A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Platinum Plus Pemetrexed Chemotherapy Plus Osimertinib Versus Platinum Plus Pemetrexed Chemotherapy Plus Placebo in Patients with EGRFm, Locally Advanced or Metastatic NSCLC who have Progressed Extracranially following First-Line Osimertinib Therapy (COMPEL)

ClinicalTrials.gov Identifier: NCT04765059

Date of Protocol: 15 July 2024

Clinical Study Protocol	
Drug Substance	Osimertinib
Study Code	D5162C00042
Version	5.0/EEA-1
Date	15 July 2024

EudraCT Number	2019-003969-18
EU CT Number	2024-516330-35-00

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Platinum Plus Pemetrexed Chemotherapy Plus Osimertinib Versus Platinum Plus Pemetrexed Chemotherapy Plus Placebo in Patients with EGFRm, Locally Advanced or Metastatic NSCLC who have Progressed Extracranially following First-Line Osimertinib Therapy (COMPEL)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Numbers:
US IND 117879
EudraCT number: 2019-003969-18
EU CT number: 2024-516330-35-00

VERSION HISTORY

Version 5.0/EEA-1, 15 July 2024

The CSP v5.0, dated 19 October 2023, has been updated to comply with the EU CTR requirements and to consolidate country-specific protocols (Germany [version DEU-4] and Italy [version ITA-4]) into the global protocol.

- **Title page:** Added EU CT number
- **Section 1.1:** Included clarification that pregnancy testing during the study treatment will be in accordance with local clinical practice.
- **Appendix A1:** Added regulatory reporting requirements for Suspected Unexpected Serious Adverse Reactions (SUSARs).
- **Appendix A6:** Updated websites where the clinical study description will be updated. Added reference to EU Clinical Trials Information System (CTIS) and clarified submission timeline.
- **Appendix I**: Added new appendix to allow for consolidation of country-specific protocols. Added cross-references to this Appendix in the respective CSP sections as appropriate.
- **Appendix J** (previously Appendix I): Updated list of abbreviations to align with latest updates in the CSP.
- **Throughout**: Minor editorial changes incorporated for consistency between sections and compliance with AstraZeneca Style Guide.

Version 5.0, 19 October 2023

This amended Clinical Study Protocol (CSP) Version 5.0 is issued to update the sample size, data cut-off (DCO), and statistical analysis due to treatment landscape changes which outpaced study recruitment; to clarify that single descriptive analysis of progression-free survival (PFS) and overall survival (OS) will be carried out at the time of the PFS DCO; to clarify that no further survival follow-up will be done after the PFS DCO. In addition, updated details of International Co-ordinating Investigator (ICI); updated text on reporting of pregnancy for consistency, updated text to clarify that patients will be considered eligible for inclusion based upon a ‘pre-existing positive local tumor tissue, cytological or circulating tumor deoxyribonucleic acid (ctDNA) epidermal growth factor receptor mutation-positive (EGFR) result’, new section added on ‘safety data collection’ describing rationale for adverse event (AE) reporting duration, and updated few sections to comply with the latest version of the CSP template and latest edition of Investigator’s Brochure (IB).

The following changes have been implemented:

- **Section 1.1, Section 7.1.1, Section 7.1.2, Section 9.4.1.2.3:** Updated table footnotes ('s' and 'k' in Table 1 and Table 2, respectively) and text to clarify that the survival follow-up will be done until death, withdrawal of consent, or the time of 'the PFS DCO' and patients should be contacted in the week after PFS DCO to establish survival status.

- **Section 1.2:** Updated details of ICI.

- **Section 1.2, Section 1.3, Section 4.1, Section 4.4, Section 6.7, Section 7.1.1, Section 7.1.2, Section 7.4, Section 9.1, Section 9.2, Section 9.4.1.1, Section 9.4.1.2.3:** Due to treatment landscape changes which outpaced study recruitment updated text to reduce the number of patients/sample size and updated schedule of PFS DCO; removed reference to 'final' analysis to clarify that primary PFS analysis and OS analysis will be done at PFS DCO; clarified that the descriptive analysis will be presented without any p-value for all PFS and OS endpoints; updated study schema.

- **Section 2.3.2.1, Section 8.3.2:** Added text on 'safety data collection' describing rationale for AE reporting duration for clarity.

- **Section 2.3.2.2:** Updated text on occurrences of Grade 3 and Grade 4 adverse reactions to 8.5% and 0.1%, respectively to align with latest IB.

- **Section 8, Section 8.1.3:** Updated text to clarify that patients will be considered eligible for inclusion based upon a 'pre-existing positive local tumor tissue, cytological or ctDNA EGFR result'.

- **Section 8.4.2.1:** Updated that all pregnancies occurring during the study and within 6 weeks of the 'last dose of osimertinib' should be reported to AstraZeneca, for consistency with Section 8.4.2.

- **Section 8.4.3:** Updated to include correct cross-reference to relevant section.

- **Section 9.4.1.1:** Deleted text 'efficacy' to improve clarity.

- Below updates were made for compliance with latest version of the CSP template.

  - **Section 6:**
    - Updated heading.
  - **Section 6.1.1:**

    - Updated Table 4 to add/revise details on type, dose formulation, unit dose strength, dosage level, use, IP/NIP, and sourcing.
  - **Section 6.2:**
    - Added text on reporting of temperature excursion situations during transit of the centrally supplied study treatments; updated that authorized site staff is also responsible for study treatment accountability, reconciliation, and record maintenance; updated text on disposal of used/unused study treatments.
  - **Section 6.2.1, Section 6.2.2:**
    - Added new subheadings on 'dose preparation' and 'dose administration', cross-references to relevant subsections included.
  - **Section 8.4.1:**
    - Added text on reporting of serious adverse events (SAEs) when Electronic Data Capturing (EDC) system is not available or temporarily not accessible.
    - Added text on reference documents for definition of expectedness/listedness of investigational products.
  - **Section 8.4.3:**
    - Updated heading.
  - **Appendix A1:**
    - Updated subheading.
  - **Appendix A4:**
    - Updated text to align with template and added text on the personal data breaches.
  - **Appendix A7:**
    - Added text on quality tolerance limits (QTLs).
- **Appendix E:** Updated text in subsection 'Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) evaluation of overall visit response at follow-up' and in 'Table 14' for clarification.
- **Appendix I**: Updated list of abbreviations to align with latest updates in the CSP.
- **Throughout**: Minor editorial changes incorporated for consistency between sections and compliance with AstraZeneca Style Guide.
    - Updated grammar, spacing, capitalization, hyphenation, and numbers for consistency within the CSP and for compliance with AstraZeneca Style Guide.
  - Updated 'investigational medicinal product (IMP)' and 'non-investigational medicinal product (NIMP)' to 'investigational product (IP)' and 'non-investigational product (NIP)', respectively, for consistency.

Version 4.0, 14 March 2023

This amended protocol is issued to update the protocol regarding inclusion and exclusion criteria for patient recruitment, and to align with the Project Specific Safety Requirements (PSSR; Version 28) and Investigator's Brochure (IB; Version 17). In addition, some updates were made to comply with the latest version of the protocol template, with minor updates and corrections added for clarification:

- **Section 1.1:** Added a footnote to the post-treatment follow-up until progression and post-progression survival follow-up to clarify that safety laboratory assessments will only be performed on patients who are still receiving study treatment.
- **Section 1.1 and Section 8.2.4**: Added that electrocardiogram (ECG) will be done in triplicate only at screening, and if clinically indicated thereafter for clarity in the procedure to be followed.
- **Section 1.2 and Section 4.1:** Updated text to allow patients with stable disease lasting ≥ 6 months in addition to complete response (CR)/partial response (PR) during first-line treatment to the study.
- **Section 2.3.2.1 and Section 2.3.2.4:** Updated the number of patients exposed to osimertinib, studies completed, and adverse drug reactions to align with IB Version 17.
- **Section 4.4**: Updated the end of study definition to comply with the latest version of the protocol template, including:
  - Definitions per the European Union and Food and Drug Administration (FDA) requirements.
  - Conditions under which a patient is considered to have completed the study and under which the study can be stopped.
  - Milestones to reach before the database can be closed.
- **Section 5.1**:
  - Inclusion criterion 6: updated requirement for CR/PR to allow patients with stable disease lasting for ≥ 6 months and updated allowance of prior adjuvant and neo-adjuvant therapies from 12 months prior to disease progression to 8 months prior, to aid with patient recruitment.
  - Inclusion criterion 11: updated definition post-menopausal age to "aged 50 years or more" to align with PSSR Version 28.

- **Section 5.2**:
  - Exclusion criterion 3: updated “extracranial diseases” to “systemic diseases” for accurate description and added restrictions on patient with hepatitis B and human immunodeficiency virus (HIV) to align with PSSR Version 28.
  - Exclusion criterion 4: rearranged to include secondary bullet list to align the PSSR Version 28.
  - Exclusion criterion 5: updated allowable ranges for absolute neutrophil count and platelet count to align with PSSR Version 28 and updated guidelines for calculation of creatinine clearance and added collection of 24-hour urine as an alternative for creatinine clearance calculation to allow older patients and patients with more extreme weight and body mass index (BMI) to participate.
  - Exclusion criterion 7: Deleted specification to extracranial therapy and adjuvant chemotherapy to align with PSSR Version 28.
  - Exclusion criterion 11: updated completion of prior therapies from 12 months prior to development of recurrent disease to 8 months to aid with patient recruitment.
  - Exclusion criterion 14: Added more detail on prohibited medication to align with PSSR Version 28.
- **Section 5.3.1:** Added “Monthly pregnancy testing and monitoring of women of childbearing potential is recommended; however, it can be modified to comply with local legislation.” to align with PSSR Version 28.
- **Section 5.3.3:** Added the subheading “Other restrictions” to add restrictions and testing guidelines for patients with chronic hepatitis B and HIV to align with PSSR Version 28.
- **Section 6.5.1**: Added guidelines for patients taking regular medications and for handling of radiation pneumonitis to align with PSSR Version 28.
- **Section 6.7**: Updated section to comply with the latest version of the protocol template, including:
  - Update to heading from “Treatment after the end of the study” to “Continued access to study treatment after the end of the study”.
  - Update to text to add more details for continued treatment options, patients’ follow-up per standard of care, and data collection after final data cut-off (DCO).

- **Section 7.1:** Added "Patients with signs/symptoms of compromised immunity due to HIV infection as evaluated by an HIV specialist and the Investigator" to align with PSSR Version 28.

- **Section 7.4**: Deleted overdose and pregnancy as information to be collected after DCO to be consistent with Section 6.7 and updated reference to specific data vendor to a general term, ie, AstraZeneca's Patient Safety data entry site, should there be a change in vendor in future.

- **Section 8.4.3**: Updated the definition of an overdose to align with PSSR Version 28.

- **Section 8.4.4 and Appendix B 8**: Added subheadings and guidelines for medication error, drug abuse, and drug misuse for compliance with the latest version of the protocol template.

- **Section 8.4.5.1**: Added that patients discontinued due to toxicities will be observed until resolution of toxicity. Added Steven's Johnsons Syndrome, toxic epidermal necrolysis, and aplastic anemia to Table 8 as adverse reactions that will lead to permanent discontinuation of osimertinib. Updated description of cardiac contractility and added aplastic anemia and toxic epidermal necrolysis as a specific adverse event to align with PSSR Version 28 and IB Version 17. Added sub section for adverse events of special interest (AESI) to define that interstitial lung disease (ILD)/pneumonitis and changes in cardiac contractility (cardiac failure) will be considered AESIs.

- **Appendix A**: Updated appendix for compliance with the latest version of the protocol template, and Appendix A9 for clarification

  - Appendix A1:
    - Added reference to indicate most recent amendment of Declaration of Helsinki.
    - Added that AstraZeneca will be responsible for obtaining authorization for regulatory authorities and the clarified the guidelines the Investigator must adhere to.
    - Added regulatory reporting requirements for serious adverse events and serious breaches.
  - Appendix A3:
    - Clarified that informed consent is voluntary.
    - Added most recent guidelines for informed consent to the study.
  - Appendix A4:

- Added clarification and information on the data protections requirements and practices that will be followed through the study.

– Appendix A5:
  - Added that information on the Trial Steering Committee will be available in a Steering Committee Charter.

– Appendix A7:
  - Added information available in the Medical Monitoring Plan, responsibility of medical oversight, and accountability for actions delegated to other parties.
  - Updated retention period of documents from 15 to 25 years, according to the Global Retention and Disposal (GRAD) schedule.

– Appendix A8:
  - Added information and clarification of source data and where to find information on this.

– Appendix A9:
  - Updated definition of study start date and procedure to follow if this study is prematurely terminated per latest version of the protocol template.
  - Added that published study data will also be considered for study-related decisions about risk/benefit ratio for clarification.

- **Appendix G:** Updated definition of post-menopausal age to "aged 50 years or more" to align with PSSR Version 28.

- **Appendix H:** Added calculation of creatinine clearance on 24-hour urine sample, the collection of which was added as an alternative in exclusion criterion 5.

- **Throughout**: Minor editorial changes for consistency between sections and compliance with AstraZeneca Style Guide and the latest version of the protocol template.

– Update grammar, eg, spacing, capitalization, hyphenation, and numbers for consistency within the protocol and for compliance with AstraZeneca Style Guide.

– Updated to US language spelling at instances where UK spelling was used for consistent language use throughout protocol.

– Updated "who have progressed" to "whose disease has progressed" for consistency in terminology and for a more accurate description.

– Updated "subject" and "participant" to "patient" for consistency throughout protocol.

– Updated “the Sponsor” to AstraZeneca throughout to comply with the latest version of the protocol template. – Updated abbreviations to AstraZeneca Style Guide and template instructions, ie, define at first use, consistent use of abbreviations, all abbreviations defined in Appendix I and abbreviation list in table and figure footnotes. – Added/removed punctuation at bullet and numbered list for consistency.

Version 3.0 Final, 09 November 2021
Protocol Amendment 2: Update as per Project Specific Safety Requirements and harmonize the protocol relating to changes in the local amendments: • **Section 1.1, Table 1**: To include clarification that pregnancy testing during the study treatment will be in accordance with local clinical practice • **Section 1.1, Table 2**: To correct the typographical error with reference to footnote ‘k’ and ‘m’ • **Section 1.2 and Section 3**: CCI [redacted] CCI [redacted] CCI [redacted] • **Section 1.2 and Section 4.4**: To update the first patient enrollment timeline • **Section 2**: To update the background information • **Section 4.4**: To update the first patient enrollment timeline and to include cross reference to Appendix A9 • **Section 5.1 and Section 8.1.3**: To delete the certification and accreditation details from the inclusion criterion no. 7 • **Section 5.3.1**: To update the duration of use of contraception to 6 months after discontinuation of chemotherapy and 6 weeks after discontinuation of osimertinib • **Section 6**: To clarify the study treatment does not include pre-treatments

- **Section 6.5.1**: To update the duration of herbal supplements restriction after the last dose of osimertinib
- **Section 8.2.1, Table 6**: To include creatinine clearance and blood creatine phosphokinase
- **Section 8.3.7**: To clarify the adverse events that are to be considered as deterioration as compared to baseline and to include reference to the list of mandated laboratory safety variables in Table 6
- **Section 8.4.5.1.1, Table 8**: To update dose modification with respect to QT interval prolongation
- **Appendix A, A 9**: To include study stopping criteria based on safety data from this and other relevant studies
- **Appendix F, F 1**: Update the withdrawal period of phenobarbitone prior to start of study treatment

Version 2.0 Final, 25 January 2021

Protocol Amendment 1:

Update the protocol relating to Biological Samples and CCI :

- **Synopsis and Table 3 Study Objectives**: To clarify the exploratory objective and endpoints relating to biological samples
- **Table 1:** To clarify that the progression sample is collected at first progression
- **Section 8.7:** To clarify the Optional Genomics Initiative research sample is not collected and therefore not applicable in this study
- **Table 1 and Section 8.8:** To update with optional consent for samples for CCI (rather than mandatory participation)
- **Section 8.8:** To clarify samples are not collected from China or where prohibited by local requirements. To update that samples will be stored for a maximum of 15 years from the date of the CSR (rather than last patient last visit)

- **Appendix A3**: To update the requirements in Appendix A3 for Investigator to explain to patients the objectives of the analysis to be done on the samples and any potential future use and they are free to refuse to participate in any optional samples or the future use and may withdraw

- **Appendix C**: To update with the latest Human Biological Sample Handling Instructions

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

The schedule of activities (SoA) is presented in Table 1 and Table 2.

Table 1 Schedule of activities

	Screening Period	Randomization and Pre-treatment Period	Treatment Period			Follow-up Period			
	Screening	**Randomization and pre-treatment**	**Cycle 1**	**Cycle 2/Day 1 and Day 1 of all subsequent cycles [a]**	**Trt Disc**	**28-day follow-up [b]**	**Post-treatment follow-up until progression (Q6W relative to randomization) [u]**	**Post-progression survival follow-up (Q12W relative to randomization) [u]**	**Details in CSP section or Appendix**
Visit	**1**	**2**	**3**	**4+**					
Day	**-28 to -1**	**< 7 days prior to Cycle 1 starting**	**1**	**22+**					
Week	**NA**	**0**	**1**	**4+**					
Window (days)	**NA**	**NA**	**0**	**± 3**	**NA**	**+ 7**	**± 7**	**± 7**	
Informed consent [c]	X								Section 5.1
Inclusion/exclusion criteria	X	X							Sections 5.1, 5.2, and 8.1.3
Routine clinical procedures [d]									
Demography and patient characteristics [e]	X								Section 5.1
Physical examination and weight	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 [f]	X	X		X		Section 8.2.6
Vital signs	X		X	X	X				Section 8.2.3
COVID-19 test [t]	←	As clinically indicated see Footnote t for a description				→			Section 8.2.7
Height	X								Section 8.2.2
ECG	X [g]		X	X	X [h]				Sections 8.2.4 and 5.4

	Screening Period	Randomization and Pre-treatment Period	Treatment Period			Follow-up Period			
	Screening	**Randomization and pre-treatment**	**Cycle 1**	**Cycle 2/Day 1 and Day 1 of all subsequent cycles [a]**	**Trt Disc**	**28-day follow-up [b]**	**Post-treatment follow-up until progression (Q6W relative to randomization) [u]**	**Post-progression survival follow-up (Q12W relative to randomization) [u]**	**Details in CSP section or Appendix**
Visit	**1**	**2**	**3**	**4+**					
Day	**-28 to -1**	**< 7 days prior to Cycle 1 starting**	**1**	**22+**					
Week	**NA**	**0**	**1**	**4+**					
Window (days)	**NA**	**NA**	**0**	**± 3**	**NA**	**+ 7**	**± 7**	**± 7**	
Echocardiogram/MUGA	X			Week 13 (± 1 week) and then every 4th cycle (± 1 week) and as clinically indicated [i]	X [h,j]				Section 8.2.5 and Appendix I 1
Concomitant medication	X	X	Conducted at every visit				X [l]		Section 6.5
Anti-cancer and surgical treatment	X								Sections 5.1 and 5.2
Routine safety measurements [d]									
Pregnancy test (serum or urine) [k]	X		Consistent with local standard clinical practice						Sections 5.1, 5.2, and 8.2.1
Adverse events	X	X	Conducted at every visit				X [l]	X [l]	Section 8.3
Safety laboratory assessments (clinical chemistry, hematology, and urinalysis)	X [g]		X [f]	X	X	Q6W (± 1 week) relative to randomization of IP until RECIST 1.1- or CNS RECIST 1.1-defined radiological disease progression or end of survival follow-up, whichever comes first			Sections 8.2.1 and 5.4
Creatinine clearance calculation	X		X [f]	X	X				Appendix H
CCI [redacted]									
CCI [redacted]			X [n]	X	X	X	X (taken at first progression)		Section 8.8

	Screening Period	Randomization and Pre-treatment Period	Treatment Period			Follow-up Period			
	Screening	**Randomization and pre-treatment**	**Cycle 1**	**Cycle 2/Day 1 and Day 1 of all subsequent cycles [a]**	**Trt Disc**	**28-day follow-up [b]**	**Post-treatment follow-up until progression (Q6W relative to randomization) [u]**	**Post-progression survival follow-up (Q12W relative to randomization) [u]**	**Details in CSP section or Appendix**
Visit	**1**	**2**	**3**	**4+**					
Day	**-28 to -1**	**< 7 days prior to Cycle 1 starting**	**1**	**22+**					
Week	**NA**	**0**	**1**	**4+**					
Window (days)	**NA**	**NA**	**0**	**± 3**	**NA**	**+ 7**	**± 7**	**± 7**	
Efficacy measurements [d]									
Brain imaging (CNS RECIST 1.1) [o]	X		Q6W (± 1 week) relative to randomization for the first 13 cycles, then Q12W (± 1 week) relative to randomization until CNS RECIST 1.1-defined radiological intracranial disease progression or end of survival follow-up, whichever comes first						Sections 7.1.3, 8.1.1 and 8.1.2 and Appendix E
Chest and abdomen imaging (RECIST 1.1) [o]	X		Q6W (± 1 week) relative to randomization for the first 13 cycles, then Q12W (± 1 week) relative to randomization until RECIST 1.1-defined radiological extracranial disease progression or end of survival follow-up, whichever comes first						Sections 8.1.1 and 8.1.2 and Appendix E
Study treatment administration [p,q]									
Randomization		X [p,q,r]							Section 6.1.2
Osimertinib/placebo treatment dispensed (daily dosing)			X	Day 1 of each cycle through Cycle 6, Q6W from Cycle 7 to 13, then Q12W thereafter					Section 6.1.2.1
Pre-treatment for pemetrexed [p,q]									
Folic acid taken orally (pre-treatment)		Begin 5 to 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	Randomization and Pre-treatment Period	Treatment Period			Follow-up Period			
	Screening	**Randomization and pre-treatment**	**Cycle 1**	**Cycle 2/Day 1 and Day 1 of all subsequent cycles [a]**	**Trt Disc**	**28-day follow-up [b]**	**Post-treatment follow-up until progression (Q6W relative to randomization) [u]**	**Post-progression survival follow-up (Q12W relative to randomization) [u]**	**Details in CSP section or Appendix**
Visit	**1**	**2**	**3**	**4+**					
Day	**-28 to -1**	**< 7 days prior to Cycle 1 starting**	**1**	**22+**					
Week	**NA**	**0**	**1**	**4+**					
Window (days)	**NA**	**NA**	**0**	**± 3**	**NA**	**+ 7**	**± 7**	**± 7**	
Corticosteroid taken orally (pre-treatment)		On the day prior to, on the day of, and on the day after pemetrexed administration							Section 6.1.2.2
Chemotherapy [p,q,r]									
Cisplatin or carboplatin IV treatment			Day 1 of Cycles 1 through 4 (inclusive)						Section 6.1.2.2
Pemetrexed IV treatment			X	X					Section 6.1.2.2
Survival follow-up									
Survival status [s]								X	Section 7.1.1 and 7.1.2

[a] Patients to attend visits on Day 1 of each 21-day cycle (± 3 days) until treatment discontinuation. At the Investigator's discretion, study treatment may continue after progression if a patient continues to derive clinical benefit per guidelines (Section 7.1.2). Patients who continue treatment following progression should maintain the Schedule of Activities at each cycle (ie, 21 days [± 3 days]).

[b] 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.

[c] Consent must be taken prior to any study-related assessments or procedures.

[d] 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 due to toxicity, all procedures except imaging will be completed relative to the adjusted cycle and not weeks on treatment.

[e] Include date of birth or age, gender, race, ethnicity, and smoking history for all patients, as per local regulations.

[f] Screening assessments that have been performed within 14 days prior to the first dose of IP do not have to be repeated on Cycle 1 Day 1 if the patient's condition has not changed.

[g] 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. The ECG should be performed in triplicate only at screening, and if clinically indicated thereafter.

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

[i] Echocardiogram/MUGA assessment to be completed at this frequency until completion of chemotherapy and pemetrexed maintenance treatment. If the last on-treatment echocardiogram/MUGA assessment is abnormal, a follow-up assessment is required. Refer to Appendix I 1 for country-specific requirements in Germany.

[j] If a patient had a MUGA or echocardiogram performed within 28 days prior to treatment discontinuation, the discontinuation visit echocardiogram/MUGA is not required unless clinically indicated. Refer to Appendix I 1 for country-specific requirements in Germany.

[k] Pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) will be conducted in women of childbearing potential only, within 14 days prior to the first dose of IP and during study treatment in accordance with local clinical practice.

[l] 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. Only concomitant medications relating to SAEs will be collected throughout follow-up (note that all concomitant medications are collected up to 28 days after CNS or Extracranial progression whichever is the latter).

[m] CCI

[n] To be collected pre-dose on Cycle 1 Day 1.

[o] The baseline radiological assessments should be performed during the 28-day screening period and preferably as close as possible to and prior to randomization. Scans obtained per the patient's standard of care prior to randomization do not need to be repeated and are acceptable to use as baseline evaluations, if the criteria in Section 8.1.1 are met. Baseline assessments include (i) CT (preferred) or MRI of the 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 Q6W (± 1 week) subsequently, relative to randomization, for the first 13 cycles, then Q12W (± 1 week), relative to randomization, until radiological disease progression as per RECIST 1.1 (for extracranial disease progression based on chest and abdomen imaging) or CNS RECIST 1.1 (for intracranial disease progression based on brain imaging), or the end of survival follow-up, whichever comes first, even if a dose is delayed due to toxicity or a patient discontinues treatment prior to progression or receives other anti-cancer treatment. Patients with intracranial progression per CNS RECIST 1.1 as their first progression event may receive open-label osimertinib if deemed appropriate by Investigator and confirmed by the study physician as described in section 7.1.3 and following confirmation in the IVRS/IWRS; if this is confirmed for patients on placebo, follow Table 2.

[p] Every effort should be made to minimize the time between randomization and starting treatment with IP; randomization must take place within 4 weeks of the patient's last dose of first-line osimertinib. Pre-treatment will take place prior to the start of IP as described above and in Section 6.1.2.2. Pre-treatment should be started as soon as possible after randomization (or started during screening if deemed appropriate by Investigator [eg, patient is already taking oral folic acid]) and whenever possible within 1 day of randomization (ie, on the same day or the day after randomization in the IVRS/IWRS).

[q] Perform all study procedures and assessments as described in above table, and ensure all eligibility criteria are met prior to randomization, IP dispensing, and administration. Pre-treatment including vitamin supplementation should begin following randomization, to support the start of pemetrexed therapy on Cycle 1 Day 1 and should be completed as described in Section 6.1.2.2. Pre-treatments may be started during screening if deemed appropriate by Investigator (eg, patient is already taking oral folic acid). Osimertinib/placebo and chemotherapy dosing should begin on the same day.

[r] Prior to randomization for each patient, the Investigator will select cisplatin or carboplatin.

[s] Patients will be contacted for survival follow-up every 12 weeks until death, withdrawal of consent, or the PFS DCO. There will be no further survival follow-up after the PFS DCO. Patients should be contacted in the week after the PFS DCO to establish survival status, refer to section 7.1.1.

[t] A COVID-19 test will be performed as clinically indicated/according to local regulations.

[u] Safety laboratory assessments (clinical chemistry, hematology, and urinalysis) in post-treatment and post-progression follow-up phases are applicable only for patients who, at the Investigator's discretion/decision are still deriving clinical benefit and continue receiving study treatment after progression.

CNS=Central nervous system; COVID-19=coronavirus disease 2019; CSP=Clinical Study Protocol; CT=Computed tomography; DCO=data cut-off; ECG=electrocardiogram; IP=Investigational product; 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; QxW=Every X weeks; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=Serious adverse event; Trt Disc=Treatment discontinuation; WHO=World Health Organization.

Table 2 Schedule of activities for open-label treatment following initial intracranial progression (only for patients who initially received placebo)

	Treatment Period		Follow-up Period			
	Cycle X/Day 1 following confirmation of intracranial progression and Day 1 of all subsequent cycles [a]	**Trt Disc**	**28-day follow-up [b]**	**Post-treatment follow-up until progression (Q6W relative to randomization) [o]**	**Post-progression survival follow-up (Q12W relative to randomization) [o]**	**Details in CSP section or Appendix**
Visit	**3+[a]**					
Day	**22+[a]**					
Week	**4+[a]**					
Window (days)	**± 3**	**NA**	**+ 7**	**± 7**	**± 7**	
Investigator determination of eligibility for open-label treatment	X [l]					Section 7.1.3
Routine clinical procedures [c]						
Physical examination and weight	X	X				Section 8.2.2
WHO performance status	X	X		X		Section 8.2.6
Vital signs	X	X				Section 8.2.3
COVID-19 test [m]	← As clinically indicated see Footnote m for a description →					Section 8.2.7
ECG	X	X [d]				Section 8.2.4
Echocardiogram/MUGA	Week 13 (± 1 week) and then every 4th cycle (± 1 week) and as clinically indicated [e]	X [d,f]				Section 8.2.5 and Appendix I 1
Concomitant medication	Conducted at every visit			X [g]	X [g]	Section 6.5
Routine safety measurements [c]						
Pregnancy test (serum or urine) [n]	Consistent with local standard clinical practice					Section 8.2.1
Adverse events	Conducted at every visit			X [g]	X [g]	Section 8.3
Safety laboratory assessments (clinical chemistry, hematology, and urinalysis)	X [h]	X	Q6W (± 1 week) relative to randomization of IP until RECIST 1.1- or CNS RECIST 1.1-defined radiological disease progression or end of survival follow-up, whichever comes first			Section 8.2.1
Creatinine clearance calculation	X	X				Appendix H

	Treatment Period		Follow-up Period			
	Cycle X/Day 1 following confirmation of intracranial progression and Day 1 of all subsequent cycles [a]	**Trt Disc**	**28-day follow-up [b]**	**Post-treatment follow-up until progression (Q6W relative to randomization) [o]**	**Post-progression survival follow-up (Q12W relative to randomization) [o]**	**Details in CSP section or Appendix**
Visit	**3+[a]**					
Day	**22+[a]**					
Week	**4+[a]**					
Window (days)	**± 3**	**NA**	**+ 7**	**± 7**	**± 7**	
Efficacy measurements [c]						
Brain imaging (CNS RECIST 1.1) [i]	Q6W (± 1 week) relative to randomization until second CNS RECIST 1.1-defined radiological intracranial disease progression or end of survival follow-up, whichever comes first					Sections 8.1.1 and 8.1.2 and Appendix E
Chest and abdomen imaging (RECIST 1.1) [i]	Q6W (± 1 week) relative to randomization for the first 13 cycles, then Q12W (± 1 week) relative to randomization until RECIST 1.1-defined radiological extracranial disease progression or end of survival follow-up, whichever comes first					Sections 8.1.1 and 8.1.2 and Appendix E
Study treatment administration						
Osimertinib treatment dispensed (daily dosing)	Day 1 of each cycle through Cycle 6, Q6W from Cycle 7 to 13, then Q12W thereafter					Section 6.1.2.1
Pre-treatment for pemetrexed						
Folic acid taken orally (pre-treatment)	Daily during treatment period and for 21 days after pemetrexed discontinuation					Section 6.1.2.2
Vitamin B_{12} intramuscular (pre-treatment)	Every 3 cycles (9 weeks) during treatment period on the day of pemetrexed administration					Section 6.1.2.2
Corticosteroid taken orally (pre-treatment)	On the day prior to, on the day of, and on the day after pemetrexed administration					Section 6.1.2.2
Chemotherapy [j]						
Cisplatin or carboplatin IV treatment	Day 1 of Cycles 1 through 4 (inclusive)					Section 6.1.2.2
Pemetrexed IV treatment	X					Section 6.1.2.2

	Treatment Period		Follow-up Period			
	Cycle X/Day 1 following confirmation of intracranial progression and Day 1 of all subsequent cycles [a]	**Trt Disc**	**28-day follow-up [b]**	**Post-treatment follow-up until progression (Q6W relative to randomization) [o]**	**Post-progression survival follow-up (Q12W relative to randomization) [o]**	**Details in CSP section or Appendix**
Visit	**3+[a]**					
Day	**22+[a]**					
Week	**4+[a]**					
Window (days)	**± 3**	**NA**	**+ 7**	**± 7**	**± 7**	
Survival follow-up						
Survival status [k]					X	Sections 7.1.1 and 7.1.2

[a] Cycle, day, visit, and week numbers for open-label treatment will continue sequentially from those during randomized treatment. Patients to attend visits on Day 1 of each 21-day cycle (± 3 days) until treatment discontinuation. At the Investigator's discretion, study treatment may continue after progression if a patient continues to derive clinical benefit per guidelines (Section 7.1.2). Patients who continue treatment following progression should maintain the Schedule of Activities at each cycle (ie, 21 days [± 3 days]).

[b] 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.

[c] 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 due to toxicity, all procedures except imaging will be completed relative to the adjusted cycle and not weeks on treatment.

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

[e] Echocardiogram/MUGA assessment to be completed at this frequency until completion of chemotherapy and pemetrexed maintenance treatment. If the last on-treatment echocardiogram/MUGA assessment is abnormal, a follow-up assessment is required. Refer to Appendix I 1 for country-specific requirements in Germany.

[f] If a patient had a MUGA or echocardiogram performed within 28 days prior to treatment discontinuation, the discontinuation visit echocardiogram/MUGA is not required unless clinically indicated. Refer to Appendix I 1 for country-specific requirements in Germany.

[g] 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. Only concomitant medications relating to SAEs will be collected throughout follow-up (note that all concomitant medications are collected up to 28 days after second CNS progression or extracranial progression whichever is the latter).

[h] Lab safety assessments should be done on Day 1 of each cycle; however, if the patient is switching to open-label osimertinib mid-cycle and safety laboratory assessments were not performed within the last 7 days, they do need to be repeated prior to starting open-label osimertinib.

[i] 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 at the timing indicated in the table, even if a dose is delayed due to toxicity or a patient discontinues treatment prior to progression or receives other anti-cancer treatment. The brain scan that was assessed as intracranial disease progression during randomized treatment should be used as the baseline CNS RECIST 1.1 assessment for the open-label period, open-label treatment should start within 28 days following the baseline scan, otherwise the patient should be discontinued from open-label treatment.

[j] Patients who receive open-label osimertinib may also receive platinum chemotherapy (if not yet completed Cycles 1 to 4) and/or pemetrexed at the Investigator's discretion.

[k] Patients will be contacted for survival follow-up every 12 weeks until death, withdrawal of consent, or the PFS DCO. There will be no further survival follow-up after the PFS DCO. Patients should be contacted in the week after the PFS DCO to establish survival status, refer to section 7.1.1.

[l] Confirm prior to first cycle of open-label treatment.

[m] A COVID-19 test will be performed as clinically indicated/according to local regulations.

[n] Pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) will be conducted in women of childbearing potential only, within 14 days prior to the first dose of IP and during study treatment in accordance with local clinical practice.

[o] Safety laboratory assessments (clinical chemistry, hematology, and urinalysis) in post-treatment and post-progression follow-up phases are applicable only for patients who, at the Investigator's discretion/decision are still deriving clinical benefit and continue receiving study treatment after progression.

Note: The AstraZeneca Core Study Team, including the statistician, study physician, data manager, and operational lead, intend to remain blinded.

CNS=Central nervous system; COVID-19=coronavirus disease 2019; CSP=Clinical Study Protocol; DCO=data cut-off; ECG=electrocardiogram; IP=Investigational product; IV=Intravenous; MUGA=Multi-Gated Acquisition Scan; NA=Not applicable; OS=overall survival; PFS=progression-free survival; QxW=Every X weeks; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=Serious adverse event; Trt Disc=Treatment discontinuation; WHO=World Health Organization.

1.2 Synopsis

International Co-ordinating Investigator:

Prof. Nir Peled, MD, PhD, FCCP, Shaare Zedek Medical Center, 12 Shmuel Beit St, Jerusalem, Israel 9103102

Protocol title: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Platinum Plus Pemetrexed Chemotherapy Plus Osimertinib Versus Platinum Plus Pemetrexed Chemotherapy Plus Placebo in Patients with EGFRm, Locally Advanced or Metastatic NSCLC who have Progressed Extracranially following First-Line Osimertinib Therapy (COMPEL)

Rationale: Despite the benefit observed for patients treated with osimertinib as first-line treatment for non-small cell lung cancer (NSCLC), the majority of patients are expected to progress. Platinum doublet chemotherapy is currently recommended following extracranial progression on first-line osimertinib (NCCN 2019, Planchard et al 2018); however, data suggest that patients who are classified as having acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have tumors containing a heterogeneous mix of cells, some of which have become resistant to the EGFR TKI, while some remain sensitive. Therefore, patients may benefit from continued treatment with EGFR TKIs, to control persistently sensitive clones of cells, while also receiving chemotherapy for suppression of resistant tumor cells. This continued treatment would be especially important for patients with central nervous system (CNS) metastases, a population in which osimertinib has been shown to have strong activity. Chemotherapy, unlike osimertinib, does not cross the blood-brain barrier, and CNS metastases are common in this population.

Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To compare the efficacy of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo based on PFS	PFS is defined as time from randomization until progression (intracranial or extracranial, whichever occurs first) per RECIST 1.1 (for extracranial progression) and CNS RECIST 1.1 (for intracranial progression) as assessed by the Investigator at local site or death due to any cause
Secondary objectives:	**Endpoints/variables:**
To compare the efficacy of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo based on intracranial PFS in patients with baseline brain metastases and patients without baseline brain metastases	Intracranial PFS is defined as time from randomization until intracranial progression per CNS RECIST 1.1 as assessed by the Investigator at local site or death due to any cause

To compare the efficacy of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo based on extracranial PFS	Extracranial PFS is defined as time from randomization until extracranial progression per RECIST 1.1 as assessed by the Investigator at local site or death due to any cause
To compare the efficacy of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo based on OS	OS is defined as the length of time from randomization until the date of death due to any cause
Safety objective:	**Endpoints/variables:**
To assess the safety and tolerability of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo in patients with locally advanced or metastatic EGFRm NSCLC whose disease has progressed extracranially on first-line osimertinib treatment	Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory assessments, ECGs, LVEF, and WHO PS. Assessments related to AEs cover • Occurrence/frequency • Relationship to IP as assessed by the Investigator • CTC grade • Seriousness • Death • AEs leading to discontinuation of IP • Other action taken related to IP • AEs of special interest • Other significant AEs
Exploratory objective:	**Endpoints/variables:**
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]

AE=Adverse event; CNS=Central nervous system; CTC=Common Terminology Criteria; ECG=electrocardiogram; EGFRm=Epidermal growth factor receptor mutation-positive; CCI [redacted] IP=Investigational product; LVEF=Left ventricular ejection fraction; NSCLC=Non-small cell lung cancer; CCI [redacted] CCI [redacted] OS=Overall survival; PFS=Progression-free survival; PS=Performance status; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; WHO=World Health Organization.

Overall design:

This is a Phase III, randomized, double-blind, placebo-controlled study of platinum plus pemetrexed chemotherapy plus osimertinib versus platinum plus pemetrexed chemotherapy plus placebo in patients with epidermal growth factor receptor mutation-positive (EGFRm), locally advanced or metastatic NSCLC with or without stable brain metastases who responded to first-line osimertinib therapy (complete response [CR] or partial response [PR]) or stable disease (SD) for ≥ 6 months during first-line osimertinib treatment, and subsequently experienced radiological, extracranial disease progression. Approximately 204 patients were to be randomized in a 1:1 ratio to treatment with platinum/pemetrexed chemotherapy plus osimertinib (Treatment Arm A) or platinum/pemetrexed chemotherapy plus placebo (Treatment Arm B). However, the number of patients was reduced to approximately 80 patients due to treatment landscape changes which outpaced study recruitment.

Patients will be stratified based on the presence of brain metastases (stable brain metastases based on CNS Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST 1.1] assessments versus no brain metastases).

Study period:

Date of first patient enrolled: Q3 2021

Estimated date of last patient completed: Q4 2024

Number of patients:

Approximately 204 patients were planned for randomization. However, the number of patients was reduced to approximately 80 patients due to treatment landscape changes which outpaced study recruitment.

Treatments and treatment duration:

The 2 randomized treatment regimens are as follows:

- Treatment Arm A: Osimertinib 80 mg once daily (QD) with pemetrexed (500 mg/m^2) (with pre-treatment) plus either cisplatin (75 mg/m^2) or carboplatin (area under the concentration-time curve [AUC] 5), both administered on Day 1 of 21-day cycles for 4 cycles, followed by osimertinib 80 mg QD plus pemetrexed maintenance (500 mg/m^2) on Day 1 of 21-day cycles
- Treatment Arm B: Placebo QD with pemetrexed (500 mg/m^2) (with pre-treatment) plus either cisplatin (75 mg/m^2) or carboplatin (AUC5), both administered on Day 1 of 21-day cycles for 4 cycles, followed by placebo QD plus pemetrexed maintenance (500 mg/m^2) on Day 1 of 21-day cycles

Study treatment will continue until RECIST 1.1- or CNS RECIST 1.1-defined progression based on Investigator assessment or another discontinuation criterion is met. Treatment through progression and treatment after intracranial progression will be permitted under the conditions described in Section 7.1.2 and Section 7.1.3. Following treatment discontinuation, subsequent therapy will be at the discretion of the Investigator, and patients will be followed for progression and survival.

Statistical methods:

The primary analysis of progression-free survival (PFS) based on Investigator assessment (according to RECIST 1.1 for extracranial progression and CNS RECIST 1.1 for intracranial progression) was to occur when approximately CCI PFS events had been observed in the 204 randomized patients (approximately CCI % maturity, allowing for a possible CCI % drop out in the first 2 months) and at least CCI months after randomization of the last patient. This was expected to occur approximately CCI months after the first patient was randomized (under an assumed CCI -month non-linear recruitment). If the true PFS hazard ratio (HR) for the comparison of chemotherapy plus osimertinib versus chemotherapy plus placebo is CCI , CCI progression events will provide at least 80% 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 CCI months, assuming exponential distribution and proportional hazards. The critical HR is CCI , which translates to an approximate median PFS improvement from CCI months.

However, the sample size was reduced to approximately 80 patients due to treatment landscape changes which outpaced study recruitment.

The PFS data cut-off (DCO) will occur when approximately 60 PFS events have been observed in approximately 80 randomized patients (approximately 75% maturity), which is expected to occur during CCI . If the 75% maturity is achieved earlier, the DCO will take place earlier, providing it is at least CCI months after randomization of the last patient.

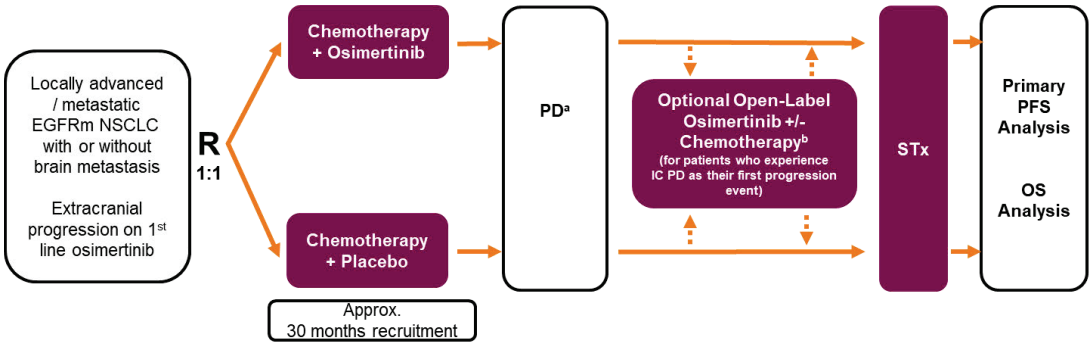
Due to the reduced sample size, the study will no longer be powered to perform a formal hypothesis test and therefore, a descriptive analysis for all PFS and overall survival (OS) endpoints will be performed. The HR and 95% confidence interval (CI) will be calculated and presented without any hypothesis testing (ie, p-value generation) for all PFS and OS endpoints.

A single analysis of OS will be carried out at the time of the DCO for PFS.

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



[a] Patients will receive randomized study treatment until RECIST 1.1- or CNS RECIST 1.1-defined progression based on Investigator assessment or another discontinuation criterion is met. At the Investigator's discretion, study treatment may continue for as long as a patient continues to derive clinical benefit through RECIST 1.1 or CNS RECIST 1.1 progression in the absence of any discontinuation criteria. Chest and abdomen imaging will continue until RECIST 1.1-defined extracranial progression; brain imaging will continue until CNS RECIST 1.1-defined intracranial progression (and until second CNS RECIST 1.1-defined intracranial progression for patients who receive open-label osimertinib).

[b] Patients who receive open-label osimertinib may also receive platinum chemotherapy and/or pemetrexed at the Investigator's discretion.

CNS=central nervous system; EGFRm=Epidermal growth factor receptor mutation-positive; IC=intracranial; NSCLC=Non-small cell lung cancer; OS=Overall survival; PD=Progressive disease; PFS=Progression-free survival; R=Randomization; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; STx=Subsequent therapy.

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 United States of America after breast cancer (NCI SEER 2018). Approximately 80% to 90% of all lung cancers are non-small cell lung cancer (NSCLC; Cataldo et al. 2011, NCCN 2019). Adenocarcinoma is the most common type of cancer 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 epidermal growth factor receptor (EGFR)-activating mutations, the most common of which are exon 19 deletions (Ex19del) and exon 21 L858R substitution mutations, is associated with responsiveness to EGFR tyrosine kinase inhibitors (TKI) therapy (erlotinib, gefitinib, afatinib, osimertinib, or dacomitinib).

Osimertinib (TAGRISSO™[1], AZD9291) is a potent, oral, irreversible, TKI targeting epidermal growth factor receptor mutation-positive (EGFRm) and T790M resistance mutations and is approved for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors have EGFR Ex19del 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.

Osimertinib is considered the preferred standard of care (SoC) for the first-line treatment of patients with metastatic EGFRm NSCLC given its superiority over the first-generation EGFR

[1] TAGRISSO is a trade name of the AstraZeneca group of companies.

TKI therapies (gefitinib/erlotinib) (NCCN 2019). However, despite the benefit observed for patients treated with osimertinib in the first-line setting, the majority of patients are expected to eventually progress on first-line osimertinib.

Platinum doublet chemotherapy is currently recommended following extracranial progression on first-line osimertinib (NCCN 2019, Planchard et al 2018). The median OS in patients post-TKI therapy typically ranges only from approximately 10 to 20 months (Mok et al 2017a, Soria et al 2015).

As described in the following sections, continued treatment with osimertinib in combination with platinum doublet chemotherapy following extracranial progression on first-line osimertinib may result in extended response and prolonged survival.

2.1 Study rationale

Knowledge regarding the exact mechanisms of acquired resistance to first-line osimertinib is limited; however, data suggest that patients who progress after first-line treatment with osimertinib have tumors containing a heterogeneous mix of cells, some of which have become resistant to the EGFR TKI, while some remain sensitive. In 13 patients who were classified as having acquired resistance to erlotinib or gefitinib, Riely et al observed a 9% increase in tumor diameter and a median 4% increase in maximum standard uptake value 3 weeks after stopping EGFR TKI treatment. Subsequently, 3 weeks after restarting EGFR TKI treatment, these patients experienced a 1% decrease in tumor diameter and a median 4% decrease in maximum standard uptake value (Riely et al 2007). Further, data from Pao and Chmielecki suggest that EGFRm tumors retain dependency on EGFR signaling even after acquiring resistance to EGFR TKIs (Pao and Chmielecki 2010). These data suggest that patients who are classified as having acquired resistance to EGFR TKIs may benefit from continued treatment with EGFR TKIs, to control persistently sensitive clones of cells, while also receiving chemotherapy for suppression of resistant cells.

Osimertinib has demonstrated strong activity against central nervous system (CNS) metastases. Brain exposure and regional brain distribution of osimertinib in the cynomolgus monkey (with an intact blood-brain barrier [BBB]) using positron emission tomography (PET) microdosing demonstrated that carbon-11 labeled 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 labeled 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 Blinded Independent Central Review (BICR; N = 128). Progression-free survival (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% confidence interval [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 once daily (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 objective response rate (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 duration of response 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 (hazard ratio [HR], 0.32; 95% CI: 0.15, 0.69; P = 0.004). In the osimertinib arm, 51% of patients (21 of 41) who achieved an extracranial 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 (PR) 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-naive 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, computed tomography (CT) and MRI may not have sufficient spatial resolution to visualize micrometastatic lesions that are likely present in many patients at the time of diagnosis, when the BBB is still intact.

Further, data suggest that tumor cells within the CNS typically do not acquire resistance to osimertinib at the same time as extracranial tumor cells. Lower therapeutic exposure in the CNS as compared to extracranial exposure results in a reduced EGFR TKI "evolutionary pressure" for new resistant tumor clones to evolve in the CNS (Baik et al 2015). 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 extracranial tumor clones have become resistant to osimertinib. Therefore, for patients with stable CNS metastases at study entry continuing osimertinib treatment may well maintain benefit with respect to their CNS lesions.

Therefore, Study D5162C00042 will evaluate the efficacy and safety of treatment with chemotherapy in combination with osimertinib compared to chemotherapy in combination with placebo in patients whose disease has progressed extracranially following first-line osimertinib treatment. Further, this study will include an option for patients who experience intracranial progression as their first progression event to receive treatment with open-label osimertinib at the discretion of the Investigator. (The AstraZeneca Core Study Team, including the statistician, study physician, data manager, and operational lead, intend to remain blinded). CCI [redacted] CCI [redacted]

It should be noted that the IMPRESS study failed to demonstrate improved efficacy with gefitinib in combination with cisplatin and pemetrexed compared to cisplatin and pemetrexed

alone in patients whose disease has progressed following first-line gefitinib treatment (Soria et al 2015). However, several factors distinguish the current study design from that of the IMPRESS study. The primary difference is that the mechanism of action of osimertinib is different from that of gefitinib, most notably allowing osimertinib more CNS permeability and therefore stronger activity against CNS metastases. Further, treatment groups in IMPRESS were imbalanced based on the number of patients with brain metastases. Since (as described above) different outcomes would be expected in patients with and without brain metastases, this may have contributed to confounding results in that study. In the current study, patients will be stratified by presence of brain metastases (stable brain metastases based on CNS Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST 1.1] assessments versus no brain metastases) to address this concern. Finally, at the time of the IMPRESS study, the main mechanism of acquired resistance to gefitinib (acquisition of the T790M mutation) was not well understood; thus, treatment groups in the IMPRESS study were not balanced based on the status of T790M mutation. Therefore, the results from the IMPRESS study are not considered to be reflective of the expected outcome of the current study.

2.2 Background

Platinum doublet chemotherapy is currently recommended following extracranial progression on first-line osimertinib (NCCN 2019, Planchard et al 2018). In this setting, use of either cisplatin or carboplatin as platinum agents is common and typically followed by maintenance pemetrexed, which has been shown to improve PFS and OS and is well tolerated (Ciuleanu et al 2009, Paz-Ares et al 2013). 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 to 5.4 months (Mok et al 2017b, Soria et al 2015, Yoo et al 2018). A meta-analysis by Cochrane concluded that there was no difference in OS between cisplatin- versus carboplatin-based chemotherapy and recommended that the choice of platinum agent be made based on the toxicity profile and each patient's specific comorbidities (de Castria et al 2013). Therefore, in the current study, patients will receive either cisplatin or carboplatin-based chemotherapy at the discretion of the Investigator, followed by pemetrexed maintenance.

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 is provided in the respective prescribing information.

2.3 Benefit/risk assessment

2.3.1 Benefit

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), and osimertinib was subsequently approved for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors have EGFR Ex19del or exon 21 (L858R) substitution mutations.

Osimertinib also demonstrated promising activity in patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy (Mok et al 2017a) and was subsequently approved in this indication.

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 there can be no certainty of clinical benefit to patients, the positive efficacy data for osimertinib from the FLAURA and AURA3 studies, supported by data in patients with CNS metastases from the AURA extension and AURA2 studies, as well as the findings from Riely et al and Pao and Chmielecki, provide support for evaluation of osimertinib with platinum/pemetrexed as treatment for patients with advanced EGFRm NSCLC whose disease has progressed extracranially on first-line osimertinib (Riely et al 2007 and Pao and Chmielecki 2010).

2.3.2 Risk

2.3.2.1 Safety data collection

Osimertinib has a defined mechanism of action and a known pharmacokinetic profile and has been dosed in over CCI patients at the recommended dose of 80 mg QD in a clinical trial program. With osimertinib in the post-marketing phase, the safety profile of osimertinib is sufficiently characterized with well-defined adverse drug reactions (ADRs), as well as adverse events of special interest which allow for complete collection of adverse events (AEs). In clinical trials osimertinib has been generally well tolerated. The majority of ADRs were Grade 1 or Grade 2 in severity and the incidences of Grade 3 and Grade 4 adverse reactions with osimertinib were 8.5% and 0.1%, respectively. Additional information on specific AEs can be found in Section 2.3.2.2 or in the osimertinib IB.

There are no proposed changes to the drug product (eg, pharmaceutical form, drug substance, excipients) or the route of administration for osimertinib in this study compared to other studies.

The safety profile of pemetrexed as monotherapy and in combination with cisplatin and carboplatin is well-defined, as described in Section 2.3.2.3. The potential for overlapping toxicity is described in Section 2.3.2.5. In the safety run-in (n = 30) of Study D5169C00001 (FLAURA2), most AEs were mild and manageable and consistent with the known safety profile of the respective treatments, with no new safety signals identified. The safety data from the randomization study period will continue to inform the use of the combination of osimertinib plus platinum + pemetrexed chemotherapy in the current study.

The safety follow-up period of 28 days (+ 7) for AEs specified in the clinical study protocol (CSP) takes into consideration the mechanism of action and half-life of osimertinib allowing monitoring of safety events until the point where no action of the drug (or presence) is to be expected.

Sections 8.3.2 and 8.3.3 provide instructions regarding safety data collection and follow-up of unresolved AEs. This accounts for any unresolved AEs at the time of treatment discontinuation and indicates that they should be followed up until resolution, to ensure that any unexpected long-term toxicities are fully characterized.

2.3.2.2 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 CCI 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 (ADAURA, 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 to 40.1 months). In the FLAURA study based on a data cut-off (DCO) of 12 June 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 most ADRs were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2 in severity. The most commonly reported ADRs were diarrhea (47%) and rash (45%). Other typical EGFR TKI ADRs include dry skin, pruritus, paronychia, and stomatitis. CTCAE Grade 3 and Grade 4 adverse reactions occurred in 8.5% and 0.1% of patients, respectively. Dose reductions due to ADRs occurred in 2.1% of the patients, and discontinuations due to ADR occurred in 4.3% of patients.

Interstitial lung disease (ILD) or ILD-like ADRs (eg, pneumonitis) were reported in 3.8% and were fatal in 0.3% (n = 5) of the CCI patients who received osimertinib 80 mg in the ADAURA, FLAURA, and AURA studies. The incidence of ILD was 10.9% in patients of Japanese ethnicity, 1.6% in patients of non-Japanese Asian ethnicity, and 2.5% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 2.8 months.

Of the CCI patients in the ADAURA, FLAURA, and AURA studies treated with osimertinib 80 mg, 0.8% (n = 12) of patients were found to have a corrected QT interval (QTc) greater than 500 msec, and CCI CCI. No QTc-related arrhythmia events were reported in the pivotal osimertinib 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 CCI patients treated with osimertinib in the ADAURA, FLAURA and AURA studies. Across clinical trials, left ventricular ejection fraction (LVEF) decreases greater than or equal to 10% and a drop to less than 50% occurred in 3.2% 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.

Further details on the clinical safety profile of osimertinib, including guidance on management of ADRs, are available in the IB.

2.3.2.3 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 as follows: neutropenia (15% of patients), anemia (6%), thrombocytopenia (4%) and febrile neutropenia (1.3%). Drug-related Grade 3 or 4 non-hematological toxicities occurred as follows: nausea (7.2%), vomiting (6.1%) and fatigue (6.7%). 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.

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.

2.3.2.4 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 investigational product (IP; pneumonitis and ILD) (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.

2.3.2.5 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 CCI patients in the ADAURA, 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 white blood cell 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 AEs (ie, neutropenia and neutrophil count decreased) were reported in 10.8% of patients receiving osimertinib, including 1.8% of patients 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 AEs.

Lymphocyte-related AEs (ie, lymphocyte count decreased and lymphopenia) were reported in 4.7% of patients receiving osimertinib, including 1.8% of patients 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 AEs (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. AEs 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. AEs of bleeding, bruising, or hemorrhage 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). ILD 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 IB. Gonadal suppression resulting in amenorrhea or azoospermia may occur in patients receiving antineoplastic therapy, and such effects may be irreversible. Moreover, chemotherapy can have genetically damaging effects. Guidance on contraception requirements and sperm donation is provided in Section 5.3.1 and Appendix G.

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 counseling on sperm storage before starting treatment.

A Japanese Phase II open-label, randomized study of osimertinib alone versus 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, and 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 transaminase (AST)/alanine transaminase (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 limited published data on the safety and tolerability of osimertinib with either cisplatin or carboplatin and pemetrexed. Study D5169C00001 (FLAURA2; NCT04035486) is a global, Phase III, open-label randomized study of osimertinib, with or without platinum plus pemetrexed chemotherapy, in patients with locally advanced or metastatic EGFRm (exon 19 deletion and/or L858R) NSCLC who have not received prior therapy for advanced disease. In the safety run-in period (prior to the phase, randomized study period), 30 patients were allocated to receive osimertinib 80 mg QD in combination with either cisplatin 75 mg/m^2 (n = 15) or carboplatin AUC5 (n = 15), plus pemetrexed 500 mg/m^2 every 3 weeks (Q3W) for 4 cycles, followed by osimertinib 80 mg QD with pemetrexed 500 mg/m^2 maintenance Q3W, until RECIST version 1.1 defined progression or discontinuation. The primary endpoints of this safety run-in include AEs; laboratory evaluations of clinical chemistry, hematology/urinalysis, vital signs, and physical examination. As of DCO date on 19 February 2020, 30 patients were enrolled across 5 countries (South Korea, Russia, Japan, Taiwan, and Australia) who received at least one dose of study treatment. All patients (100%) had metastatic disease and adenocarcinoma histology. At DCO, the majority of patients (90%) were ongoing with study treatment. Twenty-three patients (77%) had completed 4 cycles of carboplatin or cisplatin chemotherapy by DCO; total exposure time was similar for both carboplatin (2.76 months) and cisplatin (2.79 months). Total exposure time for osimertinib (3.81 months) was similar to pemetrexed (4.14 months). Adverse events were reported by 27/30 patients (90%); the majority were not serious and mild to moderate in severity. Most common AEs in all treatment groups were constipation (13/30; 43%), nausea (12/30; 40%), and diarrhea (11/30; 37%). Seven patients (23% permanently discontinued any study drug: 4 patients (27%) in the osimertinib + carboplatin + pemetrexed cohort and 3 patients (20%) in the osimertinib + cisplatin + pemetrexed cohort. The majority of AEs leading to discontinuation were single events and consistent with the known safety profile of osimertinib and chemotherapy (eg, diarrhea, laboratory related toxicities); Two patients (7%) discontinued all study treatment due to AEs or disease under study. One AE, which lead to the permanent discontinuation of osimertinib and chemotherapy, was a case of ILD (pneumonitis; CTCAE grade 2) in the osimertinib + carboplatin + pemetrexed cohort (fulfilled a study specific discontinuation criterion); the reported AE was considered moderate in severity and the patient recovered 24 days later. One discontinuation was a fatal AE (hemoptysis) attributed to NSCLC, but not considered causally related to treatment by the Investigator. Acute decreases

in key hematological parameters were noted, but these stabilized under continued study treatment and appropriate management. The results from the safety run-in period showed osimertinib plus platinum + pemetrexed chemotherapy was generally well tolerated with no new safety signals identified. Most AEs identified were mild, manageable, and consistent with the known safety profile of the respective treatments. No clear differences in safety were observed between chemotherapy regimens (Planchard et al 2020). The safety data from FLAURA2 randomization study period will continue to inform the use of the combination of osimertinib plus platinum + pemetrexed chemotherapy in current study.

2.3.3 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 platinum plus pemetrexed chemotherapy plus osimertinib followed by pemetrexed maintenance compared with platinum plus pemetrexed chemotherapy plus placebo followed by pemetrexed maintenance in patients with locally advanced or metastatic EGFRm NSCLC whose disease has progressed extracranially on first-line osimertinib treatment.

3 OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Primary objective:	**Endpoint/variable:**
To compare the efficacy of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo based on PFS	PFS is defined as time from randomization until progression (intracranial or extracranial, whichever occurs first) per RECIST 1.1 (for extracranial progression) and CNS RECIST 1.1 (for intracranial progression) as assessed by the Investigator at local site or death due to any cause
Secondary objectives:	**Endpoints/variables:**
To compare the efficacy of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo based on intracranial PFS in patients with baseline brain metastases and patients without baseline brain metastases	Intracranial PFS is defined as time from randomization until intracranial progression per CNS RECIST 1.1 as assessed by the Investigator at local site or death due to any cause
To compare the efficacy of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo based on extracranial PFS	Extracranial PFS is defined as time from randomization until extracranial progression per RECIST 1.1 as assessed by the Investigator at local site or death due to any cause
To compare the efficacy of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo based on OS	OS is defined as the length of time from randomization until the date of death due to any cause

Safety objective:	**Endpoints/variables:**
To assess the safety and tolerability of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo in patients with locally advanced or metastatic EGFRm NSCLC whose disease has progressed extracranially on first-line osimertinib treatment	Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory assessments, ECGs, LVEF, and WHO PS. Assessments related to AEs cover • Occurrence/frequency • Relationship to IP as assessed by the Investigator • CTC grade • Seriousness • Death • AEs leading to discontinuation of IP • Other action taken related to IP • AEs of special interest • Other significant AEs
Exploratory objective:	**Endpoints/variables:**
CCI	CCI CCI
CCI CCI	CCI CCI

AE=Adverse event; CNS=Central nervous system; CTC=Common Terminology Criteria; ECG=electrocardiogram; EGFRm=Epidermal growth factor receptor mutation-positive; CCI IP=Investigational product; LVEF=Left ventricular ejection fraction; NSCLC=Non-small cell lung cancer; OS=Overall survival; CCI PFS=Progression-free survival; PS=Performance status; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; WHO=World Health Organization.

4 STUDY DESIGN

4.1 Overall design

This is a Phase III, randomized, double-blind, placebo-controlled study of platinum plus pemetrexed chemotherapy plus osimertinib versus platinum plus pemetrexed chemotherapy plus placebo in patients with EGFRm, locally advanced or metastatic NSCLC with or without stable brain metastases (see Section 5.2) who responded to first-line osimertinib therapy (complete response [CR] or partial response [PR]) or stable disease (SD) for ≥ 6 months during first-line osimertinib treatment, and subsequently experienced radiological, extracranial disease progression. Approximately 204 patients were to be randomized in a 1:1 ratio to one of the below treatment arms. However, the number of patients was reduced to approximately 80 patients due to treatment landscape changes which outpaced study recruitment.

- Treatment Arm A: Osimertinib 80 mg QD with pemetrexed (500 mg/m^2) (with pre-treatment) 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 plus pemetrexed maintenance (500 mg/m^2) on Day 1 of 21-day cycles
- Treatment Arm B: Placebo QD with pemetrexed (500 mg/m^2) (with pre-treatment) plus either cisplatin (75 mg/m^2) or carboplatin (AUC5), both administered on Day 1 of 21-day cycles for 4 cycles, followed by placebo QD plus pemetrexed maintenance (500 mg/m^2) on Day 1 of 21-day cycles

Patients will be stratified based on the presence of brain metastases (stable brain metastases based on CNS RECIST 1.1 assessments versus no brain metastases).

Patients should be randomized to receive their first dose of IP (osimertinib or placebo, cisplatin or carboplatin, and pemetrexed) in the current study as soon as possible, and within a maximum of 4 weeks, following their last dose of first-line osimertinib.

Study treatment will continue until RECIST 1.1- or CNS RECIST 1.1-defined progression based on Investigator assessment or another discontinuation criterion is met (refer to Section 7.1).

Patients may continue to receive study treatment through progression if, in the judgment 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, or spinal cord compression), study treatment must be discontinued. Receipt of open-label osimertinib after intracranial progression (as first progression) will be permitted under the conditions described in Section 7.1.2 and Section 7.1.3.

Following treatment discontinuation, subsequent therapy will be at the discretion of the Investigator, and patients will be followed for progression and survival, see Table 1 and Table 2.

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.

For details on what is included in the efficacy and safety endpoints, see Section 3.

4.2 Scientific rationale for study design

4.2.1 Rationale for primary endpoint of progression-free survival

The primary endpoint of this study is PFS (intracranial or extracranial, whichever occurs first), which is widely accepted as a surrogate endpoint for clinical benefit in studies of patients with advanced NSCLC. Progression-free survival represents a direct effect of efficacy, as it is not confounded by the efficacy of subsequent therapies used after disease progression.

Overall survival will be evaluated as a secondary endpoint to support the primary PFS endpoint.

4.2.2 Rationale for PFS-related secondary endpoints

Intracranial PFS (IC-PFS) and extracranial PFS (EC-PFS) will be evaluated as secondary endpoints in this study in order to evaluate the contribution of CNS metastases to progression in this population with chemotherapy plus osimertinib compared to chemotherapy plus placebo. Evaluation of IC-PFS in the combination is especially relevant as osimertinib has demonstrated strong activity in the CNS, whereas chemotherapy, unlike osimertinib, is unable to cross the blood-brain barrier (See Section 2.1 for additional information). Intracranial PFS will allow evaluation of efficacy in patients with brain metastases at baseline as well as evaluation of prevention development of brain metastases in patients without brain metastases at baseline.

4.2.3 Rationale for treatment after intracranial progression

Patients who experience intracranial progression as their first progression event will be permitted to receive treatment with open-label osimertinib at the discretion of the Investigator (Section 7.1.2 and Section 7.1.3). The AstraZeneca Core Study Team, including the statistician, study physician, data manager, and operational lead, intend to remain blinded. Further to the rationale for osimertinib treatment provided in Section 2.1, this will allow CCI [redacted]

4.3 Justification for dose

4.3.1 Osimertinib

Osimertinib administered orally at 80 mg QD is the approved dose for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors have EGFR 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

Platinum doublet chemotherapy is the 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 National Comprehensive Cancer Network (NCCN) NSCLC 2019 guidelines include both cisplatin-plus-pemetrexed and carboplatin-plus-pemetrexed combinations as category 1 first-line extracranial 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 extracranial 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 labeling.

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

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 2017b), 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 an 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 extracranial 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 non-squamous 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, non-squamous, NSCLC and as a single-agent for the maintenance treatment of patients with locally advanced or metastatic non-squamous 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 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 non-squamous 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 4 months on placebo plus chemotherapy to 7 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 4 months, ie, approximately 5 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% of patients received ≥ 10 cycles (Paz-Ares et al 2012). Thus, the extent of pemetrexed maintenance in this study is expected to be shorter 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 80 mg daily is pemetrexed 500 mg/m^2 (with pre-treatment) 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. 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

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs under Food and Drug Administration and European Union (EU) regulatory requirements:

- EU requirements define study completion as the last visit of the last patient for any protocol related activity.
- Food and Drug Administration requirements defines 2 completion dates:

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

A patient is considered to have completed the study when they have completed all phases of the study, including their last scheduled visit or last scheduled assessment/contact shown in the Schedule of Activities (SoA; Table 1 and Table 2).

The study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings (see Appendix A 9).

The PFS DCO is planned during CCI, when approximately 60 PFS events have been observed in approximately 80 randomized patients (approximately 75% maturity). If the 75% maturity is achieved earlier, the DCO will take place earlier, providing it is at least CCI months after randomization of the last patient. A single analysis of OS will be carried out at the time of the DCO for PFS. At this time, the clinical database will close to the new data.

See Section 6.7 for details on patient management following the PFS DCO, as well as following study completion.

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

5 STUDY POPULATION

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

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be randomized. 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. "Randomized" patients are defined as those who receive a randomization number.

For procedures for withdrawal of incorrectly enrolled patients, see Section 5.5 and 7.3.

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 ICF prior to any mandatory study-specific procedures, sampling, and analyses.

The ICF process is described in Appendix A 3.

Age

3 Male or female, at least 18 years of age.

Type of patient and disease characteristics

4 Pathologically confirmed non-squamous NSCLC.

5 Locally advanced (clinical stage IIIB or 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.

6 Evidence of radiological extracranial disease progression following (Investigator-assessed) response (CR, PR) or SD for ≥ 6 months during first-line osimertinib treatment, but who have not received further, subsequent treatment.

- Prior adjuvant and neo-adjuvant therapies (chemotherapy, radiotherapy, immunotherapy, biologic therapy, or investigational agents) or definitive radiation/chemoradiation with or without regimens, including immunotherapy, biologic therapy, and investigational agents, are permitted as long as treatment was completed at least 8 months prior to the development of extracranial disease progression.

7 Tumor known to harbor 1 of the 2 or both 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.

8 World Health Organization (WHO) performance status (PS) of 0 to 1 at screening with no clinically significant deterioration in the previous 2 weeks.

9 Life expectancy > 12 weeks at Day 1.

10 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 [TL]) 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

11 Females must be using highly effective contraceptive measures, and must have a negative pregnancy test prior to start of dosing if of childbearing potential, or must have evidence of non-childbearing potential by fulfilling 1 of the following criteria at screening:

- Post-menopausal, defined as aged 50 years or more and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.
- Women under 50 years old would be considered as post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments with luteinizing hormone and follicle-stimulating hormone 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 G.

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

5.2 Exclusion criteria

Medical conditions

1 Clinical or radiological evidence of CNS progression on first-line osimertinib.

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

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 (eg, patients receiving treatment for infection) including hepatitis C, and human immunodeficiency virus (HIV), or active uncontrolled hepatitis B infection.

- Screening for chronic conditions is not required.

Should patients with hepatitis B infection be included, patients are only eligible if they meet all the following criteria:

- Demonstrated absence of hepatitis C co-infection or history of hepatitis C co-infection
- Demonstrated absence of HIV infection
- Patients with active hepatitis B infection are eligible if they are:
  - Receiving anti-viral treatment for at least 6 weeks prior to study treatment, hepatitis B virus (HBV) deoxyribonuclease (DNA) is suppressed to < 100 IU/mL, and transaminase levels are < upper limit of normal (ULN)
- Patients with a resolved or chronic hepatitis B infection are eligible if they are:
  - Negative for hepatitis B surface antigen (HBsAg) and positive for hepatitis B core antibody (anti-HBc immunoglobulin G [IgG]). In addition, patients must be receiving anti-viral prophylaxis for 2 to 4 weeks prior to study treatment

or

  - Positive for HBsAg, but for > 6 months have had transaminase levels < ULN and HBV DNA levels < 100 IU/mL (ie, are in inactive carrier state). In addition, patients must be receiving anti-viral prophylaxis for 2 to 4 weeks prior to study treatment (see Section 5.3.3)

Should patients with HIV infection be included, patients are only eligible if they meet all the following criteria:

- Undetectable viral RNA load for 6 months
- CD4+ count of > 350 cells/μL
- No history of AIDS-defining opportunistic infection within the past 12 months
- Stable for at least 4 weeks on the same anti-HIV medications

4 Any of the following cardiac criteria:

- Mean resting QTc > 470 msec, obtained from 3 ECGs, using the screening clinic ECG machine-derived QTc value
- Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG, eg, complete left bundle branch block, third-degree heart block, and 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 < LLN
  - Serum/plasma magnesium < LLN
  - Serum/plasma calcium < 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 Torsade de Pointes (TdP).

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

- Absolute neutrophil count (ANC) < 1.5×10^9/L*
- Platelet count < 100×10^9/L*
- 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 × ULN if no demonstrable liver metastases or > 5 × ULN in the presence of liver metastases
- AST > 2.5 × ULN if no demonstrable liver metastases or > 5 × ULN in the presence of liver metastases
- Total bilirubin > 1.5 × ULN if no liver metastases or > 3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases
- Serum creatinine > 1.5 × ULN concurrent with creatinine clearance < 60 mL/min, as measured or calculated by Cockcroft and Gault equation or 24-hour urine collection (refer to Appendix H for appropriate calculation). Confirmation of creatinine clearance is only required if the creatinine is > 1.5 × ULN

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 therapy greater than CTCAE Grade 1 at the time of starting IP, 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 More than 4 weeks elapsed since last dose of osimertinib by date of randomization.

10 Unable to tolerate osimertinib 80 mg first-line therapy.

11 Prior treatment with any systemic anti-cancer therapy, excluding osimertinib, 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, or investigational agents) or definitive radiation/chemoradiation with or without regimens, including immunotherapy, biologic therapies, or investigational agents, are permitted as long as treatment was completed at least 8 months prior to the development of recurrent disease.

12 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.

13 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.

14 Current use of (or unable to stop use prior to receiving the first dose of IP) medications or herbal supplements known to be strong inducers of cytochrome P450 (CYP) 3A4 (at least 3 weeks prior; Appendix F). All patients must try to avoid concomitant use of any medications, herbal supplements, and/or ingestion of foods with known inducer effects on CYP3A4.

Prior/concurrent clinical study experience

15 Participation in another clinical study with an IP (other than first-line osimertinib) during the 4 weeks prior to Day 1. Patients in the follow-up period of an interventional study are permitted.

Other exclusions

16 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and staff at the study site).

17 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 OR any conditions that, in the opinion of the Investigator, may render the patient unable to complete the study.

18 Previous randomization in the present study.

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

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

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

5.3 Lifestyle restrictions

5.3.1 Pregnancy

Monthly pregnancy testing and monitoring of women of childbearing potential is recommended; however, it can be modified to comply with local legislation. The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

1 Female patients of childbearing 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 months after discontinuing chemotherapy or at least 6 weeks after discontinuing osimertinib. Acceptable methods are provided in Appendix G.

2 Male patients must use barrier contraceptives (condoms) during sex with a female partner of childbearing 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 counseling on sperm storage before starting treatment.

5.3.2 Meals and dietary restrictions

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

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

5.3.3 Other restrictions

Patients should receive HBV anti-viral prophylaxis post-treatment as determined by their hepatologist.

In patients with resolved or chronic hepatitis B infection (inactive carrier state) or active controlled hepatitis B infection on treatment with osimertinib:

- Recommend monthly monitoring of ALT/AST, HBV DNA levels, and HBsAg (if negative at baseline)
- Where liver signs and symptoms of viral reactivation appear (HBV DNA levels exceeding 10-fold from baseline or ≥ 100 IU/mL (if baseline HBV DNA levels are undetectable) or conversion of HBsAg negative to positive):
  - Expert hepatologist/specialist oversight of the patient is required
  - Consider interruption or discontinuation of study treatment, based on risk-benefit assessment

In patients with HIV, viral RNA load, and CD4+ cell count should be monitored per local SoC (eg, every 3 months).

5.4 Screen failures

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

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened. Rescreened patients will be assigned a new E-code both in electronic database capture and interactive voice/web response system. 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 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. Use of data for patients who fail to meet eligibility criteria is detailed in the statistical analysis plan.

6 STUDY TREATMENTS AND CONCOMITANT THERAPY

Study treatment is defined as any IP(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study patient according to the study protocol (see Section 6.1.2.2.2). IP in this study refers to osimertinib, placebo, cisplatin, carboplatin, and pemetrexed.

6.1 Treatments administered

6.1.1 Investigational products

See Table 4 for further details on the study treatments.

Selection of cisplatin or carboplatin is per 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 prior to randomization.

Table 4 Study treatments for the randomized period

	Chemotherapy plus osimertinib	Chemotherapy plus placebo	Osimertinib (optional receipt of open-label osimertinib for patients with intracranial progression as their first progression event) [a]
Study treatment name	Osimertinib (AZD9291) pemetrexed cisplatin or carboplatin	Placebo for osimertinib (AZD9291) pemetrexed cisplatin or carboplatin	Osimertinib (AZD9291) pemetrexed cisplatin or carboplatin
Type	Drug	Drug	Drug
Dose formulation	Osimertinib (AZD9291): Tablet Dose formulation details on cisplatin, carboplatin, and pemetrexed can be found in the local prescribing information for these products.	Placebo: Tablet Dose formulation details on cisplatin, carboplatin, and pemetrexed can be found in the local prescribing information for these products.	Osimertinib: Tablet Dose formulation details on cisplatin, carboplatin, and pemetrexed can be found in the local prescribing information for these products.

	Chemotherapy plus osimertinib	Chemotherapy plus placebo	Osimertinib (optional receipt of open-label osimertinib for patients with intracranial progression as their first progression event) [a]
Unit dose strength	Osimertinib (AZD9291) 80 mg tablet Details on cisplatin, carboplatin, and pemetrexed can be found in the local prescribing information for these products.	Placebo tablet for osimertinib (AZD9291) Details on cisplatin, carboplatin, and pemetrexed can be found in the local prescribing information for these products.	Osimertinib (AZD9291) 80 mg tablet Details on cisplatin, carboplatin, and pemetrexed can be found in the local prescribing information for these products.
Unit dose strength, dose reduction	Osimertinib (AZD9291) 40 mg tablet Details on cisplatin, carboplatin, and pemetrexed can be found in the local prescribing information for these products.	Placebo tablet matching osimertinib (AZD9291) Details on cisplatin, carboplatin, and pemetrexed can be found in the local prescribing information for these products.	Osimertinib (AZD9291) 40 mg tablet Details on cisplatin, carboplatin, and pemetrexed can be found in the local prescribing information for these products.
Route of administration	Osimertinib (AZD9291): oral pemetrexed: IV infusion cisplatin: IV infusion carboplatin: IV infusion	Placebo for osimertinib (AZD9291): oral pemetrexed: IV infusion cisplatin: IV infusion carboplatin: IV infusion	Osimertinib (AZD9291): oral pemetrexed: IV infusion cisplatin: IV infusion carboplatin: IV infusion
Dosage level	Osimertinib 1 tablet of 80 mg QD with pemetrexed (500 mg/m^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 (With pre-treatments as detailed in Section 6.1.2.2)	Placebo for osimertinib 1 tablet QD with pemetrexed (500 mg/m^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 placebo for osimertinib QD plus pemetrexed maintenance (500 mg/m^2) every 3 weeks (With pre-treatments as detailed in Section 6.1.2.2)	Osimertinib 1 tablet of 80 mg QD with pemetrexed (500 mg/m^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 (With pre-treatments as detailed in Section 6.1.2.2)

	Chemotherapy plus osimertinib	Chemotherapy plus placebo	Osimertinib (optional receipt of open-label osimertinib for patients with intracranial progression as their first progression event) [a]
Dosage level, dose reduction	Osimertinib 1 tablet of 40 mg QD Pemetrexed, cisplatin, and carboplatin dose reduction in Section 6.6	Placebo for osimertinib 1 tablet QD Pemetrexed, cisplatin, and carboplatin dose reduction in Section 6.6	Osimertinib 1 tablet of 40 mg QD Pemetrexed, cisplatin, and carboplatin dose reduction in Section 6.6
Use	Experimental treatment combination	Placebo-active comparator	Open-label osimertinib for patients with intracranial progression as their first progression event
IP or NIP	IP	IP	IP
Packaging and labeling	Osimertinib will be provided in HDPE bottles with child-resistant closures. Each bottle will be labeled in accordance with GMP Annex 13 and per country regulatory requirement. Cisplatin, carboplatin, and pemetrexed will be sourced locally where regulatory, local procedures and timelines allow. If centrally supplied, a label will be prepared in accordance with GMP and local regulatory guidelines.	Placebo for osimertinib will be provided in HDPE bottles with child-resistant closures. Each bottle will be labeled in accordance with GMP Annex 13 and per country regulatory requirement. Cisplatin, carboplatin, and pemetrexed will be sourced locally where regulatory, local procedures and timelines allow. If centrally supplied, a label will be prepared in accordance with GMP and local regulatory guidelines.	Osimertinib will be provided in HDPE bottles with child-resistant closures. Each bottle will be labeled in accordance with GMP Annex 13 and per country regulatory requirement. Cisplatin, carboplatin, and pemetrexed will be sourced locally where regulatory, local procedures and timelines allow. If centrally supplied, a label will be prepared in accordance with GMP and local regulatory guidelines.
Sourcing	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 through AstraZeneca.	Placebo for 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 through AstraZeneca.	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 through AstraZeneca.

[a] Patients who receive open-label osimertinib may also receive platinum chemotherapy and/or pemetrexed at the Investigator's discretion.

AUC=Area under the concentration-time curve; GMP=Good Manufacturing Practice; HDPE=High-density polyethylene; IP=Investigational product; IV=Intravenous; NIP=Non-investigational product; QD=Once daily.

6.1.2 Dosing instructions

Investigational product will be dispensed to patients after all eligibility criteria have been met, randomization has completed, all pre-medication has been administered as described in Table 1 and Table 2, and all other study procedures and assessments have been performed as described in Table 1 and Table 2.

Randomization will be made in the 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. Randomization should occur within a maximum of 4 weeks following the last dose of first-line osimertinib. Every effort should be made to minimize the time between randomization and starting treatment with IP. Pre-treatment should be started as soon as possible after randomization* and whenever possible within 1 day (ie, on the same day or the day after randomization in the IVRS/IWRS). Pre-treatment will take place prior to the start of IP as described in Table 1 and Table 2 and Section 6.1.2.2.

*pre-treatments may be started during screening if deemed appropriate by Investigator for example if patient is already taking oral folic acid.

6.1.2.1 Osimertinib or matching placebo dosing

For the first 6 cycles, sufficient osimertinib or matching placebo treatment for 3 weeks will be distributed at each dispensing visit. From Cycle 7 to Cycle 13, dispensing visits will occur every 6 weeks, and sufficient osimertinib or matching placebo for 6 weeks will be distributed. From Cycle 13 onwards, dispensing visits will occur every 12 weeks, and sufficient osimertinib or matching placebo 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.

To allow for management of IP-related toxicities, the initial dose of osimertinib 80 mg QD 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. Rechallenge at 80 mg is not allowed in this study.

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

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

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

Additional information about osimertinib may be found in the IB.

6.1.2.2 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 pemetrexed dosing according to the guidelines below. Osimertinib/placebo and chemotherapy dosing should all begin on the same day. Patients should receive pre-treatment as indicated in the SoA (Table 1 and Table 2) and may receive 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 RECIST 1.1- or CNS RECIST 1.1-defined progression or another discontinuation criterion is met (see Section 7.1).

6.1.2.2.2 Pre-treatments

To reduce the severity of hematologic and gastrointestinal toxicity of pemetrexed toxicity, patients treated with pemetrexed must also receive vitamin supplementation. Pre-treatment including vitamin supplementation should begin following randomization* as indicated in the SoA (Table 1), to support the start of pemetrexed therapy on Cycle 1 Day 1. 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.

* pre-treatments may be started during screening if deemed appropriate by Investigator for example if patient is already taking oral folic acid.

6.1.2.2.3 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.

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

6.1.2.2.4 Carboplatin

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

Carboplatin dose is calculated using the Calvert formula. The carboplatin dose is not to exceed 750 mg.

Calvert Formula

Total Dose (mg) = (target AUC) × (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) × (125 + 25) = 5× 150 mL/min = 750 mg.

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

6.1.2.2.5 Antiemetics and other supportive care medications

Antiemetic pre-medication 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 pre-medication/concomitant treatments can be given according to local standards of care; additional guidance is provided in Section 6.5.

6.2 Preparation, handling, storage, and accountability

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

Only patients randomized in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. The label on the bottles specifies instruction of appropriate storage. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for osimertinib/placebo and any centrally supplied study treatments, and throughout the entire study until authorization is provided for on-site destruction or removal of the osimertinib/placebo and any centrally supplied study treatments. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying AstraZeneca (or designated party); release of osimertinib/placebo and any centrally supplied study treatments for clinical use can only occur once the event has been reviewed and approval is provided by AstraZeneca (or designated party).

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

Used/unused study treatment will in general be disposed of per local procedures and not returned to AstraZeneca or delegate for disposal. If required by local regulations, a return of used/unused drug to a centralized disposal is possible.

6.2.1 Dose preparation

See Section 6.2 for details on osimertinib, matching placebo, and chemotherapy dose preparation.

6.2.2 Dose administration

See Sections 6.1.2.1 and 6.1.2.2 for details on osimertinib, matching placebo, and chemotherapy dose administration.

6.3 Measures to minimize bias: Randomization and blinding

6.3.1 Patient enrollment and randomization

All patients will be centrally assigned to randomized IP in a 1:1 ratio (chemotherapy plus osimertinib:chemotherapy plus placebo) using IVRS/IWRS. Randomization will be stratified

by presence of brain metastases on baseline CNS scans (stable brain metastases based on CNS RECIST 1.1 assessments versus no brain metastases).

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.

- Enrollment: Upon signing informed consent, patients will be identified to the IVRS/IWRS per country regulations and PPD PPD This number is the patient's unique identifier and is used to identify the patient on the CRFs.
- Patient eligibility will then be determined (see Sections 5.1 and 5.2).
  - If the patient is eligible (all eligibility criteria have been met, including not more than 4 weeks between randomization in this study and the last dose of osimertinib):
    - Select the chemotherapy treatment (cisplatin/carboplatin-based on the most appropriate option for the patient) that the patient should receive. This must be completed for all patients in the IVRS/IWRS system.
    - Randomization: Assign a randomized treatment group via the IVRS/IWRS. Randomization codes will be assigned strictly sequentially within each stratum and site/country/region as patients become eligible for randomization. The system will randomize the eligible patient to 1 of the 2 treatment groups.
    - Initiate pre-treatments for chemotherapy as described in the SoA (Table 1).
    - Initiate IP treatment on Day 1.
  - If the patient is ineligible and not randomized, the IVRS/IWRS should be accessed to terminate the patient in the system (Screen failures may be rescreened using a new E-code if randomization within 4 weeks of last dose of osimertinib is feasible; see Section 5.4.).

6.3.2 Methods for ensuring blinding

The study will be conducted in a double-blind manner. The osimertinib and placebo tablets will be identical in size, color, weight, and appearance, and the high-density polyethylene bottles dispensed to study personnel will be identical in size, shape, color, and appearance. All osimertinib and placebo will be blinded prior to dispensing to other study personnel to maintain the double-blind conditions.

The patient, the Investigator, and the study site staff will be blinded to the osimertinib or placebo allocation.

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

The randomization code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. Refer to Section 7.1.3 for description of unblinding with regard to patients who receive open-label osimertinib after experiencing intracranial progression as their first progression event. The Investigator documents and reports the action to the study physician without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented. At primary analysis the Study Team and Contract Research Organization (CRO) will be unblinded.

6.4 Treatment compliance

The administration of all study treatment 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 study treatment at every visit will be used to assess compliance with the treatment.

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

Osimertinib and matching placebo compliance will be calculated by AstraZeneca/designee based on the drug accountability documented in the source document and eCRF by the site staff and monitored by AstraZeneca/designee. 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 screening and randomization and pre-treatment 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 a new or unresolved AE, that therapy should be recorded until the related AE is resolved, stabilized, or otherwise explained or until the 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, on medications that require close monitoring, and on washout periods is provided in Appendix F.

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

Restricted medication/Class of drug:	Usage:
Strong inducers of CYP3A4. See Appendix F: Guidance regarding potential interactions with concomitant medications	Once enrolled, all patients must try to avoid concomitant use of medications and herbal supplements and/or ingestion of foods that are known to be strong inducers of CYP3A4 whenever feasible but patients may receive any medication that is clinically indicated for the treatment of AEs. 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. All concomitant medications should be captured on the eCRF.
Patients taking regular medication	If medically feasible, patients should be maintained on their regular medication throughout the study period, with the exception of strong inducers of CYP3A4

Restricted medication/Class of drug:	Usage:
Medications whose disposition is dependent upon the BCRP and/or P-gp with a narrow therapeutic index. See Appendix F 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	Patients taking 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. Patients 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 INR frequently, if it is decided to treat the patient with oral anticoagulants. Patients taking warfarin or other anticoagulant with pemetrexed should be monitored regularly for changes in prothrombin time or INR.
Colony stimulating factors	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 white blood cell (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 F, and additional specific guidance regarding antiemetic 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 all patients.	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.

Allowed medication/Class of drug:	Usage:
Leukocyte-depleted blood transfusions	Patients can have blood transfusions during the study treatment. However, patients are not 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 patients 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 CNS RECIST 1.1 or in patients in survival follow-up.
Palliative local therapy - radiotherapy and surgical resection	Palliative local therapy, including radiation therapy [a] 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 CNS RECIST 1.1 or in patients in survival follow-up.
Vaccines	Vaccines can be administered in accordance with local labels.

[a] Given the potential risks of radiation pneumonitis associated with radiotherapy, if new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of radiation pneumonitis is observed, an interruption in study treatment dosing is recommended as clinically appropriate, and the AstraZeneca Team should be informed. It is strongly recommended to perform a full diagnostic workup to differentiate a potential drug-induced pneumonitis from radiation pneumonitis and exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. The results of full diagnostic workup (including HRCT, blood, and sputum culture, and hematological parameters) will be captured in the eCRF. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of radiation pneumonitis should be considered. Patients diagnosed with CTCAE grade 1 (asymptomatic radiation pneumonitis) should be closely followed up for clinical symptoms (including additional imaging, consider HRCT or CT as an alternative) 2 to 4 days after initial diagnosis, and monitored close thereafter (perform additional assessments as required, consider additional imaging, and additional monitoring such as additional visit or phone calls are recommended). Patient can continue treatment with osimertinib as clinically appropriate and in agreement with the AstraZeneca study physician or delegate physician. In the presence of confirmatory HRCT scans of CTCAE grade 2 or higher (symptomatic or confirmatory HRCT scans) radiation pneumonitis diagnosed, study treatment should be permanently discontinued.

AE=adverse events; BCRP=Breast Cancer Resistance Protein; CNS=central nervous system; CSF=colony-stimulating factor; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; CYP=cytochrome P450; eCRF=electronic case report form; HRCT= high-resolution computed tomography; INR=International normalized ratio; NSAIDs= Non-steroidal anti-inflammatory drugs; P-gp=P-glycoprotein; RANK-L= Receptor activator of nuclear factor kappa-B ligand; RECIST 1.1= Response Evaluation Criteria in Solid Tumors, Version 1.1.

6.5.2 Antiemetic therapy

In principle, antiemetic pre-medication 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 TdP, it is strongly recommended that antiemetic drugs from the known risk of TdP category are not given in this study.

The Arizona Center 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 5. 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 5 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

TdP=Torsades de Pointes.

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 antiemetics) with the potential for interaction with osimertinib regarding QTc interval prolongation; see Appendix F.
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 that neurokinin-1 receptor 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 well-being may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

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 treatment period.**

6.6 Dose modification

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

6.7 Continued access to study treatment after the end of the study

As described in Section 4.4, the study will remain open until all patients have discontinued study intervention and completed their last expected visit/contact.

After the PFS DCO for this study, AstraZeneca will continue to supply osimertinib to patients who were receiving osimertinib and, as judged by the Investigator, continue to derive benefit from treatment. Treatment continuity will occur for as long as the patient continues to derive benefit as judged by the Investigator or until the patient meets any other discontinuation criteria, as defined in Section 7.1.

Patients should be followed according to the institution's SoC assessments. No further data collection is required, except for reporting of SAEs.

Patients who received other study interventions (ie, SoC only/placebo), or who discontinue from the study, should continue appropriate locally available treatment (SoC therapy) at the discretion of the Investigator.

AstraZeneca will continue to supply osimertinib in the continuous supply in this study while, in the opinion of the Investigator, the patient is benefiting.

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

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

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients may be discontinued from all study treatment (osimertinib, placebo, cisplatin, carboplatin, pemetrexed, and pre-treatments) 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 and 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- or CNS 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 may discontinue pemetrexed or platinum/pemetrexed and continue to receive osimertinib or placebo alone.
- Investigator decision to withdraw the patient from treatment.
- AE – 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.
- Patients with signs/symptoms of compromised immunity due to HIV infection as evaluated by an HIV specialist and the Investigator.
- Pregnancy.
- Lost to follow-up.

See the SoA (Table 1 and 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 have an 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 the 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 and Table 2). Further follow-up procedures are detailed below and in the SoA (Table 1 and Table 2).

Patients will continue to be followed for progression as per the RECIST and CNS RECIST schedules in Table 1 and Table 2 (relative to randomization), regardless of whether or not they are continuing study treatment. Following both intracranial CNS RECIST 1.1- and extracranial RECIST 1.1-defined radiological progression, 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 1 and Table 2). (See Section 7.1.3 for a description of assessments for patients who are treated after intracranial progression.) Patients will be followed for survival status every 12 weeks until death, withdrawal of consent, or the time of PFS 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.

For patients who have not actively withdrawn consent, the status of those ongoing (in the study), withdrawn (from the study), and "lost to follow-up" at the time of the 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. Patients should be contacted in the week after the PFS DCO to establish survival status.

7.1.2 Treatment through progression

At the Investigator's discretion, study treatment may continue for as long as a patient continues to derive clinical benefit through RECIST 1.1 or CNS 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, or spinal cord compression), study treatment must be discontinued.

Patients who continue treatment following progression should maintain the SoA as shown below:

- 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, ECGs, and echocardiogram/Multi-Gated Acquisition Scan [MUGA]) and concomitant medications. Refer to Appendix I 1 for country-specific requirements in Germany.

In addition, patients who continue treatment following progression will continue to be followed up for survival status every 12 weeks until death, withdrawal of consent, or the PFS analysis DCO as per the survival follow-up column shown in the SoA (Table 1 and Table 2). Adverse events will continue to be collected throughout the treatment period and including the 28-day follow-up period (28 days after last dose of IP).

7.1.3 Treatment after intracranial progression

Patients who experience intracranial progression as defined by CNS RECIST 1.1 (as their first progression event) will be permitted to receive treatment with open-label 80 mg osimertinib at the discretion of the Investigator. Before requesting the treatment allocation, the Investigator with a patient who experiences intracranial progression as their first progression event on the study will contact the study physician to confirm that unblinding is appropriate and the Investigator should consider any ongoing toxicity. When confirmed appropriate the Investigator will request the treatment allocation for that patient (chemotherapy plus osimertinib or chemotherapy plus placebo). Investigators will then make the determination of whether or not to initiate treatment with open-label osimertinib 80 mg QD. The patients who were on chemotherapy plus placebo and are going on to receive open-label osimertinib will follow the SoA described in Table 2.

7.2 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.

7.3 Withdrawal from the study

A patient may withdraw from the study (ie, withdraw consent) (IP and assessments), 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, AstraZeneca 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 will be 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 and disposed of/destroyed, and the action is documented.
- Ensure that 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 that the organization(s) holding the samples is/are informed about the withdrawn consent immediately, the samples are disposed of/destroyed, the action is documented, and the documentation is 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.

AstraZeneca or its delegate will request Investigators to collect information on patients' vital status (dead or alive; date of death when applicable) during survival follow-up from publicly

available sources, in accordance with local regulations. Knowledge of the vital status for all patients is crucial for the integrity of the study.

See the SoA (Table 1 and 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.

7.4 Patient management following database close

The clinical study database will close to new data once the PFS analysis DCO has been reached.

After this analysis, as described in Section 6.7, patients may continue to be provided with osimertinib for as long as they continue to derive clinical benefit as judged by the Investigator or until they meet any other discontinuation criteria defined in Section 7.1. For details regarding follow-up procedures, refer to Section 7.1.1 and Section 7.1.2.

These 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 (as per Section 8.4) via paper, and such information will be emailed (preferably) or faxed directly to AstraZeneca's Patient Safety data entry site. 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 eCRF, until the event resolves, stabilizes, or is otherwise explained or until the patient is lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

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

It is recommended that the screening assessments be performed in a stepwise process beginning with verifying that the patient has a pre-existing positive local tumor tissue, cytological or circulating tumor deoxyribonucleic acid (ctDNA) EGFR result that was determined using an acceptable method (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 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 AstraZeneca immediately upon occurrence or awareness to determine whether the patient should continue or discontinue one or more of the IPs.

Adherence to the study design requirements, including those specified in the SoA (Table 1 and 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 and Table 2).

8.1 Efficacy assessments

All patients should continue to receive assigned IP until objective radiological disease progression per RECIST 1.1 (Eisenhauer et al 2009) or CNS RECIST 1.1 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) and the brain will be performed using RECIST 1.1 (Appendix E) on images from CT (preferred for the chest and abdomen) or MRI (preferred for the brain) with IV contrast, collected during screening (as close as possible to and prior to randomization). Thereafter, tumor assessments will be done every 6 weeks (± 1 week), relative to randomization, for the first 13 cycles, then every 12 weeks (± 1 week), relative to randomization. Extracranial (chest and abdomen) tumor assessments will continue until radiological extracranial disease progression per RECIST 1.1 or the end of survival follow-up, whichever comes first (see Table 1 and Table 2). Intracranial (brain) tumor assessments will continue until radiological intracranial disease progression per CNS RECIST 1.1 or the end of survival follow-up, whichever comes first (see Table 1 and Table 2), with the exception of patients who receive open-label osimertinib following initial intracranial progression while on placebo. These patients will continue intracranial (brain) tumor assessments every 6 weeks (± 1 week),

relative to randomization until their second intracranial progression. (See Section 7.1.3 for additional information.) 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.

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 randomization. Scans obtained per the patient's SoC prior to randomization 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.
- 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.
- Appropriate documentation indicating that these radiographic tumor assessments were performed as SoC 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 will not be required to have an MRI brain scan during screening if the criteria above are met.

8.1.2 RECIST 1.1 and CNS RECIST 1.1

Efficacy assessment of PFS (including whole-body PFS [intracranial or extracranial, whichever occurs first], IC-PFS, and EC-PFS) will be derived using RECIST 1.1 for extracranial progression and CNS RECIST 1.1 for intracranial progression based on Investigator evaluations. Efficacy for all patients will be assessed by objective tumor assessments according to Table 1 and Table 2 until objective radiological disease progression as defined by RECIST 1.1/CNS RECIST 1.1 (intracranial for brain imaging and extracranial for chest and abdomen imaging) and as assessed by the Investigator or until the end of

survival follow-up, whichever comes first. Patients who receive open-label osimertinib following initial intracranial progression will continue intracranial (brain) tumor assessments until their second intracranial progression. (See Section 7.1.3 for additional information.) These assessments should occur irrespective of whether a patient is receiving IP or has previously discontinued IP 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.

Modified "CNS" RECIST 1.1 guidelines are based upon the neuroimaging criteria of Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM; Lin et al 2015 supplementary appendix). Specifically, brain lesions will be assessed on a unidimensional scale according to standard RECIST 1.1 criteria (eg, a minimum longest diameter of 10 mm); however, Investigators are allowed to select up to 5 lesions in the brain as target lesions (TLs) to enable a more robust quantification of change in measurable lesions. All other lesions, including all measurable lesions not selected as TLs and small lesions (ie, < 10 mm in size) or leptomeningeal disease should be considered non-measurable. Lesions outside the CNS will not be reviewed for the purpose of intracranial efficacy assessment. Neurological symptoms or corticosteroid use will not be included in the CNS RECIST response assessment.

Response Evaluation Criteria in Solid Tumors, Version 1.1 criteria will be used to assess each patient's tumor response to treatment. The RECIST 1.1 assessments of baseline images identify 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 response, the presence of unequivocal NLs, and overall time point responses (CR, PR, SD, progressive disease [PD], or not evaluable [NE]). Further details of the RECIST 1.1 assessments can be found in Appendix E. Responses do not require confirmation.

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

8.1.2.1 Central reading of scans

All images, including unscheduled visit scans, will be collected on an ongoing basis and sent by the sites (preferably by electronic transfer) to an AstraZeneca-appointed CRO for quality control and storage. No BICR of scans from this study is planned prospectively.

8.1.3 Screening EGFR mutation analysis

In this study, patients will be considered eligible for inclusion based upon a pre-existing positive local tumor tissue, cytological or ctDNA EGFR result. Repeat EGFR mutation analysis is not required for entry into this study.

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.

Information on molecular testing results following systemic progression after first-line treatment with osimertinib from the patient's medical history should be collected in the CRF in order to understand the pattern of tumor testing (not applicable for China) in this study population.

8.2 Safety assessments

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

8.2.1 Clinical safety laboratory assessments

See Table 6 for the list of clinical safety laboratory tests to be performed for clinical chemistry, hematology, and urinalysis, and refer to the SoA (Table 1 and 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 SoA. Clinical chemistry, hematology, and urinalysis assessments that have been performed within 14 days prior to the first dose of IP 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, hematology, and urinalysis will be performed at a local laboratory in or near the Investigator site.

Table 6 Laboratory safety variables

Hematology/Hemostasis (whole blood)	Clinical chemistry (serum or plasma)
B-Hemoglobin (Hb)	S/P-Albumin
B-Red blood cell (RBC) count	S/P-Alanine transaminase (ALT)
B-Hematocrit	S/P-Aspartate transaminase (AST)

Hematology/Hemostasis (whole blood)	Clinical chemistry (serum or plasma)
B-Reticulocytes	S/P-Alkaline phosphatase (ALP)
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count) [a]	S/P-Calcium, total
Neutrophils	S/P-Creatinine
Lymphocytes	S/P-Glucose
Monocytes	S/P-Lactate dehydrogenase (LDH) [b]
Basophils	S/P-Magnesium
Eosinophils	S/P-Potassium
B-Platelet count	S/P-Sodium
Urinalysis (dipstick)	S/P-Urea/Blood urea nitrogen
U-Glucose	Creatinine clearance [c]
U-Protein	Blood creatine phosphokinase
U-Blood	

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

[b] Lactate dehydrogenase (LDH) is an additional variable collected during screening.

[c] Refer to Appendix H.

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 that collect 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), abdomen, lymph nodes, thyroid, and respiratory, cardiovascular, musculoskeletal (including spine and extremities), and neurological systems.

Height will be measured during screening only. Physical examination and weight will be performed at timelines specified in the SoA (Table 1 and 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 (ideally to be taken before blood collection 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 at the visits indicated in the SoA (Table 1 and 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. The ECG will be done in triplicate only at screening, and if clinically indicated, thereafter. A standardized ECG machine should be used, and the patient should be examined using the same machine throughout the study, if possible.

After the 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 copy 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

An echocardiogram or MUGA to assess LVEF will be performed at the visits as shown in the SoA (Table 1 and Table 2) until completion of chemotherapy and pemetrexed maintenance treatment. 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 chemotherapy or pemetrexed maintenance, a 28-day follow-up assessment will be required to confirm reversibility of the abnormality. If a patient has had a MUGA or echocardiogram

performed within 28 days prior to treatment discontinuation, the discontinuation visit echocardiogram/MUGA is not required unless clinically indicated.

Refer to Appendix I for country-specific requirements in Germany.

8.2.6 WHO performance status

Performance status will be assessed at the scheduled visits indicated in the SoA (Table 1 and 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 or office work.

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

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

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

8.2.7 COVID-19 test

Patients will be tested for COVID-19 as clinically indicated and in accordance with local procedures. If available, nucleic acid and/or immunoglobulin (Ig)M/G tests will be performed.

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. Adverse events will be reported by the patient (or, when appropriate, by a caregiver, a surrogate, or the patient's legally authorized representative). Refer to Appendix I for country-specific requirements in Germany.

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

Adverse events will be collected from time of signature of ICF throughout the treatment period and including the 28-day follow-up period (28 days after last dose of IP).

Serious adverse events will be recorded from the time of signing of ICF. Serious adverse events considered related to study treatment and/or study procedures will be collected throughout progression follow-up. Serious adverse events considered related to study treatment will be collected throughout survival follow-up.

See Section 2.3.2.1 for rationale for safety data collection in the CSP.

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

Investigators are not obligated to actively seek AEs or SAEs 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 IP or study participation, the Investigator may notify AstraZeneca.

The method of recording, evaluating, and assessing the causality of AEs and SAEs and the procedures for completing and transmitting SAE reports 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 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 until the patient is lost to follow-up.

Any AEs that are unresolved at the patient's last AE visit in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AEs/SAEs at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum CTCAE grade
- Whether the AE is serious or not

- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- 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 serious AE
- Date Investigator became aware of serious AE
- Seriousness criteria met
- Date of hospitalization
- 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 causal relationship between each 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.

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 eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol-mandated laboratory tests and vital signs will be summarized in the clinical study report (CSR). Deterioration as compared with baseline in protocol-mandated vital signs (pulse and blood pressure), laboratory values, ECGs, or LVEF should therefore only be reported as AEs if they fulfill any of the SAE criteria or 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 vital signs (pulse and blood pressure), laboratory values, ECGs, or LVEF 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 term rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s). A list of mandated laboratory safety variables can be found in Table 6.

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 Sections 8.3.9 and 8.3.10).

8.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.9 Disease under study

Symptoms of 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 IP. See Appendix B for additional information.

8.3.10 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the 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.

See Appendix B for additional information.

8.3.11 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. See Appendix B for additional information.

8.3.12 Handling of deaths

All deaths that occur during the study or within the follow-up period after the administration of the last dose of 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 time frames.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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

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

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

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

Once the Investigators or other site personnel indicate that an AE is serious in the Electronic Data Capturing (EDC) system, an automated e-mail alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports an SAE via secure method to the appropriate AstraZeneca representative.

When the EDC is temporarily not accessible, the AstraZeneca Study Representative should confirm that the Investigator/site staff enters the SAE in the AstraZeneca EDC when access resumes.

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

The reference information for definitions of expectedness/listedness is contained in the AstraZeneca TAGRISSO™ (osimertinib) IB or in the current local labels approved by country for TAGRISSO™ (osimertinib), pemetrexed, carboplatin, and cisplatin.

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 AstraZeneca within 24 hours of learning of the pregnancy.

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

8.4.2.1 Maternal exposure

If a patient becomes pregnant during the course of 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 last dose of osimertinib, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours)** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) 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 Reporting of Overdose

A maximum tolerated dose has not been established for osimertinib, therefore in context of a clinical study, an overdose is any dose which exceeds the daily dose that is defined in the Clinical Study Protocol.

The maximum dose of each IP is as follows:

- 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 IP 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 should be 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 8.4.1). 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, drug abuse, and drug misuse

8.4.4.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel must inform the appropriate AstraZeneca representatives within **1 day** ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the relevant information is completed **within 1** (initial fatal/life-threatening or follow-up fatal/life-threatening) or **5 (**other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.4.1), and **within 30 days** for all other events.

8.4.4.2 Medication error

For the purposes of this clinical study, a medication error is an **unintended** failure or mistake in the treatment process for an IP/study treatment or AstraZeneca non-IP (NIP) that either causes harm to the patient or has the potential to cause harm to the patient.

The full definition and examples of medication error can be found in Appendix B 8.

8.4.4.3 Drug abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IP/study treatment or AstraZeneca NIP for perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 8.

8.4.4.4 Drug misuse

Drug misuse is the **intentional** and inappropriate use (by a study patient) of IP/study treatment or AstraZeneca NIP for medicinal purposes outside of the authorized product information, or for unauthorized IPs/study treatment(s) or AstraZeneca NIPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 8.

8.4.5 Management of IP-related toxicities

8.4.5.1 General dose adjustments for adverse events

Platinum-based chemotherapy in combination with pemetrexed is the SoC for patients with EGFRm NSCLC whose disease has progressed extracranially on 1L osimertinib, and in the context of this trial the combination of chemotherapy with osimertinib is considered an investigational treatment.

If appropriate, the Investigator may attribute each toxicity event to cisplatin/carboplatin, pemetrexed, osimertinib/placebo, or pre-treatments alone or to a combination of study treatments and use a stepwise dose modification for IPs according to Table 7, Table 8, Table 9, and Table 10. Dose modification can be implemented for 1, 2, or 3 of the IPs 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 IP (platinum agent, pemetrexed, or osimertinib/placebo) and the dose of that IP is delayed or modified in accordance with the guidelines below, the other IPs 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 or placebo treatment. If a patient experiences a toxicity associated with osimertinib or placebo that would cause a second dose reduction, osimertinib or placebo must be discontinued. If a dose reduction for toxicity occurs with any agent, the dose of that agent may not be re-escalated.

Patients receiving pemetrexed/cisplatin or pemetrexed/carboplatin with osimertinib or placebo who discontinue cisplatin alone or carboplatin alone may, at the Investigator's discretion, be switched to the alternative platinum agent with pemetrexed and osimertinib or placebo 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 or placebo who discontinue cisplatin or carboplatin can continue to receive pemetrexed with osimertinib or placebo if considered appropriate. Patients who discontinue platinum/pemetrexed or pemetrexed can continue to receive osimertinib or placebo alone if considered appropriate. Similarly, patients may discontinue osimertinib or placebo and continue on chemotherapy alone if appropriate. Chemotherapy may be interrupted for a maximum of 3 weeks (ie, 6 weeks since the last dose of chemotherapy); osimertinib or placebo 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 7 Dose Modifications for Investigational Products

	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

AUC=Area under the concentration-time curve.

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 will be administered as required in accordance with local practice/guidelines. If the toxicity does not resolve to < Grade 2 within 3 weeks of withholding osimertinib, investigational treatment must be permanently discontinued, and the patient should be observed until resolution of toxicity. If the toxicity resolves or reverts to CTCAE Grade ≤ 1 within 3 weeks of interruption of osimertinib, 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 8 and text below.

Table 8 Dose adjustment information for adverse reactions

Adverse reaction [a]	Dose modification
ILD/Pneumonitis	Permanently discontinue osimertinib
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 reduced dose (40 mg QD) 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) [b]
QT interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Stevens Johnson Syndrome; Toxic epidermal necrolysis	Permanently discontinue osimertinib
Aplastic anemia	Permanently discontinue osimertinib

Adverse reaction [a]	Dose modification
Grade 3 or higher non-hematological adverse reaction causally related to osimertinib	Withhold osimertinib for up to 3 weeks
If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of osimertinib for up to 3 weeks	Osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg)
Grade 3 or higher adverse reaction that 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

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

[b] Refer to Appendix I 2 for country-specific requirements in Italy.

ILD=Interstitial lung disease; QD=Once daily; QTc=corrected QT interval.

Information on Specific Adverse Events

ILD/Pneumonitis-like toxicity

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of ILD is observed, an interruption in IP 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 edema, or pulmonary hemorrhage. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, and hematological parameters) will be captured by the eCRF. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD/pneumonitis should be considered, and study treatment should be permanently discontinued.

QTc prolongation

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

Patients with QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation to > 500 msec should have osimertinib or placebo interrupted, and regular ECGs should be performed until resolution to < 481 msec or recovery to baseline if baseline QTcF is ≥ 481 msec and then osimertinib or placebo should be restarted at a reduced dose of 40 mg

QD 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.

Refer to Appendix I 2 for country-specific requirements in Italy.

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.

Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis

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

Changes in cardiac contractility (Cardiac failure)

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. In the placebo-controlled ADAURA study, 1.6% (5/312) of patients treated with osimertinib and 1.5% (5/331) of patients treated with placebo experienced LVEF decreased ≥ 10% and a decrease to < 50%. Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. In patients with cardiac risk factors, and those with conditions that can affect LVEF, cardiac monitoring, including assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring, including LVEF assessment, should be considered.

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

Aplastic anemia

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

Adverse events of special interest

- ILD/Pneumonitis-like toxicity
- Changes in cardiac contractility (Cardiac failure)

Permanent discontinuation due to toxicity

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

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 ≥ 100×10^9/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 9 and Table 10, with discussion and agreement with the AstraZeneca Study Team Physician as needed. Dose adjustments for hematological 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 7 and in the text below.

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

- ANC < 1.5×10^9/L
- Platelets < 100×10^9/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 $\geq 1.5 \times 10^9$/L
- Platelets $\geq 100 \times 10^9$/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, 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 9 and Table 10. The recommended dose modifications serve as a guide and do not replace Investigator judgment and applicable local label recommendations, if more stringent.

Table 9 Recommended dose modifications for chemotherapy-associated hematological toxicity (based on nadir counts)

Hematological toxicity	Pemetrexed	Cisplatin	Carboplatin
Platelet counts $\geq 50 \times 10^9$/L and ANC $\geq 0.5 \times 10^9$/L	500 mg/m^2	75 mg/m^2	AUC5 Maximum dose 750 mg
Platelet counts $\geq 50 \times 10^9$/L and ANC $< 0.5 \times 10^9$/L	375 mg/m^2	56 mg/m^2	AUC 3.75 Maximum dose 562.5 mg
Platelet counts $\leq 50 \times 10^9$/L without bleeding and any ANC result	375 mg/m^2	56 mg/m^2	AUC 3.75 Maximum dose 562.5 mg
Any platelets and febrile neutropenia a (CTCAE v5)	375 mg/m^2	56 mg/m^2	AUC 3.75 Maximum dose 562.5 mg
Platelet counts $\leq 50 \times 10^9$/L with CTCAE Grade ≥ 2 bleeding and any ANC result	250 mg/m^2	38 mg/m^2	AUC 2.5 Maximum dose 375 mg

[a] Febrile neutropenia defined as ANC $< 1 \times 10^9$/L and single temperature of > 38.3ºC (101º Fahrenheit) or a sustained temperature of $\geq$ 38ºC (100.4º Fahrenheit) for more than 1 hour.

ANC=Absolute neutrophil count; AUC=Area under the concentration-time curve; CTCAE=Common Terminology Criteria for Adverse Events.

Table 10 Recommended dose modifications for chemotherapy-associated non-hematological 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
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] CTCAE version 5.0.

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

AUC=Area under the concentration-time curve; CTCAE=Common Terminology Criteria for Adverse Events.

8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research sample is not collected and therefore not applicable in this study.

8.8 Human Biological Sample Biomarkers

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate

measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

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

8.8.1 Collection of optional biomarker analysis

Collection of optional samples for biomarker research (not applicable for China or if prohibited by local requirements) is also part of this study as specified in the SoA (Table 1) and is subject to agreement to optional consent.

Samples will potentially be tested for the following objectives:

- To collect and store plasma for research into factors CCI [redacted]
- Plasma samples may be used CCI [redacted]

A series of blood samples to generate plasma samples will be collected, then shipped via a central laboratory and stored at a BioBank. 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 Health economics

Health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

The primary analysis of PFS based on Investigator assessment (according to RECIST 1.1 for extracranial progression and CNS RECIST 1.1 for intracranial progression) was to occur when approximately CCI PFS events had been observed in the 204 randomized patients (approximately CCI % maturity, allowing for a possible CCI % drop out in the first 2 months) and at least CCI months after randomization of the last patient. This was expected to occur approximately CCI months after the first patient was randomized (under an assumed CCI -month non-linear recruitment). If the true PFS HR for the comparison of chemotherapy plus osimertinib versus chemotherapy plus placebo is CCI , CCI progression events will provide at least 80% 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 CCI months, assuming exponential distribution and proportional hazards. The critical HR is CCI , which translates to an approximate median PFS improvement from CCI months.

However, the sample size was reduced to approximately 80 patients due to treatment landscape changes which outpaced study recruitment.

The PFS DCO will occur when approximately 60 PFS events have been observed in the approximately 80 randomized patients (approximately 75% maturity), which is expected to occur during CCI. If the 75% maturity is achieved earlier, the DCO will take place earlier, providing it is at least CCI months after randomization of the last patient.

Due to the reduced sample size, the study will no longer be powered to perform a formal hypothesis test and therefore, a descriptive analysis for all PFS and OS endpoints will be carried out. The HR and 95% CI will be calculated and presented without any hypothesis testing (ie, p-value generation) for all PFS and OS endpoints.

A single analysis of OS will be carried out at the time of the PFS DCO.

9.2 Sample size determination

Approximately 204 patients were to be recruited and randomized in a 1:1 ratio (chemotherapy plus osimertinib:chemotherapy plus placebo) to this study; a possible CCI% drop out rate in the first 2 months was to be allowed for. However, the sample size was reduced to approximately 80 patients due to treatment landscape changes which outpaced study recruitment.

The primary endpoint of the study is PFS based on Investigator assessment (according to RECIST 1.1 for extracranial progression and CNS RECIST 1.1 for intracranial progression). Progression-free survival analysis was planned to be performed at approximately CCI months after the date of first patient enrollment. However, due to treatment landscape changes which outpaced study recruitment, the PFS DCO will occur when approximately 60 PFS events have been observed in the approximately 80 randomized patients (approximately 75% maturity), which is expected to occur during CCI. If the 75% maturity is achieved earlier, the DCO will take place earlier, providing it is at least CCI months after randomization of the last patient.

Sample size estimates have been calculated using EAST® version 6.5.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All patients who sign the ICF
Full analysis set	The full analysis set consists of all randomized patients.
Safety analysis set	The safety analysis set consists of all randomized patients who have received at least 1 dose of IP. Erroneously treated patients (eg, those randomized to Treatment A but actually given Treatment B) are accounted for in the treatment arm of the treatment they actually received.

ICF=Informed consent form; IP=Investigational product.

9.3.1 Full analysis set

The full analysis set (FAS) will include all randomized patients. The FAS will be used for all efficacy analyses with the exception of CCI [redacted] (which will be analyzed using a relevant subset of the FAS defined in the statistical analysis plan [SAP]), and treatment groups will be compared on the basis of randomized IP, regardless of the treatment actually received. This is also known as the Intent to Treat analysis set.

9.3.2 Safety analysis set

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

9.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalized before database lock and will describe the patient populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR. Depending on the extent of any impact, summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued the study treatment, COVID-19 testing results, and other protocol deviations) may be generated. More details will be provided in the SAP.

9.4.1 Efficacy analyses

All efficacy analyses will be performed on the FAS.

9.4.1.1 Progression-free survival

Progression-free survival is defined as the time from randomization until the date of objective disease progression (intracranial or extracranial, whichever occurs first) as assessed by the Investigator using RECIST 1.1 for extracranial progression and CNS RECIST 1.1 for intracranial 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 whose disease has 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/CNS 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/CNS RECIST assessment. Patients who have no evaluable visits or who do not have baseline RECIST/CNS RECIST data will be censored at 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 analysis of PFS will be performed at the PFS DCO when approximately 60 PFS events have been observed in approximately 80 randomized patients (approximately 75% maturity), which is expected to occur during CCI. If the 75% maturity is achieved earlier, the DCO will take place earlier, providing it is at least CCI months after randomization of the last patient. A single analysis of OS will be carried out at the time of the DCO for PFS.

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

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

At each visit, patients will be programmatically assigned RECIST 1.1 and CNS RECIST visit responses 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 analyzed using a log-rank test stratified by brain metastases (stable brain metastases based on CNS RECIST 1.1 assessments versus no brain metastases).

The HR and CI will be obtained directly from the U and V statistics as follows (Berry et al 1991, Robins and Tsiatis 1991, Robins 1993, Selke and Siegmund 1983):

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

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

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

If there are less than 20 events in one of the strata, for example less than 20 patients with stable brain metastases based on CNS RECIST 1.1 assessments at baseline, then the stratification variable will not be included in the log-rank test.

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 plot of PFS will be presented by treatment arm.

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

9.4.1.1.1 Sensitivity analyses

(a) 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/CNS RECIST assessment (using the final date of the assessment) will be analyzed 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.

(b) 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 whose disease has 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/CNS 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 HR and 95% CI will be provided to compare the primary and sensitivity analyses of PFS.

9.4.1.1.2 Subgroup analysis

In addition to the analysis of PFS described above, subgroup analyses will be conducted by comparing PFS between treatments (ie, using a Cox-Proportional Hazards Model) and will include, but not be limited to, the following subgroups. Additional information will be provided in the SAP.

- Brain metastases at baseline (as per stratified randomization)
- Age at screening (< 65 years, ≥ 65)

9.4.1.2 Analysis of secondary variables

9.4.1.2.1 Analysis of intracranial PFS (IC-PFS)

Intracranial PFS is defined as the time from randomization until the date of intracranial disease progression or death (from any cause). Patients who withdraw from randomized therapy and receive further non-study anti-cancer therapy will be censored at the

commencement of this therapy. If patients do not receive any other non-cancer therapy at study withdrawal, they will be followed up for IC-PFS.

The IC-PFS time will be derived based on scan/assessment dates.

Intracranial PFS will be evaluated based on CNS RECIST 1.1.

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

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

Intracranial PFS will be analyzed separately for patients with baseline brain metastases and patients without baseline brain metastases. Otherwise, IC-PFS will be analyzed as described for the primary analysis of PFS (see Section 9.4.1.1) with the exception of sensitivity analyses, which will not be conducted for secondary endpoints.

9.4.1.2.2 Analysis of extracranial PFS (EC-PFS)

Extracranial PFS is defined as the time from randomization until the date of objective disease progression specific to any region other than the intracranial region or death (from any cause).

Extracranial PFS will be analyzed as described for the primary analysis of PFS.

9.4.1.2.3 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 PFS DCO and if patients are confirmed to be alive or if the death date is after the DCO date, these patients will be censored at the date of the DCO. Death dates may be found by checking publicly available death registries. There will be no further survival follow-up after the PFS DCO.

A single analysis of OS will be carried out at the time of the DCO for PFS.

This study was not sized to detect a difference in OS between the 2 treatment arms; therefore, the analysis will not include statistical hypothesis testing. Kaplan-Meier estimates of median OS together with their 95% CIs will be calculated for each treatment arm. In addition, the number and percentage of patients surviving 1 and 2 years will be calculated using the Kaplan-Meier method (by randomized treatment arm).

9.4.1.3 Analysis of exploratory variables

Exploratory variables will be described in the SAP.

9.4.2 Safety analyses

All safety analyses will be performed on the SAS.

Safety and tolerability will be assessed in terms of AEs, vital signs (pulse and blood pressure [BP]), clinical laboratory assessments, ECGs, LVEF, and WHO PS. These will be collected for all randomized patients.

Adverse events

Adverse events (both in terms of Medical Dictionary for Regulatory Activities 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 28-day 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 judgment, 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 hematological 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.

9.5 Interim analyses

No interim analysis is planned for this study.

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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 as amended at 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013, and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, revised protocols, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocols will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned regulatory authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR) 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of patients and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All Suspected Unexpected Serious Adverse Reactions (SUSARs) to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

- Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after they become aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
- AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and Investigators.
  - If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency's (EMA's) Clinical Trials Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The Investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach.
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

A 2 Financial disclosure

Investigators and Sub-Investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca 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 study and for 1 year after completion of the study.

A 3 Informed consent process

- The Investigator or their representative will explain the nature of the study to the patient or their legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulation 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date and time the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If new information requires changes to the ICF, consider if patients must be re-consented, and if so, this must be 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.
- Patients who are rescreened are required to sign a new ICF. Any intention and embarkation of rescreening should be well communicated with AstraZeneca Study Team and the reason should be reflected in the medical records. Both the previous signed ICF and rescreened ICF should be retained in original copy at study site.
- The ICF will contain a separate section that addresses and documents the collection and use of optional human biological samples. The Investigator or authorized designee will explain to each patient the objectives of the analysis to be done on the samples and any potential future use. Patients will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

Refer to Appendix I 1 for country-specific requirements in Germany.

A 4 Data protection

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

- The patient must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The patient must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorized or does not have a business need to know the information.
- The patient must be informed that in some cases their data may be pseudonymized. The General Data Protection Regulation (GDPR) defines pseudonymization as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.
- Unless previously specified, the biomarker data will have unknown clinical significance and AstraZeneca will not provide biomarker assessment results to patient, their family members, any insurance company, any employer, a clinical study Investigator, a general physician, or any other third party, unless required to do so by law. The patient's samples will not be used for any purpose other than those described in the study protocol.

Personal data breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored, or otherwise processed.

- In compliance with applicable laws, the Data Controller[2] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches, it is important that Investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The Investigator should have a process in place to ensure that:

- Allow site staff or service providers delegated by the Investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

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

AstraZeneca and the site must demonstrate that they:

- Have taken all necessary steps to avoid personal data breaches and
- Have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining, and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- Where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- Where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal data breach to patients:

- Notification to patients is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the patients. The site and/or Principal Investigator shall conduct the notification by contacting the patients using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to patients. If the personal data breach needs to be notified to the patients, the notification to patients is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the patients.
- If a personal data breach involving an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the patients. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the patients. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal

information of the patients. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.

- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for co-ordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and patients, where applicable.

A 5 Committee structure

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

A Steering Committee Charter will define the primary responsibilities of the Trial Steering Committee for this study, its members, and the purpose and timing of meetings.

A 6 Dissemination of clinical study data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

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

A 7 Data quality assurance

- All patient data relating to the study will be recorded on the eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTL) will be predefined in the Data Surveillance Plan (or in an alternative plan) to identify systematic issues that can impact patient safety and/or reliability of study results. These predefined parameters will be monitored during the

study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical Monitoring Plan.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal (GRAD) schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.
- Data entered in the eCRF 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.
- Definition of what constitutes source data and its origin can be found in the Source Document Declaration. All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Study and site closure

- The study start date is the date on which the clinical study will be open for recruitment of patients.
- The first act of recruitment is the first site open and will be the study start date.
- The AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.
- The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by AstraZeneca or Investigator may include but are not limited to:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, AstraZeneca's procedures, or GCP guidelines
  - Inadequate recruitment of patients by the Investigator
  - Discontinuation of further study intervention development
- If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.
- The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings.
- In addition, COMPEL study will use FLAURA2 (NCT04035486) Independent Data Monitoring Committee safety observations or published study data for study-related decisions about risk/benefit ratio.

A 10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a co-ordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

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

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

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

Adverse events for malignant tumors reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the ‘important medical event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a non-SAE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples include stage 1 basal cell carcinoma and stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (ie, it is not the tumor for which entry into the study is a criterion and that is

being treated by the IP and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

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 medicinal 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 Hospitalization

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

B 5 Important medical event or medical treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous 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 hospitalization
- Development of drug dependency or drug abuse

B 6 Intensity rating scale: CTCAE

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

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 etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

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

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 patient.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the patient 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 patient
- Drug not administered as indicated, eg, wrong route, dose (error > ± 10%), or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong patient received the medication (excluding Interactive Response Technology [IRT]/Randomization and Trial Supply Management [RTSM] errors)
- Wrong drug administered to patient (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM -including those which led to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging

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

Drug abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IP/study intervention or AstraZeneca NIP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the data entry site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study patient or if the drug abuse regards a person not enrolled in the study (such as a relative of the study patient).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study patient or a person not enrolled in the study).
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study patient) of IP/study intervention or AstraZeneca NIP for medicinal purposes outside of the authorized product information, or for unauthorized IPs/study interventions or AstraZeneca NIPs, outside the intended use as specified in the protocol, and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study patient or if the drug misuse regards a person not enrolled in the study (such as a relative of the study patient).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person.
- The drug is sold to other people for recreational purposes.
- The drug is used to facilitate assault in another person.
- The drug is deliberately administered by the wrong route.
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole.
- Only half the dose is taken because the study patient feels that they were feeling better when not taking the whole dose.
- Someone who is not enrolled in the study intentionally takes the drug.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AZ-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

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 analyzed when AstraZeneca receives notification of consent withdrawal, AstraZeneca is not obliged to destroy the results of this research.

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 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

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content.

Appendix D Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

D 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law (PHL) and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

Specific guidance on managing liver abnormalities can be found in Section 8.2.1 of the Clinical Study Protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits. For example, PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated total bilirubin (TBL) from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the IP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law (PHL)
Aspartate transaminase (AST) or alanine transaminase (ALT) ≥ 3 × ULN together with TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

D 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see Section D 2 within this appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

D 4 Follow-up

D 4.1 Potential Hy's Law criteria not met

If the patient does not meet PHL criteria the Investigator will perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

D 4.2 Potential Hy's Law criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section D 6 of this appendix).
- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'important medical event' and causality assessment 'yes/related' according to clinical study protocol (CSP) process for SAE reporting.

- For patients that met PHL criteria prior to starting IP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the patient's condition.
- The study physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patient' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the study physician.
  - Complete the 3 Liver CRF Modules as information becomes available.

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the study physician if there is any uncertainty.

D 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the study physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria were met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF.

- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on-study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (eg, chronic or progressing malignant disease, severe infection, or liver disease)

If No: Follow the process described in Section D 4.1 of this appendix for reporting PHL as an SAE.

If Yes: Determine if there has been a significant[#] change in the patient's condition compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in Section D 4 of this appendix for reporting PHL as an SAE.

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the study physician if there is any uncertainty.

D 7 Laboratory tests

Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgG anti-HCV HCV RNA * IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgM and IgG anti-HSV IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) **
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive

** Carbohydrate deficient transferrin (CD-transferrin) is not available in China.

Anti-CMV=cytomegalovirus antibody; anti-EBV=Epstein Barr virus antibody; anti-HBc=hepatitis B core antibody; anti-HSV-herpes simplex virus antibody; DNA=deoxyribonucleic acid; GGT=Gamma glutamyl transferase; HAV=Hepatitis A virus; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HEV=hepatitis E virus; Ig=immunoglobulin; INR=International Normalized Ratio; LDH=lactate dehydrogenase; RNA= ribonucleic acid.

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

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1) guidelines (Eisenhauer et al 2009). Investigator assessments will use the RECIST 1.1 guidelines described in this appendix for intracranial and extracranial reads separately (see also Section 8.1.2).

Imaging modalities and acquisition specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of Target Lesions (TLs), Non-Target Lesions (NTLs), and New Lesions (NLs) is provided in Table 11.

Table 11 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 (Scintigraphy)
		FDG-PET/CT

CT=Computed tomography; FDG-PET/CT=18F-Fluoro-deoxyglucose positron emission tomography/CT; MRI=Magnetic resonance imaging.

CT and MRI

Computed tomography (CT) with intravenous (IV) contrast is the preferred imaging modality (although magnetic resonance imaging [MRI] with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for extracranial tumor assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumor assessor (eg, radiologist), 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 is recommended, if possible. It is important to follow the image collection/tumor assessment schedule as closely as possible (refer to the Schedule of Activities [SoA; Table 1 and Table 2]), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient's disease has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice for extracranial scans. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artifacts (eg, heart, major blood vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions and is the preferred modality for brain imaging. 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. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. However, recommended MRI sequences for brain imaging pre-contrast administration include:

- Localizer/Scout
- T1-weighted (≤ 1.5 mm slice thickness)
- FLAIR
- T2-weighted

Suggestions for gadolinium contrast injection are: 0.1 mmol/kg or 0.2 mL/kg (20 mL maximum) via rapid hand injection + 10 mL saline flush. Ideally 20 G venous access.

Recommended sequences post-contrast include:

- T1-weighted
- FLAIR

with sequences identical to pre-contrast.

A diffusion-weighted (DW) MRI scan is optional.

The most critical CT and MRI image acquisition parameters for optimal tumor evaluation are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most extracranial solid tumors is the chest-abdomen (and if possible, 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.

Required anatomical regions to be imaged for assessment of tumor burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these timepoints are specified in the SoA (Table 1 and Table 2). Examples include the following:

- IV contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands)
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including the entire liver and both adrenal glands)
- IV contrast-enhanced CT or MRI of the head and neck
- IV contrast-enhanced MRI (preferred) or CT of the brain

For chest-abdomen imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when patients have sensitivity to IV contrast or have compromised renal function:

1 Chest-abdomen CT with IV CT contrast (most preferred)
2 Chest CT without IV contrast + abdomen MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study
3 Chest-abdomen CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the patient has compromised renal function
4 Chest-abdomen MRI with IV MRI contrast, if CT cannot be performed at any time during the study

b. IV contrast administration: Optimal visualization and measurement of metastases in solid tumors require 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 extracranial CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤ 5-mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses > 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

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 TL should be measured on the same window setting for repeated examinations throughout the study.

Chest X-ray

Chest X-ray assessment will not be used for the assessment of TLs. Chest X-ray can, however, be used to assess NTLs and to identify the presence of NLs. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTLs 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 NTLs and followed by the same method 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 that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a progressive disease (PD) assessment at that time point.

18FDG-PET/CT

18F-Fluoro-deoxyglucose positron emission tomography/CT (18FDG-PET/CT) scans may be used as a method for identifying new extrahepatic lesions (but not intrahepatic lesions) for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is positive 18F-Fluoro-deoxyglucose uptake[3] not present on baseline or prior 18FDG-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the 18FDG-PET scan. 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 18FDG-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 to verify the unequivocal presence of NLs.

At present, low dose or attenuation correction CT portions of a combined 18FDG-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

[3] 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 CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumor assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

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 the 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 for tumor assessments 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, and 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.

Furthermore, an overall assessment of complete response (all other disease disappears/reverts to normal) would be changed to partial response if an effusion remains present radiologically.

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[4] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. Please

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

see additional RECIST 1.1 guidance below on measurability of intrahepatic hepatocellular carcinoma lesions and porta hepatis lymph nodes.

Non-measurable lesions at baseline:

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component)
  - Leptomeningeal disease (all lesions to be recorded as one group in the intracranial assessment)
  - Ascites, pleural effusion, 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[5])
- Previously irradiated lesions[6]

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 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.

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

[6] Localized post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

RECIST 1.1 TL selection at baseline:

A maximum of 5 measurable lesions, with a maximum of 2 lesions per extracranial organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TLs at baseline. For the intracranial RECIST assessment, Investigators are allowed to select up to 5 lesions as TLs to enable a more robust quantification of change in measurable lesions. Cystic lesions will not be selected as intracranial TLs. Cystic lesions thought to represent cystic metastases may be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. Skull lesions and lesions outside the CNS should not be part of the intracranial assessment. Target lesions 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 that 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 nodes 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 TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases for TL assessment at baseline:

- For TLs 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.
- Tumor lesions selected for fresh screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a 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 a New Lesion.

RECIST 1.1 NTL 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.

No intracranial disease at baseline:

If the Investigator does not identify any disease at baseline within the brain (target or non-target lesions), he/she will be required to confirm that no lesions were identified.

Evaluation of tumor response and progression

RECIST 1.1 TL 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 TLs 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 TL 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, the sum of the diameters of those parts should be recorded.
- 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 separable 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.
- 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 (eg, definitive radiotherapy, embolization, surgery, transarterial chemoembolization, etc) during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 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.

Table 12 RECIST 1.1 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 the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
Progressive 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 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 PD criteria, PD overrides not evaluable as a TL response.
Not applicable (NA)	Only relevant if no TLs present at baseline.

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

RECIST 1.1 NTL assessment at follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs 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 SD or PR in TLs, the overall tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest ‘increase’ in the size of 1 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 SD or PD of target disease will therefore be extremely rare.

Table 13 RECIST 1.1 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 1 or more NTLs.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 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 1 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.
Not applicable (NA)	Only relevant if no NTLs present at baseline

CR=Complete response; NE=Not evaluable; NTL=Non-target lesion; PD=Progressive disease; TL=Target lesion.

RECIST 1.1 NL identification at follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the case report form. The presence of 1 or more NLs is assessed as progression. The finding of a 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 a 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

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs for RECIST 1.1 and CNS RECIST 1.1 uses the algorithm shown in Table 14.

Table 14 RECIST 1.1 overall visit response

Target Lesions	Non-Target Lesions	New Lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
NA *	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE or NA	No	PR
SD	Non-PD or NE or NA	No	SD
NA *	Non-CR/Non-PD	No	SD (Non-CR/Non-PD) *
NE	Non-PD or NE	No	NE
NA *	NE	No	NE
NA *	NA	No	NED *
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* Only applicable for intracranial (CNS) RECIST assessment per inclusion criteria requiring at least one non-CNS Target Lesion.

Note: Non-CR/Non-PD for Overall Response if only non-target lesions (no TLs) are present at baseline.

Note: An overall assessment of Complete Response (all other disease disappears/reverts to normal) would be changed to Partial Response if ascites remains present radiologically.

CR=Complete response; NA=Not applicable (only relevant if there were no target lesions at baseline or non-target lesions at baseline), NE=Not evaluable; NED=No evidence of diseases (only relevant if there were neither target lesions nor non-target lesions at baseline); PD=Progressive disease; PR=Partial response; SD=Stable disease; TL=Target Lesion.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For patients with TLs (at baseline): CR, PR, SD, PD, or NE
- For patients with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE
- For patients with no disease at baseline: NED (no evidence of disease; available as an option in the eCRF), PD, or NE

Central imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging Contract Research Organization (iCRO) for quality control and storage; no BICR of these scans is currently planned. Digital copies of all original scans should be stored at the Investigator site as source documents. Electronic image transfer from

the sites to the iCRO is strongly encouraged. The management of patients will be based upon the results of the tumor assessments conducted by the Investigator.

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 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.

F 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 (phenobarbitone), phenytoin, rifampicin, rifabutin, rifapentine, St John's Wort	3 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Contact AstraZeneca with any queries you have on this issue.

F 2 Medicines whose exposures may be affected by osimertinib that AstraZeneca considers may be allowed with caution

Osimertinib may increase the concentration of sensitive breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) substrates (concentration of the sensitive BCRP substrate, rosuvastatin and sensitive P-gp substrate, fexofenadine, are increased).

Exposure, pharmacological action, and toxicity may be increased by osimertinib

Warning of possible interaction	Advice
Rosuvastatin	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Refer to full prescribing information for all drugs prior to co-administration with IP.
Sulfasalazine	
Doxorubicin	
Daunorubicin	
Topotecan	
Dabigatran	
Aliskiren	
Digoxin	

IP=investigational product.

F 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 against the ArizonaCert website.

In addition, drugs intended for use during IP administration should be checked against the website.

F 3.1 Drugs with a known risk of TdP

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.

F 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.

F 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 2 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
aclarubicin, anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine terlipressin	2 days
cilostazol, cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days
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 [b], 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] Estimated value as pharmacokinetics of arsenic trioxide has not been studied.

F 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 CLQTS are excluded from this study.

F 3.3 Guidance regardless of TdP risk category

During study treatment and for a period of 2 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 G 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, 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 luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the post-menopausal range.
  - Women aged 50 years or more will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments.

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 patient 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 IUS (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
- All progesterone only pills except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing IUDs
- Fertility awareness methods
- Coitus interruptus

Appendix H Calculated Creatinine Clearance

Creatinine clearance (CrCl) 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:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}^{b}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}^{b}) \times 0.85}{0.81 \times \text{serum creatinine (µmol/L)}}$$

[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.

References:

Cockcroft and Gault 1976
Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.

Doolan et al 1962
Doolan PD, Alpen EL, Theil GB. A clinical appraisal of the plasma concentration and endogenous clearance of creatinine. Am J Med 1962; 32:65.

Appendix I Country-specific Requirements

I 1 Country-specific Requirements for Germany

Section 1.1 Schedule of Activities

Table 1 and Table 2, subsections 'Routine clinical procedures', column 1:

Revised text

Visit
Day
Week
Window (days)
[…]
Routine clinical procedures [d]
[…]
Echocardiogram~~/MUGA~~

Table 1 footnote 'i' and Table 2 footnote 'e':

Revised text

Echocardiogram~~/MUGA~~ assessment to be completed at this frequency until completion of chemotherapy and pemetrexed maintenance treatment. If the last on-treatment echocardiogram~~/MUGA~~ assessment is abnormal, a follow up assessment is required.

Table 1 footnote 'j' and Table 2 footnote 'f':

Revised text

If a patient had ~~a MUGA or~~ an echocardiogram performed within 28 days prior to treatment discontinuation, the discontinuation visit echocardiogram~~/MUGA~~ is not required unless clinically indicated.

Section 7.1.2 Treatment through progression

Revised text

Patients who continue treatment following progression should maintain the SoA as shown below:

- 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, ECGs, and echocardiogram~~/Multi-Gated Acquisition Scan [MUGA]~~) and concomitant medications

Section 8.2.5 Echocardiogram

Revised text

8.2.5 Echocardiogram~~/MUGA~~

An echocardiogram ~~or MUGA~~ to assess LVEF will be performed at the visits as shown in the SoA (Table 1 and Table 2) until completion of chemotherapy and pemetrexed maintenance treatment. 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 chemotherapy or pemetrexed maintenance, a 28-day follow-up assessment will be required to confirm reversibility of the abnormality. If a patient has had an ~~MUGA or~~ echocardiogram performed within 28 days prior to treatment discontinuation, the discontinuation visit echocardiogram~~/MUGA~~ is not required unless clinically indicated.

Section 8.3 Collection of adverse events

Revised text

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

Appendix A 3 Informed consent process

Revised text

- The Investigator or their representative will explain the nature of the study to the patient ~~or their legally authorized representative~~ and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. 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, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.
- […]
- A copy of the ICF(s) must be provided to the patient~~ or the patient's legally authorized representative~~.

I 2 Country-specific Requirements for Italy

Section 8.4.5.1.1 Dose adjustment information for osimertinib

Revised text

QTc prolongation

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

Patients with QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation to > 500 msec should have osimertinib or placebo interrupted, and regular ECGs should be performed until resolution to < 481 msec or recovery to baseline if baseline QTcF is ≥ 481 msec and then osimertinib or placebo should be restarted at a reduced dose of 40 mg QD ~~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.

Table 8

Revised text

Table 8 Dose adjustment information for adverse reactions

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 reduced dose (40 mg QD) ~~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)

Appendix J Abbreviations

Abbreviation or special term	Explanation
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
Anti-CMV	cytomegalovirus antibody
Anti-EBV	Epstein Barr virus antibody
Anti-HBc	hepatitis B core antibody
Anti-HSV	herpes simplex virus antibody
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BICR	Blinded Independent Central Review
CFR	Code of Federal Regulation
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLQTS	congenital long QT syndrome
CNS	central nervous system
COVID-19	Coronavirus disease 2019
CR	complete response
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 Events
ctDNA	circulating tumor deoxyribonucleic acid
CTIS	Clinical Trials Information System
CYP	cytochrome P450
DCO	data cut-off
DES	data entry site
DILI	Drug-induced liver injury
DNA	deoxyribonucleic acid

Abbreviation or special term	Explanation
EC-PFS	extracranial progression-free survival
eCRF	electronic case report form
EDC	Electronic Data Capturing
EGFR	epidermal growth factor receptor
EGFRm	epidermal growth factor receptor mutation-positive
EM	erythema multiforme
ESMO	European Society for Medical Oncology
EU	European Union
Ex19del	exon 19 deletions
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	gamma glutamyl transferase
GRAD	Global Retention and Disposal
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL	Hy's Law
HR	hazard ratio
HRCT	high-resolution computed tomography
IASLC	International Association for the Study of Lung Cancer
IATA	International Airline Transportation Association
IB	Investigator's Brochure
IC-PFS	intracranial progression-free survival
CCI	CCI
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobulin
ILD	interstitial lung disease
INR	International Normalized Ratio
IO	immune-oncology

Abbreviation or special term	Explanation
IP	investigational product: refers to osimertinib, placebo, or chemotherapy/pemetrexed
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intra-uterine device
IUS	intra-uterine system
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LDH	lactate dehydrogenase
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
MUGA	Multi-Gated Acquisition Scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NIP	non-investigational product
NL	new lesion
NSCLC	non-small cell lung cancer
NTL	non-target lesion
OAE	other significant AE
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PHL	potential Hy's Law
PR	partial response
PS	performance status
PSSR	Project Specific Safety Requirements
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTL	quality tolerance limit

Abbreviation or special term	Explanation
QxW	every X weeks
RANO	Response Assessment in Neuro-Oncology
RBC	Red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RNA	ribonucleic acid
RTSM	randomization and trial supply management
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	stable disease
SJS	Stevens-Johnson syndrome
SoA	Schedule of Activities
SoC	standard of care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TdP	Torsades de Pointes
TEN	Toxic epidermal necrolysis
TKI	tyrosine kinase inhibitor
TL	target lesion
ULN	upper limit of normal
US	United States of America
VATS	video-assisted thoracoscopic surgery
WBC	White blood cell
WHO	World Health Organization
WoCBP	Women of Childbearing Potential

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