Clinical Study Protocol	
Drug Substance	Osimertinib (TAGRISSO)
Study Code	D5169C00001
Version	2.0
Date	26 August 2021

A Phase III, Open-label, Randomized Study of Osimertinib with or without Platinum Plus Pemetrexed Chemotherapy, as First-line Treatment in Patients with Epidermal Growth Factor Receptor (EGFR) Mutation-Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer (FLAURA2)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Local Sponsor in Japan: AstraZeneca K.K., 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan.

Regulatory Agency Identifying Number(s): US IND 117879; EudraCT number: 2019-000650-61

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	26-Aug-2021
Original Protocol	19-Mar-2019

Amendment 1 (26-Aug-2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU.

Overall Rationale for the Amendment

The primary reason for this CSP amendment is to update the description of the timing of the primary analysis to include details of the minimum amount of follow-up required for the last recruited patient prior to conducting the primary analysis.

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 1.1 (Schedule of Activities) Table 1 and Table 2	Footnotes updated to clarify visit and data collection schedules, and to reflect update to other CSP sections.	All changes were made for clarity and avoidance of doubt.	Non-substantial
Section 1 (Introduction)	Final OS data from the FLAURA study added.	To ensure accuracy of current text.	Non-substantial
Section 2.3.2.5 (Risk-benefit summary)	Text regarding the outcome of the safety run-in period primary analysis added.	To provide an update on the risk-benefit summary following completion of the safety-run in primary analysis.	Non-substantial
Section 3 (Objectives and Endpoints) – Table 4	Addition of 'time to deterioration' to HRQoL endpoint.	To align with the study SAP.	Non-substantial
Section 4.1.1 (Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, and Appendix J	New section added to describe clinical study mitigation activities around civil crisis, natural disaster, or public health crisis (for example, COVID-19) that could impact clinical study conduct and patient safety. New Appendix J was created to provide further detailed guidance regarding changes	New information to enable mitigation strategies for clinical studies ongoing during the COVID-19 pandemic, if required, as per AstraZeneca requirements.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
	related to mitigation of study disruptions due to cases of civil crisis, natural disaster, or public health crisis.		
Section 5.1 (Inclusion criteria)	Additional text added to Inclusion Criterion #5 regarding NSCLC of mixed histology.	To clarify that patients with NSCLC of mixed histology are eligible for this study.	Non-substantial
Section 5.2 (Exclusion criteria)	Exclusion Criterion #1 reworded.	To reduce ambiguity and clarify that patients with stable brain metastases are eligible for enrollment.	Non-substantial
Section 5.2 (Exclusion criteria)	Additional text added to Exclusion Criterion #3 to define active infection.	Definition of active infection added for clarity.	Non-substantial
Section 5.2 (Exclusion criteria)	Additional text added to Exclusion Criterion #5 to include 24-hour urine collection.	Added to allow for 24-hour urine collection as alternative to Cockcroft-Gault for creatinine clearance calculation.	Non-substantial
Section 5.3.1 (Pregnancy) and Appendix H	Text added to clarify that current advice relates to osimertinib, and local label/practices should be followed for chemotherapy. Wording updated to clarify that contraception methods should be highly effective.	For clarity.	Non-substantial
Section 6.5.1 (Restricted and prohibited concomitant medications)	Timing of the avoidance of strong inducers of CYP3A4 updated from 3 months to 3 weeks	To reflect latest DDI information.	Non-substantial
Section 7.2 (Treatment through progression)	Section updated to clarify treatment through progression is only applicable to osimertinib monotherapy treatment. Timing of survival data collection updated.	For clarity.	Non-substantial
Section 8.1.3 (Screening tumor sample for EGFR mutation analysis)	Text regarding provision of archived tissue added.	To better describe tumor tissue requirements.	Non-substantial
Section 8.1.4.5 (Administration of patient-reported	Details of back-up options in the event of ePRO device failure added.	For clarity.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
outcomes questionnaires)			
Section 8.2.1 (Clinical safety laboratory assessments) – Table 8	Creatinine clearance added to Table 8 as a required laboratory variable.	Previously omitted in error.	Non-substantial
Section 8.2.3 (Vital signs)	Text regarding timing of vital signs added.	For clarity and avoidance of doubt.	Non-substantial
Section 8.2.4 (Electrocardiograms), Table 1, and Table 2	Text updated to indicate ECGs should be performed in triplicate at all timepoints.	To ensure compliance with the intended ECG data collection regimen.	Non-substantial
Section 8.3.7 (Adverse events based on examinations and tests)	Additional text added to better describe when examinations and tests should be reported as AEs.	For clarity and avoidance of doubt.	Non-substantial
Section 8.4.5.1.1 (Dose adjustment information for osimertinib)	Amendments made to dose modification criteria in Table 10. Further details of specific AEs added/updated.	To reflect latest safety data and standards.	Non-substantial
Section 8.5 (Pharmacokinetics)	Further information added in relation to PK sample data collection	To further clarify timings of PK sample collection for avoidance of doubt.	Non-substantial
Section 8.8.1 (Exploratory biomarkers), Table 1 and Table 2	Details of ctDNA sample collection added/clarified.	To ensure clarity on the timing of ctDNA sample collection, including post-primary DFS analysis collection.	Non-substantial
Section 9 (Statistical considerations)	Text added to state that additional data may be generated to summarize the impact of COVID-19 on study conduct.	To address the impact of COVID-19 on study conduct.	Non-substantial
9.2.1 Statistical hypotheses	Details of the timing of the primary analysis revised to include the requirement for at least a 16-month follow-up from the time of Last Subject In, in addition to approximately 278 PFS events.	COVID-19 has impacted study enrolment in non-Asia countries, and therefore the primary analysis will not be conducted until the specified follow-up period from the time of Last Subject In has been reached to ensure a sufficient timeframe to observe disease progression events.	Substantial
Appendix I (Calculated creatinine clearance	Creatinine clearance calculations revised.	Updated to correct a previous error in the formula, and to include 24-hour urine collection.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor; therefore, have not been summarized.	Non-substantial

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)

Table 1 Study assessments for patients in the safety run-in up to primary PFS analysis DCO of the randomized period

	Screening Period		Treatment Period										Follow-up Period			Details in CSP section or Appendix
	Screen-ing	Treat-ment Alloca-tion [a]	Cycle 1			Cycle 2 /Day 1	Cycle 3 /Day 1	Cycle 4 /Day 1	Cycle 5 /Day 1	Cycle 6 /Day 1	Cycle 7 /Day 1 onward [b]	Treat-ment Discontin-uation	28-day follow-up [c]	Progres-sion follow-up [d]	Survival follow-up	
Visit	**1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**					
Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**22**	**43**	**64**	**85**	**106**	**127+**					
Week	**NA**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**16**	**19+**					
Window (days)	**NA**	**-7**	**0**	**+/-2**	**+/-2**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**		**+7**	**+/-7**	**+/-7**	
Informed consent [e]	X															Section 5.1
Inclusion /exclusion criteria	X		X													Sections 5.1 and 5.2
Diagnostic clinical procedures																
Tumor tissue sample for central EGFR mutation analysis [f]	X															Section 8.1.3
Plasma sample for central EGFR mutation testing [f]	X															Section 8.1.3
Routine clinical procedures [g]																
Demography [h]	X															Section 5.1
Physical examination and weight	X		X [i]			X	X	X	X	X	X	X				Section 8.2.2
Medical history and comorbid conditions	X															Sections 5.1 and 5.2
WHO performance status	X		X [i]			X	X	X	X	X	X	X		X		Section 8.2.6
Vital signs	X		X [i]	X	X	X	X	X	X	X	X	X				Section 8.2.3
Height	X															Section 8.2.2
Triplicate ECG	X		X [i]	X	X	X	X	X	X	X	X	X [j]				Sections 8.2.4 and 5.4

	Screening Period		Treatment Period										Follow-up Period			Details in CSP section or Appendix
	Screen-ing	Treat-ment Alloca-tion [a]	Cycle 1			Cycle 2 /Day 1	Cycle 3 /Day 1	Cycle 4 /Day 1	Cycle 5 /Day 1	Cycle 6 /Day 1	Cycle 7 /Day 1 onward [b]	Treat-ment Discontin-uation	28-day follow-up [c]	Progres-sion follow-up [d]	Survival follow-up	
Visit	**1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**					
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Echocardiogram/ MUGA	X								at Week 13 (±1 week) and then every 12 weeks (± 1 week) relative to first dose of IP and as clinically indicated			X [k]				Section 8.2.5
Concomitant medication	X	Conducted at every visit and can be conducted by phone														Section 6.5
Anti-cancer and surgical treatment	X															Sections 5.1 and 5.2
Routine safety measurements [g]																
Pregnancy test (serum or urine)	X [l]															Sections 5.1, 5.2, and 8.2.1
Adverse events	X	Conducted at every visit and can be conducted by phone												X [m]	X [m]	Section 8.3
Safety laboratory assessments (clinical chemistry, haematology and urinalysis)	X		X[i]	X	X	X	X	X	X	X	X	X				Sections 8.2.1 and 5.4
Creatinine clearance calculation	X		X [i]			X	X	X	X	X	X	X				Appendix I
Biomarker analyses [n]																
Optional tumor biopsy for exploratory research and diagnostic development														X (taken at progress-sion)		Section 8.8
Blood sample for exploratory analysis of plasma biomarkers (ctDNA and protein analysis) [o]			X [o]	X	X	X	X	X	X	X	X	X		X (taken at progress-sion)		Section 8.8

	Screening Period		Treatment Period										Follow-up Period			Details in CSP section or Appendix
	Screen-ing	Treat-ment Alloca-tion [a]	Cycle 1			Cycle 2 /Day 1	Cycle 3 /Day 1	Cycle 4 /Day 1	Cycle 5 /Day 1	Cycle 6 /Day 1	Cycle 7 /Day 1 onward [b]	Treat-ment Discontin-uation	28-day follow-up [c]	Progres-sion follow-up [d]	Survival follow-up	
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Window (days)	**NA**	**-7**	**0**	**+/-2**	**+/-2**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**		**+7**	**+/-7**	**+/-7**	
Pharmacokinetic measurements																
Pre-dose blood sample [p]						X	X			X						Section 8.5
Post-dose blood sample [p]						X (1 hr)	X (1, 2, 4, and 6 hrs)			X (1 hr)						Section 8.5
Efficacy measurements [g]																
Brain, chest and abdomen imaging (RECIST 1.1) [q, r]	X						X		at Week 13 (±1 week) and then every 12 weeks (± 1 week) relative to first dose of IP until RECIST 1.1 defined radiological disease progression							Sections 8.1.1, 8.1.2, and Appendix E
Pharmacogenetic sampling (optional) [g]																
Genetics (Gx) blood sample (optional)			X [s]													Section 8.7
Study treatment administration [t]																
Treatment allocation		X														Section 6.1.1.1
Osimertinib treatment dispensed (daily dosing)			X			X	X	X	X	X	X					Section 6.1.2.1
Pre-treatment for chemotherapy [t]																
Folic acid (pre-treatment)		Begin 5-7 days prior to first infusion; daily during treatment period, and for 21 days after pemetrexed discontinuation														Section 6.1.2.2
Vitamin B_{12} intramuscular (pre-treatment)		Within 7 days prior to first infusion; every 3 cycles (9 weeks) during treatment period on the day of pemetrexed administration														Section 6.1.2.2

	Screening Period		Treatment Period										Follow-up Period			Details in CSP section or Appendix
	Screen-ing	Treat-ment Alloca-tion [a]	Cycle 1			Cycle 2 /Day 1	Cycle 3 /Day 1	Cycle 4 /Day 1	Cycle 5 /Day 1	Cycle 6 /Day 1	Cycle 7 /Day 1 onward [b]	Treat-ment Discontin-uation	28-day follow-up [c]	Progres-sion follow-up [d]	Survival follow-up	
Visit	**1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**					
Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**22**	**43**	**64**	**85**	**106**	**127+**					
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Corticosteroid (pre-treatment)		On the day prior to, on the day of, and on the day after pemetrexed administration														Section 6.1.2.2
Chemotherapy [g, t]																
Cisplatin or carboplatin IV treatment [u]			X			X	X	X								Section 6.1.2.2
Pemetrexed IV treatment			X			X	X	X	X	X	X					Section 6.1.2.2
Survival follow-up																
Survival status [v]															X	Section 7.1.2

CSP = clinical study protocol; ctDNA = circulating tumor deoxyribonucleic acid; DCO = data cut-off; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; hr = hour; IV = intravenous; MRI = magnetic resonance imaging; MUGA = Multi Gated Acquisition Scan; NA = not applicable; PFS = progression-free survival; PK = pharmacokinetics; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SoA = schedule of assessments; WHO = World Health Organization.

[a] Can be conducted by phone. Treatment allocation must take place within 7 days prior to Cycle 1 Day 1.

[b] Patients who have discontinued chemotherapy who are still receiving osimertinib are required to attend visits to perform assessments every 6 weeks from Cycle 7 until Cycle 17 (Week 49) and then visits every 12 weeks until disease progression, IP discontinuation or the primary PFS DCO. Patients who are receiving osimertinib + chemotherapy are also required to attend every 3 weeks for pemetrexed administration (cycles 8, 10, 12, etc.) with no protocol mandated assessments needed on those visits. Circulating tumor DNA collection timepoints should be consistent between arms (every 6 weeks) and aligned with RECIST scan visits from Cycle 7 Day 1 onwards (every 12 weeks) until progression or discontinuation.

[c] At a minimum telephone contact should be made with the patient. If an assessment was abnormal and clinically significant at treatment discontinuation, a site visit is required.

[d] At the Investigator's discretion, study treatment may continue after progression if a patient continues to derive clinical benefit per guidelines Section 7.2. Patients who continue on treatment following progression should maintain the schedule of assessments at each cycle (ie, 21 days +/-3days): Routine safety measurements (AEs, safety laboratory assessments [clinical chemistry, hematology and urinalysis], and creatinine clearance calculation); Routine clinical procedures (physical exam, WHO PS, vital signs, triplicate ECG, Echo/multi-gated acquisition (MUGA), and concomitant medications). In addition, patients will continue to be followed up for survival status every 12 weeks (calculated from the time of the treatment discontinuation visit) until death, withdrawal of consent, or the primary PFS analysis for the randomized period DCO as per the survival follow-up column. Details are provided in Section 7.2.

[e] Consent may be taken prior to 28-day window if required. The screening period of 28 days will then start with first study-related assessment. Consent must be taken prior to any study related assessments or procedures.

[f] Patients are eligible to be considered for inclusion on the basis of local pre-existing EGFR tumor tissue test results from accredited laboratories. It is mandatory for all patients to provide baseline plasma and archived tissue samples for central testing by tissue/plasma cobas® EGFR Mutation Test v2 testing post-enrollment (Section 8.1.3). The tissue sample and plasma sample will also be used for biomarker analysis (Section 8.8).

[g] In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of IP for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21 days ± 3 days). In the event that a dose of chemotherapy is delayed due to toxicity, the next dose should be given as soon as possible according to Section 8.4.5. If treatment cycles are adjusted all procedures except imaging will be completed relative to the adjusted cycle and not weeks on treatment. If chemotherapy treatment delay is due to pandemic/logistical reasons (non-AE related), a maximum of 2 weeks ([14 days]; ie, 5 weeks since the last dose of chemotherapy) delay will be allowed.

[h] Include date of birth or age, gender, race, ethnicity, and smoking history for all patients.

[i] Screening assessments that have been performed within 14 days prior to starting study treatment do not have to be repeated on Cycle 1 Day 1 if the patient's condition has not changed (this includes vital signs, physical examination, ECG, and safety laboratory assessments).

[j] A 28-day follow-up assessment will be required if an abnormal on-treatment assessment was ongoing at the time of discontinuation of study therapy to confirm reversibility of the abnormality.

[k] If a patient had a MUGA or echocardiogram performed within 28 days prior to treatment discontinuation, the discontinuation visit Echo/MUGA scan is not required unless clinically indicated.

[l] 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, within 14 days of the first dose of study treatment.

[m] SAEs considered related to study treatment and/or study procedures will be collected throughout progression follow-up. Only SAEs considered related to study treatment will be collected throughout survival follow-up.

[n] Optional blood and tumor samples for exploratory biomarker analyses are not applicable as specified by local country specific regulations, ie, China.

[o] To be taken pre-dose on Cycle 1 Day 1.

[p] Pre-dose PK samples should be collected within 1 hour before the dose on the day of collection. The osimertinib PK samples at Cycle 3 Day 1 and Cycle 6 Day 1 should be collected on the day of the chemotherapy dosing for that cycle. If the dosing for chemotherapy is altered due to interruption or modified (ie, the patient receives only a partial dose) for any other reason, the collection of this PK samples should be performed at the next scheduled dosing of chemotherapy and osimertinib.

[q] The baseline radiological assessments should be performed during the 28-day screening period and preferably as close as possible to and prior to the date of treatment allocation. Baseline assessments include (i) CT (preferred) or MRI chest/abdomen (including liver and adrenal glands) plus any other sites where disease is suspected or known at baseline and (ii) Brain imaging -MRI is preferred unless contraindicated.

Follow-up scans of anatomy imaged at baseline (as well as other sites where disease is suspected or known) are to be performed using the same modality as at baseline, after 6 weeks (±1 week), 12 weeks (±1 week), and then every 12 weeks (±1 week) subsequently, relative to first dose, until radiological disease progression as per RECIST 1.1, even if dose is delayed due to toxicity or a patient discontinues treatment prior to progression or receives other anti-cancer treatment.

[r] Brain scans using the same modality as at baseline will be performed as part of each RECIST tumor assessment visit in patients with brain metastases or a history of brain metastases until RECIST 1.1-defined disease progression. In patients without brain metastases or a history of brain metastases at baseline, brain scans will be performed only when there is a suspected CNS progression and at the point of RECIST 1.1 defined extracranial progression.

[s] 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 been provided prior to sample collection. Blood samples for genetic analyses will not be collected in China as per local regulations.

[t] Perform all study procedures and assessments as described in above table and ensure all eligibility criteria are met prior to IP dispensing and administration. Pre-treatment for chemotherapy should be completed prior to osimertinib, cisplatin, carboplatin, and pemetrexed dosing. Osimertinib and chemotherapy dosing should begin on the same day.

[u] Prior to treatment allocation for each patient, the Investigator will select cisplatin or carboplatin.

[v] Patients will be contacted for survival follow-up every 12 weeks (calculated from the time of the treatment discontinuation visit) up to the data cut-off for the primary PFS for the randomized period. Patients should be contacted in the week after data cut-off to establish survival status.

Table 2 Study assessments for patients in the randomized period

	Screening Period		Treatment Period										Follow-up Period			Details in CSP section or Appendix
	Screen-ing	Random-ization[a]	Cycle 1			Cycle 2 /Day 1	Cycle 3 /Day 1	Cycle 4 /Day 1	Cycle 5 /Day 1	Cycle 6 /Day 1	Cycle 7 /Day 1 onward [b]	Treat-ment Discontin-uation	28-day follow-up [c]	Progres-sion follow-up [d]	Survival follow-up	
Visit	**1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**					
Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**22**	**43**	**64**	**85**	**106**	**127+**					
Week	**NA**	**NA**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**16**	**19+**					
Window (days)	**NA**	**-7**	**0**	**+/-2**	**+/-2**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**		**+7**	**+/-7**	**+/-7**	
Informed consent [e]	X															Section 5.1
Inclusion /exclusion criteria	X		X													Sections 5.1 and 5.2
Diagnostic clinical procedures																
Tumor tissue sample for central EGFR mutation analysis [f]	X															Section 8.1.3
Plasma sample for central EGFR mutation testing [f]	X															Section 8.1.3
Routine clinical procedures [g]																
Demography [h]	X															Section 5.1
Physical examination and weight	X		X [i]			X	X	X	X	X	X	X				Section 8.2.2
Medical history and comorbid conditions	X															Sections 5.1 and 5.2
WHO performance status	X		X [i]			X	X	X	X	X	X	X		X		Section 8.2.6
Vital signs	X		X [i]	X	X	X	X	X	X	X	X	X				Section 8.2.3
Height	X															Section 8.2.2
Triplicate ECG	X		X [i]	X	X	X	X	X	X	X	X	X [j]				Sections 8.2.4 and 5.4

	Screening Period		Treatment Period										Follow-up Period			Details in CSP section or Appendix
	Screen-ing	Random-ization[a]	Cycle 1			Cycle 2 /Day 1	Cycle 3 /Day 1	Cycle 4 /Day 1	Cycle 5 /Day 1	Cycle 6 /Day 1	Cycle 7 /Day 1 onward [b]	Treat-ment Discontin-uation	28-day follow-up [c]	Progres-sion follow-up [d]	Survival follow-up	
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Echocardiogram/ MUGA	X								at Week 13 (± 1 week) and then every 12 weeks (± 1 week) relative to randomization and as clinically indicated [j]			X [k]				Section 8.2.5
Concomitant medication	X	Conducted at every visit and can be conducted by phone														Section 6.5
Anti-cancer and surgical treatment	X													X	X	Sections 5.1, 5.2, and 8.2.1
Routine safety measurements [g]																
Pregnancy test (serum or urine)	X [l]															Section 5.1, 5.2, and 8.2.1
Adverse events	X	Conducted at every visit and can be conducted by phone												X [m]	X [m]	Section 8.3
Safety laboratory assessments (clinical chemistry, haematology and urinalysis)	X		X [i]	X	X	X [i]	X	X	X	X	X	X				Sections 8.2.1 and 5.4
Creatinine clearance calculation	X		X [i]			X	X	X	X	X	X	X				Appendix I
Biomarker analyses [n]																
Optional tumor biopsy for exploratory research and diagnostic development														X (taken at progress-sion)		Section 8.8
Blood sample for, exploratory analysis of plasma biomarkers (ctDNA and protein analysis) [o]			X [o]	X	X	X	X	X	X	X	X	X		X (taken at progress-sion)		Section 8.8

	Screening Period		Treatment Period										Follow-up Period			Details in CSP section or Appendix
	Screen-ing	Random-ization[a]	Cycle 1			Cycle 2 /Day 1	Cycle 3 /Day 1	Cycle 4 /Day 1	Cycle 5 /Day 1	Cycle 6 /Day 1	Cycle 7 /Day 1 onward [b]	Treat-ment Discontin-uation	28-day follow-up [c]	Progres-sion follow-up [d]	Survival follow-up	
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Pharmacokinetic measurements																
Pre-dose blood sample [p]						X	X			X						Section 8.5
Post-dose blood sample [p]						X (1 hr)	X (1, 2, 4, and 6 hrs)			X (1 hr)						Section 8.5
Clinical outcome assessments [g]																
EORTC QLQ-LC13 [q]			Weekly (±1 day) starting at C1D1 until Day 57. From Day 64 every 3 weeks. (±3 days)									X		X [q]	X [q]	Section 8.1.4
EORTC QLQ-C30 [q]			C1D1, Day 22, Day 43 (±1 day). From Day 64; every 6 weeks (±3 days)									X		X [q]	X [q]	Section 8.1.4
EQ-5D-5L [q]			C1D1, Day 22, Day 43 (±1 day). From Day 64; every 6 weeks (±3 days)									X		X [q]	X [q]	Section 8.1.4
PRO-CTCAE [q]			Weekly (±1 day) starting at C1D1 until Day 57. From Day 64; every 3 weeks (±3 days)									X		X [q]	X [q]	Section 8.1.4
PGIS [q]			C1D1, Day 22, Day 43 (±1 day). From Day 64; every 6 weeks (±3 days)									X		X [q]	X [q]	Section 8.1.4
Health Resource Use Module [r]			X			X	X	X	X	X	X	X		X [r]	X [r]	Section 8.7
Efficacy measurements [g]																
Brain, chest and abdomen imaging (RECIST 1.1) [s, t]	X						X		at Week 13 (± 1 week) and then every 12 weeks (± 1 week) relative to randomization until RECIST 1.1 defined radiological disease progression							Sections 8.1.1, 8.1.2, and Appendix E
Pharmacogenetic sampling (optional) [g]																
Genetics (Gx) blood sample (optional)			X [u]													Section 8.7
Study treatment administration [v]																
Randomization		X [w]														Section 6.3

	Screening Period		Treatment Period										Follow-up Period			Details in CSP section or Appendix
	Screen-ing	Random-ization[a]	Cycle 1			Cycle 2 /Day 1	Cycle 3 /Day 1	Cycle 4 /Day 1	Cycle 5 /Day 1	Cycle 6 /Day 1	Cycle 7 /Day 1 onward [b]	Treat-ment Discontin-uation	28-day follow-up [c]	Progres-sion follow-up [d]	Survival follow-up	
Visit	**1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**					
Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**22**	**43**	**64**	**85**	**106**	**127+**					
Week	**NA**	**NA**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**16**	**19+**					
Window (days)	**NA**	**-7**	**0**	**+/-2**	**+/-2**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**		**+7**	**+/-7**	**+/-7**	
All patients																
Osimertinib treatment dispensed (daily dosing)			X			X	X	X	X	X	X					Section 6.1.2.1
Pre-treatment for chemotherapy with osimertinib arm [v]																
Folic acid (pre-treatment)		Begin 5-7 days prior to first infusion; daily during treatment period, and for 21 days after pemetrexed discontinuation														Section 6.1.2.2
Vitamin B_{12} intramuscular (pre-treatment)		Within 7 days prior to first infusion; every 3 cycles (9 weeks) during treatment period on the day of pemetrexed administration														Section 6.1.2.2
Corticosteroid (pre-treatment)		On the day prior to, on the day of, and on the day after pemetrexed administration														Section 6.1.2.2
Chemotherapy with osimertinib arm [g, v]																
Cisplatin or carboplatin IV treatment [x]			X			X	X	X								Section 6.1.2.2
Pemetrexed IV treatment			X			X	X	X	X	X	X					Section 6.1.2.2
Survival follow-up																
Subsequent response/ progression data [y]															X	Section 7.1.2
Survival status [z]															X	Section 7.1.2

C1D1 = Cycle 1, Day 1; CSP = clinical study protocol; ctDNA = circulating tumor deoxyribonucleic acid; DCO = data cut-off; ECG = electrocardiogram; 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; hr = hour; IV = intravenous; IVRS = interactive voice response system; IWRS = interactive web response system; MRI = magnetic resonance imaging; MUGA = Multi Gated Acquisition Scan; NA = not applicable; OS = overall survival; PFS = progression-free survival; PFS2 = time from randomization to second progression on a subsequent treatment; PGIS=Patients Global Impression of Severity; PK = pharmacokinetic; PRO = patient-reported outcome; PRO-CTCAE = Patient Reported Outcome version of the Common Terminology Criteria

for Adverse Event; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SoA = schedule of assessments; WHO = World Health Organization.

[a] Can be conducted by phone. Randomization must take place within 7 days prior to Cycle 1 Day 1.

[b] Patients on osimertinib treatment (osimertinib only arm or who have discontinued chemotherapy who are still receiving osimertinib) are required to attend visits to perform assessments every 6 weeks from Cycle 7 until Cycle 17 (Week 49) and then visits every 12 weeks until disease progression, IP discontinuation or primary PFS DCO. Patients who are receiving osimertinib + chemotherapy are also required to attend every 3 weeks for pemetrexed administration (cycles 8, 10, 12, etc.) with no protocol mandated assessments needed on those visits. Circulating tumor DNA collection timepoints should be consistent between arms (every 6 weeks) and aligned with RECIST scan visits from Cycle 7 Day 1 onwards (every 12 weeks) until progression or discontinuation.

[c] At a minimum telephone contact should be made with the patient. If an assessment was abnormal and clinically significant at treatment discontinuation, a site visit is required.

[d] At the Investigator's discretion, study treatment may continue after progression if a patient continues to derive clinical benefit per guidelines Section 7.2. Patients who continue on treatment following progression should maintain the schedule of assessments at each cycle (ie, 21 days +/-3days): Routine safety measurements (AEs, safety laboratory assessments [clinical chemistry, hematology and urinalysis], and creatinine clearance calculation); Routine clinical procedures (physical exam, WHO PS, vital signs, triplicate ECG, Echo/MUGA, and concomitant medications); and PROs every 8 weeks post progression until PFS2 or DCO for the primary PFS analysis, whichever is sooner. In addition, patients will continue to be followed up for survival status every 12 weeks (calculated from the time of the treatment discontinuation visit) until death, withdrawal of consent, or the final OS analysis DCO as per the survival follow-up column. Details are provided in Section 7.2.

[e] Consent may be taken prior to 28-day window if required. The screening period of 28 days will then start with first study-related assessment. Consent must be taken before any study related assessments or procedures.

[f] Patients are eligible to be considered for inclusion on the basis of local pre-existing EGFR tumor tissue test results from accredited laboratories. It is mandatory for all patients to provide baseline plasma and archived tissue samples for central testing by tissue/plasma cobas® EGFR Mutation Test v2 testing post-enrollment (Section 8.1.3). The tissue sample and plasma sample will also be used for biomarker analysis (Section 8.8).

[g] In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of IP for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21 days ± 3 days). In the event that a dose of chemotherapy is delayed due to toxicity, the next dose should be given as soon as possible according to Section 8.4.5. If treatment cycles are adjusted all procedures except imaging and clinical outcome assessments (PROs and Health Resource Use Module) will be completed relative to the adjusted cycle and not weeks on treatment. If chemotherapy treatment delay is due to pandemic/logistical reasons (non-AE related), a maximum of 2 weeks (ie, 5 weeks since the last dose of chemotherapy) delay will be allowed.

[h] Include date of birth or age, gender, race, ethnicity, and smoking history for all patients.

[i] Screening assessments that have been performed within 14 days prior to starting study treatment do not have to be repeated on Cycle 1 Day 1 if the patient's condition has not changed (this includes vital signs, physical examination, ECG, and safety laboratory assessments). Additionally, in the event a patient's visit 4 (Cycle 1 Day 15) and visit 5 (Cycle 2 Day 1) (per allowable protocol timeframes) are within 72 hours of each other, then a repeat of safety laboratory assessments at visit 5 is exempted.

[j] A 28-day follow-up assessment will be required if an abnormal on-treatment assessment was ongoing at the time of discontinuation of study therapy to confirm reversibility of the abnormality.

[k] If a patient had a MUGA or echocardiogram performed within 28 days prior to treatment discontinuation, the discontinuation visit Echo/MUGA scan is not required unless clinically indicated.

[l] 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, within 14 days of the first dose of study treatment.

[m] SAEs considered related to study treatment and/or study procedures will be collected throughout progression follow-up. Only SAEs considered related to study treatment will be collected throughout survival follow-up.

[n] Optional blood and tumor samples for exploratory biomarker analyses are not applicable as specified by local country specific regulations, ie, China.

[o] To be taken pre-dose on Cycle 1 Day 1. Post primary PFS analysis, ctDNA samples will continue to be collected at treatment discontinuation and at progression only.

[p] Pre-dose PK samples should be collected within 1 hour before the dose on the day of collection. The osimertinib PK samples at Cycle 3 Day 1 and Cycle 6 Day 1 should be collected on the day of the chemotherapy dosing for that cycle. If the dosing for chemotherapy is altered due to interruption or modified (ie, the patient receives only a partial dose) for any other reason, then, the collection of this PK samples should be performed at the next scheduled dosing of chemotherapy and osimertinib. If chemotherapy dosing is discontinued, PK collection could be stopped in consultation with the AstraZeneca Study Physician. If the dosing of osimertinib is altered due to interruption or modified for any other reason, then the collection of these PK samples should be performed at the next scheduled visit, after at least 7 continuous days of dosing of osimertinib. No further PK samples are required if osimertinib dosing is discontinued.

[q] PRO handheld devices should be assigned to patients only on the day of Cycle 1, Day 1. Baseline ePROs should be completed by patients prior to dosing when they are still in the clinic to ensure that the device is correctly set up and working properly. Thereafter, ePROs should be completed by the patients at home. PROs to be collected at treatment discontinuation visit following disease progression and every 8 weeks post progression until PFS2. For patients who discontinue study treatment prior to progression, PROs should be collected at the study treatment discontinuation visit and continue to be collected at the same frequency as the treatment period until disease progression, then at disease progression and every 8 weeks post progression until PFS2 or DCO for the primary PFS analysis, whichever is sooner. After the data cut-off for the primary PFS analysis, patients who have not had progression, regardless of whether study treatment is ongoing, should stop ePROs. PRO CTCAE will be administered only in the languages where a linguistically validated version exists.

[r] Patients who discontinue study treatment for a reason other than progression should have healthcare resource use module collected at that time of study treatment discontinuation until progression. Following progression, healthcare resource use module will be collected every 12 weeks (calculated from the time of the treatment discontinuation visit) during survival follow-up for all patients until the primary PFS analysis DCO. See Section 8.9 for further details.

[s] The baseline radiological assessments should be performed during the 28-day screening period and preferably as close as possible to and prior to the date of randomization. Baseline assessments include (i) CT (preferred) or MRI chest/abdomen (including liver and adrenal glands) plus any other sites where disease is suspected or known at baseline and (ii) Brain imaging - MRI is preferred unless contraindicated.
Follow-up scans of anatomy imaged at baseline (as well as other sites where disease is suspected or known) are to be performed using the same modality as at baseline, after 6 weeks (±1 week), 12 weeks (±1 week), and then every 12 weeks (±1 week) subsequently, relative to randomization, until radiological disease progression as per RECIST 1.1, even if dose is delayed due to toxicity or a patient discontinues treatment prior to progression or receives other anti-cancer treatment.
Following RECIST 1.1 defined progression, 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 is to be collected every 12 weeks up to the data cut off for the primary PFS analysis.

[t] Brain scans using the same modality as at baseline will be performed as part of each RECIST tumor assessment visit in patients with brain metastases or a history of brain metastases until RECIST 1.1-defined disease progression. In patients without brain metastases or a history of brain metastases at baseline, brain scans will be performed only when there is a suspected CNS progression and at the point of RECIST 1.1 defined extracranial progression.

[u] 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 been provided prior to sample collection. Blood samples for genetic analyses will not be collected in China as per local regulations.

[v] Perform all study procedures and assessments as described in above table and ensure all eligibility criteria are met prior to IP dispensing and administration. Pre-treatment for chemotherapy should be completed prior to osimertinib, cisplatin, carboplatin, and pemetrexed dosing. For the osimertinib with chemotherapy arm, osimertinib and chemotherapy dosing should begin on the same day.

[w] 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 for the osimertinib monotherapy arm or premedication for the osimertinib with chemotherapy arm. It is recommended that patients commence study treatment for the osimertinib monotherapy arm or premedication for the osimertinib with chemotherapy arm as soon as possible after randomization and whenever possible within one day. (ie, on the same day after randomization in the IVRS/IWRS).

[x] Prior to randomization for each patient, the Investigator will select whether the patient is to receive cisplatin or carboplatin in the event that they are randomized to the osimertinib with chemotherapy arm.

[y] Following progression, 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 DCO for the primary PFS analysis.

[z] Patients will be contacted for survival follow-up every 12 weeks (calculated from the time of the treatment discontinuation visit) up to the data cut-off for the final OS analysis. Patients should be contacted in the week after DCO for each study analysis (primary PFS and OS) to establish survival status.

Note: Following the primary PFS analysis (ie, during the OS follow-up phase), PRO and PK data will no longer be collected. All other study assessments will continue per the SoA.

1.2 Synopsis

International Co-ordinating Investigators

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Protocol Title:

A phase III, open-label, randomized study of osimertinib with or without platinum plus pemetrexed chemotherapy, as first-line treatment in patients with epidermal growth factor receptor (EGFR) mutation-positive, locally advanced or metastatic non-small cell lung cancer (FLAURA2)

Rationale:

Osimertinib is a potent, oral, irreversible tyrosine kinase inhibitor (TKI) of EGFR mutation-positive (EGFRm) and T790M mutation-positive forms of EGFR with demonstrated clinical activity on central nervous system (CNS) metastases. Osimertinib is designed to have limited activity against wild-type (WT) EGFR. Osimertinib is approved globally, and marketed as Tagrisso®, for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions (Ex19del) or exon 21 (L858R) substitution mutations and the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy.

First-line monotherapy with EGFR-TKIs (such as erlotinib, afatinib, gefitinib, osimertinib, or dacomitinib) has replaced chemotherapy as the standard of care (SoC) for patients with advanced NSCLC harboring EGFR activating mutations (NCCN 2019, Planchard et al 2018). Chemotherapy has been reserved for later-line therapy after failure of targeted therapy.

However, in a recently published study conducted in Japan (North East Japan Study Group [NEJ]009), the addition of carboplatin and pemetrexed to gefitinib as first-line treatment of patients with untreated advanced EGFRm NSCLC markedly improved the progression-free survival (PFS) and overall survival (OS) of patients, with an acceptable toxicity profile (Nakamura et al 2018, Seike et al 2018). In addition, data from 4 prospective Phase II studies (2 randomized, 2 single arm) of gefitinib in combination with pemetrexed monotherapy or carboplatin/pemetrexed doublet therapy followed by pemetrexed maintenance and a

retrospective study of erlotinib with chemotherapy (predominantly platinum/pemetrexed), further support the concept of adding chemotherapy to EGFR-TKI therapy in the first-line treatment of patients with advanced EGFRm NSCLC (Cheng et al 2016, Dudnik et al 2014, Han et al 2017, Oizumi et al 2017, Sugawara et al 2015, Yang et al 2018, Yoshimura et al 2015).

In the FLAURA study, osimertinib demonstrated superior PFS compared to first-generation EGFR-TKIs (gefitinib and erlotinib) (Soria et al 2018). The addition of platinum and pemetrexed chemotherapy to osimertinib may extend the benefit of osimertinib therapy and provide a new therapeutic option for the first-line treatment of patients with advanced EGFRm NSCLC.

Safety Run-in Objectives and Endpoints

Primary Objective:	**Endpoint/Variable:**
To evaluate the safety and tolerability of osimertinib plus chemotherapy	Adverse events graded by CTCAE v5; Clinical chemistry, hematology and urinalysis; Vital signs (pulse and blood pressure); physical examination; weight; LVEF; ECG parameters; WHO Performance Status
Secondary Objectives:	**Endpoint/Variable:**
To assess the efficacy of osimertinib plus chemotherapy	ORR, DoR; depth of response; DCR by Investigator; OS; Landmark OS at 1, 2, and 3 years
To assess the PK of osimertinib when given with chemotherapy	Steady-state plasma concentrations and appropriate PK parameters (CL_{ss}/F, $C_{max,ss}$ $C_{min,ss}$ and AUC_{ss}) of osimertinib and its metabolite, AZ5104 will be summarized. *
Exploratory Objectives:	**Endpoint/Variable:**
To explore how changes in plasma-based biomarkers (eg, ctDNA, proteomic) correlate with response	Quantitative ctDNA analysis using specific EGFR biomarkers or broader cancer biomarker panel in longitudinal plasma samples, to assess ctDNA clearance and correlate with response (eg, PFS)
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	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety or response observed in patients treated with osimertinib plus chemotherapy
To explore efficacy biomarkers and biomarker changes in baseline, longitudinal and progression samples (plasma and tumor tissue) for correlation with response	Assessment of innate and acquired resistance mechanisms and biomarkers of response including but not limited to mutations in, amplifications and expression of EGFR, TP53, HER2, MET and relevant pathway genes Proteomic and/or gene expression analysis eg, biomarkers of inflammation

Safety Run-in Objectives and Endpoints

To collect and store tumor, serum and plasma samples for potential exploratory research into factors that may influence susceptibility to development of NSCLC and/or response to osimertinib and/or chemotherapy (where response is defined broadly to include efficacy, tolerability or safety) and to assess the relationship between tissue and/or bloodborne biomarkers and selected efficacy endpoints. Tissue and plasma samples may be used to support diagnostic development.	Key genetic, gene expression and proteomic markers to include, but not limited to, EGFR mutations, HER, and proto-oncogene encoding cMET expression and/or amplification. Relationship between PK and blood-borne biomarkers. Diagnostic development.

* If feasible, further PK parameters may be derived using population PK analysis and reported separately from the CSR. Data from this study may also form part of a pooled analysis with data from other studies

AUC_{ss}=area under plasma concentration-time curve during any dosing interval at steady state [amount·time/volume]; CL_{ss}/F=apparent total body clearance at steady state; cMET = hepatocyte growth factor receptor; CSR=clinical study report; $C_{max,ss}$ =maximum plasma concentration at steady state; $C_{min,ss}$ =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; HER2=human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; MET=tyrosine-protein kinase Met; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic(s); WHO=World Health Organization.

Randomized Period Objectives and Endpoints

Primary Objective:	**Endpoint/Variable:**
To assess the efficacy of osimertinib plus chemotherapy treatment compared with osimertinib	PFS using Investigator assessment as defined by RECIST 1.1; Sensitivity analysis of PFS using BICR assessment as defined by RECIST 1.1
Secondary Objectives:	**Endpoint/Variable:**
To further assess the efficacy of osimertinib plus chemotherapy compared with osimertinib	OS; Landmark OS at 1, 2, and 3 years; ORR, DoR; depth of response; DCR by Investigator
To further assess the efficacy of osimertinib plus chemotherapy compared with osimertinib post progression	PFS2; TFST; TSST
To assess disease-related symptoms and health-related QoL in patients treated with osimertinib plus chemotherapy compared with osimertinib	Change from baseline and time to deterioration in EORTC QLQ-C30; Change from baseline and time to deterioration in EORTC QLQ-LC13

Randomized Period Objectives and Endpoints

To assess the PK of osimertinib when given with or without chemotherapy	Steady-state plasma concentrations and appropriate PK parameters (CL_{ss}/F, $C_{max,ss}$ $C_{min,ss}$ and AUC_{ss}) of osimertinib and its metabolite, AZ5104 will be summarized. *
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	Concordance of EGFR mutation status between the local EGFR mutation test and the central cobas® EGFR Mutation Test v2 results from tumor samples with evaluable results
To determine efficacy of osimertinib monotherapy vs. osimertinib combined with chemotherapy based on the cobas® EGFR Mutation Test v2 plasma screening test result for Exon 19 deletions or L858R EGFR mutations	PFS by Investigator by plasma EGFR mutation status
Safety Objective:	**Endpoint/Variable:**
To evaluate the safety and tolerability of osimertinib plus chemotherapy compared with osimertinib	Adverse events graded by CTCAE v5; Clinical chemistry, hematology and urinalysis; Vital signs (pulse and blood pressure); physical examination; weight; LVEF; ECG parameters; WHO Performance Status
Exploratory Objectives:	**Endpoint/Variable:**
To assess the impact of osimertinib plus chemotherapy compared with osimertinib on patient reported treatment related symptoms	PRO-CTCAE symptoms
To assess patients' overall impression of severity of cancer symptoms	PGIS
To compare health resource use associated with osimertinib plus chemotherapy treatment versus osimertinib	Health Resource Use Module
To assess the impact of osimertinib plus chemotherapy compared with osimertinib on patient reported health state utility	EQ-5D-5L

Randomized Period Objectives and Endpoints

To assess the efficacy of osimertinib plus chemotherapy treatment compared with osimertinib on CNS metastases in patients with CNS metastases at baseline	Neuro-radiologist assessments according to CNS RECIST 1.1 to calculate: • CNS PFS; CNS ORR; CNS DoR; CNS DCR; • Best percentage change in CNS tumor size (target lesion)
To assess the efficacy of osimertinib plus chemotherapy treatment compared with osimertinib on the prevention of CNS metastases	Neuro-radiologist assessments according to CNS RECIST 1.1 to determine the presence/absence of CNS lesions at progression in patients without CNS metastases at baseline.
To compare concordance of the cobas® EGFR Mutation Test v2 versus alternative EGFR tissue testing methods for diagnostic development	Concordance of EGFR mutation status between the cobas® EGFR Mutation Test v2 and an alternative devices.
To explore how changes in plasma-based biomarkers (eg, ctDNA, proteomic) correlate with response	Quantitative ctDNA analysis using specific EGFR biomarkers or broader cancer biomarker panel in longitudinal plasma samples, to assess ctDNA clearance and correlate with response (eg, PFS).
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	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety or response observed in patients treated with osimertinib and osimertinib plus chemotherapy
To explore efficacy biomarkers and biomarker changes in baseline, longitudinal and progression samples (plasma and tumor tissue) for correlation with response	Assessment of innate and acquired resistance mechanisms and biomarkers of response including but not limited to mutations in, amplifications and expression of EGFR, TP53, HER2, MET and relevant pathway genes Proteomic and/or gene expression analysis eg, biomarkers of inflammation

Randomized Period Objectives and Endpoints

To collect and store tumor, serum and plasma samples for potential exploratory research into factors that may influence susceptibility to development of NSCLC and/or response to osimertinib and/or chemotherapy (where response is defined broadly to include efficacy, tolerability or safety) and to assess the relationship between tissue and/or bloodborne biomarkers and selected efficacy endpoints. Tissue and plasma samples may be used to support diagnostic development.	Key genetic, gene expression and proteomic markers to include, but not limited to, EGFR mutations, HER, and proto-oncogene encoding cMET expression and/or amplification. Relationship between PK and blood-borne biomarkers. Diagnostic development.

* If feasible, further PK parameters may be derived using population PK analysis and reported separately from the CSR. Data from this study may also form part of a pooled analysis with data from other studies

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; cMET = hepatocyte growth factor receptor; CNS=central nervous system; CSR=clinical study report; $C_{max,ss}$ =maximum plasma concentration at steady state; $C_{min,ss}$ =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; 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 Questionnaire; HER2=human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; MET=tyrosine-protein kinase Met; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PFS2=time from randomization to second progression on a subsequent treatment; PGIS=Patients Global Impression of Severity; PK=pharmacokinetic(s); 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; WHO=World Health Organization.

Overall design:

This is a global phase III, open-label, randomized study of osimertinib with or without platinum plus pemetrexed chemotherapy conducted in patients with locally-advanced or metastatic EGFRm (Ex19del and/or L858R) NSCLC who have not received any prior therapy for advanced disease.

Prior to the start of the randomized period of the study, a non-randomized safety run-in will allocate study treatment to approximately 30 patients to evaluate the safety and tolerability of osimertinib with platinum (carboplatin or cisplatin) and pemetrexed.

Following a positive recommendation by the Safety Review Committee based on the evaluation of data from the safety run-in period, approximately 556 new patients will be randomized in a 1:1 ratio to receive osimertinib alone or osimertinib with pemetrexed and either cisplatin or carboplatin (hereafter, referred to as the randomized period). Patients will be stratified by race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), World Health Organization (WHO) performance status (PS) (0 or 1), and method for tissue testing (central vs. local) for generation of the p-value, using the Breslow approach for handling ties. It is anticipated that approximately 60% Asian patients and 40% non-Asian patients will be recruited. The Investigator will decide before randomization which chemotherapy regimen (carboplatin/pemetrexed or cisplatin/pemetrexed) a patient would receive in case the patient is assigned to the osimertinib plus chemotherapy arm.

Study Period:

Safety run-in

Estimated date of first patient enrolled is Q3 2019

Estimated date of last patient completed is Q1 2023

Randomized

Estimated date of first patient enrolled is Q1 2020

Estimated date of last patient completed (OS cut-off) is Q1 2026

Number of Patients:

Approximately 30 patients will be allocated to the non-randomized safety run-in.

Approximately 556 patients will be randomized, globally, in a 1:1 ratio (osimertinib:osimertinib with chemotherapy) to the randomized period of this study.

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

Treatments and treatment duration:

During the safety run-in, 2 cohorts of patients (osimertinib plus cisplatin/pemetrexed and osimertinib plus carboplatin/pemetrexed) will be studied in a non-randomized fashion. Approximately 15 patients per cohort will receive osimertinib 80 mg once daily (QD) with either cisplatin (75 mg/m^2) or carboplatin (AUC of 5 mg/mL/min [AUC5]), and pemetrexed (500 mg/m^2), both administered every 3 weeks (Q3W) for 4 cycles, followed by osimertinib 80 mg once daily plus pemetrexed maintenance (500 mg/m^2) Q3W until RECIST 1.1-defined progression or another discontinuation criterion is met.

Data from the safety run-in will be reviewed by a Safety Review Committee. Following a positive recommendation, the randomized period of the study will begin, in which a new group of patients will be randomized to receive osimertinib alone or with pemetrexed and either cisplatin or carboplatin. Patients who were involved in the safety run-in period will not be included in the randomized period, but may continue the treatment they received during the safety run in, with procedures continuing as shown in the schedule of assessments (SoA) Table 1.

The 2 randomized treatment regimens will be as follows:

- osimertinib 80 mg QD OR
- osimertinib 80 mg QD with pemetrexed (500 mg/m^2) (with vitamin supplementation) plus either cisplatin (75 mg/m^2) or carboplatin (AUC5), both administered on Day 1 of 21-day cycles for 4 cycles, followed by osimertinib 80 mg QD with pemetrexed maintenance (500 mg/m^2) Q3W.

Randomized treatment will continue until RECIST 1.1-defined progression or until another discontinuation criterion is met. Following treatment discontinuation, choice of subsequent therapy will be at the discretion of the Investigator. Patients will be followed for second progression on a subsequent treatment, defined according to local practice, and for survival.

Safety Review Committee:

During the safety run-in, safety and tolerability data will be reviewed by a Safety Review Committee, which will convene when safety data are available from at least 12 patients in each cohort who have either received ≥3 cycles of study treatment (osimertinib, cisplatin or carboplatin, and pemetrexed) or who have discontinued study treatment due to unacceptable toxicity. All data, including, safety, tolerability, and available pharmacokinetic (PK) data from all patients, will be reviewed. The Safety Review Committee will include independent experts with relevant experience in clinical trial conduct, methodology, and procedures in patients with NSCLC, and AstraZeneca personnel. The Safety Review Committee will recommend whether the data support the initiation of the randomized period of the study after which it will end its function.

Oversight of safety and tolerability of the randomized period of the study will be provided by an Independent Data Monitoring Committee (IDMC), with fully independent members. The IDMC will meet periodically to review safety data and will make recommendations to continue, amend, or stop the study based on findings. The IDMC will convene at the beginning of the randomized period, but will have access to up to date data from patients ongoing in the safety run-in period as well as the randomized period to inform their recommendations.

The IDMC will meet after data are available from approximately 60 patients across both treatment arms with at least 28 days of follow-up. Thereafter, the IDMC will meet after data

are available from approximately 150 patients across both treatment arms with at least 28 days of follow-up, after 300 patients across both treatment arms with at least 28 days of follow-up, after completion of recruitment, and approximately every 6 months until the primary PFS analysis data cut-off (DCO).

The IDMC will also meet for the planned futility analysis when approximately 83 PFS events have occurred to provide a recommendation for the continuation of this study based on efficacy observed in the randomized period.

Statistical methods

No formal statistical analysis is planned for efficacy within the safety run-in, and the data will be reviewed in its entirety by Safety Review Committee to advise on safety. A formal database lock will be required to facilitate this data review. Patients included in the safety run-in will be excluded from the analysis of the randomized period.

After the safety run-in, patients will be randomized in a 1:1 ratio in the randomized period to receive osimertinib alone or osimertinib with pemetrexed and either cisplatin or carboplatin.

The primary analysis of PFS based on Investigator assessment (according to RECIST 1.1) will occur when approximately 278 PFS events and at least 16 months of follow-up after LSI, has occurred in the 556 randomized patients (approximately 50% maturity). This was initially expected to occur approximately 33 months after the first patient is randomized (under an assumed 15-month exponential recruitment); however, the actual DCO for the primary PFS analysis will be determined such that both criteria are met. Progression-free survival will be analyzed using a log-rank test stratified by race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1), and method for tissue testing (central vs. local) for generation of the p-value, using the Breslow approach for handling ties. The assumption of proportionality will be assessed. A sensitivity analysis of PFS will be performed based on data assessed by blinded independent central review (BICR) for all randomized patients.

A prespecified subgroup analysis will be conducted in patients who have a centrally confirmed EGFRm status. The central confirmation of a pre-existing EGFR test - as performed in a Clinical Laboratory Improvement Amendments (CLIA) accredited laboratory (United States) or in a locally accredited laboratory (outside of United States [US]) - can be determined by cobas® tissue and/or cobas® plasma tests.

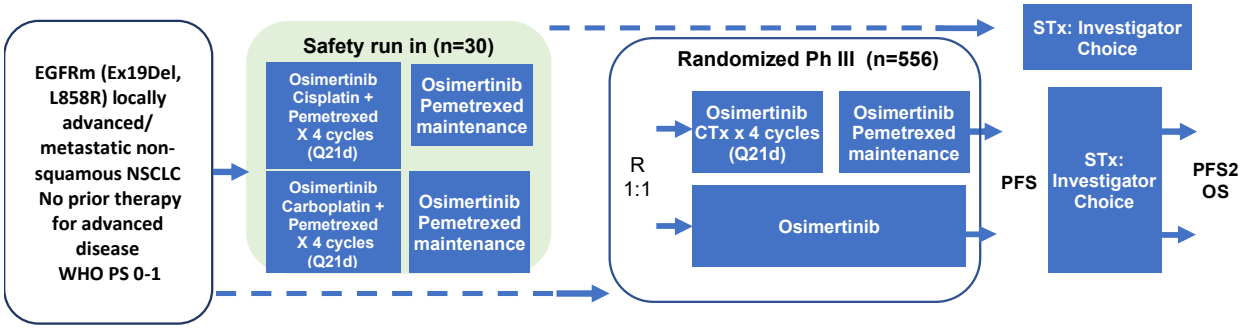
The key secondary endpoint of OS will be tested after the primary PFS analysis in a hierarchical procedure at the time of the PFS analysis and when the data are approximately 60% mature (approximately 334 death events across both arms). Alpha will be controlled across the 2 OS analyses; ie, at the time of the primary PFS analysis and at the final OS analysis, with the overall Type 1 error strongly controlled at 5% (2 sided) for the testing of OS under an O'Brien and Fleming spending rule.

Additional efficacy endpoints will be included such as objective response rate (ORR), duration of events (DoR) and time from randomization to second progression on a subsequent treatment (PFS2) (Section 3).

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



CTx = chemotherapy; EGFRm = epidermal growth factor receptor mutation-positive; Ex19del = exon 19 deletions; OS = overall survival; PFS = progression-free survival; PFS2 = time from randomization to second progression or death on a subsequent treatment; NSCLC = non-small cell lung cancer; Q21d = every 21 days; STx = subsequent treatment; WHO = World Health Organization.

2 INTRODUCTION

Primary lung cancer is the most frequent form of cancer worldwide (estimated at ~13.5% of all new cancer cases in 2018) and the most frequent form of cancer in the US after breast cancer (NCI SEER 2018). Despite the regional differences in incidence, lung cancer remains the leading cause of cancer-related death globally (25.3% of all deaths from cancer) with only 18.6% of patients, irrespective of the stage, surviving 5 years (NCI SEER 2018, NCCN 2019). Approximately 80% to 90% of all lung cancers are NSCLC (Cataldo et al. 2011, NCCN 2019). Adenocarcinoma is the most common type in the US and also the most frequent histological type in non-smokers.

Despite recent progress in early detection, in 70% to 80% of patients, lung cancer is diagnosed at a locally advanced or metastatic stage when it is no longer amenable to surgical resection (NCI SEER 2018). Advanced NSCLC is an incurable condition. Despite the development of new therapies, the prognosis remains dismal, with a mean 5-year survival rate of approximately 5% in patients with unselected NSCLC (NCI SEER 2018).

In current clinical practice, therapeutic decisions for patients with advanced NSCLC are informed by the molecular subtypes of tumors (Keedy et al 2011, Leighl et al. 2014, NCCN 2019, Planchard et al 2018, Travis et al 2011). Molecular profiling of patients with advanced NSCLC for biomarkers is standard clinical practice based on international guidelines and is conducted to detect the presence of predictive and prognostic biomarkers for NSCLC (NCCN 2019).

Numerous gene mutations or alterations have been identified as molecular therapeutic targets that impact the choice of therapy. These mutations/alterations are generally not overlapping, although 1% to 3% of NSCLC tumors may harbor concurrent alterations (NCCN 2019). Among these mutations, the presence of EGFR-activating mutations, the most common of which are Ex19del and exon 21 L858R substitution mutations, is associated with responsiveness to EGFR-TKI therapy (erlotinib, gefitinib, afatinib, osimertinib, dacomitinib).

Activating mutations in exons 18-21 of the kinase domain of EGFR are found in approximately 15% of patients with lung cancer in the US (Keedy et al 2011), 10% of patients with lung cancer in the European Economic Area (Barlesi et al 2013, Esteban et al 2015, Gahr et al 2013, Herbst et al 2008), and 30% to 50% of patients with lung cancer in Asia (Han et al 2015, Shi et al 2014, Tokumo et al 2005, Yoshida et al 2007). Overall, EGFR mutations have been found to be more frequent in never-smokers, in patients with the adenocarcinoma histological subtype, and in women. As stated above, the prevalence of the EGFR mutations is also higher in East Asian patients than in Caucasian patients (Marchetti et al 2005, Planchard et al 2018). The T790M exon 20 substitution mutation is rarely found in EGFR-TKI-naïve patients (less than 5%; Beau-Faller et al 2014, Inukai et al 2006), but is the most frequent cause (50% to 60%) of resistance to EGFR-TKIs other than osimertinib.

The established first-line therapy in patients with advanced NSCLC and a tumor harboring activating EGFR mutations discovered prior to first-line systemic therapy is 1 of the following EGFR-TKIs: osimertinib (labelled as preferred by the National Comprehensive Cancer Network [NCCN] panel), erlotinib, afatinib, gefitinib, or dacomitinib (Planchard et al 2018, NCCN 2019). Patients with advanced EGFRm NSCLC who receive EGFR-TKIs have a median OS of more than 2 years, in contrast with the survival of unselected patients receiving platinum-based chemotherapy (approximately 12 months; Heuckmann et al 2012). Five-year survival in patients with advanced EGFRm NSCLC is approximately 15% (Lin et al 2016). In patients with activating EGFR mutations, response rates of 50% to 80% have been reported with first-line EGFR-TKI treatment, compared with 15% to 34% in patients receiving platinum-doublet chemotherapy as first-line therapy or as second-line therapy following progression on first-line treatment with EGFR-TKIs (Maemondo et al 2010, Mok et al 2017, Rosell et al 2012, Sequist et al 2013, Soria et al 2015, Wu et al 2014).

The Phase III FLAURA study compared the efficacy and safety of osimertinib administered as first-line therapy to patients with advanced EGFRm (Ex19del or L858R) NSCLC versus (vs.) either gefitinib or erlotinib. FLAURA showed a statistically and clinically significant improved median PFS in the osimertinib arm (18.9 months [95% confidence interval [CI]: 15.2, 21.4]) compared to erlotinib or gefitinib (10.2 months [95% CI: 9.6, 11.1]), with a hazard ratio (HR) of 0.46 (95% CI: 0.37, 0.57; $p < 0.0001$). The results of the interim OS analysis showed an HR of 0.63 (95% CI: 0.45, 0.88). There was a clinically meaningful improvement in OS for patients on osimertinib compared to patients on erlotinib or gefitinib ($p = 0.0068$), which did not reach formal statistical significance for the interim analysis. At the time of initiation of the FLAURA2 study, the OS results from FLAURA were immature (25.4%) and a final OS analysis was awaited. Since this time, final OS analysis data have become available (DCO2 date of 25 June 2019), which demonstrated a 20% lower risk of death in the osimertinib arm compared with the SoC arm (OS HR: 0.799; adjusted 95.05% CI: 0.6406, 0.9968). The difference between treatment arms in favor of osimertinib was statistically significant (p-value of 0.0462, which was below the pre-defined level of 0.0495 required at this analysis). Median OS was 38.6 (95% CI: 34.5, 41.8) months in the osimertinib arm, and 31.8 (95% CI: 26.6, 36.0) months in the SoC arm, a difference of 6.8 months. These data demonstrate that most of the benefit of osimertinib seen in the PFS analysis at DCO1 was preserved in the final OS analysis at DCO2.

On the basis on the results of the primary analysis of the FLAURA study, osimertinib was recommended by the NCCN Panel as preferred first-line therapy in these patients. Osimertinib is approved for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy. Country specific variations in approved indications may apply.

Prior to the discovery of EGFR activating mutations in 2004 (Lynch et al 2004, Paez et al 2004), Phase III studies of first-line treatment of patients with advanced NSCLC assessed either cisplatin/gemcitabine or carboplatin/paclitaxel, with gefitinib or placebo (Giaccone et al 2004 [INTACT1], Herbst et al 2004 [INTACT2]) or erlotinib or placebo (Gatzemeier et al 2007 [TALENT], Herbst et al 2005 [TRIBUTE]). Combination therapy was not found to be superior in any of the studies with respect to the primary endpoint of OS or secondary endpoints of time to progression and ORR. Never smokers treated with erlotinib and chemotherapy seemed to experience an improvement in survival in the TRIBUTE study. EGFR mutation testing was conducted retrospectively in a subgroup of patients with available archival tissue (n = 274) in the TRIBUTE study (Eberhard et al 2005). EGFR mutations were detected in 13% of patients and were associated with longer survival irrespective of treatment. Among erlotinib-treated patients, EGFR mutations were associated with an improved response rate ($p<0.05$) and there was a trend toward an erlotinib benefit on time to progression ($p = 0.092$) but without improved survival ($p = 0.96$). A numerical increase in adverse events (AEs) leading to death was observed with combination treatment in the TRIBUTE study, but not in the TALENT, INTACT1 and INTACT2 studies. Overall, with the exception of an increased incidence of rash and diarrhea in the combination arms, the adverse event (AE) profile was similar for patients on chemotherapy/EGFR-TKI and those on chemotherapy/placebo.

2.1 Study rationale

Osimertinib is considered the preferred SoC for the first-line treatment of patients with metastatic EGFRm NSCLC given its superiority over the first-generation EGFR-TKI therapies (gefitinib/erlotinib) (NCCN 2019). However, despite the benefit observed for patients treated with osimertinib in the first-line setting, the vast majority of patients are expected to develop resistance. Thus, there remains a significant unmet medical need for new treatment options for patients in this disease setting.

Knowledge regarding the exact mechanisms of resistance to first-line osimertinib is limited but it is evident that heterogeneous mechanisms could be responsible. It is conceivable that the addition of chemotherapy to osimertinib therapy may achieve killing of different cell populations in the cancer, thereby controlling several routes of resistance at the point of maximal response, ie, restrict the development of drug tolerance.

On the basis of this hypothesis, in conjunction with data from the FLAURA trial and supportive data from trials of 1st generation EGFR TKI therapies in combination with platinum/pemetrexed chemotherapy in patients with advanced EGFR-mutation positive NSCLC, it is considered reasonable to test whether the addition of platinum/pemetrexed chemotherapy to osimertinib monotherapy can delay the development of acquired resistance, thereby prolonging PFS and potentially also OS.

The study will also look to understand whether specific subsets of patients are most likely to gain benefit from receiving combination therapy based on clinical and/or molecular characteristics.

2.2 Background

First-line monotherapy with EGFR-TKIs (such as erlotinib, afatinib, gefitinib, osimertinib, or dacomitinib) has replaced chemotherapy as the SoC for patients with advanced NSCLC harboring EGFR activating mutations (NCCN 2019, Planchard et al 2018). In the FLAURA study, osimertinib demonstrated superior PFS compared to first-generation EGFR-TKIs (gefitinib and erlotinib) (Soria et al 2018).

The hypothesis that the addition of platinum and pemetrexed chemotherapy to osimertinib could extend the benefit of osimertinib therapy is supported by a recently published study conducted in Japan (North East Japan Study Group [NEJ]009; Nakamura et al 2018; Seike et al 2018). In this study 344 patients with newly diagnosed stage III/IV/ recurrent NSCLC harboring an EGFR activating mutation (exon 19 deletion or exon 21 L858R) were randomized 1:1 to receive gefitinib 250 mg orally once daily or gefitinib 250 mg orally once daily in combination with carboplatin AUC5 and pemetrexed 500 mg/m^2 every 3 weeks for 4 cycles followed by pemetrexed maintenance. Progression-free survival was statistically significantly longer in the gefitinib in combination with chemotherapy arm than in the gefitinib monotherapy arm (20.9 months [95% CI: 18.0-24.2] vs. 11.2 months (95% CI: 9.0-13.4), respectively). The HR was 0.49 (95% CI: 0.390, 0.623; p<0.001).

Second PFS was similar in both arms, with a median of 20.9 months (95% CI: 18.0, 24.2) in the gefitinib in combination with chemotherapy arm vs. 21.1 months (95% CI:1 7.9, 24.9) in the gefitinib monotherapy arm (HR= 0.891 [95% CI: 0.708, 1.122]; p = 0.806). Overall survival was longer in the gefitinib in combination with chemotherapy arm than in the gefitinib monotherapy arm, with a median OS of 52.2 months (95% CI: 41.8, 62.5) vs. 38.8 months (95% CI: 31.1, 47.3), respectively (HR = 0.70 [95% CI: 0.58, 0.95]; p = 0.013).

In addition, data from 4 prospective Phase II studies (2 randomized, 2 single arm) of gefitinib in combination with pemetrexed monotherapy or platinum/pemetrexed doublet therapy followed by pemetrexed maintenance and a retrospective study of erlotinib with chemotherapy (predominantly platinum/pemetrexed), further support the concept of adding chemotherapy to EGFR-TKI therapy in the first-line treatment of patients with advanced EGFRm NSCLC (Cheng et al 2016, Dudnik et al 2014, Dudnik et al 2018, Han et al 2017, Oizumi et al 2017, Sugawara et al 2015, Yang et al 2018, Yoshimura et al 2015).

It is noted that NCCN 2019 guidelines for NSCLC do not recommend adding EGFR-TKIs to current chemotherapy (NCCN 2019). The guideline is based on data from a subgroup of randomized Phase II study CALGB 30406 which compared erlotinib alone vs. erlotinib

combined with chemotherapy with carboplatin plus paclitaxel as first-line treatment for patients with advanced EGFRm NSCLC who were never- or light-former smokers (Jänne et al 2012). In the subgroup of patients with EGFR mutations PFS and OS was similar in both arms of the study and the combination was associated with more side effects than erlotinib monotherapy. However, this study was not designed to make a formal comparison of efficacy endpoints between the regimens in patients with EGFRm NSCLC. It is also noted that the chemotherapy regimen in this study did not include pemetrexed nor the incorporation of maintenance chemotherapy.

Currently, knowledge regarding the mechanisms of acquired resistance to first-line osimertinib is limited. A preliminary analysis of paired plasma samples (baseline and following progression according to Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1] and/or treatment discontinuation) analyzed using next-generation sequencing was recently presented (Ramalingam et al 2018). In the osimertinib arm, there was no evidence of acquired EGFR T790M. The most common acquired resistance mechanism detected was tyrosine-protein kinase Met (MET) amplification (14/91 [15%]), followed by EGFR C797S mutation (6/91 [7%]). Other mechanisms included human epidermal growth factor receptor (HER2) amplification, phosphatidylinositol-4,5-biphosphonate 3-kinase, catalytic subunit alpha (PIK3CA) mutations, and RAt Sarcoma virus (RAS) mutations (2-7%). No unexpected resistance mechanisms were observed in osimertinib-treated patients. While these data are preliminary, it is evident that heterogeneous mechanisms are responsible for acquired resistance to first-line osimertinib. Some of these mechanisms of resistance are potentially actionable, but there are no approved targeted therapies for use in this setting.

In a previous study of osimertinib, patients with tissue T790M positive NSCLC and detectable baseline plasma EGFR mutations (Ex19del/L858R/T790M) assessed by droplet digital PCR (Biodesix) who received osimertinib, the continued detection of EGFR mutations at weeks 3 and 6 was associated with lower progression-free survival in comparison with patients with clearance of plasma mutations (Shepherd et al 2018). In the present study, mutation clearance at various intervals after treatment with osimertinib and chemotherapy in the safety run-in, and osimertinib monotherapy or osimertinib and chemotherapy in the randomized period, will be assessed and correlated with PFS or other measures of response.

Platinum doublet chemotherapy is currently recommended following systemic progression on osimertinib (NCCN 2019, Planchard et al 2018). In studies in patients with disease progression on first-generation EGFR-TKI therapy, platinum/pemetrexed chemotherapy ± pemetrexed maintenance has demonstrated modest efficacy, including an ORR of 31% to 35% and a median PFS of 4.2 months to 5.4 months (Mok et al 2017, Soria et al 2015, Yoo et al 2018). At the time of writing there are no published studies regarding the efficacy of platinum/pemetrexed chemotherapy in patients whose disease has progressed on first-line osimertinib therapy.

Although molecular mechanisms of acquired resistance to EGFR inhibitors have been identified, little is known about how resistant clones evolve during drug therapy (Hata et al 2016). In some cases, clones with clinically validated genetic resistance mechanisms may exist prior to drug exposure and may be selected by treatment (Turke et al 2010, Bhang et al 2015, Su et al 2012, Ye et al 2013). Alternatively, it has been hypothesized that drug-tolerant (or "persister") cells without bona fide resistance mechanisms may survive initial drug treatment by epigenetic adaptations (Lee et al 2014, Sharma et al 2010, Wilson et al 2012) and undergo further evolution over time to acquire validated genetic resistance mechanisms.

Although there is evidence that cells that have developed tolerance to EGFR-TKIs are also cross-resistant to cisplatin (Sharma et al 2010), it is conceivable that some drug-tolerant persister cells are sensitive to chemotherapy and, hence, chemotherapy in combination with osimertinib may achieve killing of different cell populations in the cancer, leading to greater overall log cell kill and superior efficacy compared with osimertinib alone. While drug-tolerant cells can exhibit cross-tolerance to other agents, there is a possibility that, firstly, osimertinib plus chemotherapy might reduce the number of drug-tolerant cells at the point of maximal response, ie, restrict the development of drug tolerance; and secondly, that de novo drug-resistant clones emerging from the tolerant state could be susceptible to the chemotherapy.

In addition to the concept that upfront chemotherapy with osimertinib may be more effective than sequential osimertinib followed by chemotherapy, an additional advantage of treating first-line patients with osimertinib and chemotherapy is that it guarantees that all patients receive chemotherapy during their treatment journey. This is important since, despite the proven efficacy of platinum-based chemotherapy, not all patients who progress on first-line EGFR-TKI therapy subsequently receive platinum doublet chemotherapy or single-agent chemotherapy as second- or later-line therapy. In an individual patient data meta-analysis of OS in trials of gefitinib or erlotinib vs. platinum-doublet-chemotherapy for EGFRm NSCLC, only ~66% of patients randomized to receive EGFR-TKIs who developed disease progression (n = 493) received any chemotherapy in the ≥ second-line setting and 9% received no further treatment (Lee et al 2017). Similarly, in a retrospective analysis of subsequent therapy outcomes in 553 patients with common EGFR mutations from 3 Phase III studies of first-line afatinib (LUX-Lung 3 [Sequist et al 2013], LUX-Lung 6 [Wu et al 2014], and LUX-Lung 7 [Park et al 2016]), only 71% of patients were fit enough to receive subsequent therapies. (Sequist et al 2017); 46% of patients received platinum-based chemotherapy. Given that patients in the proposed trial are required to have a PS of 0 or 1, those randomized to combination treatment will, by definition, be fit enough to receive platinum/pemetrexed chemotherapy.

A detailed description of the chemistry, pharmacology, efficacy, and safety of osimertinib is found in the Investigator's Brochure (IB). A detailed description of the pharmacology,

pharmacokinetics, efficacy, and safety of , cisplatin, carboplatin, and pemetrexed are provided in the respective prescribing information.

2.3 Benefit/risk assessment

2.3.1 Benefit

Although there can be no certainty of clinical benefit to patients, the positive efficacy data for osimertinib from FLAURA, supported by the Phase III NEJ009 study and Phase II studies of first generation EGFR TKI studies in combination with pemetrexed or carboplatin/pemetrexed in patients with EGFR mutation-positive NSCLC, provide support for evaluation of osimertinib with platinum/pemetrexed as first-line treatment for advanced EGFRm NSCLC.

2.3.2 Risk

2.3.2.1 Osimertinib

The tolerability profile of osimertinib when given as monotherapy is well characterized and suitable for long term dosing. In a pooled dataset that incorporated data from 1142 patients with EGFR mutation-positive NSCLC who received 80 mg osimertinib in all lines of therapy (first-, second-, and ≥third-line) in Phase I-III studies FLAURA, AURA Phase I, AURA extension, AURA2, and AURA3), the median duration of osimertinib therapy was 12.9 months (mean, 13.9 months; range, <0.1 – 40.1 months). In the FLAURA trial based on a data cut-off of June 12th 2017, the median duration of treatment with osimertinib was 16.1 months. Osimertinib exposure was ≥12 months in 194 (69.5%) patients, ≥18 months in 106 (38.0%) patients, and ≥24 months in 13 (4.7%) patients.

In the above pooled dataset that incorporated data from of 1142 patients treated with osimertinib at a dose of 80mg, most adverse drug reactions (ADRs) were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2 in severity. The most commonly reported ADRs were diarrhea (49%) and rash (47%). Other typical EGFR TKI ADRs include dry skin, pruritis, paronychia and stomatitis. CTCAE Grade 3 and Grade 4 adverse reactions occurred in 9.7% and 0.9% of patients, respectively. Dose reductions due to ADRs occurred in 2.1% of the patients and discontinuations due to ADR in 4.3% of patients.

Interstitial Lung Disease (ILD) or ILD-like ADRs (eg, pneumonitis) were reported in 3.9% and were fatal in 0.4% (n=5) of the 1142 patients who received osimertinib 80mg 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.

Of the 1142 patients in FLAURA and AURA studies treated with osimertinib 80 mg, 0.9% were found to have a corrected QT interval (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/pharmacodynamic

analysis with osimertinib predicted a drug-related QTc interval prolongation at 80 mg of 14 msec with an upper bound of 16 msec (90% CI).

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

AEs of leukopenia, lymphopenia, neutropenia and thrombocytopenia have been reported, most of which were mild or moderate in severity and did not lead to dose interruptions.

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

Across clinical trials in the pooled dataset of 1142 patients, left ventricular ejection fraction (LVEF) decreases greater than or equal to 10% and a drop to less than 50% occurred in 3.9% 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.

Further details on the clinical safety profile of osimertinib including guidance on management of ADRs is available in the Investigator's Brochure.

2.3.2.2 Chemotherapy

The safety profile of pemetrexed as monotherapy and in combination with cisplatin and carboplatin is well defined.

In a Phase III study of cisplatin and pemetrexed administered up to 6 cycles (but without pemetrexed maintenance), Grade 3 or 4 drug-related hematological toxicities occurred in the following: neutropenia (15% of patients), anemia (6%), and thrombocytopenia (4%). Drug-related Grade 3 or 4 non-haematological toxicities occurred in the following: nausea (7.2%), vomiting (6.1%), fatigue (6.7%), and febrile neutropenia (1.3%). In addition, alopecia of any grade was reported in 11.9% of patients and dehydration in 3.6% of patients (Scagliotti et al 2008).

In a placebo-controlled Phase III study of pemetrexed maintenance following completion of 4 cycles of cisplatin and pemetrexed in patients with EGFR unselected NSCLC, the most common Grade 3 or 4 ADRs included anemia (4.8% of patients), neutropenia (3.9%), fatigue (4.5%), nausea (0.3%)and mucositis/stomatitis (0.3%) (Paz-Ares et al 2012). In this study the median number of cycles of pemetrexed maintenance was 4; 47% of patients received ≥6 cycles and 28% received ≥10 cycles.

It should be noted that the present study of osimertinib alone or osimertinib with platinum/pemetrexed chemotherapy is powered to demonstrate an improvement in median PFS from 19 months to 28 months. Assuming 3 months for the first 4 cycles of platinum/pemetrexed doublet therapy, this equates to a median duration of pemetrexed of 25 months (ie, approximately 36 cycles assuming patients receive pemetrexed maintenance and do not discontinue for reasons other than disease progression); thus, the average duration of pemetrexed treatment is anticipated to be longer than has been observed in previous studies in which the median PFS was 18.3-20.9 months (Sugawara et al 2015, Nakamura et al 2018). In the NEJ005 study, the median number of cycles of pemetrexed maintenance was 13 (range 1-49) (Sugawara et al 2015). Gefitinib in combination with platinum/pemetrexed with pemetrexed maintenance was generally well tolerated in these studies which provides reassurance for the present study.

There is evidence of cumulative nephrotoxicity in patients receiving pemetrexed therapy(Visser et al 2018, Middleton et al 2018). With this in mind, in order to maximize the potential to administer prolonged pemetrexed maintenance, patients will be required to have a screening creatinine clearance of ≥60 mL/min. Careful monitoring of renal function will be carried out during administration of study medication in the present study. Pemetrexed will be interrupted if creatinine clearance is <45 mL/min and permanently discontinued if creatinine clearance has not returned to ≥45 mL/min within 42 days of the previous dose.

Platinum agents, most notably cisplatin, are associated with nephrotoxicity, ototoxicity and neuropathy; therefore, careful monitoring will be carried out.

2.3.2.3 Safety data from studies of chemotherapy with first generation EGFR TKI therapies.

In Phase III studies of platinum-based chemotherapy (cisplatin/gemcitabine and carboplatin/paclitaxel) with or without EGFR-TKIs in patients with EGFR unselected NSCLC, there is no clear evidence that combination treatment increases the incidence of hematological toxicity or non-hematological toxicity other than the expected EGFR-TKI toxicities of rash and diarrhea (Giaccone et al 2004, Herbst et al 2004, Herbst et al 2005, Gatzemeier et al 2007).

In studies of EGFR-TKIs with or without pemetrexed-based chemotherapy in patients with EGFR mutation positive NSCLC, including the Phase III study of gefitinib with or without carboplatin/pemetrexed chemotherapy (Nakamura et al 2018) and Phase II studies (Cheng et al 2016, Dudnik et al 2014, Han et al 2017, Oizumi et al 2017, Sugawara et al 2015, Yang et al 2018, Yoshimura et al 2015), hematological toxicities were more common in patients receiving combination therapy compared with EGFR-TKI therapy alone. In 1 study 2/127 (1.6%) patients receiving pemetrexed and gefitinib died as a result of AEs that were considered related to IP (pneumonitis and interstitial lung disease) (Cheng et al 2016). However, across studies combination therapy was not clearly associated with a marked

increased incidence of severe ILD. Overall, the safety profile of first-line EGFR-TKI therapy in combination with platinum/pemetrexed chemotherapy is manageable.

2.3.2.4 Potential for osimertinib and chemotherapy overlapping toxicity

The theoretical potential for overlapping toxicity between osimertinib and platinum/pemetrexed chemotherapy exists and includes the potential for additive hematological toxicity.

Decreases from baseline in median values for platelets, neutrophils, lymphocytes and leukocytes have been observed early in treatment with osimertinib. Median values appear to stabilize after the initial decrease with the majority of patients experiencing a single CTCAE grade change or no grade change.

Of the 1142 patients in the FLAURA and AURA studies treated with osimertinib 80 mg, the incidence of CTCAE all grade shifts and CTCAE ≥Grade 3 shifts in laboratory values includes the following: leukocytes decreased all grades 68% and ≥Grade 3 1.5%; neutrophils decreased all grades 35% and ≥Grade 3 4.1%; lymphocytes decreased all grades 67% and ≥Grade 3 7.2%; and platelet count decreased, all grades 54% and ≥Grade 3 1.6%. Dose reductions due to AEs of neutropenia and thrombocytopenia were reported in 0.4% and 0.3% of patients, respectively.

In the FLAURA study, leukocyte-related AEs (ie, leukopenia or WBC count decreased) occurred in 15.4% of patients receiving osimertinib, including 0.4% with a CTCAE Grade 3 AE. No Grade 4 or 5 events occurred. AEs leading to interruption, dose reduction or discontinuation occurred in 0.7%, 0.4 % and 0% of patients, respectively.

Neutrophil-related adverse events (ie, neutropenia and neutrophil count decreased) were reported in 10.8% of patients receiving osimertinib including 1.8% with a CTCAE Grade 3 event; no Grade 4 or 5 events occurred. AEs leading to dose interruption, dose reduction and discontinuation occurred in 1.4%, 0.4% and 0.4% of patients, respectively. There were no AEs of febrile neutropenia. Colony stimulating factors were administered to 2.5% of patients for AEs of neutrophil-related AEs or leukocyte-related adverse events.

Lymphocyte-related adverse events (ie, lymphocyte count decreased and lymphopenia) were reported in 4.7% of patients receiving osimertinib including 1.8% with a Grade 3 event; no Grade 4 or 5 events occurred. AEs leading to interruption, dose reduction or discontinuation occurred in 1.4 %, 0% and 0%, respectively.

Platelet-related adverse events (ie, thrombocytopenia and platelet count decreased) were reported in 14.3% of patients receiving osimertinib. Most of the events were reported as Grade 1; 0.7% of patients had a Grade 3 event and no Grade 4 or 5 events occurred. Adverse events leading to interruption, dose reduction or discontinuation occurred in 0.7 %, 0% and

0% of patients, respectively. One patient required heparin for an event of thrombocytopenia-related change. Adverse events of bleeding, bruising or haemorrhage occurring concomitantly with platelet count below the lower limit of normal (LLN) were reported in 3.2% of patients; the majority of which were Grade 1 or 2.

Platinum agents and pemetrexed are associated with myelosuppression. Carboplatin is associated with a higher incidence of severe thrombocytopenia than cisplatin (Ardizzoni et al 2007).

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

There is also the potential for overlapping toxicity with respect to effects on fertility. Based on studies in animals, male fertility and female fertility may be impaired by treatment with osimertinib. For further details see the osimertinib Investigator's Brochure. Gonadal suppression resulting in amenorrhea or azoospermia may occur in patients receiving antineoplastic therapy and such effects may be irreversible. Moreover, chemotherapy can have genetically damaging effects. Guidance on contraception requirements and sperm donation is provided in Section 5.3.1 and Appendix H.

Due to the possibility of platinum-based chemotherapy and pemetrexed treatment causing irreversible infertility, men allocated/randomized to receive osimertinib and chemotherapy are advised to seek counselling on sperm storage before starting treatment.

A Japanese Phase II open-label, randomized study of osimertinib alone vs. osimertinib plus carboplatin/pemetrexed for patients with locally-advanced or metastatic NSCLC whose disease has progressed with previous EGFR-TKI therapy and whose tumors harbor a T790M mutation within the EGFR gene is ongoing (TAKUMI Study LOGIK1604/NEJ032A; UMINCTR: UMIN). An interim safety review was conducted based on data from the first cycle in 24 patients (12 on monotherapy and 12 on combination therapy). One ≥Grade 3 AE was reported in the osimertinib arm (Grade 3 decreased neutrophil count); whereas, in the combination arm, 4 episodes each of Grade 3 or 4 decreased white blood cell count, decreased neutrophil count, decreased platelet count, and anemia; 2 episodes of Grade 3 skin rash, and 1 episode each of Grade 3 bronchial infection, oral mucositis, hypertension, and hypokalemia were reported. The authors stated that "The event frequency in the combination arm was similar to that in previous studies of carboplatin/pemetrexed. Exaggeration of AEs by osimertinib or previously unobserved events were not apparent in the combination arm." The authors concluded "The combination treatment was safe in the selected patient population"

(Okada et al 2018) and the Safety Review Committee for the study recommended that the study continue to enroll patients.

In a retrospective analysis of patients with advanced EGFRm NSCLC treated off-label with concurrent chemotherapy and osimertinib, 18 patients received 25 chemotherapy regimens in combination with osimertinib, including 10 platinum doublets (8 on carboplatin/pemetrexed) and 15 monotherapy regimens (6 on pemetrexed) (Piotrowska et al 2018). All patients had progressed on third-generation EGFR-TKI monotherapy before the addition of chemotherapy. One Grade 4 neutropenia (pemetrexed) and 5 Grade 3 neutropenia (1 carboplatin/pemetrexed; 2 pemetrexed; 1 gemcitabine; 1 carboplatin/nab-paclitaxel) were reported; 3 patients received support with granulocyte colony stimulating factors. Other Grade 3 toxicities were rare and all were reversible: 1 aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) elevation (carboplatin/pemetrexed), 1 thrombocytopenia (carboplatin/pemetrexed), and 1 anemia (carboplatin/pemetrexed). Adverse events led to treatment delay in 5 patients, osimertinib dose-reduction in 2 patients, and discontinuation of regimen in 2 patients. There were no cases of pneumonitis. The authors concluded that osimertinib does not appear to add significant toxicity to the various chemotherapy regimens.

There are no published data on the safety and tolerability of osimertinib with cisplatin and pemetrexed, and information on the safety and tolerability of osimertinib with carboplatin and pemetrexed is limited. As such, in order to provide sufficient confidence in the safety of osimertinib with platinum/pemetrexed, the proposed study will include a safety run-in period prior to conducting the Phase III evaluation, as described in Section 4.

2.3.2.5 Risk-benefit summary

Based on a review of the potential benefits and risks, it is considered to be reasonable and appropriate to evaluate the concurrent use of osimertinib and platinum plus pemetrexed chemotherapy followed by pemetrexed maintenance compared with osimertinib monotherapy in the first-line treatment of patients with locally-advanced or metastatic EGFRm NSCLC.

Furthermore, following the primary analysis of the Safety run-in period, no new safety signals were identified, and no new clinically relevant toxicities with osimertinib given in combination with chemotherapy were noted. On a population level, a decrease in key haematological parameters (haemoglobin, leucocytes, platelets, and neutrophils) was noted after the initiation of study treatment; however, these decreases were acute in nature and stabilized with continued study treatment. Consequently, the results of the safety run-in period support the continued investigation of osimertinib in combination with chemotherapy agents in the randomized study period.

3 OBJECTIVES AND ENDPOINTS

Prior to the start of the randomized period of the study, a non-randomized safety run-in will allocate approximately 30 patients to evaluate the safety and tolerability of osimertinib with platinum (carboplatin or cisplatin) and pemetrexed (Section 4.1).

The objective for the safety run-in is shown in Table 3.

Table 3 Study objectives for the safety run-in

Primary Objective:	**Endpoint/Variable:**
To evaluate the safety and tolerability of osimertinib plus chemotherapy	Adverse events graded by CTCAE v5; Clinical chemistry, hematology and urinalysis; Vital signs (pulse and blood pressure); physical examination; weight; LVEF; ECG parameters; WHO Performance Status
Secondary Objectives:	**Endpoint/Variable:**
To assess the efficacy of osimertinib plus chemotherapy	ORR, DoR; depth of response; DCR by Investigator; OS;
To assess the PK of osimertinib when given with chemotherapy	Steady-state plasma concentrations and appropriate PK parameters (CL_{ss}/F, $C_{max,ss}$ $C_{min,ss}$ and AUC_{ss}) of osimertinib and its metabolite, AZ5104 will be summarized. *
Exploratory Objectives:	**Endpoint/Variable:**
To explore how changes in plasma-based biomarkers (eg, ctDNA, proteomic) correlate with response	Quantitative ctDNA analysis using specific EGFR biomarkers or broader cancer biomarker panel in longitudinal plasma samples, to assess ctDNA clearance and correlate with response (eg, PFS)
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	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety or response observed in patients treated with osimertinib plus chemotherapy
To explore efficacy biomarkers and biomarker changes in baseline, longitudinal and progression samples (plasma and tumor tissue) for correlation with response	Assessment of innate and acquired resistance mechanisms and biomarkers of response including but not limited to mutations in, amplifications and expression of EGFR, TP53, HER2, MET and relevant pathway genes Proteomic and/or gene expression analysis eg, biomarkers of inflammation

To collect and store tumor, serum and plasma samples for potential exploratory research into factors that may influence susceptibility to development of NSCLC and/or response to osimertinib and/or chemotherapy (where response is defined broadly to include efficacy, tolerability or safety) and to assess the relationship between tissue and/or bloodborne biomarkers and selected efficacy endpoints. Tissue and plasma samples may be used to support diagnostic development.	Key genetic, gene expression and proteomic markers to include, but not limited to, EGFR mutations, HER, and proto-oncogene encoding cMET expression and/or amplification. Relationship between PK and blood-borne biomarkers. Diagnostic development.

* If feasible, further PK parameters may be derived using population PK analysis and reported separately from the CSR. Data from this study may also form part of a pooled analysis with data from other studies

AUC_{ss}=area under plasma concentration-time curve during any dosing interval at steady state [amount·time/volume]; CL_{ss}/F=apparent total body clearance at steady state; cMET = hepatocyte growth factor receptor; CSR=clinical study report; $C_{max,ss}$ =maximum plasma concentration at steady state; $C_{min,ss}$ =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; HER2=human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; MET=tyrosine-protein kinase Met; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic(s); WHO=World Health Organization.

Objectives for the randomized period are shown in Table 4.

Table 4 Study objectives for the randomized period

Primary Objective:	**Endpoint/Variable:**
To assess the efficacy of osimertinib plus chemotherapy treatment compared with osimertinib	PFS using Investigator assessment as defined by RECIST 1.1; Sensitivity analysis of PFS using BICR assessment as defined by RECIST 1.1
Secondary Objectives:	**Endpoint/Variable:**
To further assess the efficacy of osimertinib plus chemotherapy compared with osimertinib	OS; Landmark OS at 1, 2, and 3 years; ORR, DoR; depth of response; DCR by Investigator
To further assess the efficacy of osimertinib plus chemotherapy compared with osimertinib post progression	PFS2; TFST; TSST
To assess disease-related symptoms and health-related QoL in patients treated with osimertinib plus chemotherapy compared with osimertinib	Change from baseline and time to deterioration in EORTC QLQ-C30; Change from baseline and time to deterioration in EORTC QLQ-LC13

To assess the PK of osimertinib when given with or without chemotherapy	Steady-state plasma concentrations and appropriate PK parameters (CL_{ss}/F, $C_{max,ss}$ $C_{min,ss}$ and AUC_{ss}) of osimertinib and its metabolite, AZ5104 will be summarized. *
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	Concordance of EGFR mutation status between the local EGFR mutation test and the central cobas® EGFR Mutation Test v2 results from tumor samples with evaluable results
To determine efficacy of osimertinib monotherapy vs. osimertinib combined with chemotherapy based on the cobas® EGFR Mutation Test v2 plasma screening test result for Exon 19 deletions or L858R EGFR mutations	PFS by Investigator by plasma EGFR mutation status
Safety Objective:	**Endpoint/Variable:**
To evaluate the safety and tolerability of osimertinib plus chemotherapy compared with osimertinib	Adverse events graded by CTCAE v5; Clinical chemistry, hematology and urinalysis; Vital signs (pulse and blood pressure); physical examination; weight; LVEF; ECG parameters; WHO Performance Status
Exploratory Objectives:	**Endpoint/Variable:**
To assess the impact of osimertinib plus chemotherapy compared with osimertinib on patient reported treatment related symptoms	PRO-CTCAE symptoms
To assess patients' overall impression of severity of cancer symptoms	PGIS
To compare health resource use associated with osimertinib plus chemotherapy treatment versus osimertinib	Health Resource Use Module
To assess the impact of osimertinib plus chemotherapy compared with osimertinib on patient reported health state utility	EQ-5D-5L
To assess the efficacy of osimertinib plus chemotherapy treatment compared with osimertinib on CNS metastases in patients with CNS metastases at baseline	Neuro-radiologist assessments according to CNS RECIST 1.1 to calculate: • CNS PFS; CNS ORR; CNS DoR; CNS DCR; • Best percentage change in CNS tumor size (target lesion)
To assess the efficacy of osimertinib plus chemotherapy treatment compared with osimertinib on the prevention of CNS metastases	Neuro-radiologist assessments according to CNS RECIST 1.1 to determine the presence/absence of CNS lesions at progression in patients without CNS metastases at baseline

To compare concordance of the cobas® EGFR Mutation Test v2 versus alternative EGFR tissue testing alternative methods for diagnostic development	Concordance of EGFR mutation status between the cobas® EGFR Mutation Test v2 and an alternative devices.
To explore how changes in plasma-based biomarkers (eg, ctDNA, proteomic) correlate with response	Quantitative ctDNA analysis using specific EGFR biomarkers or broader cancer biomarker panel in longitudinal plasma samples, to assess ctDNA clearance and correlate with response (eg, PFS)
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	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety or response observed in patients treated with osimertinib plus chemotherapy compared with osimertinib
To explore efficacy biomarkers and biomarker changes in baseline, longitudinal and progression samples (plasma and tumor tissue) for correlation with response	Assessment of innate and acquired resistance mechanisms and biomarkers of response including but not limited to mutations in, amplifications and expression of EGFR, TP53, HER2, MET and relevant pathway genes Proteomic and/or gene expression analysis eg, biomarkers of inflammation
To collect and store tumor, serum and plasma samples for potential exploratory research into factors that may influence susceptibility to development of NSCLC and/or response to osimertinib and/or chemotherapy (where response is defined broadly to include efficacy, tolerability or safety) and to assess the relationship between tissue and/or bloodborne biomarkers and selected efficacy endpoints. Tissue and plasma samples may be used to support diagnostic development.	Key genetic, gene expression and proteomic markers to include, but not limited to, EGFR mutations, HER, and proto-oncogene encoding cMET expression and/or amplification. Relationship between PK and blood-borne biomarkers. Diagnostic development.

* If feasible, further PK parameters may be derived using population PK analysis and reported separately from the CSR. Data from this study may also form part of a pooled analysis with data from other studies

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; cMET = hepatocyte growth factor receptor; CNS=central nervous system; CSR=clinical study report; $C_{max,ss}$ =maximum plasma concentration at steady state; $C_{min,ss}$ =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; 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 Questionnaire; HER2=human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; MET=tyrosine-protein kinase Met; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PFS2=time from randomization to second progression on a subsequent treatment; PGIS=Patients Global Impression of Severity; PK=pharmacokinetic(s); 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; WHO=World Health Organization.

4 STUDY DESIGN

4.1 Overall design

This is a global Phase III, open-label, randomized study of osimertinib with or without platinum plus pemetrexed chemotherapy conducted in patients with locally-advanced or metastatic EGFRm (Ex19del and/or L858R) NSCLC who have not received any prior therapy for advanced disease.

The proposed study will include patients with EGFRm NSCLC who have either: (1) a pre-existing positive (Ex19del or L858R) tissue test result obtained from a CLIA-certified local laboratory (for US sites) or from an accredited local laboratory (for sites outside of the US); or (2) have a positive tissue Ex19del or L858R EGFR mutation test based on the cobas® EGFR Mutation Test v2 conducted prospectively in a central laboratory. Further details are provided in Section 4.2.3. The options for randomization of patients on the basis of a pre-existing EGFR result vs. prospective central testing may be modified during the trial to ensure that an adequate proportion of patients that are randomized on the basis of a pre-existing EGFR result are centrally confirmed by the cobas® EGFR Mutation Test v2 retrospectively. If a modification to not allow further randomization of patients on the basis of a pre-existing EGFR result is made, this change will be communicated to participating sites in a timely manner. Prospective analysis of EGFR mutation status of FFPE tumor tissue using central laboratory testing by the cobas® EGFR Mutation Test v2 is encouraged.

Prior to the start of the randomized period, approximately 30 patients will be studied in a non-randomized fashion in 2 cohorts of patients to evaluate the safety and tolerability of osimertinib with platinum-based chemotherapy (carboplatin or cisplatin) and pemetrexed chemotherapy (Figure 1). Approximately 15 patients per cohort will receive osimertinib 80 mg QD with either cisplatin (75 mg/m^2) or carboplatin (AUC5), and pemetrexed (500 mg/m^2), both administered Q3W for 4 cycles, followed by osimertinib 80 mg QD plus pemetrexed maintenance (500 mg/m^2) Q3W until RECIST 1.1-defined progression or another discontinuation criterion is met.

When at least 12 patients in each cohort have either received ≥3 cycles of study treatment (osimertinib, cisplatin or carboplatin, and pemetrexed) or have discontinued study treatment due to unacceptable toxicity, a Safety Review Committee will convene. A formal database lock will be required to facilitate this data review. Full details of the Safety Review Committee procedures and processes can be found in the Safety Review Committee Charter. All data, including safety, tolerability, and available PK data from all patients, will be reviewed. The Safety Review Committee will include independent experts with relevant experience in clinical trial conduct, methodology, and procedures in patients with NSCLC,

and AstraZeneca personnel. Based on these data and taking into consideration data from other sources (eg, any updated information from the Phase II study of osimertinib alone vs. osimertinib plus carboplatin/pemetrexed [TAKUMI Study LOGIK1604/NEJ032A]), the Safety Review Committee will recommend whether the data support the initiation of the randomized period of the study after which it will end its function (Section 4.2.1).

Following Safety Review Committee evaluation and recommendation, patients who participated in the safety run-in will not be included among the patients in the randomized period, but may continue on their allocated treatment per protocol, with procedures continuing as shown in the SoA Table 1.

Following a recommendation by the Safety Review Committee based on the evaluation of data from the safety run-in period, the randomized period will begin to randomize approximately 556 new patients randomized in a 1:1 ratio to receive osimertinib alone or osimertinib with pemetrexed and either cisplatin or carboplatin. Patients will be stratified by race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1), and method for tissue testing (central vs. local) for generation of the p-value, using the Breslow approach for handling ties. It is anticipated that approximately 60% Asian patients and 40% non-Asian patients will be recruited. The Investigator will decide before randomization which chemotherapy regimen (carboplatin/pemetrexed or cisplatin/pemetrexed) a patient would receive in case the patient is assigned to the osimertinib plus chemotherapy arm. In the event that the Safety Review Committee deems one of the study treatments to be inappropriate, only one study treatment may be recommended for the randomized period (eg, osimertinib with pemetrexed and cisplatin or osimertinib with pemetrexed and carboplatin).

The 2 randomized treatment regimens will be as follows:

- Osimertinib 80 mg once daily OR
- Osimertinib 80 mg once daily with pemetrexed (500 mg/m^2) (with vitamin supplementation) plus either cisplatin (75 mg/m^2) or carboplatin (AUC5), with both treatments administered on Day 1 of 21-day cycles for 4 cycles, followed by osimertinib 80mg daily plus pemetrexed maintenance (500 mg/m^2) Q3W.

Randomized treatment will continue until RECIST 1.1-defined progression by Investigator or until another discontinuation criterion is met.

Patients can continue to receive study treatment through progression if, in the judgement of the Investigator, they are receiving clinical benefit and do not meet any of the discontinuation criteria. However, if the patient is deemed to have clinically significant unacceptable or irreversible toxicities, rapid tumor progression, or symptomatic progression requiring urgent medical intervention (eg, CNS metastases, respiratory failure, spinal cord compression) study treatment must be discontinued.

Following treatment discontinuation, subsequent therapy will be at the discretion of the Investigator. Patients will be followed for second progression on a subsequent treatment, defined according to local practice, and for survival.

Oversight of safety and tolerability of the randomized period of the study will be provided by an IDMC. Safety run-in data will not be included in the analysis of the randomized period; however, during the randomized period, the IDMC will review data from the safety run-in separately as part of the ongoing review process.

A futility analysis is planned to occur when approximately 83 PFS events have occurred in the randomized period of the study, which is predicted to occur approximately 15 months after the start of randomization. The futility analysis will be conducted and reviewed by the IDMC in order to recommended whether the study should continue. The rationale for conducting a futility analysis is to minimize patient exposure in the event that osimertinib with pemetrexed and cisplatin or carboplatin shows insufficient evidence of an efficacy benefit when compared with osimertinib monotherapy.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints. See details on the planned statistical analysis in Section 4.2.4.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with Good Clinical Practice, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the ICF should be signed at the patient's next contact with the study site).

- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened patients. The investigator should confirm this with the designated study physician.

- Home or Remote visit: Performed by a site qualified HCP or HCP provided by a TPV.

- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

- At-home IP administration: Performed by a site qualified HCP, HCP provided by a TPV, or by the patients or the patient's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, see Appendix J.

4.2 Scientific rationale for study design

4.2.1 Rationale for safety run-in

The safety run-in is intended to evaluate the safety of the study treatment in a limited number of patients prior to larger numbers of patients being recruited for the randomized period of the study, given that: (i) there is the potential for overlapping toxicity between osimertinib and chemotherapy, (ii) there are no published data on the safety and tolerability of osimertinib with cisplatin and pemetrexed, and (iii) there is only limited information on the safety and tolerability of osimertinib with carboplatin and pemetrexed. Section 2.3.2 provides detailed information on the risks associated with osimertinib and chemotherapy.

4.2.2 Rationale for primary endpoint of progression-free survival

The primary endpoint of this study is PFS, which is widely accepted as a surrogate endpoint for clinical benefit in studies of patients with advanced NSCLC. PFS represents a direct effect of the efficacy of osimertinib with or without platinum plus pemetrexed chemotherapy as it is not confounded by the efficacy of subsequent therapies used after disease progression. Overall survival will be evaluated as a key secondary endpoint.

4.2.3 Testing for activating EGFR mutations

Only patients with tumors harboring the common activating Ex19del or L858R EGFR mutations will be eligible for inclusion in the study.

A patient can be considered eligible for the study on the basis of one of the following:

- a pre-existing EGFR-mutation positive tissue test result obtained by a CLIA-certified or locally accredited laboratory, meeting the requirements as specified in the Laboratory Manual, OR
- a positive tissue EGFR test result obtained prospectively at a CLIA-certified central laboratory using the cobas® EGFR Mutation Test v2 according to its instructions for use.

For patients eligible for inclusion in the study based on a pre-existing EGFRm tissue sample result, the local EGFR tissue testing laboratory methods will be documented by questionnaires before study start and for each individual subject in the respective electronic case report forms (eCRF). Pre-existing EGFR mutation tests obtained at the locally accredited laboratory will be confirmed post-enrollment using the cobas® EGFR Mutation Test v2 in a CLIA-certified central laboratory, using a formalin-fixed paraffin-embedded (FFPE) tissue sample.

Central confirmation will not be mandated before randomization (or before first dose for the safety run-in) for patients with a positive tissue test result obtained from a CLIA-certified or locally accredited laboratory.

The options for inclusion of patients on the basis of a pre-existing EGFR result vs. prospective central testing may be modified during the trial to ensure that an adequate proportion of patients that are allocated/randomized on the basis of a pre-existing EGFR result are centrally confirmed by the cobas® EGFR Mutation Test v2 retrospectively. If a modification to not allow further eligibility of patients on the basis of a pre-existing EGFR result is made, this change will be communicated to participating sites in a timely manner. Prospective analysis of EGFR mutation status of FFPE tumor tissue using central laboratory testing by the cobas® EGFR Mutation Test v2 is encouraged.

In addition, all patients are mandated to provide a plasma sample during screening for retrospective central testing of EGFR mutations in order to assess concordance with tissue test results, to assess outcome based on plasma EGFRm positivity and to assess outcome based on a positive EGFR test either by tumour or plasma. However, study entry criteria are based exclusively on positive tumor tissue tests. Further details are provided in Section 8.1.3.

4.2.4 Planned statistical analysis

No formal statistical analysis is planned within the safety run-in. At the time of the Safety Review Committee assessment of the approximately 30 patients allocated in the safety run-in, a listing of RECIST responses will be produced along with safety summaries. Based on a positive assessment from the Safety Review Committee, approximately 556 patients will be randomized in a 1:1 ratio in the randomized period to receive osimertinib monotherapy or osimertinib with pemetrexed and either cisplatin or carboplatin. Data for IDMC review will

not combine data from the safety run-in and randomized period to assess safety. The data will be reviewed separately.

The primary analysis of PFS based on Investigator assessment (according to RECIST 1.1) will occur when approximately 278 PFS events and at least 16 months of follow-up after LSI, has occurred in the 556 randomized patients (approximately 50% maturity). This was initially expected to occur approximately 33 months after the first patient is randomized (under an assumed 15-month exponential recruitment); however, the actual DCO for the primary PFS analysis will be determined such that both criteria are met.

At the primary PFS DCO for the randomized period, data will be analysed for patients who received osimertinib vs patients who received osimertinib plus chemotherapy, pooling the data across the type of chemotherapy (ie, cisplatin/pemetrexed and carboplatin/pemetrexed data will be presented together). The safety run-in patients will be analysed separately from the randomized patients. In addition, further safety summaries will be produced for the safety-run in patients at the time of the primary PFS DCO.

Progression-free survival will be analyzed using a log-rank test stratified by race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1), and method for tissue testing (central vs. local) for generation of the p-value, using the Breslow approach for handling ties. The assumption of proportionality will be assessed. A sensitivity analysis of PFS will be performed based on data assessed by BICR for all patients. A prespecified subgroup analysis will be conducted in patients who have a centrally confirmed EGFRm status by cobas® tissue or cobas® plasma tests, either used for eligibility into the study or retrospectively if eligibility was per a locally accredited test.

The key secondary endpoint of OS will be tested in a hierarchical procedure, at the time of the PFS analysis and analyzed again when the data are approximately 60% mature (334 death events across both arms) at the final OS analysis. Alpha will be controlled across the 2 OS analyses; ie, at the time of the primary PFS analysis and at the final OS analysis, with the overall Type 1 error strongly controlled at 5% (2 sided) for the testing of OS under an O'Brien and Fleming spending rule.

Stratification in this study will include central or local EGFR method for tissue testing to allow for any potential differences in EGFR mutation detection. In addition, stratification will include race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian) which is commonly assessed in studies of EGFR-TKI therapy, and WHO performance status (0 vs. 1) which is a known prognostic factor with respect to OS in patients with NSCLC (NCCN 2019, Kawaguchi et al 2010).

4.2.5 Rationale for CNS efficacy exploratory endpoints

The vast majority of patients with advanced EGFRm NSCLC treated with first- and second-generation EGFR TKIs develop disease progression within 1 year. In approximately 30% of patients, this includes the development of CNS metastases (How et al 2017, Chooback et al 2018). CNS metastases are associated with a worsening quality of life, higher healthcare costs and poorer survival in patients with NSCLC (Peters et al 2016). There is a high unmet medical need for effective, non-invasive, and well tolerated treatments for patients with brain metastases associated with EGFRm NSCLC. The CNS is known as a sanctuary site due to the presence of an active blood brain barrier (BBB). Many systemic therapies, including EGFR-TKIs, are unable to provide optimal CNS therapeutic exposure, resulting in limited CNS activity. For EGFR-TKIs, suboptimal therapeutic exposure in the CNS results in an insufficient EGFR-TKI "evolutionary pressure" for new resistant tumor clones to evolve in the CNS. This situation may result in a discordant tumor biology between extracranial and CNS lesions, where the CNS lesions are still being driven by the primary tumor biology, while new resistant tumor clones develop secondary TKI-resistant mutations such as T790M in extracranial lesions. It is hypothesized that to be effective in CNS metastases, an EGFR TKI needs to be effective against the activating EGFRm that are driving the primary tumor biology and be able to cross the BBB to inhibit aberrant EGFR signalling.

Brain exposure and regional brain distribution of osimertinib in the cynomolgus monkey (with an intact BBB) using positron emission tomography (PET) microdosing demonstrated that carbon-11 labelled osimertinib ([^{11}C]osimertinib) penetrated the BBB of non-human primates and that [^{11}C]osimertinib exhibited a superior level of brain exposure compared to that of the active metabolite [^{11}C]AZ5104 and other EGFR TKIs (Ballard et al 2016). Similar to non-human primates, PET examinations after microdose administration of [^{11}C]osimertinib, performed to examine the distribution of the labelled compound in the brain and whole body in healthy volunteers with intact BBBs, showed excellent exposure of osimertinib in human brain (Varrone et al 2018). Distribution of [^{11}C]osimertinib to the brain was fast (within 10 minutes) and exposure of [^{11}C]osimertinib in humans was similar to that demonstrated for non-human primates and similar to well-established CNS drugs (Colclough et al 2019).

The clinical activity of osimertinib in CNS metastases was demonstrated in global Phase II (AURA extension and AURA2) and randomized Phase III (AURA3) studies conducted in patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC after progression on prior EGFR TKI therapy and in patients with untreated EGFR mutated advanced NSCLC (Goss et al 2018, Soria et al 2018, Wu et al 2018). In the FLAURA study, a subset of patients who had CNS baseline brain scans (N=200 out of 556) had metastases as assessed by neuroradiologic BICR (N=128). PFS benefit of osimertinib compared with EGFR SoC was observed both in patients with and without brain metastases at baseline (Reungwetwattana et al 2018). The probability of experiencing a CNS progression event was

consistently lower with osimertinib compared with SoC (gefitinib or erlotinib). At 12 months, it was 8% (95% CI: 3%, 16%) with osimertinib, vs. 24% (95% CI: 15%, 35%) with SoC.

The AURA3 study showed the first comparative evidence of osimertinib's CNS efficacy versus platinum- based chemotherapy/pemetrexed (Wu et al 2018). In AURA 3, patients with T790M positive NSCLC following prior EGFR TKI therapy were randomly assigned 2:1 to receive osimertinib 80 mg QD or platinum-pemetrexed. A pre-planned subgroup analysis was conducted in patients with measurable and/or non-measurable CNS lesions on baseline brain scans (as assessed by BICR). Of 419 patients randomly assigned to treatment, 116 had measurable and/or non-measurable CNS lesions, including 46 patients with measurable CNS lesions. CNS ORR in patients with 1 or more measurable CNS lesions was 70% (21/30 patients; 95% CI: 51%, 85%) with osimertinib and 31% (5/16 patients; 95% CI: 11%, 59%) with platinum pemetrexed (odds ratio, 5.13; 95% CI: 1.44, 20.64; P=0.015). The ORR was 40% (30/75 patients; 95% CI: 29%, 52%) and 17% (7/41 patients; 95% CI: 7%, 32%), respectively, in patients with measurable and/or non-measurable CNS lesions (odds ratio, 3.24; 95% CI: 1.33, 8.81; P=0.014). Median CNS DoR in patients with measurable and/or non-measurable CNS lesions was 8.9 months (95% CI: 4.3, not calculable [NC]) for osimertinib and 5.7 months (95% CI: 4.4, 5.7) for platinum pemetrexed; median CNS PFS was 11.7 and 5.6 months, respectively (HR, 0.32; 95% CI: 0.15, 0.69; P=0.004). In the osimertinib arm, 51% of patients (21 of 41) who achieved a systemic response also responded in the CNS, compared with 31% of patients (four of 13) in the platinum-pemetrexed arm.

There are few randomized clinical trials that have investigated the efficacy of chemotherapy for the treatment of brain metastasis in NSCLC (Inno et al 2016). A retrospective study by Bearz et al. (Bearz et al 2010) reported a partial response in 11 out of 39 patients (28%) in NSCLC patients with CNS metastases treated with pemetrexed as second- or third-line therapy. In a study of 43 chemotherapy-naïve NSCLC patients with asymptomatic inoperable CNS metastases cisplatin and pemetrexed was associated with an intracranial response rate of 42% (Barlesi et al 2011).

Pharmacokinetic studies of cisplatin, carboplatin and pemetrexed cerebrospinal fluid concentrations in the range of 2.6% to 5% suggest limited CNS penetration (Jacobs et al 2005; Kumthekar et al 2013). Chemotherapy molecules are generally large, hydrophilic, protein-bound molecules, and therefore unable to cross an intact BBB that comprises endothelial cells with tight junctions. The protective role of the BBB is compromised structurally and functionally in the presence of brain metastases larger than 1–2 mm in diameter within the brain parenchyma (Eichler et al 2011). However, despite a potentially 'leaky' BBB, evidence from clinical studies has not demonstrated significant CNS uptake of first- and second-generation TKIs (Bohn et al 2016). Furthermore, although uptake of contrast enhancement on magnetic resonance imaging (MRI) can provide visual evidence of disruption of the BBB, the barrier may remain intact at the leading edge of a tumor, which prevents drug distribution to

cancerous cells (Van Tellingen et al 2015). Importantly, computerized tomography (CT) and MRI may not have sufficient spatial resolution to visualise micrometastatic lesions that are likely present in many patients at the time of diagnosis, when the BBB is still intact.

To date no study has been performed that has systematically assessed the CNS efficacy of osimertinib in all patients enrolled in a Phase 3 trial. The present study aims to extend the evidence of osimertinib CNS efficacy by collecting brain scans for all subjects at baseline and at progression, in order to assess the incidence rate of patients with CNS lesions in both treatment arms at progression. In addition, by collecting brain scans in all patients at baseline, patients with CNS metastases will be followed on study to allow objective assessment of measurable and/or non-measurable lesions at each timepoint. Given that chemotherapy is associated with evidence of activity in patients with CNS metastases this study will also explore the hypothesis that osimertinib and chemotherapy may be more effective than osimertinib alone in controlling existing CNS metastases and in preventing new CNS metastases.

4.3 Justification for dose selection/regimen

4.3.1 Osimertinib

Osimertinib administered orally at 80 mg QD is the approved dose for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions (Ex19del) or exon 21 L858R substitution mutations, as detected by an approved test

4.3.2 Choice of chemotherapy and pemetrexed maintenance regimen

4.3.2.1 Choice of platinum agent

It is not standard practice to give chemotherapy as a first-line treatment to patients with advanced EGFRm NSCLC. However, platinum-doublet chemotherapy is the NCCN-recommended second-line treatment for a) patients with EGFRm NSCLC whose disease has progressed on first-line osimertinib, and b) patients whose disease has progressed on first-generation EGFR-TKI therapy and whose tumors do not harbor the EGFR T790M mutation. The NCCN NSCLC 2019 guidelines include both cisplatin-plus-pemetrexed and carboplatin-plus-pemetrexed combinations as category 1 first-line systemic therapy options for patients with adenocarcinoma of the lung (NCCN 2019). European Society for Medical Oncology (ESMO) 2018 guidelines state that for patients with nonsquamous NSCLC, the combination of carboplatin with pemetrexed can be an option in case of a contraindication to cisplatin (Planchard et al 2018). The American Society of Clinical Oncology (ASCO) Clinical Practice Guideline update on systemic therapy for stage IV NSCLC notes that cisplatin and carboplatin-based combinations are acceptable options and state that “cisplatin was slightly superior in efficacy to carboplatin in meta-analysis but perhaps not worth the added toxicity in the palliative care setting” (Masters et al 2015).

In this study, Investigators may choose either carboplatin or cisplatin as the platinum-based therapy for each patient.

4.3.2.2 Platinum dose

The cisplatin dose of 75 mg/m^2 is in accordance with approved product labelling.

The administration of carboplatin at a dose for a target AUC of 5 mg/mL/min (AUC5) is in accordance with approved product labelling.

Carboplatin has been administered in combination with pemetrexed, taxanes, or gemcitabine at a dose for a target AUC5 (Gronberg et al 2009, Rodrigues-Pereira et al 2011) or target AUC 6 mg/mL/min (AUC6) (Okamoto et al 2013, Patel et al 2013, Sandler et al 2006, Scagliotti et al 2005, Schuette et al 2013, Socinski et al 2010, Zinner et al 2005). In recent global Phase III studies in first-line treatment of NSCLC that include carboplatin and pemetrexed, alternative options for carboplatin dosing have been employed; eg, AUC5 only (Gandhi et al 2018, Mok et al 2017), a choice of AUC5 or AUC6 (Reck et al 2016, MYSTIC- NCT02453282), and AUC6 only (Carbone et al 2017).

No prospective comparison of the carboplatin dose regimens in combination with pemetrexed has been performed, but in a meta-analysis comparing the AUC5 (n = 105) and AUC6 (n = 384) regimens in the first-line treatment of advanced NSCLC with carboplatin/pemetrexed, an improved safety profile was observed in patients receiving the AUC5 regimen, while efficacy was similar between the 2 groups (Okamoto et al 2017).

The NEJ005 study included up to 6 cycles of carboplatin AUC6 with pemetrexed and concurrent or sequential gefitinib. The study authors commented that the combination of gefitinib and carboplatin/pemetrexed does not appear to have additive toxicity. "However, 41.5% of patients in the concurrent regimen group required dose reductions of carboplatin/ pemetrexed. A lower incidence of adverse hematological events is preferred, as such, and an AUC of 5 has been adopted in the NEJ009 study" (Sugawara et al 2015). In addition, the ongoing randomized study of osimertinib with and without platinum/pemetrexed therapy includes carboplatin AUC5.

Both carboplatin AUC5 and AUC6 dosing regimens are considered to represent a SoC; However, due to better tolerability and similar efficacy, AUC5 has been chosen as the carboplatin dose regimen in the proposed study.

4.3.2.3 Pemetrexed

NCCN 2019 guidelines include pemetrexed in combination with cisplatin or carboplatin as category 1 first-line systemic therapy options for patients with adenocarcinoma (NCCN 2019). ESMO 2018 guidelines recommend pemetrexed in preference to gemcitabine or docetaxel for use in combination with platinum-based chemotherapy in patients with nonsquamous tumors

(level II, Grade A; Planchard et al 2018). Per the ASCO guideline, platinum/pemetrexed combinations are acceptable options for patients with stage IV NSCLC (Masters et al 2015).

Pemetrexed is approved by the Food and Drug Administration (FDA) for use in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, nonsquamous, NSCLC and as a single agent for the maintenance treatment of patients with locally-advanced or metastatic nonsquamous NSCLC whose disease has not progressed after 4 cycles of platinum-based first-line chemotherapy. The recommended dose of pemetrexed for maintenance treatment of NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous (IV) infusion over 10 minutes on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity, to be administered after 4 cycles of platinum-based first-line chemotherapy until disease progression or unacceptable toxicity.

Moreover, international guidelines recommend pemetrexed maintenance. ESMO 2018 guidelines recommend 4 cycles of platinum-based doublets followed by less toxic maintenance monotherapy as first-line treatment of NSCLC without actionable oncogenic driver regardless of programmed death ligand 1 (PD-L1) status (Planchard et al 2018). The NCCN 2019 guidance includes single-agent pemetrexed as a category 1 recommendation as a continuation maintenance therapy in patients with nonsquamous NSCLC and negative or unknown results for mutations (NCCN 2019).

It appears that there are no prospective studies that have assessed whether pemetrexed maintenance is superior to no maintenance treatment (or placebo) specifically in patients with EGFRm disease who have been treated with 4 cycles of platinum-pemetrexed therapy.

The NCCN 2019 guidelines support pemetrexed maintenance in the second- and later-line setting in patients with EGFRm NSCLC (NCCN 2019).

In the present study, pemetrexed maintenance will continue until a discontinuation criterion is met (Section 7). The proposed study is powered to demonstrate an improvement in median PFS from 19 months on osimertinib to 28 months on osimertinib with chemotherapy. Assuming 3 months for the first 4 cycles of platinum/pemetrexed doublet therapy, this equates to a median duration of pemetrexed maintenance of 25 months, ie, approximately 36 cycles (assuming patients receive pemetrexed maintenance and do not discontinue for reasons other than disease progression). In comparison, in the Phase III study of pemetrexed maintenance, the median number of cycles of pemetrexed maintenance was 4; 47% of patients received ≥6 cycles and 28% received ≥10 cycles (Paz-Ares et al 2012). Thus, the extent of pemetrexed maintenance in this study is expected to be significantly longer than would be expected based on a study of patients with EGFR wild type or EGFR-unknown NSCLC.

4.3.2.4 Summary

The proposed chemotherapy regimen for use with osimertinib is pemetrexed 500 mg/m^2 (with vitamin supplementation) plus cisplatin 75 mg/m^2 or carboplatin AUC5, both administered on Day 1 Q3W for 4 cycles, followed by osimertinib 80 mg daily and pemetrexed 500 mg/m^2 Q3W until progression or another discontinuation criterion is met. While administration of chemotherapy with an EGFR-TKI is not SoC as first-line treatment for patients with EGFRm NSCLC, the proposed chemotherapy part of the regimen is consistent with approved labels, national and international cancer guidelines, global clinical trials, and standard clinical practice.

4.4 End-of-study definition

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

The study is expected to start patient enrolment Q3 2019 and to end by approximately Q1 2026.

The study may be terminated at individual study sites if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. The study may be terminated due to futility. AstraZeneca may also terminate the entire study prematurely if concerns for patient safety arise within this study or in any other study with osimertinib.

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

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

5 STUDY POPULATION

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

Inclusion and exclusion criteria are the same for the safety run-in period and the randomized period. Each patient must meet all of the inclusion criteria and none of the exclusion criteria in order to be allocated/randomized to a study treatment. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures, refer to Section 5.4.

In this protocol, “enrolled” patients are defined as those who sign informed consent. “Allocated” patients are defined as those in the safety run-in who are assigned to treatment.

"Randomized" patients are defined as those who receive a randomization number in the randomized period of the study.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.4.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria (Section 5.2) apply:

Informed consent

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

2 Provision of signed and dated, written informed consent form prior to any mandatory study-specific procedures, sampling, and analyses.

3 For patients who agree to the optional genetic testing, provision of signed and dated genetic testing section of the written Main ICF prior to collection of a sample for genetic analysis for inclusion in the optional genetic research as allowed by local regulations.

The ICF process is described in Appendix A 3.

Age

4 Male or female, at least 18 years of age; patients from Japan at least 20 years of age.

Type of patient and disease characteristics

5 Pathologically confirmed nonsquamous NSCLC. NSCLC of mixed histology is allowed.

6 Newly diagnosed locally advanced (clinical stage IIIB, IIIC) or metastatic NSCLC (clinical stage IVA or IVB) or recurrent NSCLC (per Version 8 of the International Association for the Study of Lung Cancer [IASLC] Staging Manual in Thoracic Oncology), not amenable to curative surgery or radiotherapy.

7 The tumor harbors 1 of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del or L858R), either alone or in combination with other EGFR mutations, which may include T790M, assessed by a CLIA-certified (US sites) or an accredited (outside of the US) local laboratory or by central prospective tissue testing.

8 Mandatory provision of a baseline plasma sample and an unstained, archival tumor tissue sample in a quantity sufficient to allow for central confirmation of the EGFR mutation status.

9 Patients must have untreated advanced NSCLC not amenable to curative surgery or radiotherapy. Prior adjuvant and neo-adjuvant therapies (chemotherapy, radiotherapy, immunotherapy, biologic therapy, investigational agents), or definitive radiation/chemoradiation with or without regimens including immunotherapy, biologic

therapy, investigational agents, are permitted as long as treatment was completed at least 12 months prior to the development of recurrent disease.

10 WHO PS of 0 to 1 at screening with no clinically significant deterioration in the previous 2 weeks.

11 Life expectancy >12 weeks at Day 1.

12 At least 1 lesion, not previously irradiated that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis of ≥15 mm) with CT or MRI, and that is suitable for accurate repeated measurements. If only 1 measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously irradiated and as long as it has not been biopsied within 14 days of the baseline tumor assessment scans.

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 highly effective contraceptive measures, must not be breast feeding, and must have a negative pregnancy test prior to first dose of IP or must have evidence of non-child-bearing potential by fulfilling 1 of the following criteria at screening:

- Post-menopausal, defined as more than 50 years of age and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
- Women under 50 years old would be considered as postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and have luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the post-menopausal range for the institution
- Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

Further information is available in Appendix H (Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods).

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

5.2 Exclusion criteria

Medical conditions

1 Spinal cord compression and unstable brain metastases. Patients with stable brain metastases who have completed definitive therapy, are not on steroids, and have a stable neurological status for at least 2 weeks after completion of the definitive therapy and steroids can be enrolled. Patients with asymptomatic brain metastases can be eligible for inclusion if in the opinion of the Investigator immediate definitive treatment is not indicated.

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

3 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 jeopardize compliance with the protocol, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required. Active infection will include any patients receiving treatment for infection.

4 Any of the following cardiac criteria:

- Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine-derived QTcF value;
- Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG; eg, complete left bundle branch block, third-degree heart block, second-degree heart block;
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as electrolyte abnormalities including serum/plasma potassium*, magnesium* and calcium* below the LLN, heart failure, congenital long QT syndrome, 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. See Section 6.5.2 and Appendix G.
  * correction of electrolyte abnormalities to within normal ranges can be performed during screening

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

- Absolute neutrophil count below the lower limit of normal (<LLN) *
- Platelet count below the LLN*
- Hemoglobin <90 g/L*

  *The use of granulocyte colony stimulating factor support, platelet transfusion and blood transfusions to meet these criteria is not permitted.

- ALT >2.5 x the upper limit of normal (ULN) if no demonstrable liver metastases or >5 x ULN in the presence of liver metastases
- AST >2.5 x ULN if no demonstrable liver metastases or >5 x ULN in the presence of liver metastases
- Total bilirubin >1.5 x ULN if no liver metastases or >3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases

- Creatinine clearance <60 mL/min calculated by Cockcroft and Gault equation or 24-hour urine collection (refer to Appendix I for appropriate calculation)

6 Any concurrent and/or other active malignancy that has required treatment within 2 years of first dose of IP.

7 Any unresolved toxicities from prior systemic therapy (eg, adjuvant chemotherapy) greater than CTCAE Grade 1 at the time of starting study treatment, with the exception of alopecia and Grade 2 prior platinum-therapy related neuropathy.

8 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

9 Prior treatment with any systemic anti-cancer therapy for advanced NSCLC not amenable to curative surgery or radiation including chemotherapy, biologic therapy, immunotherapy, or any investigational drug. Prior adjuvant and neo-adjuvant therapies (chemotherapy, radiotherapy , immunotherapy, biologic therapy, investigational agents), or definitive radiation/chemoradiation with or without regimens including immunotherapy, biologic therapies, investigational agents are permitted as long as treatment was completed at least 12 months prior to the development of recurrent disease.

10 Prior treatment with an EGFR-TKI.

11 Major surgery within 4 weeks of the first dose of IP. Procedures such as placement of vascular access, biopsy via mediastinoscopy or biopsy via video assisted thoracoscopic surgery (VATS) are permitted.

12 Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of IP.

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

Prior/concurrent clinical study experience

14 Participation in another clinical study with an investigational product during the 4 weeks prior to Day 1. Patients in the follow-up period of an interventional study are permitted.

Other exclusions

15 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and 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 Previous treatment allocation (safety run in) or randomization (randomization period) in the present study.

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

19 History of hypersensitivity to active or inactive excipients of IP or drugs with a similar chemical structure or class to IP.

20 Contraindication for pemetrexed and cisplatin/carboplatin according to local approved label.

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

- Prior allogeneic bone marrow transplant
- 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 any study treatment and for the specified times before and after.

5.3.1 Pregnancy

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

1 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 highly effective methods of contraception from screening until at least 6 weeks after discontinuing study treatment. Highly effective methods are provided Appendix H (Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods).

2 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 at least 6 months after discontinuing chemotherapy or at least 4 months after discontinuing osimertinib. In addition, patients must refrain from donating sperm from the start of dosing until at least 6 months after discontinuing chemotherapy or at least 4 months after discontinuing osimertinib.

3 Due to the possibility of platinum-based chemotherapy and pemetrexed treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment (see Section 2.3.2.4).

For patients receiving chemotherapy, all guidance in the local label and/or in general use by the investigating site should be followed.

5.3.2 Meals and dietary restrictions

Osimertinib can be taken without regard to food. The use of any natural/herbal products or other "folk remedies" should be discouraged and in particular patients should avoid taking dietary supplements or herbal medicines with known strong inducers of CYP3A4 whenever feasible (see Section 6.5).

The use of any natural/herbal products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications should be recorded in the eCRF.

5.4 Screen failures

Screen failures are defined as patients who signed the informed consent form to participate in the clinical study but are not subsequently entered into the safety run-in or randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of patients who fail screening to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened, with the exception of patients with a central EGFR test negative for Exon19 deletions or L858R. Rescreened patients should be assigned a new E-code both in electronic database capture and interactive voice/web response system, while the unique subject identifier assigned at the first time of screening should remain the same to easily identify rescreened patients. Rescreening should be documented so that its effect on study results, if any, can be assessed.

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

5.5 Procedures for handling incorrectly enrolled or randomized patients

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

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed combination product) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to osimertinib monotherapy and osimertinib with pemetrexed and either cisplatin or carboplatin.

6.1 Treatments administered

6.1.1 Investigational products

See Table 5 for further details on the investigational products (IPs) in the safety run-in period and see Table 6 for further details on the IPs in the randomized period.

6.1.1.1 Safety run-in

Study treatments for the safety run-in are shown in Table 5. Selection of cisplatin or carboplatin is the Investigator's choice. The investigational site should declare (in interactive voice response system [IVRS]/interactive web response system [IWRS]) their choice of chemotherapy for each patient. Each treatment will have a maximum number of patients that can be allocated (approximately 15 patients per cohort).

Table 5 Study treatments for the safety run-in

	Osimertinib plus Cisplatin/pemetrexed	Osimertinib plus Carboplatin/pemetrexed
Study treatment name	osimertinib (AZD9291) pemetrexed cisplatin	osimertinib (AZD9291) pemetrexed carboplatin
Dosage formulation	osimertinib 80 mg tablet pemetrexed 500 mg/m^2 cisplatin 75 mg/m^2	osimertinib 80 mg tablet pemetrexed 500 mg/m^2 carboplatin (AUC of 5 mg/mL/min [AUC5])
Dosage formulation, dose reduction	40 mg tablet for oral administration pemetrexed and cisplatin dose reduction in Section 6.6	40 mg tablet for oral administration pemetrexed and carboplatin dose reduction in Section 6.6
Route of administration	osimertinib: oral pemetrexed: IV infusion cisplatin: IV infusion	osimertinib: oral pemetrexed: IV infusion carboplatin: IV infusion

	Osimertinib plus Cisplatin/pemetrexed	Osimertinib plus Carboplatin/pemetrexed
Dosing instructions	osimertinib 1 tablet of 80 mg QD with pemetrexed (500 mg/m^2, with vitamin supplementation as detailed in Section 6.1.2) plus cisplatin (75 mg/m^2) on Day 1 of 21-day cycles (every 3 weeks) for 4 cycles, followed by osimertinib 80 mg QD plus pemetrexed maintenance (500 mg/m^2) every 3 weeks	osimertinib 1 tablet of 80 mg QD with pemetrexed (500 mg/m^2, with vitamin supplementation as detailed in Section 6.1.2) plus carboplatin (AUC5) on Day 1 of 21-day cycles (every 3 weeks) for 4 cycles, followed by osimertinib 80 mg QD plus pemetrexed maintenance (500 mg/m^2) every 3 weeks
Dosing instructions, dose reduction	osimertinib 1 tablet of 40 mg QD pemetrexed and cisplatin dose reduction in Section 6.6	osimertinib 1 tablet of 40 mg QD pemetrexed and carboplatin dose reduction in Section 6.6
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. Cisplatin and pemetrexed will be sourced locally where country regulations allow. If centrally supplied, a label will be prepared in accordance with GMP and local regulatory guidelines.	Osimertinib will be provided in in HDPE bottles with child-resistant closures. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. Carboplatin and pemetrexed will be sourced locally where country regulations allow. If centrally supplied, a label will be prepared in accordance with GMP and local regulatory guidelines.
Provider	osimertinib: AstraZeneca pemetrexed and cisplatin: sourced locally by site where country regulations allow, under certain circumstances when local sourcing is not feasible a chemotherapy treatment may be supplied centrally through AstraZeneca	osimertinib: AstraZeneca pemetrexed and carboplatin: sourced locally by site where country regulations allow, under certain circumstances when local sourcing is not feasible a chemotherapy treatment may be supplied centrally through AstraZeneca

6.1.1.2 Randomized Period

Study treatments for the randomized period are shown in Table 6. Selection of cisplatin or carboplatin is per Investigator's choice. The investigational site should declare (in

IVRS/IWRS) their choice of chemotherapy for each patient prior to randomization to cover the eventuality that the patient is randomized to the osimertinib plus chemotherapy arm. Randomization will be made in IVRS/IWRS system as soon as all the eligibility criteria are met as confirmed by the Investigator and should be documented in the medical records.

Table 6 Study treatments for the randomized period

	Osimertinib plus chemotherapy	Osimertinib
Study treatment name	osimertinib (AZD9291) pemetrexed cisplatin or carboplatin	osimertinib (AZD9291)
Dosage formulation	osimertinib 80 mg pemetrexed 500 mg/m^2 cisplatin 75 mg/m^2 OR carboplatin (AUC of 5 mg/mL/min [AUC5])	80 mg tablet
Dosage formulation, dose reduction	40 mg tablet for oral administration pemetrexed, cisplatin, and carboplatin dose reduction in Section 6.6	40 mg tablet for oral administration
Route of administration	osimertinib: oral pemetrexed: IV infusion cisplatin: IV infusion carboplatin: IV infusion	oral
Dosing instructions	osimertinib 1 tablet of 80 mg QD with pemetrexed (500 mg/m^2, with vitamin supplementation as detailed in Section 6.1.2) plus either cisplatin (75 mg/m^2) or carboplatin (AUC5) on Day 1 of 21-day cycles (every 3 weeks) for 4 cycles, followed by osimertinib 80 mg QD plus pemetrexed maintenance (500 mg/m^2) every 3 weeks	osimertinib 1 tablet of 80 mg QD
Dosing instructions, dose reduction	osimertinib 1 tablet of 40 mg QD pemetrexed, cisplatin, and carboplatin dose reduction in Section 6.6	osimertinib 1 tablet of 40 mg QD

	Osimertinib plus chemotherapy	Osimertinib
Packaging and labelling	Osimertinib will be provided in in HDPE bottles with child-resistant closures. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. Cisplatin, carboplatin, and pemetrexed will be sourced locally where country regulations allow. If centrally supplied, a label will be prepared in accordance with GMP and local regulatory guidelines.	Osimertinib will be provided in in HDPE bottles with child-resistant closures. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.
Provider	osimertinib: AstraZeneca pemetrexed, cisplatin, and carboplatin: sourced locally by site where country regulations allow, under certain circumstances when local sourcing is not feasible a chemotherapy treatment may be supplied centrally through AstraZeneca	osimertinib: AstraZeneca

6.1.2 Dosing instructions

6.1.2.1 Osimertinib dosing

For the first 6 cycles, sufficient osimertinib treatment for 3 weeks will be distributed at each dispensing visit. From Cycle 7 to Cycle 17, dispensing visits will occur every 6 weeks and sufficient osimertinib for 6 weeks will be distributed. From Cycle 17 onwards, dispensing visits will occur every 12 weeks and sufficient osimertinib will be dispensed for 12 weeks. Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

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

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

Study drug will be dispensed to patients at Cycle 1 Day 1 (safety run-in) or randomization (randomized period) only after all study procedures and assessments have been performed as described in Table 1 or Table 2 and all eligibility criteria have been met.

For the randomized period only, 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 treatment allocation (safety run-in) or randomization (randomized period) and starting study treatment. If study treatment includes chemotherapy, pre-treatment should be started as soon as possible and will take place prior to the start of study treatment as described in Table 1, Table 2 and Section 6.1.2.2. It is recommended that patients commence study treatment or chemotherapy pre-treatment as soon as possible after treatment allocation (safety run-in) or randomization (randomized period) and whenever possible within 1 day. (ie, for the randomized period, on the same day after randomization in the IVRS/IWRS).

To allow for management of IP-related toxicities, the initial dose of osimertinib 80 mg once daily can be reduced to 40 mg QD (see Section 6.6 and Section 8.4.5). Once the dose of osimertinib is reduced to 40 mg once per day, the patient will remain on the reduced dose until termination from study treatment. Re-challenge at 80 mg is not allowed in this study.

On site visit days on which PK samples are scheduled, the dosing should be delayed until the patient arrives 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 each day. Doses should not be missed. If a patient misses taking a scheduled dose, it is acceptable to take the dose within a window of 12 hours. If it is more than 12 hours after the scheduled dose time, the missed dose should not be taken, and the patient should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking the IP, he/she should not make up for this dose, but should take the next dose at the scheduled time.

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

Any change from the dosing schedule, dose interruptions, or dose reductions should be recorded in the electronic Case Report Form (eCRF).

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

6.1.2.2 Chemotherapy dosing

Full details on cisplatin, carboplatin and pemetrexed can be found in the local prescribing information for these products. Pre-treatment for chemotherapy should be completed prior to

osimertinib, cisplatin, carboplatin, and pemetrexed dosing according to the guidelines below. For the osimertinib and chemotherapy arm, osimertinib and chemotherapy dosing should begin on the same day. Patients may receive pre-treatment and concomitant treatment (eg, antiemetics) as recommended by the approved label for pemetrexed, carboplatin or cisplatin as clinically indicated by the Investigator; however, additional information provided in Section 6.5 should be reviewed.

6.1.2.2.1 Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes Q3W as per local practice and labels until RECIST1.1-defined progression or another discontinuation criterion is met (see Section 7.1).

To reduce the severity of hematologic and gastrointestinal toxicity of pemetrexed toxicity, patients treated with pemetrexed must also receive vitamin supplementation. Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1000 mcg) on a daily basis. At least 5 doses of folic acid should be taken during the 7 days preceding the first dose of pemetrexed. Folic acid dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients should also receive an intramuscular injection of vitamin B_{12} (1000 mcg or 1 mg) in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as pemetrexed. Do not substitute oral vitamin B_{12} for intramuscular vitamin B_{12}.

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

6.1.2.2.2 Cisplatin

Cisplatin 75 mg/m^2 will be administered as an IV infusion according to local practice and labels approximately 30 minutes after the pemetrexed infusion, Q3W for 4 cycles, and should be immediately preceded and followed by hydration.

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

6.1.2.2.3 Carboplatin

Carboplatin AUC5 mg/mL/min will be administered as an IV infusion over 15-60 minutes, after the pemetrexed infusion, Q3W for 4 cycles, according to local practice and labels.

Carboplatin dose is calculated using the Calvert formula. Glomerular filtration rate in the Calvert formula is estimated by calculated creatinine clearance using the Cockcroft-Gault Equation. The carboplatin dose is not to exceed 750 mg.

Calvert Formula

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

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

6.1.2.2.4 Antiemetics and other supportive care medications

Antiemetic premedication will be administered according to local standards of care; however, given the potential for an interaction between osimertinib and some antiemetic therapies with respect to prolongation of the QTc interval, additional guidance is provided in Section 6.5.

Additional supportive premedication/concomitant treatments can be given according to local standards of care; additional guidance is provided in Section 6.5.

6.2 Preparation/handling/storage/accountability

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

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments should be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff. The investigational product label on the bottles specifies instruction of appropriate storage. The Investigator or designee should confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

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

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

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

6.3 Measures to minimise bias: randomization and blinding

In the randomized period of the study, all patients will be centrally assigned to randomized study treatment in a 1:1 ratio, osimertinib:osimertinib with chemotherapy, using IVRS/IWRS.

All patients will be stratified prior to randomization by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO PS (0 vs. 1), and method for tissue testing (central vs. local) for generation of the p-value, using the Breslow approach for handling ties.

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 his/her patient number cannot be reused. Withdrawn patients will not be replaced.

This is an open-label study for the personnel at study sites; however, the Sponsor/Global Study Team are blinded during the randomized period and the specific treatment to be taken by a patient will be assigned using an IVRS/IWRS. Blinded and unblinded access and notifications will be controlled using the IVRS/IWRS. The site will contact the IVRS/IWRS prior to the start of study treatment administration for each patient. The site will record the treatment assignment on the applicable case report form (CRF). Potential bias will be reduced by use of central randomization and blinding of the Sponsor/Global Study Team.

6.4 Treatment compliance

The administration of all IP including chemotherapy should be recorded in the source document and appropriate sections of the eCRF. Any change and the reason for changing the dosing schedule, dose interruption, dose delay, dose reduction, dose discontinuation, overdosing or omission will also be recorded in the source document and eCRF. This information plus drug accountability for all IP at every visit will be used to assess compliance with the treatment.

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

6.5 Concomitant therapy

Any concomitant treatment, procedures, medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient receives within 4 weeks prior to the first dose of IP or receives during the study until 28-day follow-up visit (28 days after last dose of IP) should be recorded in the source document and the applicable section of eCRF. If any concomitant therapy is administered due to new or unresolved AE, that therapy 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 in the table below. For questions related to specific medications, contact the Study Physician. Guidance on medications to avoid, medications that require close monitoring, and on washout periods are provided in Appendix G.

Prohibited Medication/Class of drug:	Usage:
Other anti-cancer agents, investigational agents and non-palliative radiotherapy	Should not be given while the subject is on IP.

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

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

Allowed Medication/Class of drug:	**Usage:**
Pre-medication will be allowed for subjects receiving osimertinib with chemotherapy. It is also allowed for subjects randomized to osimertinib after the first dose of osimertinib.	To be administered as directed by the Investigator. This includes management of diarrhea, nausea and vomiting.
Calcium folinate/folinic acid	The use of calcium folinate/folinic acid in the management of pemetrexed overdose should be considered.

Leukocyte-depleted blood transfusions	Patients can have blood transfusions during the study treatment. However, patients aren't allowed to receive blood transfusions or platelet transfusions in order meet the inclusion criteria of the study.
Corticosteroids /bisphosphonates/Rank-ligand inhibitors	Please see Section 6.1.2.2 for details relating to corticosteroid pre-medication for subjects receiving chemotherapy. Corticosteroids can be used for the management of bone metastases. Regular, concomitant use of bisphosphonates and RANK-L inhibitors for management of bone metastases is permitted if therapy is initiated prior to first dose of study therapy. Initiation of therapy after allocation/randomization is permitted in patients with no evidence of overall clinical or radiographic progression per RECIST 1.1. or in patients in survival follow-up.
Palliative local therapy-radiotherapy and surgical resection	Palliative local therapy, including radiation therapy and surgical resection for non-target lesions is permitted in patients with no evidence of overall clinical or radiographic progression per RECIST 1.1 or in patients in survival follow-up.
Vaccines	Vaccines can be administered in accordance with local labels.

6.5.2 Antiemetic therapy

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

The Arizona Centre for Education and Research on Therapeutics (https://www.crediblemeds.org/) is a website that categorizes drugs based on the risk of causing QT prolongation or TdP. Information on these categories and antiemetic therapies is provided in Table 7. The list of drugs may not be exhaustive; moreover the information regarding drugs in the table below is subject to change as new information on drugs becomes available. As such investigators should review the up-to-date website.

Table 7 QT/TdP risk category for antiemetic therapies

QT/TdP risk Category	Definition	Antiemetic therapies
Known risk of TdP	These drugs prolong the QT interval **AND** are clearly associated with a known risk of TdP, even when taken as recommended	domperidone droperidol haloperidol levomepromazine levosulpiride ondansetron
Possible risk of TdP	These drugs can cause QT prolongation **BUT** currently lack evidence for a risk of TdP when taken as recommended.	dolasetron granisetron palonosetron tropisetron
Conditional Risk of TdP	These drugs are associated with TdP **BUT** only under certain conditions of their use (eg, excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) **OR** by creating conditions that facilitate or induce TdP (eg, by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).	metoclopramide

An additional risk category applies to Drugs to Avoid in Congenital Long QT Syndrome (cLQTS); however, patients with congenital long QT syndrome are not permitted to enroll in this study.

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

1 At screening patients are required to have serum electrolytes ≥LLN; ie, potassium, magnesium and calcium in the normal range. If during screening patients have electrolyte levels <LLN, measures can be taken to bring these into the normal range. During study treatment, electrolyte levels should be maintained in the normal range.

2 Investigators should review guidance that applies to all drugs (ie, not just anti-emetics) with the potential for interaction with osimertinib regarding QTc interval prolongation - see Appendix G.

3 In this study it is strongly recommended that antiemetic drugs from the **known risk of TdP** category are not given, ie, ondansetron, domperidone, droperidol, haloperidol, levomepromazine, or levosulpiride. If it is considered essential to give a 5-HT_3 receptor-antagonist, one of the following agents should be given if available: granisetron,

dolasetron, tropisetron or palonosetron. However, as these drugs are categorized as having a possible risk of TdP, careful monitoring of ECGs and electrolytes is recommended. If it is essential to give a 5-HT_3 receptor- antagonist and ondansetron is the only available 5-HT_3 receptor- antagonist, careful monitoring with ECGs and electrolytes is recommended.

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

6.5.3 Other concomitant treatment

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

6.5.4 Prior immune-oncology therapy

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

6.6 Dose modification

Dose modifications are permitted in the management of IP-related toxicities as described in Section 8.4.5.

6.7 Treatment after the end of the study

After the final OS analysis, patients may continue on study treatment until disease progression occurs as judged by the Investigator or until the patient meets any other discontinuation criteria as defined in Section 7.1.

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients may be discontinued from all IP (osimertinib, cisplatin, carboplatin, and pemetrexed) for the situations listed below. A patient continuing on at least 1 IP will not be considered discontinued from study treatment and will continue assessments per the SoA (Table 1 or Table 2). Note that discontinuation from study treatment is NOT the same as a complete withdrawal from the study. Patients who discontinue study treatment will continue in follow-up per the protocol.

- RECIST 1.1-defined progression if patient is no longer receiving clinical benefit
- Patient decision - the patient is free to discontinue treatment at any time, without prejudice to further treatment. Patients randomized to receive osimertinib with chemotherapy treatment can discontinue pemetrexed or platinum/ pemetrexed and continue to receive osimertinib alone.
- Investigator decision to withdraw the patient from treatment
- Adverse event – specific criteria requiring discontinuation of osimertinib and platinum/pemetrexed chemotherapy are provided in Section 8.4.5
- Severe non-compliance with the Clinical Study Protocol
- Patients who are incorrectly initiated on IP
- Pregnancy.

See the SoA (Table 1 or Table 2) 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

The Investigator should instruct the patient to contact the site before or at the time study treatment is stopped. A patient who decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the eCRF. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF. All study treatment should be returned by the patient at the next on-site study visit or unscheduled visit. Patients permanently discontinuing study treatment should be given locally available SoC therapy, at the discretion of the Investigator.

Discontinuation of study treatment, for any reason, does not impact on the patient´s participation in the study. The patient 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 should be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

The discontinuation visit assessments should be performed as soon as the patient permanently discontinues from study treatment and/or the study (Table 1 or Table 2). Further follow-up procedures are detailed below and in the SoA (Table 1 or Table 2).

7.1.2 Procedures for follow-up

7.1.2.1 Prior to primary PFS analysis DCO

Progression follow-up

In the event that a patient discontinues IP for reasons other than RECIST 1.1 defined progression prior to the primary PFS analysis DCO, that patient will continue to be followed for progression as per the RECIST schedule in Table 1 or Table 2 (relative to first dose for the safety run-in and relative to randomization for the randomized period). The investigator will continue to assess for progression according to RECIST 1.1, and scans will be sent for BICR assessment, up to disease progression or until the primary PFS analysis DCO, whichever occurs first. Refer to Section 7.1.2.2 for patients who have not had disease progression after the primary PFS DCO.

OS follow-up

Patients assessed as having RECIST 1.1 defined progression by the Investigator prior to the primary PFS analysis DCO will continue to be followed as per the survival follow up column of the SoA (Table 1 or Table 2). Survival information may be obtained via telephone contact with the patient or the patient's family or by contact with the patient's current physician.

For the safety run-in, patients will be followed for survival status every 12 weeks until death, withdrawal of consent, or the primary PFS DCO, whichever occurs first.

For the randomized period, patients will be followed for survival status every 12 weeks until death, withdrawal of consent, or the final OS DCO, whichever occurs first.

The following assessments apply to the randomized period only, as the assessments are not applicable for the safety run-in period. Assessments will be collected as below with further details provided in Table 2:

- Subsequent progression will be collected up to the primary PFS analysis DCO as assessed by the Investigator and defined according to local standard practice (Table 2). Investigator assessment of subsequent response/progression is to be collected every 12 weeks up to the DCO for the primary PFS analysis.
- Electronic patient-reported outcome (ePRO) data will be collected at disease progression and then every 8 weeks post progression until primary PFS analysis DCO or PFS2, whichever is sooner.
- Healthcare resource use module will be collected every 12 weeks during survival follow-up for all patients until primary PFS DCO.

Patients should be contacted in the week following primary PFS analysis DCO to provide 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 primary PFS

analysis DCO should be obtained by the site personnel by checking the patient notes and hospital records, contacting the patient's general practitioner, and checking publicly available death registries. If the patient has actively withdrawn consent to the processing of his/her 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.

7.1.2.2 After primary PFS analysis DCO

For the safety run-in, refer to Section 7.5. For the randomized period, follow the guidance below.

At the time of the primary PFS analysis DCO the collection of progression data according to RECIST 1.1 will cease. Scans will no longer be sent for BICR assessment. PFS2 data, ePRO, and health resource module will cease to be collected. The patients should return the ePRO devices to the site at their next visit and site staff should perform the "End LogPad Use," so that this is recorded in the database.

Progression follow-up

Patients who have not yet had disease progression will continue to be followed for progression defined as per local clinical practice. Investigator assessment of response/progression will be collected every 12 weeks up to disease progression or until the final OS analysis DCO.

OS follow-up

Following progression defined by local clinical practice, the patient will enter into survival follow up and will continue to be followed as per the survival follow up column of the SoA (Table 2). Patients will be followed for survival status every 12 weeks until death, withdrawal of consent or the time of final OS analysis DCO. Survival information may be obtained via telephone contact with the patient or patient's family, or by contact with the patient's current physician.

Patients should be contacted in the week following the final OS analysis DCO to provide 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 DCO should be obtained by the site personnel by checking the patient notes and hospital records, contacting the patient's general practitioner, and checking publicly available death registries. If the patient has actively withdrawn consent to the processing of his/her 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 through progression

At the Investigator's discretion, study treatment with osimertinib monotherapy may continue for as long as a patient continues to derive clinical benefit after RECIST 1.1 progression in the

absence of any discontinuation criteria. However, if the patient is deemed to have clinically significant, unacceptable or irreversible toxicities, rapid tumor progression, or symptomatic progression requiring urgent medical intervention (eg, CNS metastases, respiratory failure, spinal cord compression) study treatment must be discontinued.

Patients who continue on osimertinib treatment following progression should maintain the schedule of assessments as shown below:

- Routine safety measurements (AEs, safety laboratory assessments [clinical chemistry, haematology and urinalysis], and creatinine clearance calculation);
- Routine clinical procedures (physical exam, WHO PS, vital signs, ECGs, Echo/ MUGA), and concomitant medications;
- PROs every 8 weeks post progression until PFS2 or DCO for the primary PFS analysis, whichever is sooner

In addition, patients who continue on osimertinib treatment following progression will continue to be followed up for survival status every 12 weeks (calculated from the time of the treatment discontinuation visit) until death, withdrawal of consent, or the primary PFS analysis DCO for the randomized period (for patients in the safety run-in) or the final OS analysis DCO (for patients in the randomized period) as per the survival follow-up column shown in the SoA (Table 1 or Table 2). AEs will continue to be collected throughout the treatment period and including the 28-day follow-up period (28 days after last dose of IP).

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 should 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; eg, by 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. If the patient is 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 the latest follow-up contact.

7.4 Withdrawal from the study

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

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

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 consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator has the following responsibilities:

- Ensure that AstraZeneca is notified immediately of the patients' withdrawal of informed consent for the use of donated samples
- Ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensure the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action is documented and the signed document is returned to the study site
- Ensure that the patient and AstraZeneca are informed about the sample disposal. AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately, samples are disposed of/destroyed, the action documented, and the documentation returned to the study site.

A patient who withdraws consent will always be asked about the reason(s) for the withdrawal and the presence of any AEs. The Investigator will follow up patients as medically indicated. The patient will return all unused study treatment and ePRO devices.

The Sponsor or its delegate will request Investigators to collect information on patients' vital status (dead or alive; date of death when applicable) during survival follow up from publicly available sources, in accordance with local regulations. Knowledge of the vital status for all patient is crucial for the integrity of the study.

See SoA (Table 1 or Table 2) 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 following database close

The clinical study database will close to new data from the safety run-in once the final PFS analysis DCO has been reached and will close to new data from the randomized period once the final OS analysis DCO has been reached.

Patients can continue to receive study treatment until disease progression occurs as judged by the Investigator, or they meet any other discontinuation criteria defined in Section 7.1. For details regarding follow-up procedures, refer to Section 7.1.2.

Patients will be monitored in accordance with the Investigator's standard clinical practice or national product label. 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, overdose and pregnancy (as per Section 8.4) via paper and emailed (preferably) or faxed directly to Tata Consulting Services Data Entry Site (TCS DES) (also known as AZ DES). Drug accountability information will be recorded in the source documents.

If an Investigator learns of any SAEs, 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 AE that is unresolved at the patient's last AE visit in the study will be followed by the Investigator for as long as medically indicated, but without further recording in the CRF, until the event resolves, stabilizes, or is otherwise explained, or the patient is lost to follow up.

8 STUDY ASSESSMENTS AND PROCEDURES

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

It is recommended that the screening assessments be performed in a stepwise process beginning with the confirmation of EGFR mutation status (see Section 8.1.3). However, screening assessments may be done in parallel to the EGFR mutation assessment, as appropriate.

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

The Investigator ensures the accuracy and completeness of the eCRFs 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 and a copy will be archived at the study site.

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

Adherence to the study design requirements, including those specified in the SoA (Table 1 or Table 2), is essential and required for study conduct.

All screening evaluations 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 (eg, blood count or CT scan) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1 or Table 2).

8.1 Efficacy assessments

All patients should continue to receive assigned study treatment until objective radiological disease progression per RECIST 1.1 (Eisenhauer et al 2009) as assessed by the Investigator, or until another discontinuation criterion is met as per Section 7.1.

8.1.1 Imaging acquisition

Tumor assessments of the chest and abdomen (including the entire liver and both adrenal glands) will be performed using RECIST 1.1 (Appendix E) on images from CT (preferred) or MRI with IV contrast, collected during screening (as close as possible to and prior to the date of randomization or first dose for the safety run-in), Thereafter, tumor assessments will be done after 6 weeks (±1 week), 12 Weeks (±1 week), and then every 12 weeks (±1 week), relative to randomization for the randomized period or relative to first dose for the safety run-in until radiological disease progression per RECIST 1.1 (see Table 1 or Table 2). Tumor assessments will be done on this schedule even if a patient discontinues treatment prior to progression or receives other anti-cancer treatment. If patients are contraindicated to CT contrast agents, a non-contrast CT otherwise MRI will be acceptable. Tumor assessments of the brain will be part of the RECIST 1.1 assessment for Investigators (recorded as non-target lesions), using images from contrast-enhanced T1 MRI (preferred over CT) that are collected at screening and at progression for all patients (see Section 8.1.2.1). In addition, patients with brain metastases or a history of brain metastases at screening should be followed up with repeated imaging assessments using the same frequency as the extracranial scans to allow whole-body RECIST assessments until progression. Any areas of disease involvement should

be additionally imaged based on known metastasis sites or by the signs and symptoms of individual patients. In those patients who are contraindicated to contrast agents based on gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA), a non-contrast MRI would be sufficient. In those patients with a contraindication to MRI, a (contrast-enhanced) CT of the brain would be sufficient. Further details of the CT and MRI acquisition parameters will be documented in a separate image acquisition guidelines document. The same imaging modality used for baseline tumor assessment should be used for each subsequent follow-up assessment throughout the study if possible.

The baseline assessment is part of the screening procedures and ideally should be performed as close as possible to and prior to the start of study treatment. Scans obtained per the patient's SoC prior to randomization (or first dose for the safety run-in) do not need to be repeated and are acceptable to use as baseline evaluations, if the following criteria are met:

- the scan is obtained within 28 days before randomization (or first dose for the safety run-in);
- the scan is performed using the method requirements outlined in RECIST 1.1 (contrast-enhanced CT is recommended for imaging the chest and abdomen, including liver and adrenal glands, whereas contrast-enhanced MRI is recommended for brain scans);
- the same technique/modality can be used to follow identified lesions throughout the trial for a given patient; and
- appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

Patients with a CT scan of the brain obtained per the patient's SoC prior to randomization (or first dose for the safety run-in) will not be required to have an MRI brain scan during screening if the criteria above are met.

8.1.2 RECIST 1.1

Efficacy assessments of PFS, ORR, DoR, disease control rate (DCR) and depth of response will be derived (by AstraZeneca) using RECIST 1.1 assessments based on Investigator evaluation. Efficacy for all patients will be assessed by objective tumor assessments according to Table 1 or Table 2 until objective radiological disease progression as defined by RECIST 1.1 and as assessed by the Investigator. These assessments should occur irrespective of whether a patient is receiving study treatment or has previously discontinued study treatment for another discontinuation criterion and has started alternative anti-cancer treatment. 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.

RECIST 1.1 criteria will be used to assess each patient's tumor response to treatment. The RECIST 1.1 assessments of baseline images identify Target Lesions (TLs; defined as measurable) and Non-Target Lesions (NTLs). On-study images are evaluated for TLs and NTLs chosen at baseline, and for New Lesions (NLs) when they appear. This allows determination of follow-up TL response, NTL lesion response, the presence of unequivocal NLs, and overall time point responses (complete response [CR], partial response [PR], stable disease [SD], PD, or not evaluable [NE]). Further details of the RECIST 1.1 assessments can be found in Appendix E. Responses do not require confirmation for the randomized period. However, for the safety run-in period, objective response (per RECIST 1.1 using Investigator assessments) is defined as at least 1 visit response of CR or PR that is subsequently confirmed as CR or PR on a subsequent scan (acquired at least 4 weeks later). Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue study treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the analysis of ORR.

If the Investigator is in doubt as to whether progression has occurred, particularly with response on NTLs or the appearance of a NLs, it is advisable to continue treatment until the next scheduled assessment (or sooner assessment, if clinically indicated) and reassess the subject's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

Following Investigator-assessed 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 (see Section 8.1.2.3). These local-practice scans should not be sent to the appointed contact research organization (CRO) for BICR.

8.1.2.1 Imaging of brain metastases

For all patients in either the safety run-in or the randomized period, brain scans should be performed (preferably with MRI) at screening and progression using the same modality. The presence of brain metastases at screening will be based on the Investigator assessment of the brain scan. Patients who have brain metastases or a history of brain metastases at screening are to be followed-up at every imaging visit, and will have tumor assessments according to RECIST 1.1 until overall PD. If brain metastases are not detected (within 28 days prior to randomization [or first dose for the safety run-in]), or if the patient does not have a history of brain metastases, the patient is not required to undergo further imaging of the brain *unless* metastases are suspected by the Investigator, or until (extracranial) PD is assessed with RECIST 1.1 by the Investigator. Once PD is assessed in patients without brain metastases, a brain scan should be performed within 4 weeks, but preferably as soon as possible, to allow the assessment of new lesions in the brain. If an unscheduled imaging assessment was

performed, for example due to suspected CNS progression, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled scan. For patients without a history of brain metastases, the scheduled brain scan will be performed once extracranial progression has been assessed.

8.1.2.2 Central reading of scans

For the safety run-in, all images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organization for QC and storage. There is no BICR of the safety run-in scans.

For the randomized period, all images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organization to enable BICR up to the point of the primary PFS analysis DCO. After the primary PFS analysis DCO, images will no longer be collected centrally. Guidelines for image acquisition, de-identification, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. In addition to a whole-body BICR according to RECIST 1.1, all CNS scans will have a CNS BICR using modified CNS RECIST guidelines, which allow the selection of up to 5 lesions in the brain as target lesions. The CNS BICR is separate from the BICR and is comprised of independent neuroradiologists. Further details of the BICR and CNS BICR will be documented in the Independent Review Charter (also referred to as "Imaging Charter"). Results of the independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based wholly upon the results of the RECIST 1.1 assessment conducted by the Investigator.

8.1.2.3 Assessment of second progression

During the randomized period following objective radiological progression, patients will have their progression status recorded every 12 weeks per local standard clinical practice to assess time to PFS2 up to the DCO for the primary PFS analysis. A patient's progression status will be defined according to the local practice and may involve any of the following: objective radiological progression (preferred), symptomatic progression, or death. Formal RECIST 1.1 measurements will not be collected for assessment of PFS2. The PFS2 event must have occurred after discontinuation of study treatment and subsequent treatment administered after the initial PFS event. 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. After the primary PFS analysis DCO, PFS2 will no longer be collected.

8.1.3 Screening tumor sample for EGFR mutation analysis

In this study patients can be considered eligible for inclusion in the study based upon either (i) a pre-existing positive local tumor tissue EGFR result obtained in CLIA-certified (for US

sites) or accredited laboratories (for sites outside of the US) meeting the testing method requirement specified in the Laboratory Manual or (ii) prospective central tumor tissue analysis of EGFR mutation status performed using the cobas® EGFR Mutation Test v2 according to its instructions for use.

The options for eligibility for inclusion of patients on the basis of a pre-existing EGFR result vs. prospective central testing may be modified during the trial to ensure that an adequate proportion of patients that are allocated/randomized on the basis of a pre-existing EGFR result are centrally confirmed by the cobas® EGFR Mutation Test v2 retrospectively. If a modification to not allow further eligibility of patients on the basis of a pre-existing EGFR result is made, this change will be communicated to participating sites in a timely manner. Prospective analysis of EGFR mutation status of FFPE tumor tissue using central laboratory testing by the cobas® EGFR Mutation Test v2 is encouraged.

For patients entering the study based upon a pre-existing local tumor tissue result the pre-existing local EGFR laboratory results and detailed information on the test method should be collected and maintained as a source document and captured in the eCRF. The type of EGFR laboratory methods that are acceptable and qualify to be used to inform a pre-existing EGFR status are detailed in the Laboratory Manual. Patients entering the study based upon a pre-existing local tumor tissue result are still mandated to provide a FFPE tumor tissue for retrospective central confirmation testing with the cobas® EGFR Mutation Test v2. This includes patients whose local positive test result was obtained from the cobas® EGFR Mutation Test v2. Central confirmation will not be mandated before randomization (or first dose for the safety run-in) for patients with a positive tissue EGFR test result obtained from a locally accredited laboratory.

In addition, all patients are mandated to provide a plasma sample during screening for retrospective central testing of EGFR mutations in order to assess concordance with tissue test results and to assess outcome based on plasma positivity. However, study entry criteria is based exclusively on positive tumor tissue tests.

Investigators are mandated to provide FFPE tumor tissue and plasma sample for all patients for central testing with the cobas® EGFR Mutation Test v2 as outlined below. Further guidance is provided in the Laboratory Manual.

The Investigator will be asked to provide:

- FFPE tumor tissue blocks, not older than 12 months. 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 part of the planned management of the patient and if it is considered a medically acceptable risk by the investigator; or

- An absolute minimum of 6 but preferably at least 15 unstained sections from FFPE tumor tissue block for EGFR mutation testing, exploratory biomarker and diagnostic (optional) studies, mounted on glass slides for not more than 60 days. Each section is to be 5 µm thick. The minimum number of slides will be re-iterated in the Laboratory Manual.
- A plasma sample- guidance is provided in the Laboratory Manual regarding the blood collection, volume requirement, processing to plasma and storage.

Tumor tissue blocks should be provided wherever possible for further analysis, except for China study sites, who will submit only unstained sections from the tissue block. Mutation testing residual tissue samples collected in China will be destroyed or repatriated maximally 5 years after the indication of this study is approved for marketing in China. Mandatory tissue and plasma samples will also be used for exploratory biomarker analysis (except in China, as per local regulations).

Samples may be collected from primary or metastatic tumour deposits. The tumour sample must not have been taken from a previously irradiated lesion. The sample must not have been be taken from a lesion(s) selected for inclusion criterion #12 (unless only one measurable lesion exists, in which case the baseline tumour assessment scans are to be done at least 14 days after the screening tumour sample was taken). Cytology samples (slides or cell blocks) including fine-needle aspirates, transbronchial needle aspirates, bronchial washings, bronchial lavage, bone marrow aspirates, and expectorated sputum are NOT acceptable samples and should not be sent. Needle core biopsies in which the tissue architecture is maintained are acceptable.

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

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

8.1.4 Clinical outcome assessments

A Clinical Outcome Assessment (COA) is any assessment that may be influenced by human choices, judgement, or motivation and may support either direct or indirect evidence of treatment benefit. COAs can be reported by patients (PRO), clinicians (ClinRo), or observers (ObsRo).

A patient-reported outcome (PRO) is any report of the status of a patient's health condition that comes directly from the patient, without interpretation by anyone else. PROs have become a significant tool for evaluating effectiveness of treatments in clinical studies.

The following PROs will be collected during the randomized period of the study until PFS2 or up to the DCO for the primary PFS analysis, whichever is sooner: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13), Patient Reported Outcome version of the Common Terminology Criteria for Adverse Event (PRO-CTCAE), Patients Global Impression of Severity (PGIS), and EuroQoL 5-Dimension 5-Levels (EQ-5D-5L) (see Appendix F).

8.1.4.1 EORTC QLQ-C30 and QLQ-LC13

The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population that was developed by the EORTC Quality of Life Group 1993. It consists of 30 items and measures cancer patients' symptoms, functioning, and health-related quality of life (HRQoL) (Aaronson et al 1993) for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social); 3 multi-item symptom scales (fatigue, pain, nausea/vomiting); a 2-item global HRQoL scale; 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea); and 1 item on the financial impact of the disease.

The 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). The QLQ-LC13 includes questions assessing cough, hemoptysis, dyspnea, site-specific pain (symptoms), sore mouth, dysphagia, peripheral neuropathy, alopecia (treatment-related side effects), and pain medication.

8.1.4.2 PRO-CTCAE

The PRO-CTCAE will be administered only in countries where a linguistically validated version exists.

The PRO-CTCAE was developed by the National Cancer Institute (NCI) in recognition that collecting treatment-related symptom data directly from patients can improve 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 (Basch et al 2009, Litwin et al 1998, Sprangers and Aaronson 1992). To date, 78 symptoms of the PRO-CTCAE (version 4) have been identified to be amenable to patient reporting, but not all items are administered in any clinical study. Response options vary in frequency, severity, and interference with usual activities. For this study, 9 symptoms are considered relevant for this cancer treatment (mouth or throat sores, nausea, vomiting, loose

or watery stools, pain in the abdomen, loss of control of bowel movements, dry skin, hair loss, and numbness or tingling in hands or feet; see Appendix F).

8.1.4.3 Patient Global Impression of Severity

The PGIS is a 1-item scale that assesses how a patient perceives his/her overall current severity of cancer symptoms. Patients will choose from response options from "No symptoms" to "Very severe."

8.1.4.4 EQ-5D-5L

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

Since 2009, the EuroQol group has been developing a more sensitive version of the EQ-5D (the EQ-5D-5L), which expands the range of responses to each dimension from 3 to 5 levels of increasing severity (Herdman et al 2011). Each dimension has 5 response options that reflect increasing levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems) (EuroQol Group 2013). Preliminary studies indicate that the 5-level version improves upon the properties of the 3-level version in terms of reduced ceiling effect, increased reliability and an improved ability to differentiate among different levels of health (Pickard et al 2007, Janssen et al 2008a, Janssen et al 2008b).

The questionnaire also includes a visual analogue scale, on which the subject will be asked to rate current health status on a scale of zero to 100, with zero being the worst imaginable health state (see Appendix F).

8.1.4.5 Administration of patient-reported outcomes questionnaires

The PRO instruments will be self-administered by the patients using a handheld electronic device. To ensure that the device is correctly set up and working properly, baseline PRO assessments should be completed by patients while they are in the study site on Cycle 1 Day 1, prior to the first dose of study treatment and prior to any other assessments. Thereafter, PRO assessments should be completed by the patients at home according to the SoA in Table 2. Multiple PRO assessments scheduled for the same time do not have to be completed on the same day, but should be completed within a window of ±1 day or ±3 days as specified in Table 2. The patient will be instructed to bring the PRO device to site at each visit for compliance check. If technical or other issues prohibit completion on the device, an

appropriate back-up option may be considered for the study with prior approval and instruction from the sponsor.

Each study site must allocate the responsibility for the administration of the PRO instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover in case that individual is absent. It is important that the site staff explains that PRO data are important and relevant because it allows patients to directly indicate how they feel. The following best practice guidelines should be followed:

- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the patient has any medical problems, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided in the ePRO device.
- The research nurse or appointed site staff must provide guidance on whom to call if there are problems with the device when the patient is completing the ePRO at home.
- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and should not clarify items (to avoid introducing bias). The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires.
- If the patient is unable to read the questionnaire (eg, patient is blind or illiterate), that patient should be exempted from completing PRO questionnaires but may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff in the source documents and in designated eCRF.

A key aspect of study success is to have high PRO compliance. To minimize missing data, compliance must be checked and discussed with the patient at each site visit, and the reason(s) why the patient could not complete assessments should be documented in source documents and in eCRF. If compliance drops below 90%, a check-in call from the site to ask the patient if he/she has any difficulties is highly recommended.

8.2 Safety assessments

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

8.2.1 Clinical safety laboratory assessments

See Table 8 for the list of clinical safety laboratory tests to be performed for clinical chemistry, hematology and urinalysis and refer to the SoA (Table 1 or Table 2) 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. Clinical chemistry, hematology, and urinalysis assessments that have been performed within 14 days

prior to starting study treatment do not have to be repeated on Cycle 1 Day 1 if the patient's condition has not changed.

The Investigator should provide an assessment of whether abnormal results are clinically relevant. The laboratory results should be signed and dated and retained at the study site as source data for laboratory variables.

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

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory in or near the Investigator site.

Table 8 Laboratory safety variables

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

[a] LDH is an additional variable collected during screening.

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

Total mandatory blood volume for patients in the first 4 cycles is approximately 350 mL excluding optional genetics (Gx) sample. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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 and volume of blood are, therefore, subject to site-specific change.

8.2.2 Physical examinations

Physical examination will include an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems.

Height will be measured during screening only. Physical examination and weight will be performed at timelines as specified in the SoA (Table 1 or Table 2). Investigators should pay special attention to clinical signs related to previous serious illnesses. New or worsening abnormalities may qualify as AEs, see Section 8.3.7 for details.

8.2.3 Vital signs

Vital signs (allowing an interval of at least 30 minutes after blood collection [if applicable] for laboratory tests) will be measured in a supine position after 5 minutes rest for the patient in a quiet setting and will include systolic and diastolic blood pressure, and pulse rate.

Changes in vital signs as compared to baseline may qualify as an AE, see Section 8.3.7.

8.2.4 Electrocardiograms

Twelve-lead ECG will be performed in triplicate at the visits indicated in the SoA (Table 1 or Table 2) and should also 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 5 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. At each time point at which ECG are required, three individual ECG tracings should be obtained in succession, no more than two minutes apart. The full set of triplicates should be completed within five minutes. A standardized ECG machine should be used and the patient should be examined using the same machine throughout the study, if possible.

After paper ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local cardiologist, if appropriate. The paper copies should be filed in the patient's medical records as source documents. If the Investigator considers an abnormal ECG finding at screening or baseline to be clinically significant, that finding should be reported as a concurrent condition. For all ECGs, details of rhythm, ECG intervals and an overall evaluation will be recorded.

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

8.2.5 Echocardiogram/MUGA scan

An echocardiogram or MUGA scan to assess LVEF will be performed at the visits as shown in the SoA (Table 1 or Table 2). The modality of the cardiac function assessments must be consistent within a patient; ie, if echocardiogram is used for the screening assessment, then echocardiogram should also be used for subsequent scans. The patients should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken. If an on-treatment assessment is abnormal at the time of discontinuation of study therapy, a 28-day follow-up assessment will be required to confirm reversibility of the abnormality. If a patient has had a MUGA scan or echocardiogram performed within 28 days prior to treatment discontinuation, the discontinuation visit Echo/MUGA scan is not required unless clinically indicated.

8.2.6 WHO performance status

Performance status will be assessed at the scheduled visits indicated in the SoA (Table 1 or Table 2) 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, eg, 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 Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B. AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized

representative). The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE.

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

AEs will be collected from time of signature of informed consent form throughout the treatment period and including the 28-day follow-up period (28 days after last dose of IP).

SAEs will be recorded from the time of signing of informed consent form. SAEs considered related to study treatment and/or study procedures will be collected throughout progression follow-up. SAEs considered related to study treatment will be collected throughout survival follow-up.

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 the data 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.

The methods of recording, evaluating, and assessing causality of AE and SAE are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow up on each patient at subsequent visits/contacts. Any new or unresolved AE observed at 28-day follow-up should be followed until the event resolves, stabilizes, or is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the patient's last AE visit in the study will be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE/SAE 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 the date it stopped
- Maximum CTCAE grade
- Whether the AE is serious
- Investigator causality rating against the IP(s) (yes or no)
- Action taken with regard to IP(s)
- AE caused patient's withdrawal from study (yes or no)
- Outcome.

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Seriousness criterion met
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed (yes or no)
- Causality assessment in relation to study procedure(s) (yes or no)
- Causality assessment to other medication (yes or no)
- Description of SAE.

8.3.5 Causality collection

The Investigator will assess the causal relationship between the 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 investigational product?"

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

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

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/you were last asked?" or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) over 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 clinical study protocol (CSP)-mandated laboratory tests and vital signs will be summarized in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs (pulse and blood pressure [BP]) should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the IP, or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or study intervention interruption).

If deterioration in a laboratory value, vital sign, ECG, or echocardiogram/MUGA scan is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator will use the clinical, rather than the laboratory term (eg, "anemia" rather than "low haemoglobin value"). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs. A list of mandated Laboratory safety variables can be found in Table 8.

Deterioration of a laboratory value that 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 Section 8.3.8.

8.3.8 Disease-under study

Symptoms of the disease-under study are those that might be expected to occur as a direct result of locally advanced or metastatic NSCLC. Events that 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.

8.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. Disease progression 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 that 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 an SAE. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE.

8.3.10 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least 1 of the serious criteria. New cancers are those that are NOT the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

8.3.11 Handling of deaths

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

- Death that 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 an SAE during the study.
- Where death is not clearly due to disease progression of the disease under study, 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 an 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 to an AstraZeneca representative within the usual expedited 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 the Investigator considers them to be causally related to the IP or to the study procedure(s). All SAEs will be recorded in the CRF.

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

The designated AstraZeneca representative will work 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 must be undertaken immediately. Investigators or other site personnel should inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day (ie, immediately but **no later than 24 hours**) of when he or she becomes aware of it.

Once the Investigator or other site personnel indicates 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 study site staff must report an SAE to the appropriate AstraZeneca representative by telephone.

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

For further guidance on the definition of an SAE, see Appendix B of the Clinical Study Protocol.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy that occur during the course of the study and within 6 weeks of the last dose of osimertinib should be reported to AstraZeneca.

If a pregnancy is reported, the Investigator should inform the Sponsor **no later than 24 hours** of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, 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 study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital 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 during the study or within 6 weeks of the final dose of the investigational product, then the Investigator or other site personnel must inform the appropriate AstraZeneca representative within 1 day (ie, immediately but **no later than 24 hours)** of when he or she becomes aware of it.

The designated AstraZeneca representative will work 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 a patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented if possible.

To capture information about a pregnancy from the partner of a male patient, consent from the male patient's partner must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 4 months after dosing ends should be followed up and documented.

8.4.3 Overdose

An overdose is defined as any dose higher than the protocol-mandated dose.

The maximum dose of each study treatment is:

- Osimertinib 80 mg within a 24-hour period
- Pemetrexed 500 mg/m^2 in 1 treatment cycle
- Cisplatin 75 mg/m^2 in 1 treatment cycle
- Carboplatin AUC5 750 mg in 1 treatment cycle

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

Additional guidance regarding overdose for each study treatment is below:

- Osimertinib: There is no specific treatment in the event of osimertinib overdose. In case of suspected overdose, osimertinib should be withheld and symptomatic treatment initiated
- Pemetrexed: In the event of suspected overdose, patients should be monitored with blood counts and should receive supportive therapy as necessary. The use of calcium folinate/folinic acid in the management of pemetrexed overdose should be considered.
- Cisplatin: There is no specific antidote in the event of a cisplatin overdose and an overdose may be fatal. Due to a strong and rapid fixation of cisplatin to proteins hemodialysis, even if initiated within 4 hours after the overdose, has little effect on the elimination of cisplatin from the body.
- Carboplatin: There is no known antidote for carboplatin overdose. Patients may need supportive treatment relating to myelosuppression, renal, hepatic and auditory function impairment.

Full details on cisplatin, carboplatin and pemetrexed overdose can be found in the local approved labels.

If an overdose on an IP occurs during the study, then the Investigator or other site personnel must inform appropriate AstraZeneca representatives immediately but **no later than 24 hours** of when he or she becomes aware of it. The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site. For overdoses associated with an SAE, the standard expediting reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

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

8.4.4 Medication error

All medication errors must be reported. If any medication error occurs during the study, then Investigators or other site personnel must inform the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours**) of when he or she becomes aware of it.

The designated AstraZeneca representative will work 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 Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening medication errors, **within 5 calendar days** of initial receipt if there is an SAE

associated with the medication error (see Section 8.3.2), and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.4.5 Management of IP-related toxicities

8.4.5.1 General dose adjustments for adverse events

Osimertinib is the standard of care for patients with treatment-naïve EGFR mutation positive NSCLC and in the context of this trial the combination of chemotherapy with osimertinib is considered an investigational treatment. As such, in order to maintain the dose intensity of the standard of care, it is recommended that if clinically appropriate, and where osimertinib interruption is not mandated, for the management of potential overlapping toxicities, dose interruption/dose reduction of chemotherapy is prioritized above dose interruption/dose reduction of osimertinib.

If appropriate, the Investigator may attribute each toxicity event to cisplatin/carboplatin, pemetrexed or osimertinib alone or to a combination of study treatments and use a stepwise dose modification according to Table 9, Table 10, Table 11, and Table 12. Dose modification can be implemented for 1, 2 or 3 of the study treatment components depending upon the Investigator's assessment of causality. If, in the opinion of the Investigator, a toxicity is considered to be due predominantly to 1 component of the study treatment (platinum agent, pemetrexed or osimertinib) and the dose of that component is delayed or modified in accordance with the guidelines below, the other components may be administered if there is no contraindication. If a patient experiences several toxicities and there are conflicting recommendations for those toxicities, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Dose modifications for toxicities must be based on the maximum toxicity experienced during a cycle. Toxicity must resolve to CTCAE Grade ≤1 or baseline prior to resumption of study treatment (see Sections 8.4.5.1.1 and 8.4.5.1.2 for exceptions).

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

Patients receiving pemetrexed/cisplatin or pemetrexed/carboplatin with osimertinib who discontinue cisplatin alone or carboplatin alone may, at the Investigator's discretion, be switched to the alternative platinum agent with pemetrexed and osimertinib for the remainder

of the platinum doublet cycles, up to a maximum of 4 cycles of platinum (eg, 2 cycles of pemetrexed/cisplatin followed by 2 cycles of pemetrexed/carboplatin is acceptable). Patients receiving pemetrexed/cisplatin or pemetrexed/carboplatin, with osimertinib who discontinue cisplatin or carboplatin can continue to receive pemetrexed with osimertinib if considered appropriate. Patients who discontinue platinum/pemetrexed or pemetrexed can continue to receive osimertinib alone if considered appropriate. Similarly, patients may discontinue osimertinib and continue on chemotherapy alone if appropriate. Chemotherapy may be interrupted for a maximum of 3 weeks (ie, 6 weeks since the last dose of chemotherapy); osimertinib may be interrupted for a maximum of 3 weeks.

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

Table 9 Dose Modifications for Study Treatments

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

8.4.5.1.1 Dose adjustment information for osimertinib

If a patient experiences a CTCAE Grade 3 or higher and/or unacceptable toxicity not attributable to the disease or disease-related processes under investigation, not covered by the specific guidance below, where the investigator feels that there is a reasonable possibility of a causal relationship with osimertinib, dosing of osimertinib will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. If the toxicity does not resolve within 3 weeks, osimertinib must be permanently discontinued. If the toxicity resolves or reverts to ≤CTCAE Grade 1 within 3 weeks of onset, treatment with osimertinib may be restarted at the same dose, 80 mg QD or a lower dose (osimertinib 40 mg QD), with discussion and agreement with the AstraZeneca Study Team Physician as needed. Following restart of treatment, the patient should be closely monitored for recurrence. Further guidance is provided in Table 10 and text below.

Table 10 Dose adjustment and dose discontinuation information for adverse reactions

Adverse reaction*	Dose modification
ILD/Pneumonitis	Permanently discontinue osimertinib

Adverse reaction*	Dose modification
QT interval >500 msec on at least 2 separate ECGs	Withhold osimertinib 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).
QT interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Grade 3 or higher non-hematological adverse reaction causally related to osimertinib	Withhold osimertinib for up to 3 weeks. If adverse reaction improves to Grade 0 - 2 after withholding of osimertinib for up to 3 weeks, osimertinib may be restarted at the same dose (80mg) or a lower dose (40mg). If adverse reaction does not improve to Grade 0 - 2 after withholding for up to 3 weeks, permanently discontinue osimertinib.
Grade 4 hematological laboratory value or grade 3 hematological laboratory value with clinical sequelae, regardless of causality, specific parameters are listed below	Withhold osimertinib for up to 3 weeks. If adverse reaction improves to Grade 0 - 2 after withholding of osimertinib for up to 3 weeks, osimertinib may be restarted at the same dose (80mg) or a lower dose (40mg). If adverse reaction does not improve to Grade 0 - 2 after withholding for up to 3 weeks, permanently discontinue osimertinib.

* The intensity of the clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Information on Specific Adverse Events

Erythema Multiforme and Stevens-Johnson Syndrome

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

ILD/Pneumonitis-like toxicity

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of ILD is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca study team should be informed. It is strongly recommended to perform a full

diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema or pulmonary haemorrhage. The results of full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, haematological parameters) will be captured by eCRF. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and study treatment permanently discontinued.

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 monitored during study treatment.

Patients with QTcF prolongation to >500 msec should have study treatment interrupted and regular ECGs performed until resolution to <481 msec, or recovery to baseline, and then restarted at a reduced dose of 40 mg, or 80 mg at the discretion of the investigator. If the toxicity does not resolve to ≤ CTCAE Grade 1 within 21 days the patient will be permanently withdrawn from study treatment.

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.

Changes in cardiac contractility

Across clinical trials, LVEF decreases ≥10% and a decrease to <50% occurred in 3.2% (40/1233) of patients treated with osimertinib who had baseline and at least 1 follow-up LVEF assessment. Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. However, LVEF will be monitored in all patients by way of Echo/MUGA scans.

Hematological parameters

Patients meeting any of the criteria below must have osimertinib interrupted until the toxicity resolves to ≤CTCAE Grade 1. Osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg) at the discretion of the investigator.

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

8.4.5.1.2 Dose adjustment information for chemotherapy

If a patient experiences a CTCAE Grade 3 or higher and/or unacceptable toxicity not attributable to the disease or disease-related processes under investigation where the investigator feels that there is a reasonable possibility of a causal relationship with chemotherapy, dosing of chemotherapy should be delayed and supportive therapy administered as required in accordance with local practice/guidelines. If the toxicity resolves or reverts to ≤CTCAE Grade 1 (platelet count ≥100 x 10^9/L) within 3 weeks of onset, treatment with chemotherapy may be restarted at the same dose, or at a reduced dose in accordance with Table 11 and Table 12, with discussion and agreement with the AstraZeneca Study Team Physician as needed . Dose adjustments for haematological toxicity should be based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Following restart of treatment, the patient should be closely monitored for recurrence. Further guidance is provided in Table 9 and in the text below.

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

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

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

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

- ANC ≥1.5 x 10^9/L
- Platelets ≥100 x 10^9/L
- Creatinine clearance ≥45 ml/min
- Resolution of ≥Grade 2 AST, ALT or bilirubin to ≤Grade 1
- Resolution of ≥Grade 3 drug-related AEs to ≤Grade 1 or baseline (chemotherapy can be given in the presence of Grade 2 alopecia and fatigue)

In the event that a dose of chemotherapy is delayed due to toxicity, the next dose should be given as soon as possible according to Section 8.4.5.1. If treatment cycles are adjusted due to toxicity, all procedures, except imaging and clinical outcome assessments (PROs and Health

Resource Use Module, will be completed relative to the adjusted cycle and not weeks on treatment. Imaging will be completed relative to weeks on treatment. All 4 doses of cisplatin or carboplatin should be given if clinically appropriate.

Specific dose modification advice is provided in Table 11 and Table 12. The recommended dose modifications serve as a guide and do not replace Investigator judgment and applicable local label recommendations, if more stringent.

Table 11 Recommended dose modifications for chemotherapy-associated hematological toxicity (based on nadir counts)

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

ANC = absolute neutrophil count

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

Table 12 Recommended dose modifications for chemotherapy-associated non-haematological toxicity

Adverse event	CTCAE Grade[a]	Pemetrexed	Cisplatin	Carboplatin
Diarrhea	Any diarrhea requiring hospitalization (irrespective of grade) or Grade 3 or 4	375 mg/m^2	56 mg/m^2	AUC5 Maximum dose 750 mg
Mucositis	Grade 3 or 4	250 mg/m^2	75 mg/m^2	AUC5 Maximum dose 750 mg
Neurotoxicity	Grade 2	500 mg/m^2	38 mg/m^2	AUC5 Maximum dose 750 mg
	Grade 3 or 4	Discontinue	Discontinue	Discontinue
Interstitial lung disease/pneumonitis	Any Grade	Discontinue	Discontinue	Discontinue

Table 12 Recommended dose modifications for chemotherapy-associated non-haematological toxicity

Adverse event	CTCAE Grade[a]	Pemetrexed	Cisplatin	Carboplatin
Other non-hematological toxicity [b]	Grade 3 or 4	375 mg/m^2	56 mg/m^2	AUC 3.75 Maximum dose 562.5 mg

[a] Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

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

8.5 Pharmacokinetics

Plasma samples of approximately 2 mL will be collected for measurement of plasma concentrations and PK parameters of osimertinib and its metabolite AZ5104 as specified in the SoA (Table 1 or Table 2).

Safety run-in sample collection will occur at the following time points: at pre-dose and 1 hr after dosing on Day 22 (Cycle 2/Day 1); at pre-dose and at 1, 2, 4 and 6 hours after dosing on Day 43 (Cycle 3/Day 1); and at pre-dose and 1 hr after dosing on Day 106 (Cycle 6/Day 1).

In the randomized period, sample collection will occur at the following time points: at pre-dose and 1 hr after dosing on Day 22 (Cycle 2/Day 1), at pre-dose and at 1, 2, 4 and 6 hours after dosing on Day 43 (Cycle 3/Day 1), and at pre-dose and 1 hr after dosing on Day 106 (Cycle 6/Day 1).

If the dosing of osimertinib is altered due to interruption or modified for any other reason, then the collection of these PK samples should be performed at the next scheduled visit, after at least 7 continuous days of dosing of osimertinib. No further PK samples are required if osimertinib dosing is discontinued.

The osimertinib PK samples at Cycle 3 Day 1 and Cycle 6 Day 1 should be collected on the day of the chemotherapy dosing for that cycle. If the dosing for chemotherapy is altered due to interruption or modified (ie, the patient receives only a partial dose) for any other reason, then, the collection of this PK samples should be performed at the next scheduled dosing of chemotherapy and osimertinib. If chemotherapy dosing is discontinued, PK collection could be stopped in consultation with the AstraZeneca Study Physician.

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, provided they are aligned with local regulations. Instructions for the collection and handling of biological samples will be provided by the Sponsor or analytical test site. The actual date and time (24-hour clock time) of each sample along with the dosing time on the PK day and the day prior to the PK day will be recorded.

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

8.5.1 Determination of drug concentration

Samples for determination of osimertinib (and AZ5104) concentrations in plasma will analyzed by Covance Labs (at Harrogate, UK; Shanghai, China; or its affiliate), on behalf of AstraZeneca using validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report. All samples within the known stability of the analytes of interest (ie, osimertinib and AZ5104) at the time of receipt by the bioanalytical laboratory will be analyzed.

In addition, the PK samples may be subjected to further analyses by AstraZeneca to further investigate the presence and/or identity of additional drug metabolites and 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 will be reported separately from the CSR.

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 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

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

Incurred sample reproducibility analysis, if any, will be performed with the bioanalysis of the test samples. The results from the evaluation will not be reported in a bioanalytical report.

Except for patients from China, samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual to Covance Laboratories Clinical Bioanalysis Alliance for bioanalysis. Samples from China will be analyzed at Covance Shanghai.

All PK samples and PK testing residual samples collected in China will be managed according to local laws and regulations, and will be destroyed or repatriated at the end of the study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

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.

8.7.1 Optional exploratory genetic samples

Blood samples for genetic analyses will be obtained participating in the safety run-in period and also the randomized period of the study as specified in the SoA (Table 1 or Table 2), except in China and other selected countries and study sites, as per local regulations. Approximately 6 mL of blood for deoxyribonucleic acid (DNA) isolation will be collected from patients who have consented to participate in the optional genetic analysis component of the study. Only one blood sample per patient should be collected during the study for this assessment. 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 this consent was included in the original consent form.

See Appendix D for information regarding genetic research.

8.7.2 Storage and destruction of genetic sample

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.

Details on processes for collection and shipment and destruction of these samples can be found in Appendix D or in the Laboratory Manual.

8.8 Biomarkers and exploratory research

Mandatory collection of blood samples (30 mL sample per timepoint) and analysis of residual tumor from samples provided for EGFR mutation testing, for biomarker research and diagnostic development (optional) is also part of this study. Blood and tissue samples for biomarker and exploratory research will be collected during the safety run-in period and the randomized period of the study as specified in the SoA (Table 1 or Table 2), 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.

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 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 objective response rate. Samples may also be used to monitor changes in cancer related biomarkers over time.

Further details of exploratory biomarkers are provided in Section 8.8.1.

8.8.1 Exploratory biomarkers

Tumor tissue biomarkers

Exploratory Biomarker analysis may be conducted using mandated or optional samples. Exploratory analysis described in the objectives and relating to clinical outcomes is a mandatory part of the study. Additional biomarker analyses, unrelated to clinical outcome on this study, that may be performed on residual samples (for example, to understand how lung cancer develops) is optional and consent for this must be provided specifically. Use of residual samples for diagnostic development is also optional and must be consented to specifically.

Based on availability of tissue, archival tumor material at baseline after central testing of EGFR mutation status (see Section 8.1.3) will be used to assess exploratory biomarkers. Baseline measures will be correlated with outcomes including time to progression and objective response rate. Markers tested may include but will not be limited to EGFR mutations (sensitizing and non-sensitizing), HER2, TP53 and 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 the Laboratory Manual.

Blood-based biomarkers

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 circulating tumor deoxyribonucleic acid (ctDNA) and will be used to explore the relationship between changes

in biomarkers and response to treatment. In addition, innate and acquired resistance mechanisms may be explored. Markers tested may include but will not be limited to EGFR mutations such as T790M and C797S, TP53 mutations, EGFR amplification, MET amplification, HER2 amplification, and alterations in other genes involved in EGFR signalling. Similarly, the relationship between other blood-borne biomarkers and drug response and/or disease progression may be explored. These markers may include but will not be limited to growth factors or cytokines.

Plasma samples will be taken as described in the SoA (see Table 1 and Table 2). Post primary PFS analysis for patients in the randomized period, ctDNA samples will continue to be collected at treatment discontinuation and at progression.

8.8.2 Additional research

Residual tumor and plasma samples from samples provided for mandatory research may be used for exploratory research, including analyses not directly linked to drug response eg, to explore factors that may influence susceptibility to/development of NSCLC/. In addition, the samples may be used to support the development of companion 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 Patient's Last Visit, after which they will be destroyed, all as per local regulation. 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 IP to generate hypotheses to be tested in future research.

8.9 Medical resource utilization and health economics

During the randomized period of the study, medical resource utilization and health economics data, associated with medical encounters, will be collected and recorded in the CRF by the Investigator and study-site personnel for all patients until the primary PFS analysis DCO or PFS2, whichever comes first. The data may be used as input to cost analyses; eg, cost utility analysis or cost effectiveness analysis. Protocol-mandated procedures, tests, and encounters are excluded.

The Healthcare Resource Use Module will be completed by the investigational site for any healthcare resource use between visits. The site will ask patients for any health resource use between visits (ie, excluding routine follow-up clinic visits associated with the clinical trial but including both planned and unplanned admissions).

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 (hospitalisations, 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 come mainly from the patient's medical record and will be captured by site staff using WBDC.

9 STATISTICAL CONSIDERATIONS

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized around the time of first patient in (FPI). The aim of the study is to compare the efficacy and safety of osimertinib with chemotherapy versus osimertinib monotherapy.

Depending on the extent of any impact, summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued IP, and other protocol deviations) may be generated. More detail will be provided in the SAP.

9.1 Safety run-in period

9.1.1 Population for analysis

The only analysis set associated with the safety run-in period of this study is the Safety Analysis Set.

The safety-run in Safety Analysis Set (Safety run-in SAS) contains all patients allocated to the safety run-in period of this study, who receive at least 1 dose of study treatment (osimertinib, cisplatin, carboplatin, or pemetrexed).

All safety and efficacy summaries will be produced on the Safety run-in SAS. Available PK data will also be summarized.

9.1.2 Efficacy analyses

No formal statistical testing is planned within the safety run-in. A formal database lock will be required to facilitate this data review. At the Safety Review Committee assessment for the safety run-in, a small number of efficacy summaries and analyses will be produced to report on the efficacy data collected to that point.

9.1.2.1 RECIST response summaries

All patients in the safety run-in will be included in a summary of confirmed RECIST (version 1.1) response data for the Safety Review Committee assessment of the safety run-in.

Objective response rate

Confirmed ORR (per RECIST 1.1 using Investigator assessments) is defined as the number (%) of patients with at least 1 visit response of CR or PR, where each CR or PR must be subsequently confirmed at least 4 weeks later. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR calculation, where the denominator will be the safety run-in SAS.

Duration of response

DoR will be defined as the time from the date of first documented response until the date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If a patient does not progress following a response, then his/her duration of response will use the PFS censoring time as the endpoint for their DoR calculation.

Descriptive data will be provided for the duration of response in responding patients, including the associated Kaplan-Meier curves (without any formal comparison or p-value attached).

Overall Survival (OS)

OS will not be summarized at the Safety Review committee safety run-in assessment. A listing of OS data at the time of the primary PFS DCO for the randomized period, will be produced.

Progression-free survival (PFS)

PFS will not be summarized at the Safety Review Committee safety-run in assessment. A listing of PFS times will be produced. The listing will be updated at the time of the primary PFS DCO.

9.1.2.2 Safety run-in analysis at the primary randomized DCO for PFS

At the primary PFS DCO for the randomized period, the safety run-in patients will be analysed separately to the randomized patients, with all safety run-in patients being analysed together regardless of chemotherapy received for consistency with the randomized period.

The clinical study database will close to new data for patients in the safety run-in period after the primary PFS analysis DCO.

9.1.3 Safety analyses

At the Safety Review Committee assessment for the safety, summaries will be produced to be reviewed in its entirety by the Safety Review Committee to advise on safety. During the randomized period, data for IDMC review will not combine data from the safety run-in and randomized period to assess safety. The data will be reviewed separately.

Adverse events, deaths, laboratory data, vital signs (pulse and BP), ECG, LVEF, WHO performance status, and ophthalmologic assessment will be summarized for the SAS population and by patient listings for each choice of chemotherapy with osimertinib where relevant for the Safety Review Committee, in order to inform their decision.

At the primary PFS DCO for this study, no safety data from the safety run-in will be combined with the randomized period. However, the additional safety data for the safety run-in period will be summarized once more at this point.

9.1.4 Safety Review Committee

A Safety Review Committee for the safety run-in will be utilized for this study.

When at least 12 patients in each cohort have either received ≥3 cycles of osimertinib with chemotherapy (osimertinib, cisplatin or carboplatin, and pemetrexed) or have discontinued study treatment due to unacceptable toxicity, a Safety Review Committee will convene. A formal database lock will be required to facilitate this data review. All data, including, safety, tolerability, and available PK data from all patients, will be reviewed. The Safety Review Committee will include independent experts with relevant experience in clinical trial conduct, methodology, and procedures in patients with NSCLC, and AstraZeneca personnel. Based on these data and taking into consideration data from other sources (eg, any updated information from the Phase II study of osimertinib alone vs. osimertinib plus carboplatin/pemetrexed [TAKUMI Study LOGIK1604/NEJ032A]), the Safety Review Committee will recommend whether the data support the initiation of the randomized period of the study after which it will end its function (Section 4.2.1).

In the event that the Safety Review Committee deems 1 of the study treatments to be inappropriate, only 1 combination can be recommended for the randomized period (eg, osimertinib with pemetrexed and cisplatin or osimertinib with pemetrexed and carboplatin).

Full details of the Safety Review Committee procedures and processes can be found in the Safety Review Committee Charter. Appendix A 5 provides more details on the rationale for and the remit of the Committee.

9.2 Randomized period

9.2.1 Statistical hypotheses

A futility analysis will be conducted prior to the primary analysis of PFS or OS for the randomized period to assess for a potential lack of efficacy in the osimertinib with chemotherapy arm when compared with osimertinib monotherapy. An IDMC will review the efficacy and safety data of the randomized period when approximately 83 PFS events have occurred, which is currently predicted to take place at approximately 15 months after the start of randomization. This is an Information Fraction (IF) of 0.30 (83/278 events that are required for the primary PFS analysis).

The futility boundary will be based on the conditional probability of showing statistical significance for the primary endpoint of PFS, which is based on 278 events in approximately 556 patients. If the conditional probability that the final study result will be statistically significant, given the data observed thus far and assuming the original design effect for the remainder of the study is less than 30%, the IDMC will consider the option of declaring futility. The exact figure used for the futility boundary will be calculated by the AZ statistician or delegate and sent to the IDMC at the time of the interim analysis, based on the number of events which have occurred at that time using appropriate software such as EAST. As an example, if exactly 83 of approximately 278 final events have occurred at the time of the interim analysis, then the HR that corresponds to 30% conditional power for the interim analysis will be 1.262. Further details will be provided in the SAP and IDMC charter.

The primary analysis of PFS based on Investigator assessment (according to RECIST 1.1) will occur when approximately 278 PFS events and at least 16 months of follow-up after LSI, has occurred in the 556 randomized patients (approximately 50% maturity). This was initially expected to occur approximately 33 months after the first patient is randomized (under an assumed 15-month exponential recruitment); however, the actual DCO for the primary PFS analysis will be determined such that both criteria are met. If the true PFS HR for the comparison of osimertinib with chemotherapy vs. osimertinib monotherapy is 0.68, 278 progression events will provide 90% power to demonstrate a statistically significant difference in PFS at a 5% two-sided significance level. This translates to an improvement in median PFS from 19 months to 28 months, assuming exponential distribution and proportional hazards. The minimum critical HR is 0.79, which translates to an approximate median PFS improvement from 19 months to 24 months.

The key secondary endpoint of OS will be tested in a hierarchical procedure, at the time of the PFS analysis and after the primary PFS analysis when the OS data are approximately 60% mature (approximately 334 death events across both arms). Alpha will be controlled across the 2 OS analyses; ie, at the time of the primary PFS analysis and at the final OS analysis, with the overall Type 1 error strongly controlled at 5% (2 sided) for the testing of OS under an

O'Brien and Fleming spending rule. Under assumed medians of 40 months and 52 months (HR = 0.77) for osimertinib monotherapy and osimertinib with chemotherapy, respectively, 170 observed events (information fraction of 0.51) are expected at the time of the primary PFS analysis with 2-sided alpha of 0.0034, with the remaining alpha assigned to the final OS analysis (0.0490).

9.2.2 Sample size determination

Approximately 556 patients will be randomized, in a 1:1 ratio (osimertinib with chemotherapy: osimertinib) to this study. The primary endpoint of the study is PFS based on Investigator assessment (according to RECIST 1.1). Progression-free survival analysis was initially planned to be performed at approximately 33 months after FPI for an assumed 15-month exponential recruitment; however, the actual timing of the primary PFS analysis will occur when approximately 278 PFS events and at least 16 months of follow-up after LSI have occurred.

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

9.2.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Full analysis set (FAS)	All randomized patients
Safety analysis set (SAS)	All randomized patients who received at least 1 dose of study treatment.
Pharmacokinetic analysis set (PAS)	All patients in the FAS who have at least 1 measurable PK concentration without any protocol deviation that affects the PK, supported by the relevant date and time of this sample; and, for each time a PK sample was taken, the dosing data for that day, and for samples taken after multiple dosing, the dosing data for the day prior to the sample day is required

9.2.3.1 Full analysis set

The full analysis set (FAS) will include all randomized patients. 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.

9.2.3.2 Safety analysis set

The safety analysis set (SAS) will consist of all patients randomized who received at least 1 dose of study treatment. Safety data will not be formally analysed but summarized, according to the treatment received; eg, a patient who is randomized to osimertinib plus

chemotherapy but who only received osimertinib will be summarized under the osimertinib monotherapy arm.

9.2.3.3 Pharmacokinetic analysis set

Pharmacokinetic Analysis Set (PAS) is defined as patients in the FAS who have at least 1 measurable PK concentration, without any protocol deviation that affects PK, supported by the relevant date and time of this sample. For each time a PK sample is taken, the dosing data for that day should be recorded and the dosing data for the previous day prior to the sample day as well as the sample day should be recorded.

The pharmacokineticist will agree to the strategy for dealing with data affected by deviations from planned sample collections before any formal statistical analysis is performed. Important 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 are not limited to, 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 any such 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 that affect the PK will be listed and summarized in the CSR.

9.2.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalized by first patient in and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.2.4.1 Efficacy analyses

All efficacy analyses will be performed on the FAS.

9.2.4.1.1 Progression-free survival

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

However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. Patients who have no evaluable visits or who do not have baseline RECIST data will be censored at study day 1

unless they die within 2 visits of baseline, in which case their date of death will be used as an event.

The primary efficacy analysis of PFS will be performed by Investigator assessment (RECIST 1.1), when approximately 278 PFS events have occurred at the primary PFS DCO. A sensitivity analysis will be performed for PFS by BICR assessment.

The PFS time will always be derived based on the scan/assessment dates, not visit dates. RECIST assessments/scans contributing toward a particular visit may be performed on different dates.

The following rules will be applied:

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

Investigator RECIST-based assessments

From the Investigators review of the imaging scans, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST 1.1.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE, unless there is any evidence of progression, in which case the response will be assigned as PD.

Refer to Appendix E for the definitions of CR, PR, SD, and PD.

Progression free survival per the Investigator assessment for patients in the FAS will be analysed using a log rank test stratified by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO PS (0 vs. 1), and method used for tissue testing (central vs. local) for generation of the p-value, using the Breslow approach for handling ties.

If the resulting strata are too small (ie, <20 events) the strata will be collapsed in the following pre-defined order to allow analysis. The China cohort strata will be collapsed first (to Asian vs. Non-Asian), followed by race, and then WHO PS, and finally central/local tissue testing.

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 SAS LIFETEST procedure with a term for the stratification.

The assumption of proportionality will be assessed. In the event of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. Proportionality will be tested firstly by examining the plots of complementary log-log(event times) versus log(time) and, if necessary, a time dependent covariate will be fitted to assess the extent to which this represents random variation.

A Kaplan-Meier (KM) plot of PFS will be presented by treatment group.

The treatment effect HR and two-sided 95% CIs will also be presented on a forest plot, alongside subgroup analyses.

Blinded independent central review of RECIST-based assessments

The BICR of radiological imaging data will be carried out using RECIST 1.1. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows) will be provided to the BICR. All imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 criteria and will be adjudicated if required. The independent reviewers will be blinded to treatment.

Duplicate images will be collected for the BICR. For each patient, the BICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each time point (ie, for visits where response or progression is not identified). If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is any evidence of progression in which case the response will be assigned as PD). Progression free survival will be derived from the overall visit response data and the scan dates.

Further details of the BICR will be documented in the Independent Review Charter.

9.2.4.1.2 Sensitivity analyses

(a) Quantitative interactions

A Cox proportional hazards model will be employed to assess the effect of the pre-specified covariates listed in Section 9.2.4.1.3 on the PFS HR estimate. A model will be constructed, containing treatment and the stratification factor(s) alone, to ensure that any output from the Cox model is likely to be consistent with the results of the primary analysis using the stratified log-rank test. The results from the initial model and the model containing additional covariates (in the MODEL statement) will be presented.

This analysis evaluates the treatment effect, adjusting for any potential imbalances in baseline prognostic factors that are not balanced by stratification.

The model will include all additional covariates regardless of whether their inclusion significantly improves the fit of the model, providing there is enough data to make them meaningful. Missing covariate data will be imputed using the mean (for continuous variables) or the most common category (for categorical factors).

(b) Ascertainment bias

Ascertainment bias will be assessed by analysing the BICR data. The stratified log rank test will be repeated on PFS using the BICR data based upon RECIST. The HR and CI will be presented.

If there is an important discrepancy between the primary analysis using the Investigator data and this sensitivity analysis using BICR data, then the proportion of patients with Investigator assessment but no central confirmation of progression will be summarized; such patients have the potential to induce bias in the central review due to informative censoring. An approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value (Fleischer et al 2011), but only if an important discrepancy exists.

Disagreements between Investigator and central reviews of RECIST progression will be presented for each treatment group.

(c) Evaluation-time bias

A sensitivity analysis will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) will be analysed using a stratified log-rank test, as described for the primary analysis of PFS. For patients whose death was treated as a PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust to even highly asymmetric assessment schedules (Sun and Chen 2010). To

support this analysis, the mean of patient-level average inter-assessment times will be tabulated for each treatment. This approach will use the Investigator RECIST assessments.

(d) Attrition bias

Attrition bias will be assessed by repeating the 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, and within the same sensitivity analysis, patients who take subsequent therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) prior to their last evaluable RECIST assessment or progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a Kaplan-Meier plot of the time to censoring using the PFS data from the primary analysis and where the censoring indicator of the PFS analysis is reversed.

A forest plot illustrating the hazard ratio and 95% confidence interval will be provided to compare the primary and sensitivity analyses of progression free survival.

9.2.4.1.3 Subgroup analysis

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

- Gender (Male, Female)
- Race (Chinese/Asian, non-Chinese/Asian, non-Asian)
- Age at screening (<65 years, ≥65)
- Smoking history
- EGFR mutation (Exon 19 Deletion or L858R)
- EGFR by ctDNA (Positive, Negative, Missing)
- Centrally confirmed tissue EGFR (Positive, Negative, Missing)
- WHO performance status (0, 1)
- CNS status at baseline (yes, no)
- Central confirmation of EGFR mutation (centrally confirmed tissue or ctDNA EGFR positive result, no central confirmation)

9.2.4.2 Analysis of secondary variables

9.2.4.2.1 Analysis of overall survival

Overall survival 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 from the SURVIVAL CRF page only.

Note: Survival calls will be made in the 1 week following the date of the DCO for each OS analysis and for the planned futility analysis, and if subjects are confirmed to be alive. If the death date is after the data cut-off date, these subjects will be censored at the date of the data cut-off. Death dates may be found by checking publicly available death registries.

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 334 death events (across both arms) have occurred.

Overall survival data will be analyzed using the same methodology and model as for the analysis of PFS, provided there are sufficient events (≥ 20 deaths) available for a meaningful analysis; otherwise, descriptive summaries will be provided.

An exploratory analysis will be conducted to report the 5 year overall survival rate. The data cut-off will occur 5 years after the last patient has been randomized or all patients have died, whichever occurs first. No p-value will be presented as this analysis is excluded from the alpha spending rule.

9.2.4.2.2 Analysis of objective response rate

ORR (per RECIST 1.1 using Investigator assessments) is defined as the number (%) of patients with at least 1 visit response of CR or PR. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR calculation, where the denominator will be the FAS.

Objective Response rate by Investigator will be analyzed using a logistic regression stratified by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO PS (0 vs. 1), and method used for tissue testing (central vs. local). The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood CI and 2-sided p-value.

9.2.4.2.3 Analysis of duration of response

DoR is defined as the time from the date of first documented response until the date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing toward the first visit response of PR or CR. If a patient does not progress following a response, then his/her duration of response will use the PFS censoring time as the end point for their DoR calculation.

Descriptive data will be provided for the duration of response in responding patients, including the associated Kaplan-Meier curves (without any formal comparison or p-value attached).

9.2.4.2.4 Analysis of disease control rate

Disease control rate (DCR) is defined as the percentage of subjects who have a best overall response of CR or PR or SD by RECIST 1.1 as assessed by the Investigator. For patients with a best overall response of SD, a RECIST assessment of SD must have been observed at least 6 weeks following randomization to be included in the numerator of the calculation for disease control rate. This is to enable sufficient follow-up to establish SD.

Disease Control Rate will be analyzed using a logistic regression. The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood CI and 2-sided p-value.

9.2.4.2.5 Analysis of depth of response

Depth of response (ie, tumor shrinkage / change in tumor size) by Investigator is defined as the relative change in the sum of the longest diameters of RECIST target lesions at the nadir in the absence of NLs or progression of NTLs when compared to baseline. The best absolute change in target lesion tumor size from baseline, and best percentage change in target lesion tumor size from baseline will be summarized using descriptive statistics and presented by randomized treatment group. The best change in tumor size will include all assessments prior to progression or start of subsequent anti-cancer therapy.

9.2.4.2.6 Analysis of post progression outcomes

For details of PFS2 refer to Section 8.1.2.3. Analysis of PFS2 will take place at the time of the primary PFS analysis only.

Time to second progression (PFS2), time to first subsequent treatment (TFST) and time to second subsequent treatment (TSST) will be analyzed in the FAS using a log rank test stratified by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO PS (0 vs. 1), and method used for tissue testing (central vs. local). The HR and CI will be obtained as for PFS.

Time from randomization to second progression or death (exploratory)

PFS2 is defined as the time from the date of randomization to the earliest of the progression events subsequent to that used for the primary PFS, or death in absence of a first or second progression. The second progression event must have occurred after discontinuation of study treatment and subsequent treatment administered after the initial PFS event. Patients alive and for whom a second disease progression has not be observed should be censored at the last time known to be alive and without a second disease progression; ie, censored at the last progression assessment date if the patient has not had a second progression or death.

Time to first subsequent therapy or death

Time to first subsequent therapy (TFST) or death is defined as the time from the date of randomization to the earlier of the date of anti-cancer therapy start date following IP discontinuation or death. Any patient not known to have had a subsequent therapy or not known to have died at the time of the analysis will be censored at the last known time to have not received subsequent therapy; ie, the last follow-up visit where this was confirmed.

Time to second subsequent therapy or death

Time to second subsequent therapy (TSST) or death is defined as the time from the date of randomization to the earlier of the date of second subsequent anti-cancer therapy start date following IP discontinuation 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, ie, the last follow-up visit where this was confirmed.

9.2.4.2.7 EORTC QLQ-C30 and QLQ-LC13

Symptoms and overall quality of life will be assessed using EORTC QLQ-C30 and QLQLC13. Questionnaires will be scored according to published guidelines or the developer's guidelines, if published guidelines are not available. All PRO analyses will be based on the FAS. Further details of the statistical analysis methods 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 be used only if all 3 items have been scored; otherwise, the items are treated as single-item measures.

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

Higher scores on the global health status/QoL and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity. Changes in score compared with baseline will be evaluated. For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number

of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Definition of compliance and evaluability rates

Compliance with the EORTC QLQ-C30 and EORTC QLQ-LC13 will be calculated separately for each questionnaire:

- Compliance rate = number of evaluable forms/number of expected forms × 100
- Evaluability rates for the EORTC QLQ-C30 and EORTC QLQ-LC13 will also be calculated, separately for each questionnaire:
- Evaluability rate = number of evaluable forms/number of received forms × 100
- An expected form = a questionnaire that is expected to be completed at a scheduled assessment time, ie, 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 1 subscale that is non-missing.
- A received form = a questionnaire that has been received and has a completion date and at least 1 individual item completed.

Definition of clinically meaningful changes

Changes in score compared to baseline will be evaluated. A minimum clinically relevant change is defined as a change in the score from baseline of ≥10 for scales/items from the QLQ-C30 and the QLQ-LC13 (Obosa et al 1998). For example, a clinically relevant deterioration or worsening in chest pain (as assessed by QLQ-LC13) is defined as an increase in the score from baseline (defined as Day 1, pre-dose) of ≥10. A clinically relevant improvement in fatigue (as assessed by QLQ-C30) is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, change in symptoms/functioning from baseline will be categorized as improved, stable, or worsening as shown in Table 13. Patients with no baseline data will be excluded from analyses.

Table 13 Mean change and assessment response in symptoms and health-related quality of life

Score	Change from baseline	Visit response
EORTC QLQ-LC13/QLQ-C30 symptom scales/items	≥+10	Deterioration
	≤-10	Improvement

Table 13 Mean change and assessment response in symptoms and health-related quality of life

Score	Change from baseline	Visit response
	Otherwise	No change
EORTC QLQ-C30 functional scales	≥+10	Improvement
	≤-10	Deterioration
	Otherwise	No change

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.

Change from baseline and time to symptom and HRQoL/function deterioration (QLQ-C30 and QLQ-LC13)

Change from baseline and time to symptom and HRQoL/function deterioration (QLQ-C30 and QLQ-LC13) will be evaluated, more details will be specified in the SAP.

9.2.4.2.8 Safety analyses

All safety analyses will be performed on the SAS.

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs (pulse and BP), ECG, LVEF, WHO PS, and ophthalmologic assessment. These will be collected for all randomized patients.

Adverse events

Adverse events (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient.

Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs.

Any AE occurring within 28 days of discontinuation of IP and prior to start of a new anti-cancer treatment will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after

consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs (pulse and BP)/ECG data will be performed for identification of OAEs.

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

9.2.4.3 Exploratory analyses

9.2.4.3.1 CNS Analysis

CNS analyses and summaries will be conducted at the primary PFS DCO for this study and will be described in more detail in the SAP. The main exploratory endpoints for the CNS analysis are CNS PFS by CNS BICR, and the number of patients without CNS metastases at RECIST progression.

The CNS FAS (cFAS) will be a subset of the FAS population. It will include all patients who undertook a brain scan in the screening/baseline period, had their scan sent for CNS BICR review and were identified by that review as having non-measurable and/or measurable brain disease at baseline (ie, at least 1 non-measurable and/or 1 measurable brain lesion noted at baseline).

CNS PFS by BICR assessment

Central Nervous System Progression-Free Survival (CNS PFS) is defined as the time from randomization until the date of objective CNS progression or death (by any cause in absence of CNS progression) regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to CNS progression. Patients who have not progressed in the CNS or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable brain scan.

The cFAS analysis set will be used for the CNS PFS analysis by CNS BICR assessment. A summary of the number and percentage of patients experiencing a CNS PFS event, and the type of event (CNS progression or death) will be provided, along with medians (and 95% CI), and quartiles per treatment arm.

CNS PFS will be analysed using a KM analysis. Median PFS (calculated from the KM plot, with 95% CIs), and the percentage of patients alive and CNS progression free at 6-monthly intervals will be evaluated until there are no data available at that timepoint. The analysis method will be per the primary PFS analysis (described in Section 9.2.4.1.1) but without stratification.

CNS lesions at overall RECIST progression

Each patient, regardless of presence of CNS metastases at baseline, will undergo a brain scan at RECIST progression per the primary PFS endpoint. The number of patients with and without CNS metastases at RECIST progression will be tabulated by CNS disease status at baseline (present/absence).

CNS ORR by CNS BICR assessment

CNS ORR is defined as the number (%) of patients who had at least 1 visit with CNS response of PR or CR by CNS BICR assessment. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of CNS ORR. Patients who discontinue treatment without CNS progression, receive a subsequent therapy, and then respond will not be included as responders in the CNS ORR calculation.

A summary of the best objective CNS response will be presented by treatment group. CNS ORR will be analyzed using a logistic regression and the results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood.

CNS BICR assessment – reason for CNS progression

A summary table will be included to present the number/percentage of patients with RECIST progression by whether there was documented progression in the CNS. The summary table will indicate whether the progression was in a target, non-target, or a new lesion. The table will present the data by treatment group.

For patients with CNS progression due to a new CNS lesion, a summary will be provided to show the extent of CNS disease at baseline, and the response of target/non-target lesions at the time of the appearance of the new lesion.

9.2.4.3.2 EQ-5D-5L health state utility

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses). Where values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied. In addition to the descriptive system, respondents will also assess their health on the day of assessment on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

9.2.4.3.3 Patient reported outcome version of the Common Terminology Criteria for Adverse Event System (PRO-CTCAE)

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

9.2.4.3.4 PGIS

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

9.2.4.3.5 Health Resource Utilization

Health resource utilisation will be assessed in terms of hospitalization, outpatient visits and emergency department visits

9.2.4.4 Other analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the SAP. The population PK analysis and pharmacodynamic analyses may be presented separately from the main clinical study report (CSR).

9.2.5 Independent Data Monitoring Committee (IDMC)

An IDMC for the randomized period will be utilized for this study.

Oversight of safety and tolerability of the randomized period of the study will be provided by an IDMC which will be comprised of fully independent members. The IDMC will meet periodically to review safety data and will make recommendations to continue, amend, or stop the study based on findings. Serious AEs, AEs, and other safety data will be reviewed, and individual and aggregated safety data will be evaluated by the IDMC. The IDMC will convene at the beginning of the randomized period, but will have access to the up to date data from patients ongoing in the safety run-in period as well as the randomized period to inform their recommendations.

The IDMC will also meet for the planned futility analysis when approximately 83 PFS events have occurred to provide a recommendation for the continuation of this study based on efficacy observed in the randomized period.

Full details of the IDMC procedure and processes can be found in the IDMC Charter, Appendix A 5 provides more details on the rationale and remit of the Committee.

9.3 Interim analysis

There is a planned interim analysis to assess for futility. The futility analysis will be described in detail in the SAP and IDMC charter.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's 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.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- 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), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

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 centre.

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 patient's partner becomes pregnant during or within 4 months after the study, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

Patients who are rescreened are required to sign a new ICF. 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 or optional samples for optional exploratory research, ie, research that does not directly relate to response to the IP. Note that exploratory research relating to response to the IP is mandatory. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate in the broader exploratory research (for example, to understand disease susceptibility) 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 that does not directly relate to response to IP. Patients who decline to participate in

this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analysed at the time the request is communicated to AstraZeneca, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

Each patient will be assigned a unique identifier by the sponsor. Any patient records or data sets transferred to the sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

A Safety Review Committee for the safety run-in and an IDMC for the randomized period will be utilized for this study.

Safety Review Committee

When at least 12 patients in each cohort have either received >3 cycles of osimertinib with chemotherapy (osimertinib, cisplatin or carboplatin, and pemetrexed) or have discontinued IP due to unacceptable toxicity, a Safety Review Committee will convene. All data, including, safety, tolerability, and available PK data from all patients, will be reviewed. The Safety Review Committee will include independent experts with relevant experience in clinical trial conduct, methodology, and procedures in patients with NSCLC, and AstraZeneca personnel. Based on these data and taking into consideration data from other sources (eg, any updated information from the Phase II study of osimertinib alone vs. osimertinib plus carboplatin/pemetrexed [TAKUMI Study LOGIK1604/NEJ032A]), the Safety Review Committee will recommend whether the data support the initiation of the randomized period of the study after which it will end its function (Section 4.2.1). In the event that the Safety Review Committee deems one of the IP to be inappropriate, only one IP may be recommended for the randomized period (eg, osimertinib with pemetrexed and cisplatin or osimertinib with pemetrexed and carboplatin).

Full details of the Safety Review Committee procedures and processes can be found in the Safety Review Committee Charter.

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 Clinical Study Protocol and letters to Investigators.

IDMC

Oversight of safety and tolerability of the randomized period of the study will be provided solely by an Independent Data Monitoring Committee (IDMC) which will be comprised of fully independent members. The IDMC will meet periodically to review safety data and will make recommendations to continue, amend, or stop the study based on findings. Serious AEs, AEs, and other safety data will be reviewed, and individual and aggregated safety data will be evaluated by the IDMC. The IDMC will convene at the beginning of the randomized period, but will have access to the up to date data from patients ongoing in the safety run-in period as well as the randomized period to inform their recommendations.

The IDMC will meet after data are available from approximately 60 patients across both treatment arms with at least 28 days of follow-up. Thereafter, the IDMC will meet after data are available from approximately 150 patients across both treatment arms with at least 28 days of follow-up, after 300 patients across both treatment arms with at least 28 days of follow-up, after completion of recruitment, and approximately every 6 months until the primary PFS analysis DCO.

The IDMC will also meet for the planned futility analysis when approximately 83 PFS events have occurred to provide a recommendation for the continuation of this study based on efficacy observed in the randomized period.

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

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov 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.

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

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 15 years after study completion unless local regulations or institutional policies require a longer retention period. 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 multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

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

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 (eg, hepatitis that resolved without hepatic failure).

B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

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, hospitalisation, 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.

Examples of important medical events or medical treatment are as follows:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B 6 Intensity rating scale: CTCAE

The grading scale found in the revised National Cancer Institute 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.

Intensity is assessed according to the following scale:

- Grade 1 Mild - asymptomatic or mild symptoms or clinical or diagnostic observations only or intervention not indicated;
- Grade 2 Moderate - minimal, local or non-invasive intervention indicated or limiting age-appropriate instrumental activities of daily living;
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated or disabling or limiting self-care activities of daily living;
- Grade 4 Life-threatening consequences or urgent intervention indicated;
- Grade 5 Death related to AE.

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 aetiology 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

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca IP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the 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) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

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 centre 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.

C 2 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed when AstraZeneca receives notification of consent withdrawal, AstraZeneca is not obliged to destroy the results of this research. If any samples are remaining after the results are obtained, they will be disposed of/destroyed.

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 aetiology; 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, ie, the entire genome.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on IP 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 fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant;
- Non-leukocyte depleted whole blood transfusion in 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 Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from patients participating in the safety run-in period and also the randomized period of the study. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, 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 organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the patient enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. 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 A.

Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time.

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 analyse the samples.

AstraZeneca and its designated organisations 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 organisations 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 Statistical Analysis Plan may be prepared where appropriate.

Appendix E Guidelines for evaluation of objective tumor response using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

E 1 Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for this study with regard to Investigator assessment of tumor burden including protocol-specific requirements for this study. Additional special guidance is provided for assessing follow-up scans acquired after RECIST 1.1-defined radiological progression.

E 2 Imaging modalities and acquisition specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of TLs, NTLs, and New Lesions (NLs) is provided below.

Summary of imaging modalities for tumor assessment

Target Lesions	Non-Target Lesions	New Lesions
CT	CT	CT
MRI	MRI	MRI
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan
		FDG-PET/CT

CT=Computed tomography; MRI=Magnetic resonance imaging; FDG-PET/CT=2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography/CT;

It is essential that the same imaging modality [computed tomography (CT) or magnetic resonance imaging (MRI)] and image acquisition parameters (eg, imaged anatomy, IV contrast imaging phases, etc.), imaging facility, and method of tumor assessment (eg, RECIST 1.1) are used consistently for each patient throughout the study. The use of the same scanner for serial scans, if possible, is highly recommended. It is important to follow the image collection/tumor assessment schedule as closely as possible (Table 1 or Table 2). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression), every attempt should be made to perform the subsequent scan acquisitions during scheduled visits.

CT and MRI

CT and MRI, each preferably with IV contrast, are generally considered to generate the best currently available and reproducible anatomical images for measurement of TL, assessment of NTL, and identification of New Lesions. The most critical CT and MRI image acquisition

parameters for optimal tumor evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

For standard (extracranial) RECIST 1.1 assessments, it is recommended that IV contrast-enhanced CT examinations of the chest, abdomen (including the entire liver and both adrenal glands), and pelvis (only if clinically indicated) will be used to assess tumor burden at baseline and follow-up visits. In patients who are sensitive to IV CT contrast, a non-contrast CT examination of the chest and an MRI with IV MRI contrast of the abdomen and pelvis is appropriate. In patients who develop sensitivity to both CT and MRI IV contrast or have significantly compromised renal function, a non-contrast CT examination of the chest, abdomen, and pelvis is appropriate. Any other areas of disease involvement (eg, brain) should be additionally imaged based on the signs and symptoms of individual patients. For brain lesion assessment, MRI with IV contrast is the preferred method over IV contrast-enhanced CT.

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 eg, neck) with T1 and T2 weighted imaging preferably with fat suppression along with T1 weighted imaging with fat suppression following IV injection of gadolinium-based contrast agent is 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 scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans for each patient. Body scans should be performed with breath-hold scanning techniques if possible. For these reasons, CT is typically the imaging modality of choice.

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 time points. This will enable better consistency not only of tumor measurements but also identification of new disease. Coverage

should also encompass the brain at baseline and at progression. In addition, for those patients with (a history of) brain metastases at baseline, brain scans should be performed at each follow up imaging time point, preferably with contrast enhanced MRI.

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. An adequate volume of a suitable contrast agent should be given so that the tumor lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. Oral contrast is recommended to help visualize and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/ reconstructed as contiguous (no gap) with ≤5 mm slice thickness for optimal lesion measurements. 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. Many patients with brain metastases present with small sub-centimetre lesions and therefore it is recommended that MRIs of the brain are performed with 3 mm slice thickness or less.

For CT 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 measurements should be performed using the same window setting for repeated examinations throughout the study.

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 NLs.

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.

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 (CT, MRI, or X-ray).

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. NLs may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan which 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/CT

^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography/CT (FDG-PET/CT) scans may be used as a method for identifying new lesions, according to the following algorithm: New Lesions (NLs) will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake not present on baseline or a prior FDG-PET scan or in a location corresponding to an NL on a companion CT/MRI collected close in time to the FDG-PET scan. A positive FDG-PET scan lesion should be reported only when an uptake (eg, SUV) greater than twice that of the surrounding tissue or liver is observed. The PET portion of the PET/CT introduces additional data that may bias an Investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior FDG-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule in order to verify the unequivocal presence of NLs.

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 intravenous 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.

Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation and may not provide an accurate assessment of true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Other Tumor Assessments

Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used as they are not validated in the context of tumor assessment.

Histology and Cytology

Histology or tumor markers 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 (eg, ascites, pericardial effusion, pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment as per RECIST 1.1.

E 3 Measurability of Tumor Lesions at Baseline

RECIST 1.1 measurable lesions at baseline:

A tumor lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis[1] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements.

Non-measurable lesions at baseline:

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component)
  - Leptomeningeal disease
  - Ascites, pleural, or pericardial effusion
  - Inflammatory breast disease
  - Lymphangitic involvement of skin or lung
- 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]).
- Previously irradiated lesions
- Brain metastasis

[1] The short axis is defined as the longest in-plane axis perpendicular to long axis

[2] Lymph nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

Special considerations regarding lesion measurability at baseline:

- Bone lesions
  - Bone scan, PET scan or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - 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 bone lesions are considered non-measurable.
- Cystic lesions thought to represent 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 over cystic lesions as TLs.

E 3.1 RECIST 1.1 Target Lesion Selection at Baseline:

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 TLs at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter 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.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph node locations as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented as well as the longest axis diameter for non-nodal lesions (or short axis diameter 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.

A previously irradiated lesion may be selected as a Target Lesion provided it fulfils the criteria for reproducible measurability and is the only lesion available.

E 3.2 Special cases for Target Lesion assessment at baseline:

- 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 diameter.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non- nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- 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.
- Tumor lesions selected for fresh screening biopsy should not be selected as TLs, unless imaging occurred at least ~2 weeks after biopsy, allowing time for healing.

A tumor lesion selected for fresh screening biopsy should not be selected as a Target Lesion unless it is the only lesion available and imaging occurred at least ~2 weeks after biopsy, allowing time for healing.

E 3.3 RECIST 1.1 Non-Target Lesion selection at baseline:

All other lesions, including non-measurable lesions and surplus measurable lesions not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

E 4 Evaluation of tumor response and progression

RECIST 1.1 Target Lesion assessment at follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimeters. The sum of the diameters for all TL at each follow-up visit will be compared to the baseline sum of diameters (for response or stable disease) or to the smallest prior (nadir) sum of diameters (for progression).

Special cases for Target Lesion assessment at follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.

- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.

- If 2 or more TLs merge then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually discernable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter of the nodal mass.

- 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. The choice of 'Too large to measure' in the case report form will trigger an overall visit response of PD.

- When a TL has had any intervention during the study (eg, definitive radiotherapy, embolization, surgery, etc.) that is not part of the planned IP, the size of the TL should still be provided where possible and the intervention recorded in the RECIST case report form for the current imaging visit and all subsequent visits. If a TL has been completely removed (surgery) or disappears, the longest diameter should be recorded as 0 mm.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see table below).

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 diameter 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 decrease in sum of diameters 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 previous sum of diameters (nadir) – 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 from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg, missing anatomy) or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; TL Target lesion.

RECIST 1.1 Non-Target Lesion assessment at follow-up

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.

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 stable disease or partial response in TLs, the overall tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest ‘increase’ in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of stable disease (SD) or progressive disease (PR) of target disease will therefore be extremely rare.

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 below).

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.

RECIST 1.1 New Lesion identification at follow-up

Details including the imaging modality, the date of scan, and the location of any NLs will be recorded in the case report form. The presence of 1 or more NLs is assessed as progression. The finding of an NL should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. If an NL is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously (pre-existing) new lesion has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

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

RECIST 1.1 Evaluation of overall visit response at follow-up

The overall visit response will be derived using the algorithm shown in the table below.

Overall visit response algorithm

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

Overall visit response algorithm

Target lesions	Non-target lesions	New lesions	Overall response
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 or non-target lesions at baseline), NED No Evidence of Disease (only relevant if there were neither target nor non-target lesions at baseline).

* Non-CR/Non-PD for Overall Response if only non-target lesions (no TLs) are present at baseline.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For subjects with TLs (at baseline): CR, PR, SD, PD, or NE
- For subjects with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE
- For subjects with no disease at baseline: NED (no evidence of disease; available as an option in the electronic case repot form), PD, or NE

Symptomatic deterioration

Symptomatic (clinical) deterioration is not a descriptor of an objective 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 scan acquisitions and tumor assessments where clinically feasible.

E 5 Central Review

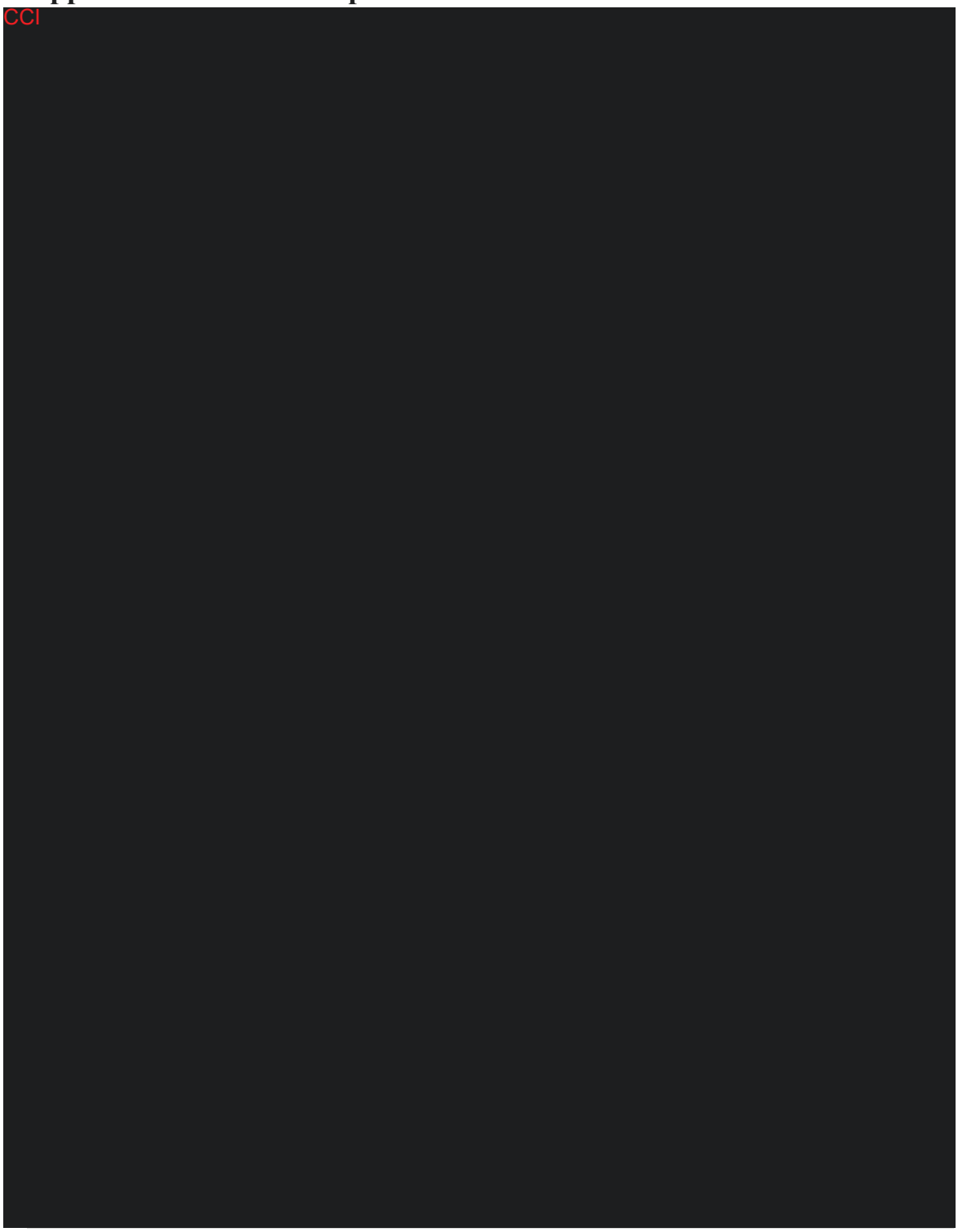
Refer to Section 8.1.2.2 for details regarding the central review of imaging. Guidelines for image acquisition, de-identification, storage at the investigative site as source data, and transfer to the iCRO will be provided in a separate document. Further details of the BICR will be documented in the Independent Review Charter (also referred to as “Imaging Charter”).

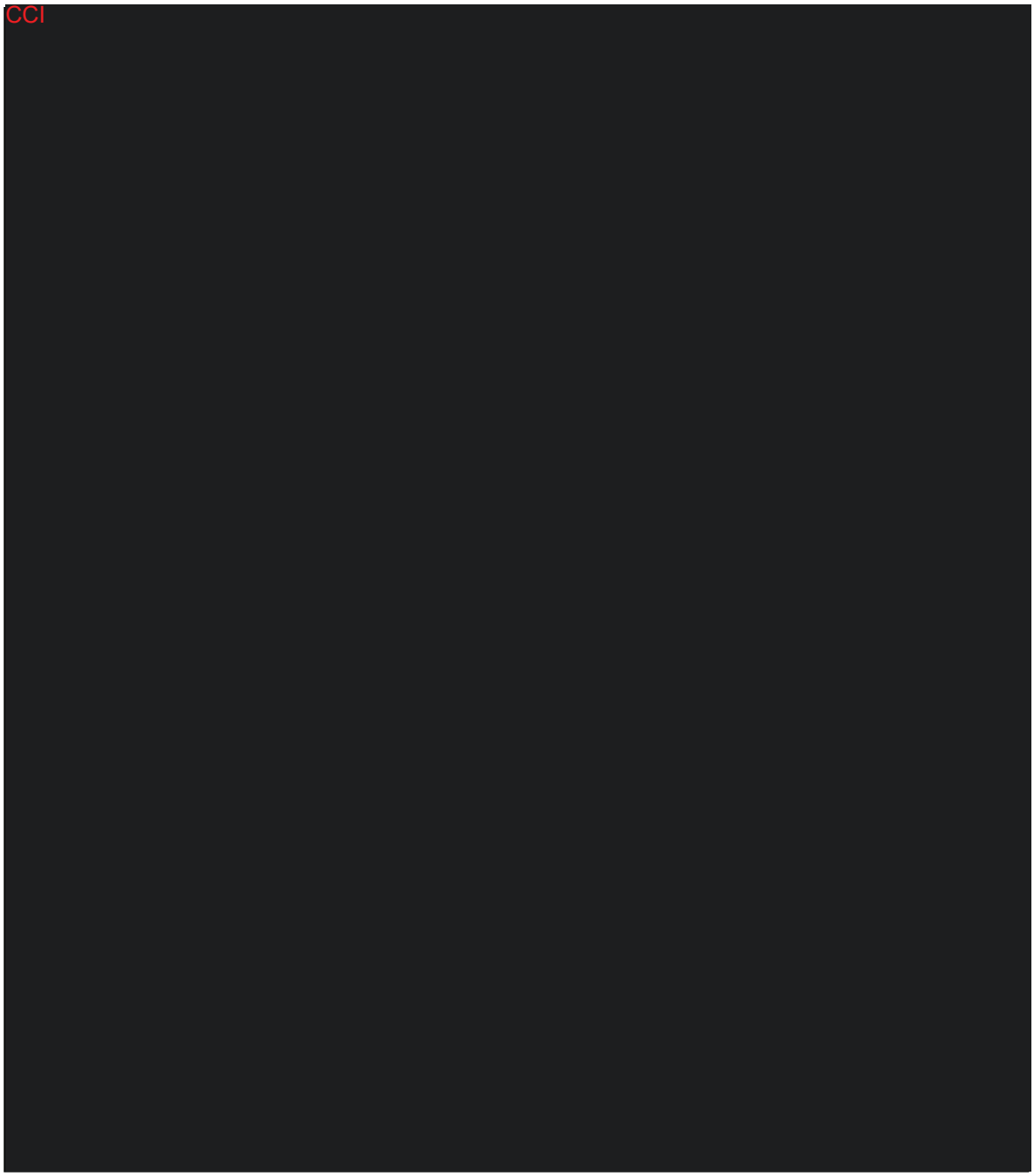
E 6 References

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 F Patient Reported Outcomes

CCI

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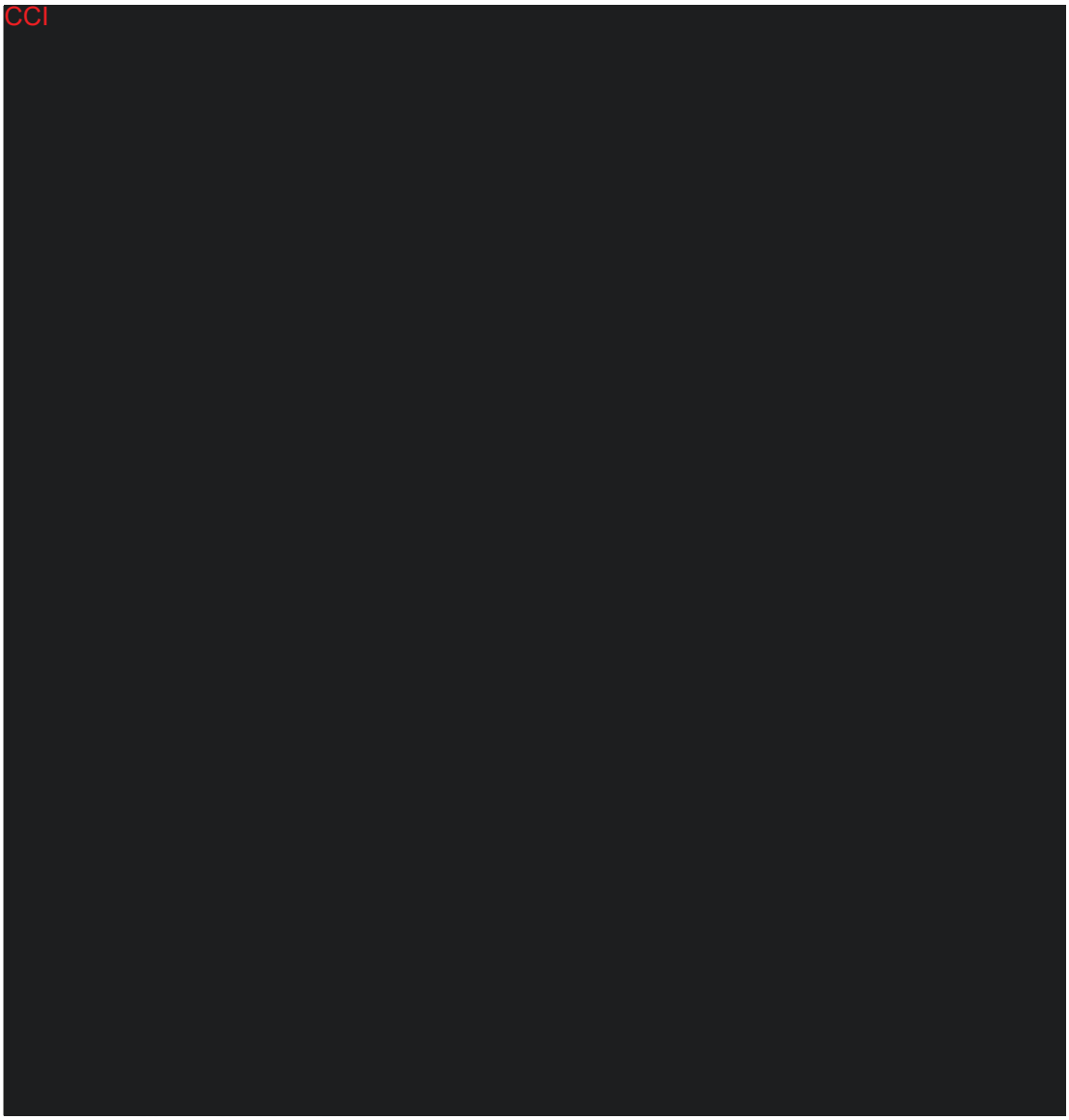

CCI

Patient Global Impression of Severity for Cancer Symptoms

Overall, how would you rate the severity of your cancer symptoms today?

- ☐ No symptoms
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

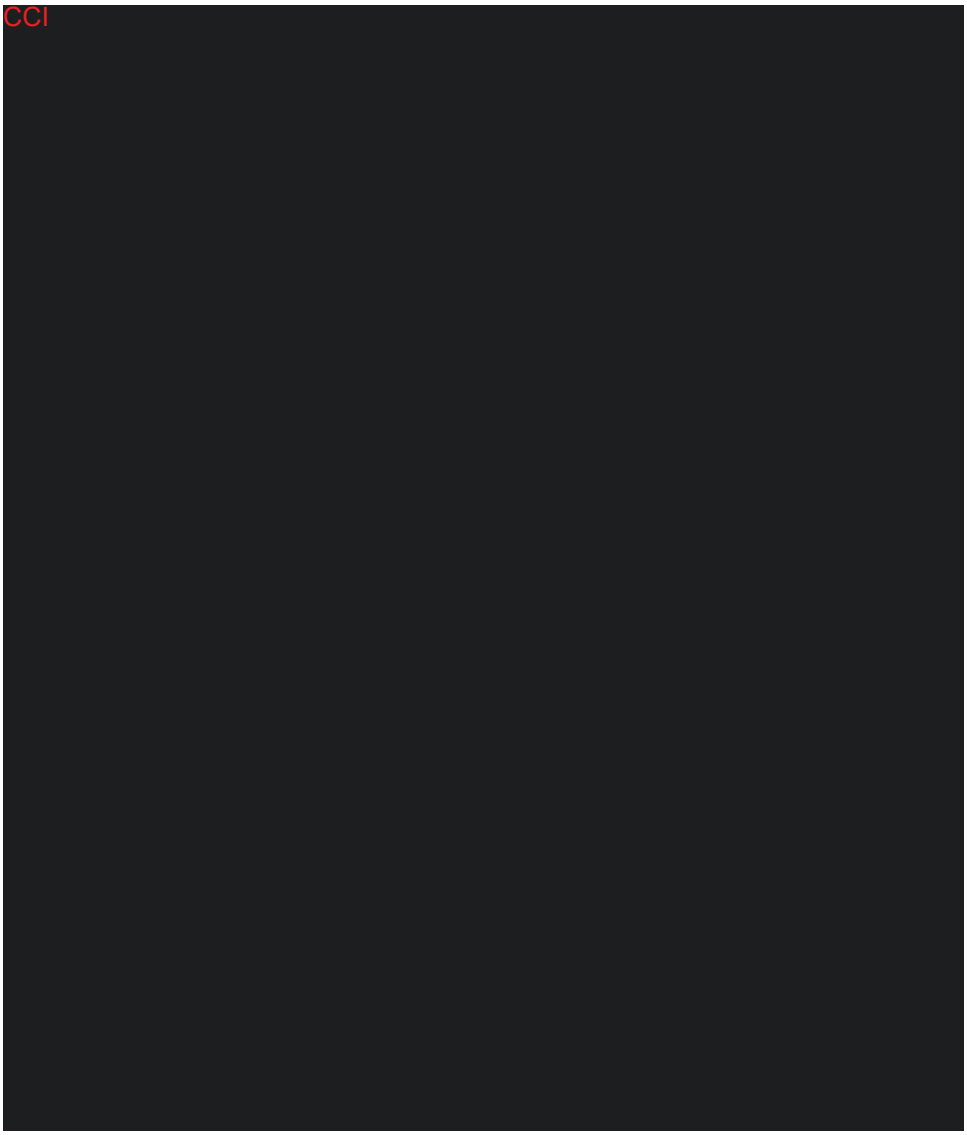
CCI

[redacted]

CCI

[redacted]

CCI



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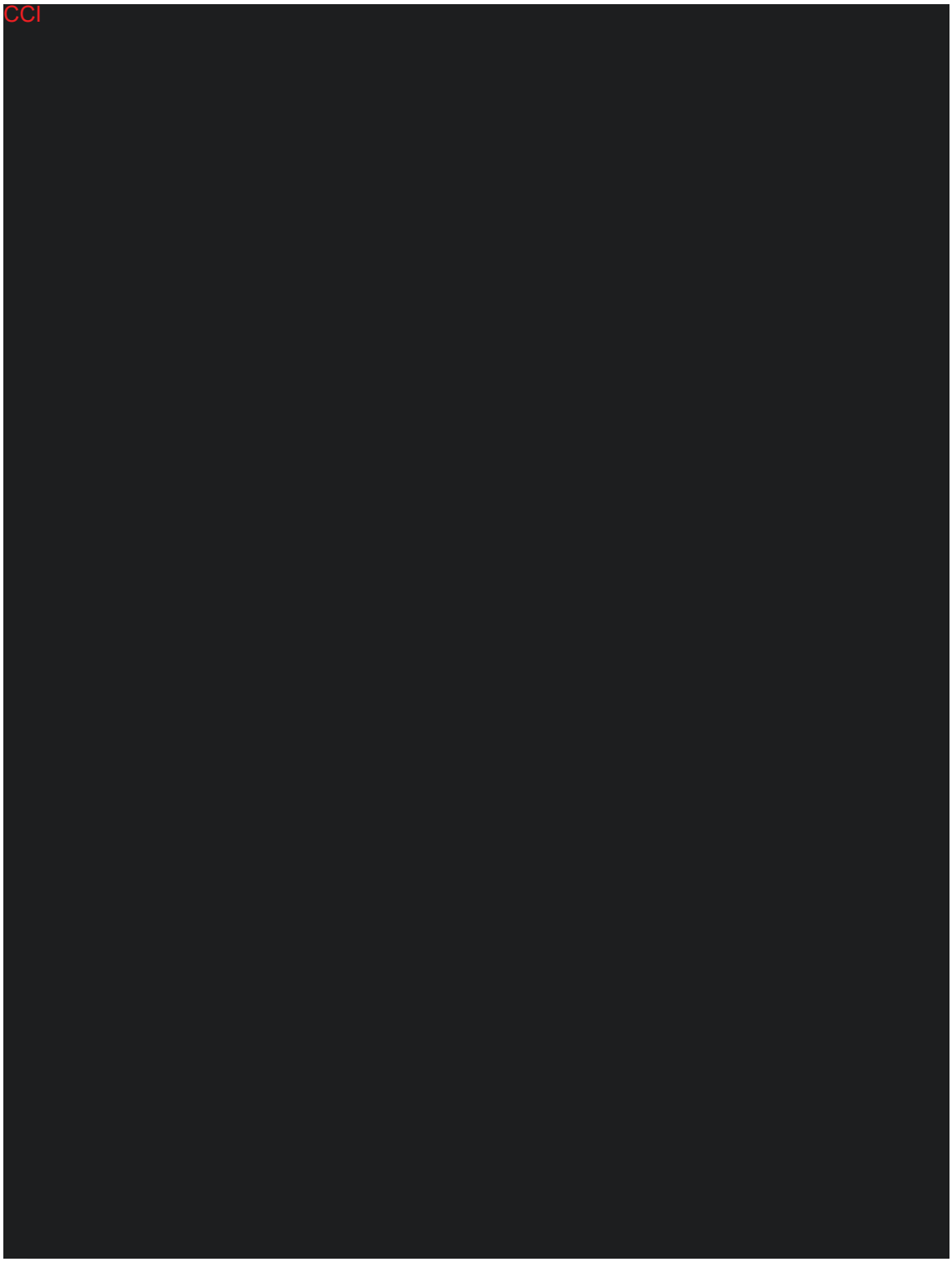
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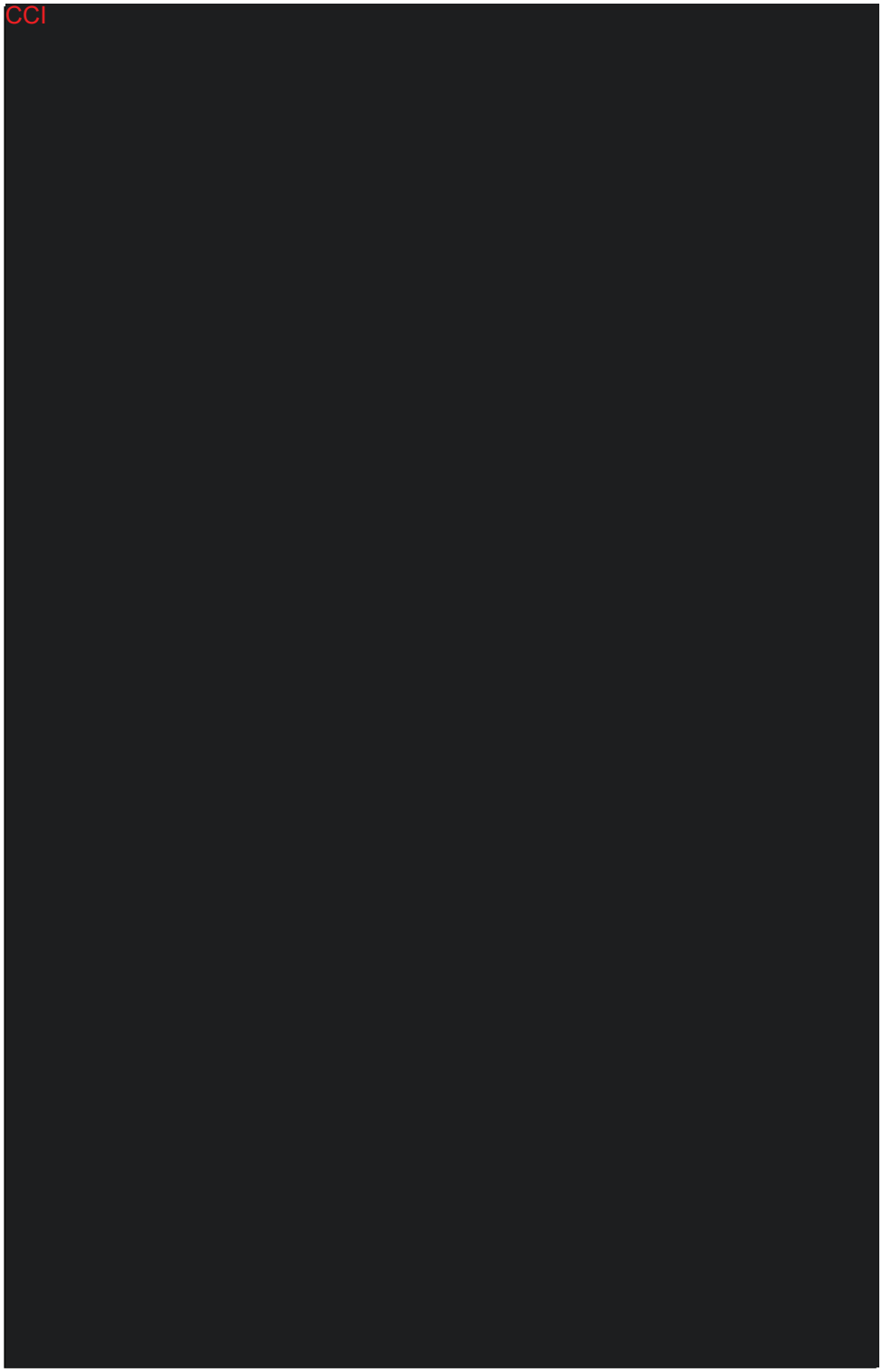
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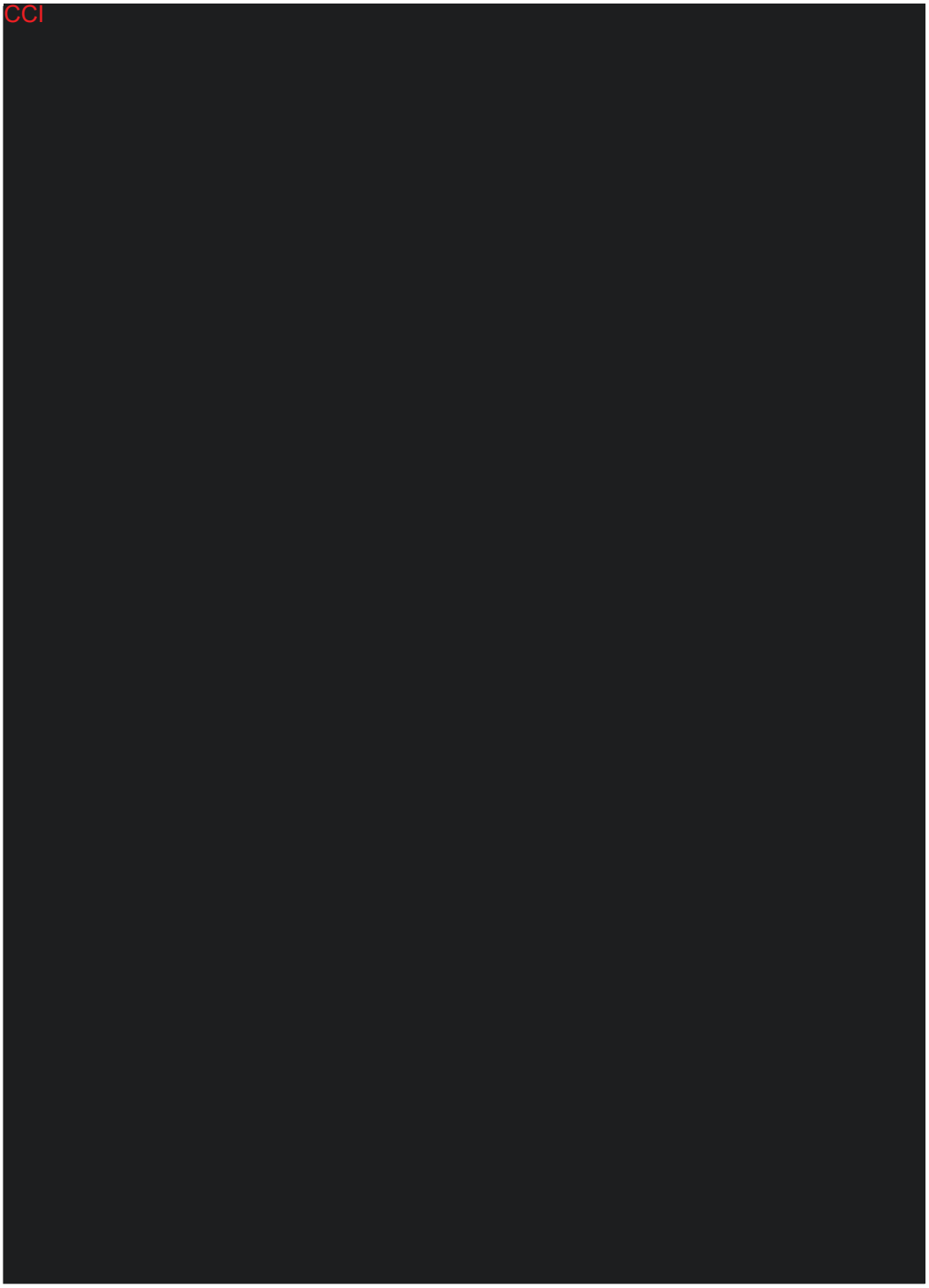
CCI

Appendix G Guidance regarding Potential Interactions With Concomitant Medications

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

G 1 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 IP.

Drugs inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to Study treatment start
Carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentin St John's Wort	3 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Contact AstraZeneca with any queries you have on this issue.

G 2 Medicines whose exposures may be affected by osimertinib that AstraZeneca considers may be allowed with caution

Osimertinib may increase the concentration of sensitive BCRP and Pgp substrates (concentration of the sensitive BCRP substrate, rosuvastatin and sensitive Pgp substrate, fexofenadine, are increased).

Exposure, pharmacological action and toxicity may be increased by Osimertinib

Warning of possible interaction	Advice
Rosuvastatin	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Refer to full prescribing information for all drugs prior to co-administration with IP.
Sulfasalazine	
Doxorubicin	
Daunorubicin	

Exposure, pharmacological action and toxicity may be increased by Osimertinib

Warning of possible interaction	Advice
Topotecan Dabigatran Aliskiren Digoxin	

G 3 Drugs that prolong QT interval

The drugs listed in this section are taken from information provided by the Arizona Center for Education and Research on Therapeutics website: https://www.crediblemeds.org/. The website categorizes drugs based on the risk of inducing TdP.

During screening the drugs that patients are currently receiving (prescription and non-prescription) should be checked opposite the ArizonaCert website.

In addition, drugs intended for use during IP should be checked opposite the website.

G 3.1 Drugs with a known risk of Torsades de Pointes

Drugs in this category are known to prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended.

G 3.1.1 Before commencing study treatment

Drugs in the category of known risk of TdP **must** have been discontinued prior to the start of administration of IP in accordance with guidance provided in the table below.

G 3.1.2 During study treatment

It is recommended that drugs in the category of known risk are not co-administered with IP (osimertinib) and for a period of two weeks after discontinuing IP, however if it is considered essential for patient management to co-administer these drugs with IP (osimertinib), close monitoring with ECGs and electrolytes is recommended.

The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such Investigators are recommended to search the CredibleMeds® website (https://www.crediblemeds.org/) to provide the most up to date information.

Drugs with a known risk of TdP[a]

Drug name	Withdrawal period prior to IP start[b]
aclarubicin, anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron[c], papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine terlipressin	2 days
cilostazol, cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days
azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
donepezil, terodiline	3 weeks
levomethadyl, methadone, pimozide	4 weeks
arsenic trioxide[d], ibogaine	6 weeks
pentamidine	8 weeks
astemizole, probucol, vandetanib	4 months
amiodarone, chloroquine	1 year

[a] This list should be checked against the full and most current list presented in the CredibleMeds® website (https://www.crediblemeds.org/).

[b] Values determined from comprehensive review (internal AZ) of each compounds PK half-life and determination of the washout period.

[c] For further details of ondansetron usage, refer to Section 6.5.2 (bullet point #3).

[d] Estimated value as pharmacokinetics of arsenic trioxide has not been studied.

G 3.2 Other TdP risk categories

Patients receiving drugs that prolong QT interval or may increase the risk of TdP from other TdP risk categories can be eligible for inclusion in the study, 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.

G 3.3 Guidance regardless of TdP risk category

During study treatment and for a period of two weeks after discontinuing IP if it is considered essential for patient management to co-administer drugs known to prolong QTc interval,

regardless of TdP risk category, close monitoring with ECGs and electrolytes is recommended.

Appendix H 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 (eg, undergo pregnancy testing etc., as required by the study protocol).
- Women will be considered post-menopausal if they are amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:
- Women under 50 years old will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range.
- Women 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.

Highly effective contraception methods

Highly effective method of birth control is defined in Note 3 in ICH Guidance M3 (Nonclinical Safety Studies for the conduct of Human Clinical trials for Pharmaceuticals) as one that results in a low failure rate (eg, less than 1 percent per year) when used consistently and correctly.

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.

Acceptable 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 Intra-Uterine Devices (IUDs)
- Fertility awareness methods
- Coitus interruptus

Appendix I Calculated Creatinine Clearance

Creatinine clearance calculation should preferably be by Cockcroft-Gault formula. Glomerular filtration rate (GFR) estimation by 24-hour urine collection or Tc99m-DTPA serum clearance may be used as an alternative method if acceptable per local standards.

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Men

For serum creatinine concentration in mg/dL:

$$\textbf{CrCl} \text{ (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}^{b}) \times 1.0}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\textbf{CrCl} \text{ (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}^{b}) \times 1.0}{0.81 \times \text{serum creatinine (µmol/L)}}$$

[a] Age in years.

[b] Weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Women

For serum creatinine concentration in mg/dL:

$$\textbf{CrCl} \text{ (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}^{b}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\textbf{CrCl} \text{ (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}^{b}) \times 0.85}{0.81 \times \text{serum creatinine (µmol /L)}}$$

[a] Age in years.

[b] Weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

Calculation of creatinine clearance from 24-hour urine collection:

$$\text{CrCl (mL/min)} = \frac{\text{urine creatine} \times \text{24-hour urine volume (ml)}}{\text{serum creatinine} \times 1440}$$

Source: Doolan et al 1962.

Serum and urine creatine concentration must be in same units. The use of internet-based calculators is allowed.

I 1 References

Cockcroft and Gault 1976
Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.

Doolan et al 1962
Doolan PD, Alpen EL, Theil GB. A clinical appraisal of the plasma concentration and endogenous clearance of creatinine. Am J Med 1962; 32:65.

Appendix J Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the participant's safety. If in doubt, please contact the AZ Study Physician.

J 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in the sections below. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

J 2 Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with study intervention. If this delay is outside the screening window specified in Table 1 and Table 2 the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4. The procedures detailed in Table 1 and Table 2 must be undertaken to confirm eligibility using the same randomization number as for the participant.

J 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TVP service will visit the participants home or other remote location as per local Standard Operating Procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the clinical study protocol (CSP).

J 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs, concomitant medication, and targeted physical examination to be reported and documented. Site personnel to also ensure that ePROs are being completed by participant as per SoA.

J 5 Data Capture During Telemedicine Visits

Data collected during telemedicine or home / remote visits will be captured by the qualified HCP (or site delegate) from the study site or TVP service in the source documents.

Appendix K Abbreviations

Abbreviation or special term	Explanation
[^{11}C]osimertinib	carbon-11 labelled osimertinib
AE	adverse event
ADR	adverse drug reaction
ALT	alanine aminotransaferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferaminase
AUC_{ss}	area under plasma concentration-time curve during any dosing interval at steady state [amount·time/volume]
AUC5	AUC of 5 mg/mL/min
AUC6	AUC of 6 mg/mL/min
BBB	blood brain barrier
BICR	blinded independent central review
BP	blood pressure
CDx	companion diagnostic
cFAS	CNS full analysis set
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CL_{ss}/F	Apparent total body clearance at steady state
$C_{max,ss}$	Maximum plasma concentration at steady state
cMET	Hepatocyte growth factor receptor
$C_{min,ss}$	Minimum plasma concentration at steady state
CNS	central nervous system
COA	Clinical Outcome Assessment
CR	complete response
Crcl	creatinine clearance
CRF	case report form
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	circulating tumor deoxyribonucleic acid
CYP	cytochrome P450
DCO	data cut-off

Abbreviation or special term	Explanation
DCR	disease control rate
DNA	deoxyribonucleic acid
DoR	duration of response
EC	ethics committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
ECG	electrocardiogram
eCRF	electronic Case Report Form
EGFR	epidermal growth factor receptor
EGFRm	epidermal growth factor receptor mutation-positive
EM	erythema multiforme
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
ESMO	European Society for Medical Oncology
Ex19del	exon 19 deletions
FAS	full analysis set
FFPE	formalin-fixed paraffin-embedded
FPI	first patient in
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Gx	genetics
HDPE	high-density polyethylene
HER2	human epidermal growth factor receptor
HR	hazard ratio
HRCT	high resolution computed tomography
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
ILD	interstitial lung disease
INR	International Normalized Ratio

Abbreviation or special term	Explanation
IO	immune-oncology
IP	investigational product
ITT	intent-to-treat
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
L858R	leucine-to-arginine substitution at amino acid position 858 (L858R) in exon 21 of EGFR gene
LH	luteinizing hormone
LLN	lower limit of normal
LSI	Last subject in
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MET	tyrosine-protein kinase Met
MRI	magnetic resonance imaging
MUGA	Multi Gated Acquisition Scan
NA	not applicable
NCCN	National Comprehensive Cancer Network
NE	not evaluable
NL	new lesion
NSAID	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
NTL	non-target lesion
OAE	other significant adverse event
ORR	objective response rate
OS	overall survival
PAS	pharmacokinetic analysis set
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PFS2	time from randomization to second progression on a subsequent treatment
PGIS	Patients Global Impression of Severity
PK	pharmacokinetics
PR	partial response
PRO	patient-reported outcome

Abbreviation or special term	Explanation
PRO-CTCAE	Patient Reported Outcome version of the Common Terminology Criteria for Adverse Event approximately 17 items
PS	performance status
Q	quater
Q3W	every 3 weeks
QD	Once daily
QoL	quality of life
QTc	corrected QT interval
QTcF	Frederica's corrected QT interval
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	stable disease
SoA	schedule of assessments
SoC	standard of care
SJS	Stevens-Johnson syndrome
T790M	an amino acid substitution at position 790 in EGFR, from a threonine (T) to a methionine (M)
TdP	Torsades de Pointes
TFST	time to first subsequent treatment
TKI	tyrosine kinase inhibitor
TSST	time to second subsequent treatment
ULN	upper limit of normal
US	United States
WBDC	web based data capture
WHO	World Health Organization
WT	wild-type

Appendix L Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

SIGNATURE PAGE

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Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.