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)

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ASA	American Statistical Association
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CNS	Central Nervous System
CNS RECIST	Central Nervous System Response Evaluation Criteria in Solid Tumors
CR	Complete Response
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database Lock
DBP	Diastolic Blood Pressure
DCO	Data Cut-off
DP	Decimal Places
ECG	Electrocardiogram
EC	Extracranial
EC-PFS	Extracranial Progression Free Survival
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
COVID-19	Corona Virus Disease-2019
eCRF	Electronic Case Report Form

FAS	Full Analysis Set
HB	Hemoglobin
HR	Hazard Ratio
IC	Intracranial
ICF	Informed Consent Form
ILD	Interstitial Lung Disease
CCI	CCI
CCI	CCI
IC-PFS	Intracranial Progression Free Survival
CCI	CCI
IP	Investigational Product
IPD	Important Protocol Deviation
ITT	Intent to Treat
IV	Intravenous
IVRS	Interactive Voice Recording System
LD	Longest Diameter
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MUGA	Multi-Gated Acquisition Scan
NA	Not applicable
NE	Not evaluable
NED	No Evidence of Disease
NSCLC	Non-Small Cell Lung Cancer
NTL	Non-target Lesion
OAE	Other Significant Adverse Event
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free survival
PR	Partial Response
PS	Performance Status
PT	Preferred Term
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors

SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Stable Disease
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TL	Target Lesion
TNM	Tumor, Node and Metastasis
TKI	Tyrosine Kinase Inhibitor
WHO	World Health Organization
WHO/ECOG PS	World Health Organisation/Eastern Cooperative Oncology Group Performance Status

AMENDMENT HISTORY

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	Click or tap here to enter text.	Initial approved SAP	N/A	N/A
Primary endpoint(s)	22 Nov 2023	Timing of analysis changed in section 3.1 and 4.2.1.4	Yes	CSP updated
Primary endpoint(s)	22 Nov 2023	P-value removed from log rank test in section 4.2.1.4 and 4.2	Yes	CSP udpated, as the study is no longer powered for a formal comparison.

1 INTRODUCTION

The purpose of the document is to give details for the statistical analysis of study D5162C00042 supporting the clinical study report. The reader is referred to the V5.0 of clinical study protocol (CSP) and the case report form (CRF) for details of objectives, study design, study conduct and data collection.

The study design schema is presented in Figure 1 and Schedule of Activities (SoA) are presented in Table 1 and Table 2 of CSP.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

Approximately 204 patients were to be recruited and randomised 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 has been reduced to approximately 80 patients due to treatment landscape changes which outpaced study recruitment.

The primary analysis of progression-free survival (PFS) based on Investigator assessment (according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for extracranial progression and central nervous system (CNS) RECIST 1.1 for intracranial progression) was planned to be performed at approximately CCI months after the date of first patient randomised. However, due to treatment landscape changes which outpaced study recruitment, the PFS data cut off date (DCO) will occur when approximately 60 PFS events have been observed in the approximately 80 randomised 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 randomisation of the last patient.

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

3.2 Analysis Populations

For purposes of analysis, the following populations are defined:

Table 1 Study Population

Population	Description
Enrolled	All patients who sign the informed consent form (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 investigational product (IP). Erroneously treated patients (eg, those randomized to Treatment A but actually given Treatment B) are accounted for in the treatment group of the treatment they actually received.

Full Analysis Set

The full analysis set (FAS) will include all randomized patients. The FAS will be used for all efficacy analyses and treatment groups will be compared on the basis of randomized IP, regardless of the treatment actually received. Patients who were randomised but did not subsequently receive treatment are included in the FAS. The analysis of data using the FAS therefore follows the principles of Intention to Treat (ITT) .

The FAS will be used for all efficacy analyses with the exception of CCI [redacted] (which will be analyzed using the subset of FAS defined in section 4.2.5.1), and treatment groups will be compared on the basis of randomized treatment group, regardless of the treatment actually received.

Safety Analysis Set

The safety analysis set 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 first treatment received (eg, a patient who is randomized to chemotherapy plus osimertinib but who received chemotherapy plus placebo as their first dose will be summarized under the chemotherapy plus placebo group).

3.3 General Considerations

- Continuous variables will be summarized by the number of observations (n), mean, standard deviation, median, lower and upper quartiles where indicated, minimum, and maximum.
- For the continuous data, the summary statistics will be displayed with the following accuracy (number of decimal places (dps)):

- The minimum and maximum with same accuracy as the raw data.
- The mean and median will be rounded to 1 additional dp more than the number of dps in the raw data.
- The standard deviation will be rounded to 2 additional dps more than the number of dps in the raw data.
- If the number of observations is 1, the standard deviation will not be derived.

- Categorical variables will be summarized by frequency counts and percentages for each category and percentages will be rounded to one dp.
- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment group. Overall totals will be calculated for baseline summaries only. SAS® version 9.4 or higher will be used for all analyses.
- Exact CIs for proportions will be calculated using the Clopper-Pearson method.
- For percentiles of survival times based on the Kaplan-Meier method (eg, median survival), CIs will be calculated using the default method available in the SAS LIFETEST procedure (ie, the Klein and Moeschberger extension of the Brookmeyer-Crowley method).
- For point-estimates of survival based on the Kaplan-Meier method (eg, for PFS), CIs will be calculated using the default method available in the SAS LIFETEST procedure (ie, using Greenwood's estimate of standard error and a log-log transformation).
- If relevant for the study, the following will be included due to the COVID-19 pandemic: participants affected by the COVID-19 pandemic will be listed including category for study disruption due to the pandemic and details of the disruption. If required, the study disruptions due to the pandemic will also be summarized. Subject disposition will be summarized including number (%) of participants who discontinued treatment due to the pandemic and who withdrew from study due to the pandemic. Important protocol deviations will be summarized including number (%) of participants with at least one important protocol deviation related to the pandemic.

3.3.1 General Study Level Definitions

Study Day Definition

Study Day 1 is defined as the date of first dose of study treatment. For visits (or events) that occur on or after first dose, study day is defined as (date of visit [event] - date of first dose of study treatment + 1). For visits (or events) that occur prior to first dose, study day is defined as (date of visit [event] - date of first dose of study treatment). There is no Study Day 0.

For listings (such as for AEs) that include the derivation of "days since last dose," this is defined as (event date - date of last dose). Events that occur on the same day as the last dose

of study drug will therefore be described as occurring zero days from the last dose of study drug.

Baseline measurements and change from baseline derivation

In general, for efficacy endpoints the last observed measurement prior to randomisation will be considered the baseline measurement. Baseline for safety assessments will generally be the last value obtained prior to the first dose of study medication. Alternatively, if two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose with no washout or other intervention in the screening period), the average can be taken as a baseline value. For non-numeric laboratory tests (i.e. some of the urinalysis parameters) where taking an average is not possible then the best value would be taken as baseline as this is the most conservative. In the scenario where there are two assessments on day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. For % change from baseline, calculate as:

$$\frac{(\text{post-baseline value} - \text{baseline value})}{\text{baseline value}} \times 100$$

Imputation of missing dates

Missing start date/end date will be imputed for concomitant medication or AEs for the purpose of identifying them as treatment emergent. The rules are described below:

If the start date of the concomitant medication or AE is missing, the following rules will be applied:

- If the year is available and the month and day are missing, then impute the month as January and the day as 01.
- If the year and month are available and the day is missing, impute the day as 01 (the first day of the month).
- If the start date is completely missing, impute as the first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

If the stop date of the concomitant medication or AE is missing, the following rules will be applied:

- If the year is available and the month and day are missing, then impute the month as December and the day as 31, unless this is after the date of death in which case date of death will be used instead.
- If the year and month are available and the day is missing, impute the day as the last day of the month (eg, 28, 29, 30 or 31), unless this is after the date of death in which case date of death will be used instead.

Imputation of safety data

Missing safety data will generally not be imputed. However, safety assessment values of the form of "<x" (ie, below the lower limit of quantification) or >x (ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings.

Imputation of date of death

If a patient is known to have died where only a partial death date is available then the date of death will be imputed as:-
a. For Missing day only – using the 1st of the month
b. For Missing day and Month – using the 1st of January
unless this date is before the last date the patient is known to be alive then the date of death will be imputed as the last date known to be alive +1.
If death has been recorded but the date is entirely missing, then date of death will be imputed as the date the patient was last known to be alive +1.

Derivation of RECIST Visit Responses

The baseline assessment is part of the screening procedures and ideally should be performed as close as possible to and prior to randomization (the scan should be obtained within 28 days before randomization).

Efficacy assessment of progression free survival (PFS) (including whole-body PFS [intracranial or extracranial, whichever occurs first], intracranial PFS (IC-PFS), and extracranial PFS (EC-PFS)) will be derived using RECIST 1.1 for extracranial progression and CNS RECIST 1.1 for intracranial progression based on Investigator evaluations.

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 of CSP) on images from CT (preferred for the chest and abdomen) or MRI (preferred for the brain) with IV contrast, collected during screening. 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. 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, with the exception of patients who receive open-label osimertinib following initial intracranial progression whilst on placebo. These patients will continue intracranial (brain) tumor assessments every 6 weeks (±1 week), relative to randomization until their second intracranial progression. Tumor assessments will be done on this schedule even if a patient discontinues treatment prior to progression or receives other anti-cancer treatment.

If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

From the investigator's review of the imaging scans, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST version 1.1 and CNS RECISIT 1.1. At each visit, patients will be programmatically assigned a visit response of complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), using the information from target lesions (TLs), non-target lesions (NTLs) and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumor assessment which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

RECIST outcomes (ie, PFS and ORR etc.) will be calculated programmatically from site investigator data from overall visit responses.

Site Investigator Assessments Using RECIST 1.1

Target Lesions

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥10 mm in the longest diameter (LD), (except lymph nodes which must have short axis ≥15 mm) with IV contrast-enhanced CT or MRI and which is suitable for accurate repeated measurements.

A maximum of five measurable lesions (with a maximum of two lesions per organ for extracranial RECIST 1.1), representative of all lesions involved and suitable for accurate repeated measurement, should be identified as TLs at baseline. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement. In which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

If more than one baseline scan is recorded, then measurements from the one that is closest and prior to randomization will be used to define the baseline sum of TLs.

All other measurable lesions not recorded as TL, and all non-measurable lesions (or sites of disease) should be identified as non-target lesions (NTLs) at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

For patients who do not have measurable disease at entry (ie, no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions. If a patient does not have measurable disease at baseline, then the TL visit response will be not applicable (NA).

Table 2 Target Lesion Visit Responses

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 as long as criteria for PD are not met.
Stable disease (SD)	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir). This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.
Not applicable (NA)	Only relevant if no TLs present at baseline.

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

Rounding of Target Lesion Data

For calculation of PD and PR for TLs, percentage changes from baseline and previous minimum should be rounded to 1 decimal place (dp) before assigning a target lesion response. For example, 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%

Missing TL Data

For a visit to be evaluable then all target lesion measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred

- A new lesion is recorded
- A NTL visit response of PD is recorded
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm, from nadir even assuming the non-recorded TLs have disappeared

Note: the nadir (i.e., the smallest measurement based on the same set of lesions at baseline and on a given visit) can only be taken from assessments where all the TLs had a LD recorded.

If there is at least one TL measurement missing and a visit response of PD cannot be assigned, the visit response is NE.

If all TL measurements are missing, then the TL visit response is NE. Overall visit response will also be NE, unless there is a progression of non-TLs or new lesions, in which case the response will be PD.

Lymph Nodes

For lymph nodes, if the size reduces to <10mm then these are considered non-pathological. However, a size will still be given, and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are <10mm and all other TLs are 0mm then although the sum may be > 0mm the calculation of TL response should be over-written as a CR.

Target Lesion Visit Responses Subsequent to Complete Response

A CR response can only be followed by CR, PD or NE. If a CR has occurred, then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (ie, 0mm or <10mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met ie, if a lymph node LD increases by 20% but remains <10mm.
- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (ie, 0mm or <10mm for lymph nodes) then response will be set to NE irrespective of whether when referencing the sum of TL diameters, the criteria for PD is also met.
- Step 3: If not all lesions meet the CR criteria (i.e. a pathological lymph node selected as TL has short axis > 10mm or the reappearance of previously disappeared lesion) or a new lesion appears then response will be set to PD
- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR

Target Lesion Too Big to Measure

If a target lesion becomes too big to measure this should be indicated in the database and a size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of target lesion response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team blinded to treatment assignment. It is expected that a visit response of PD will remain in the vast majority of cases.

Target Lesion Too Small to Measure

If a TL becomes too small to measure, then this will be indicated as such on the case report form and a value of 5mm will be entered into the database and used in TL calculations. However, a smaller value may be used if the radiologist has not indicated 'too small to measure' on the case report form and has entered a smaller value that can be reliably measured. If a TL response of PD results, then this will be reviewed by the study team blinded to treatment assignment.

Irradiated Lesions/Lesion Intervention

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention in addition to study treatment during the study (eg, irradiation / palliative surgery / embolization), should be handled in the following way and once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumors:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.
- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.
- Step 3: If, after both steps, PD has not been assigned, then, if appropriate (ie, if ≤1/3 of the TLs have missing measurements), the scaled sum of diameters calculated in step 2 should be used, and PR or SD then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10mm for lymph nodes) and the lesions that have been subject to intervention have a value of 0 (or <10mm for lymph nodes) recorded. If scaling up is not appropriate due to too few non-missing measurements, then the visit response will be set as NE.

At subsequent visits the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2 above).

Scaling of the Sum of Target Lesions

Scaling of the sum of target lesion diameters is used when one or more target lesion diameter is missing because of on-study target lesion intervention.

If > 1/3 of target lesion measurements are missing (because of intervention) then target lesion response will be NE, unless the sum of diameters of non-missing target lesion would result in PD (ie, if using a value of 0 for missing lesions, the sum of diameters has still increased by 20% or more compared to nadir and the sum of target lesions has increased by ≥ 5mm from nadir).

If ≤1/3 of the target lesion measurements are missing (because of intervention) then the results will be scaled up based on the sizes at the nadir visit to give an estimated sum of diameters and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

Example of Scaling

Lesion	Longest diameter (mm) at nadir visit	Longest diameter (mm) at follow-up visit
1	16	18
2	14	16
3	14	16
4	18	18
5	12	Intervention
Sum	**74**	**68**

Lesion 5 has had an intervention at the follow-up visit. The sum of the Baseline measures is 74 mm. The sum of lesions 1-4 at the follow-up is 68 mm. The sum of the corresponding lesions at nadir visit is 62 mm. Scale up as follows to give an estimated follow-up visit TL sum of 81mm:

$$\frac{68}{62} \times 74 = 81mm$$

Lesions that Split in Two or more Parts

If a TL splits in two or more parts, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that Merge

If two or more target lesions merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL sizes should be recorded as 0mm.

Change in Method of Assessment of Target Lesions

CT and MRI are the only methods of assessment that can be used within this trial for the assesment of TLs. If a change in method of assessment between CT and MRI occurs this will be considered acceptable and no adjustment within the programming is needed.

Note, if a change in method involves clinical examination (eg, CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

Non-Target Lesions and New Lesions

At each visit an overall assessment of the NTL response should be recorded by the investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.Non-target lesion response will be derived based on the Investigator's overall assessment of NTLs as follows:

Table 3 NTL Visit Responses

Visit Responses	Description
Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of one or more NTLs with no evidence of progression.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable (NA)	Only relevant if there are no NTLs at baseline.

CR: Complete response; NA: Not applicable; NE: Not evaluable; NTL non-target lesion; PD: Progressive disease; TL: target lesion.

To achieve 'unequivocal progression' based on NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in TLs, the overall tumor burden has increased sufficiently to merit a determination of disease

progression. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression, so the overall visit response will be PD irrespective of the TL and NTL response.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present, and should be queried.

Symptomatic deterioration is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumor assessments where possible until objective disease progression is observed.

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.

For patients with no evidence of disease in the brain (NED ie, no TLs and no NTLs), evaluation of overall visit responses will be based on absence/presence of new lesions. If no TLs and no NTLs are recorded at a visit, both the TL and NTL CNS visit response will be recorded as NA and the overall CNS visit response will be NED.

Overall Visit Response

Table 4 Overall Visit Response defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 4 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.

3.3.2 Visit Window

For visit-based summaries of vital signs, laboratory data and ECG data, visits will be assigned to calculated 'analysis' visit windows (using study day) in the following way:

The time windows should be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the visit window should be based on the actual date and not the intended date of the visit. For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit-based summary, when deriving a patient level statistic such as a maximum.

The window for the visits following baseline (including unscheduled visits) will be constructed in such a way that the upper limit of the interval falls half-way between the two visits (the lower limit of the first post-baseline visit will be Day 2, ie. the day after the first dose of study drug). The visits Screening, Cycle 1 Day 1, Treatment Discontinuation, 28-Day Follow-up and Survival Follow-up visits will be excluded from remapping. The equation to be used to calculate the time windows for each post-baseline visit is:

Lower limit of interval=Upper limit of previous visit's time window +1

Upper limit of interval=Nominal day at visit + ([nominal day at visit*i+1* - nominal day at visit*i*]/2), where *i* = 3, 4, 5, 5.1, 5.2..., etc.

If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day.

For example, the visit windows for vital signs data are:

- Cycle 2 Day 1; planned day 22, visit window 2 – 32
- Cycle 3 Day 1; planned day 43, visit window 33 – 53
- Cycle 4 Day 1; planned day 64, visit window 54 – 74
- Cycle 5 Day 1; planned day 85, visit window 75 – 95

…

For visit-based summaries:

- If there is more than one value per patient within a visit window then the closest to the planned study day value should be summarized, or the earlier in the event the values are equidistant from the planned study day. The visit will be missing if no assessment was reported within the specified visit window around the planned study day.
- To prevent very large tables or plots being produced that contain many cells with meaningless data, summary statistics will be presented where at least 10 patients in either treatment group have data recorded at a particular visit.

For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval). Values from scheduled and unscheduled visits will be included.

Listings should display all values contributing to a time point for a patient; they should also highlight the value for that patient that was used in the visit-based summary table, wherever feasible.

3.3.3 Handling of Unscheduled Visits

All unscheduled visit data have the potential to be included in the summaries. More details are given in section 3.3.2.

3.3.4 Multiplicity/Multiple Comparisons

All of the analyses in this study are exploratory. Therefore, no adjustment to the Type I error rate to account for multiple testing is planned for this study.

3.3.5 Handling of Protocol Deviations in Study Analysis

According to ICH E3 guidelines version dated 1995 (ICH 1995),

> "Protocol deviations consist of any change, divergence or departure from the study design or procedures defined in the protocol. Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety or well-being."

A list of protocol deviations that are regarded as important are in Table 5 below.

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

Table 5 Important deviations

Criteria type	Important Deviation Description
Inclusion	No pathologically confirmed non-squamous NSCLC (criteria 4).
Inclusion	No locally advanced or metastatic NSCLC, or recurrent NSCLC, not amenable to curative surgery or radiotherapy (criteria 5).
Inclusion	No confirmation that the tumor harbours an EGFR mutation known to be associated with EGFR TKI sensitivity (including exon 19 deletion or L858R) (criteria 7).
Inclusion	No lesions that have not either been previously irradiated or biopsied during the study screening period; that can be accurately measured at baseline as ≥ 10mm in the longest diameter (except lymph nodes which must have short axis ≥ 15mm) with computerised tomography (CT) or magnetic resonance imaging (MRI); and which is suitable for accurate repeated measurements (criteria 10).
Inclusion	World Health Organization (WHO) performance status (PS) of 2 at screening with clinically significant deterioration in the previous 2 weeks (criteria 8).
Exclusion	Clinical or radiological evidence of CNS progression on first-line Osimertinib (criteria 1).

Criteria type	Important Deviation Description
Exclusion	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 regiments, 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 (criteria 11).
Exclusion	Past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD (criteria 2).
Exclusion	More than 4 weeks elapsed since last dose of osimertinib from date of randomization (criteria 9).
Exclusion	Unable to tolerate osimertinib 80 mg first-line therapy (criteria 10).
IP Administration/ Study treatment	Patient received /used incorrect investigational product
IP Administration/ Study treatment	Patient did not receive any study medication but was randomized
Withdrawal criteria	The patient met discontinuation criteria but did not discontinue osimertinib (eg, patient withdrew consent, patient became pregnant)
Disallowed medications	Other anticancer agents, investigational agents, and non-palliative radiotherapy which are prohibited while the patient is on study treatment
Procedures /tests	Baseline tumor assessments (RECIST1.1) performed more than 42 days before randomization.
Procedures /tests	RECIST scans performed outside of the scheduled window on more than 2 occasions
Procedures /tests	Methods/Procedures for tumor assessment are not compliant with CSP or RECIST1.1.
Procedures /tests	Missing RECIST assessments for efficacy for two consecutive assessments.

Criteria type	Important Deviation Description
COVID-19	Missed visits, assessments, or treatments that, in the opinion of the principal investigator, • were due to the 2020 COVID-19 global pandemic and • there was a significant effect on either completeness, accuracy, and/or reliability of the patient' data, or the patient's rights, safety or well-being.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per endpoint.

4.1 Study Population

4.1.1 Subject Disposition and Completion Status

Patient disposition will be listed and summarized by treatment group and overall for all enrolled patients. Summaries will include the number and percentage of patients in each of the following categories:

- Enrolled (informed consent received)
- Randomized / Not randomized
- Treated / Not treated
- Discontinued treatment i.e. discontinued any part of the study treatment (osimertinib/placebo; cisplatin/carboplatin; pemetrexed)
- Reasons for treatment discontinuation (including the reason due to COVID-19 pandemic) - presented separately for each study treatment
- Patients ongoing study treatment at the data cut-off
- Patients ongoing study at the data cut-off
- Discontinued study (including the reason due to COVID-19 pandemic)
- Reasons for study discontinuation
- Patients randomized to receive placebo who had intercranial progression as their first progression and received open label osimertinib after unblinding.

In addition, the following summaries will be provided by treatment group and overall for all randomized patients:

- Number of patients by region, country and center
- Interactive voice recording system (IVRS) stratification factor at randomization
- Disruptions due to COVID-19

Listings will be presented for:

- Disposition details for discontinued patients and patients ongoing in the study
- Randomization scheme and codes
- COVID-19 study disruptions.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

With the exception of some summaries of patient disposition and particular individual patient data listings, which will be produced for all patients who provided informed consent and who were enrolled in the study, three analysis sets will be used for listings, summaries, and analyses in the study. Details of the definition is given in section 3.2.

4.1.2.2 Presentation

The number and percentage of patients in each analysis set will be presented by randomized treatment group for all enrolled patients.

A listing of patients excluded from each analysis set will be presented.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Important protocol deviations are those that could have a heavy influence on the interpretation of any analysis based on addressing the primary efficacy and secondary safety objectives of the trial. The list of the IPDs are given in section 3.3.5

Programmable protocol deviations will be detected from the data recorded in the clinical database and will be reviewed at regular protocol deviation review meetings. At this meeting, the programmatically derived protocol deviations will be checked to ensure that they have been correctly classified as important or other study deviations.

On an ongoing basis throughout the study, monitoring notes or summaries will also be reviewed to determine any important post-entry deviations that are not identifiable via programming.

If the number of deviations which are considered to have the potential to impact the primary analysis is considered important, sensitivity analyses may be performed on subgroups. This will be decided during the data review meeting and before the DBL.

The final classification of IPDs will be made prior to PFS DCO.

4.1.3.2 Presentation

The number and percentage of patients in the following categories will be summarized by randomized treatment group using the FAS:

- Number of patients with at least 1 important protocol deviation by criteria type
- Number of patients with at least 1 COVID-19 related important protocol deviation by criteria type
- Number of patients with at least 1 important protocol deviation, excluding COVID-19 related IPDs by criteria type

Important protocol deviations will be listed.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

The following demographic variables will be collected:

- Age (years).
- Age group (years) (grouped as <50, ≥50-<65, ≥65-<75, ≥75)
- Sex
- Race
- Ethnic group

4.1.4.2 Presentation

Demographic characteristics mentioned in section 4.1.4.1 will be summarized by randomized treatment group using the FAS. Standard descriptive statistics will be presented for the continuous variables. Counts and percentages of patients will be presented for the categorical variables.

Demographic data will be listed.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

The following baseline characteristics variables are of interest:

- Weight (kg)
- Weight group (<70 kg, 70 kg to 90 kg, >90 kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2), calculated as: $\frac{weight}{height^2}$
- BMI group [Normal (<25), Overweight (25-30), Obese (>30)]
- Nicotine consumption (number of pack years)
- Smoking status (current, former, never)
- Comparison of stratification factor between eCRF and IVRS.

4.1.5.2 Presentation

The variables mentioned in section 4.1.5.1 will be summarized by randomized treatment group using the FAS.

Standard descriptive statistics will be presented for the continuous variables. Counts and percentages of patients will be presented for the categorical variables.

Baseline characteristics (height, weight and BMI) data will be listed.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

The following disease characteristics are of interest:

- WHO/ECOG performance status
- Primary tumor location at diagnosis and study entry
- Histology type at diagnosis and study entry
- American Joint Committee on Cancer (AJCC) staging at diagnosis and study entry
- Tumor grade at the time of diagnosis
- TNM classification for primary tumor, regional lymph nodes and distant metastases at the time of diagnosis and study entry.
- Time from original diagnosis to randomization (years) calculated as (Date of Randomization-Date of diagnosis)/365.25
- Time from diagnosis of metastatic disease to randomization (years) calculated as (Date of randomization-Date of diagnosis of metastatic disease)/365.25

The extent of disease at entry to the study will be summarized including:

- Evidence of disease (yes/no)

- Number of metastatic sites at study entry
- Metastatic/Locally Advanced
- Sites of Local/Metastatic Disease
- Brain metastases at baseline (per CRF)

4.1.6.2 Presentation

Variables mentioned for disease characteristics in section 4.1.6.1 will be summarized by randomized treatment group using the FAS.

Standard descriptive statistics will be presented for the continuous variables. Counts and percentages of patients will be presented for the categorical variables.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history and relevant surgical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

4.1.7.2 Presentation

The number and percentage of patients with any medical history (past and current) will be summarized for the FAS by randomized treatment group, system organ class (SOC) and preferred term (PT).

Medical history data will also be listed.

All relevant surgical history will be listed and summarized similarly.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

All prior and concomitant medications will be captured in the eCRF.

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

The latest version of the World Health Organization (WHO) Drug Dictionary will be used for coding medication terms.

For the purpose of inclusion in prior and/or concomitant mediation or therapy summaries, incomplete medication or radiotherapy start and stop dates will be imputed as detailed in Section 3.3.1.

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

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

4.1.8.2 Presentation

The following summaries will be produced by randomized treatment group using the FAS:

- Summary of prior medications
- Summary of prior anti-cancer therapies
- Summary of all allowed concomitant medications
- Summary of post study treatment cancer therapies
- Summary of prohibited/disallowed concomitant medications (section 6.5.1 of CSP).
- Summary of radiotherapy

Medications will be summarized (in terms of frequency and percentage of patients) by anatomical therapeutic chemical (ATC) dictionary text and generic term. Each unique drug will be counted once per participant. The summary will be ordered by decreasing total frequency of use.

All concomitant and other treatment data (folic acid and vitamin B12 and oral corticosteroid) will be listed.

4.1.9 Study Drug Compliance

Not applicable.

4.2 Endpoint Analyses

All efficacy analyses will be performed on the FAS. Results of all statistical analyses will be presented using a 95% confidence interval (CI) .

Table 6 Estimand

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To compare the efficacy of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo based on PFS					
Primary	PFS	FAS	Included in analysis regardless of treatment discontinuation/ introduction of non-study anti-cancer therapy (Treatment policy strategy)	Hazard Ratio (HR) from log rank statistic	4.2.1.4
Sensitivity	PFS accounted for evaluation time bias	FAS	Included in analysis regardless of treatment discontinuation/ introduction of non-study anti-cancer therapy (Treatment policy strategy)	Hazard Ratio (HR) from log rank statistic	4.2.1.5
Sensitivity	PFS accounted for attrition bias	FAS	Patients censored at commencement of non-study anti-cancer therapy (Hypothetical strategy)	Hazard Ratio (HR) from log rank statistic	4.2.1.5
Subgroup analysis (with/without baseline metastasis)	PFS	FAS	Included in analysis regardless of treatment discontinuation/ introduction of non-study anti-cancer therapy (Treatment policy strategy)	Hazard Ratio and 95% CI from Cox model	4.2.1.7
Subgroup analysis (<65 years, ≥65 years)	PFS	FAS	Included in analysis regardless of treatment discontinuation/ introduction of non-study anti-cancer therapy (Treatment policy strategy)	Hazard Ratio and 95% CI from Cox model	4.2.1.7
Objective 2: 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					

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary	Intracranial progression (IC-PFS)	FAS	Patients censored at commencement of non-study anti-cancer therapy (Hypothetical strategy)	Hazard Ratio (HR) from log rank statistic	4.2.2.4
Objective 3: To compare the efficacy of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo based on extracranial PFS					
Secondary	Extracranial progression (EC-PFS)	FAS	Included in analysis regardless of treatment discontinuation/ introduction of non-study anti-cancer therapy (Treatment policy strategy)	HR from from log rank statistic	4.2.3.4
Objective 4: To compare the efficacy of chemotherapy plus osimertinib treatment relative to chemotherapy plus placebo based on OS					
Secondary	OS	FAS	Included in analysis regardless of treatment discontinuation/ introduction of non-study anti-cancer therapy (Treatment policy strategy)	HR and 95% CI from log rank statistic	4.2.4.4
Objective 5: CCI [redacted]					
CCI [redacted]					CCI
CCI [redacted]					CCI

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
CCI					CCI

The translational science objective analysis will be described outside of the SAP/CSR.

4.2.1 Primary Endpoint - Progression-Free Survival (PFS)

4.2.1.1 Definition (PFS)

PFS is defined as the time from randomisation 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 who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST/CNS RECIST assessment.

4.2.1.2 Derivations (PFS)

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

RECIST 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 PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

4.2.1.3 Handling of Dropouts and Missing Data (PFS)

If the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST/CNS RECIST assessment. The following rules will be applied for both RECIST/CNS RECIST:

Given the scheduled visit assessment scheme (i.e. six-weekly for the first 36 weeks then twelve-weekly thereafter) the definition of 2 missed visits will change.

1. If the previous RECIST assessment is baseline then two missing visits will equate to 13 weeks since the previous RECIST assessment, allowing for a late visit (i.e. 2 x 6 weeks + 1 week for a late assessment = 13 weeks).
2. If the previous RECIST assessment is post baseline and < study day 203 (i.e. week 29) then two missing visits will equate to 14 weeks since the previous RECIST assessment, allowing for early and late visits (i.e. 2 x 6 weeks + 1 week for an early assessment + 1 week for a late assessment = 14 weeks).
3. If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from six-weekly to twelve-weekly this will equate to 20 weeks (i.e. take the average of 6 and 12 weeks which gives 9 weeks and then apply same rationale, hence 2 x 9 weeks + 1 week for an early assessment + 1 week for a late assessment = 20 weeks). The time period for the previous RECIST assessment will be from study days 203 to 245 (i.e. week 29 to week 35).
4. From week 35 onwards (when the scheduling changes to twelve-weekly assessments), two missing visits will equate to 26 weeks (i.e. 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks).

If the patient has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within two visits of baseline (on or before study day 92 (2 x 6 weeks x 7 +7 days for late assessment)), in which case their date of death will be used as an event.

4.2.1.4 Primary Analysis of Primary Endpoint (PFS)

The primary analysis of PFS will be performed at the PFS DCO when approximately 60 PFS events have been observed in approximately 80 randomised patients (approximately 75% maturity), which is expected to occur during [redacted]. If the 75% maturity is achieved earlier, the DCO will take place earlier, providing it is at least [redacted] months after randomisation of the last patient. A single analysis of OS will be carried out at the time of the DCO for PFS.

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 following SAS code may be used:

```
PROC LIFETEST DATA=...;
TIME pfsTime*censor (1);
STRATA Brainm;
TEST trtn;
RUN;
```

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 standard deviation obtained from the LIFETEST procedure with a STRATA term for the stratification variable.

The covariates in the statistical modelling will be based on the values entered into IVRS at randomisation, even if it is subsequently discovered that these values were incorrect.

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 strata will not be included in the log rank test.

The log-rank test statistic and the HR (osimertinib vs placebo) together with corresponding 95% CI will be presented (a HR less than 1 will favor osimertinib).

A Kaplan-Meier (KM) plot of PFS will be presented by treatment group. The total number of events, and the percentage PFS at 4, 6, 12, and 18 months (or as appropriate for the maturity of the data) will be summarized. The median PFS (calculated from the Kaplan-Meier plot, with 95% CIs) will be presented if the data are sufficiently mature. The progression status at the time of the PFS analysis will also be summarized, including the number and percentage of patients who progressed due to RECIST/CNS RECIST progression or due to death, or did not progress due to being progression free or due to being lost to follow up. This will also provide distribution of number of days prior to progression for the patients who have discontinued treatment.

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

The assumption of proportionality will be assessed. Proportional hazards will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time dependent covariate *(adding a treatment-by-time or treatment-by ln(time) interaction term)* to assess the extent to which this represents random variation. If there is evidence of non-proportional hazard, the HR from the primary analysis can still be meaningfully interpreted as an average HR over the observed extent of follow-up.

The following SAS code may be used to check whether the proportionality assumption is valid:

```
PROC PHREG DATA=...;
CLASS trtn (REF='placebo') / PARAM=REFERENCE;
MODEL pfs_Time *censor (1) =trtn timeDependent/ TIES=EFRON;
STRATA Brainm;
timeDependent = trtn*LOG (pfs_Time);
proportionality_test: TEST timeDependent;
RUN;
```

4.2.1.5 Sensitivity Analyses of the Primary Endpoint (PFS)

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.

Attrition bias

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following 2 or more non-evaluable tumor assessments will be included. In addition, and within the same sensitivity analysis, patients who take subsequent therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) prior to their last evaluable RECIST / 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.

4.2.1.6 Supplementary Analyses of the Primary Endpoint (PFS)

Summary statistics will be given for the number of days from censoring to DCO for all censored patients.

A summary of the duration of follow-up will be summarised using median time from randomisation to date of censoring (date last known to have not progressed) in censored

(not progressed) patients only, presented by treatment group.

Additionally, summary statistics for the number of weeks between the time of progression and the last evaluable RECIST assessment prior to progression will be presented for each treatment group.

Summaries of the number and percentage of patients who missed two or more consecutive RECIST assessments will be presented for each treatment group.

All of the collected RECIST 1.1 data will be listed for all randomised patients. In addition, a summary of new lesions (i.e. sites of new lesions) will be produced.

4.2.1.7 Subgroup Analyses (PFS)

Subgroup analysis will be performed comparing PFS between treatments (ie, using a Cox-Proportional Hazards Model) and will include the following subgroups.

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

For each subgroup level of a factor, the HR and 95% CI will be calculated from a Cox proportional hazards model that only contains a term for treatment.. The Cox models will be fitted using SAS® PROC PHREG with the Efron method to control for ties, and using a BY statement for the subgroup factor.

These HRs and associated two-sided 95% CIs will be summarized and presented on a forest plot, along with the results of the overall primary analysis.

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

4.2.2 Secondary Endpoint-Intracranial Progression-Free Survival (IC-PFS)

4.2.2.1 Definition (IC-PFS)

IC-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.

4.2.2.2 Derivations (IC-PFS)

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

IC-PFS will be evaluated based on CNS RECIST 1.1.

CNS 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.

4.2.2.3 Handling of Dropouts and Missing Data (IC-PFS)

Handling of missed visits will be dealt similarly as the primary end point described in section 4.2.1.3.

4.2.2.4 Primary Analysis of Secondary Endpoint (IC-PFS)

IC-PFS will be analyzed similarly as the primary end point described in section 4.2.1.4 using the FAS, separately for patients with baseline brain metastases and without baseline brain metastases.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint (IC-PFS)

No sensitivity analysis is planned for this endpoint.

4.2.2.6 Supplementary Analyses of the Secondary Endpoint (IC-PFS)

No supplementary analysis is planned for this endpoint.

4.2.2.7 Subgroup Analyses (IC-PFS)

No subgroup analysis is planned for this endpoint.

4.2.3 Secondary Endpoint-Extracranial Progression-Free Survival (EC-PFS)

4.2.3.1 Definition (EC-PFS)

EC-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 due to any cause.

4.2.3.2 Derivations (EC-PFS)

EC-PFS will be evaluated based on RECIST 1.1. The derivation will be performed similarly as primary end point described in section 4.2.1.2.

4.2.3.3 Handling of Dropouts and Missing Data (EC-PFS)

Handling of missed visits will be performed similarly as the primary end point described in section 4.2.1.3.

4.2.3.4 Primary Analysis of Secondary Endpoint (EC-PFS)

EC-PFS will be analyzed similarly as the primary analysis of PFS described in section 4.2.1.4 using the FAS.

4.2.3.5 Additional Analyses of the Secondary Endpoint (EC-PFS)

No additional analyses are planned for this endpoint.

4.2.3.6 Subgroup Analyses (EC-PFS)

No subgroup analysis is planned for this endpoint.

4.2.4 Secondary Endpoint-Overall Survival (OS)

4.2.4.1 Definition (OS)

OS is defined as the time from the date of randomization until death due to any cause.

4.2.4.2 Derivations (OS)

OS (days) = (date of death or censoring) – (date of randomization) + 1

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. Survival calls will be made in the 1 week following the date of 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.

4.2.4.3 Handling of Dropouts and Missing Data (OS)

The censoring rule for OS analysis is provided in section 4.2.4.2. If the survive form is not completed for certain patients it may be necessary to use all relevant CRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment. The last date of each individual patient is defined as the latest among the following dates recorded on the eCRF:

- AE start and stop dates
- Study treatment date
- End of treatment date
- Laboratory test date
- Date of vital signs
- Disease assessment dates on RECIST CRF
- Start and stop dates of alternative anti-cancer therapy
- Date last know alive on survival status CRF

- End of study date

4.2.4.4 Primary Analysis of Secondary Endpoint (OS)

This study was not sized to detect a difference in OS between the 2 treatment groups; therefore, the analysis will not include statistical hypothesis testing. The number and percentage of patients surviving 12, 18 and 24 months (or as appropriate for the maturity of the data) will be calculated using the Kaplan-Meier method (by randomized treatment group) using the FAS. In addition Kaplan-Meier estimates of median OS together with their 95% CIs will be calculated for each treatment group, providing there are sufficient events.

4.2.4.5 Additional Analyses of the Secondary Endpoint (OS)

No additional analysis is planned for this endpoint.

4.2.4.6 Subgroup Analyses (OS)

No subgroup analysis is planned for OS.

4.2.5 Exploratory Endpoint-IC Objective Response Rate CCI

4.2.5.1 Definition CCI

CCI [redacted]

4.2.5.2 Derivations CCI

CCI [redacted]

CCI [redacted]

4.2.5.3 Handling of Dropouts and Missing Data CCI

Not applicable

4.2.5.4 Primary Analysis of Exploratory Endpoint CCI

CCI

CCI

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4.2.5.5 Additional Analyses of the Exploratory Endpoint CCI

CCI

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4.2.5.6 Subgroup Analyses of Exploratory Endpoint CCI

CCI

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4.2.6 Exploratory Endpoint- CCI CCI

4.2.6.1 Definition CCI

CCI

4.2.6.2 Derivations CCI

CCI

CCI

CCI

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CCI

CCI

CCI [redacted].

4.2.6.3 Handling of Dropouts and Missing Data CCI [redacted]

Not applicable

4.2.6.4 Primary Analysis of Exploratory Endpoint CCI [redacted]

CCI [redacted]

4.2.6.5 Additional Analyses of the Exploratory Endpoint CCI [redacted]

CCI [redacted].

4.2.6.6 Subgroup Analyses of Exploratory Endpoint CCI [redacted]

CCI [redacted].

4.2.7 Exploratory Endpoint- CCI [redacted]

4.2.7.1 Definition CCI [redacted]

CCI [redacted].

4.2.7.2 Derivations CCI [redacted]

CCI [redacted]

CCI [redacted].

4.2.7.3 Handling of Dropouts and Missing Data CCI [redacted]

CCI [redacted].

4.2.7.4 Primary Analysis of Exploratory Endpoint

[redacted]

4.2.7.5 Additional Analyses of the Exploratory Endpoint

No additional analysis is planned for this endpoint.

4.2.7.6 Subgroup Analyses of Exploratory Endpoint

No subgroup analysis is planned for this endpoint.

4.3 Pharmacodynamic Endpoint(s)

Not applicable.

4.4 Pharmacokinetics

Not applicable

4.5 Immunogenicity

Not applicable

4.6 Safety

All the safety variables will be summarized using the safety analysis set.

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs (pulse and blood pressure [BP]), ECG, LVEF, physical exam, and WHO performance status.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Exposure of osimertinib/placebo

Total exposure time (months) of osimertinib/placebo will be calculated from the first dose to the last dose:

- Total (or intended) exposure = min(last dose date where dose > 0 mg, date of death, date of DCO) – first dose date +1)/30.4375

Actual exposure time (months) of osimertinib/placebo will be calculated from first dose to the last dose, taking account of dose interruptions.

- Actual exposure = (Total exposure in days-total duration of dose interruption (i.e. number of days with dose = 0)/30.4375

Exposure of chemotherapy (pemetrexed, cisplatin, and carboplatin)

Duration of treatment of chemotherapy will be in terms of the number of cycles and total exposure.

A cycle corresponds to a period of 21 days. If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if chemotherapy is started, even if the full dose is not delivered. The total exposure (month) will be calculated as the (min(last dose date where dose > 0 mg for any of pemetrexed, cisplatin, and carboplatin, date of death, date of DCO)-first dose date+21)/30.4375.

Exposure of third-line osimertinib

Total exposure time (months) during the third line of osimertinib will be calculated as follows:

- Total exposure in days calculated as = min(last dose date where dose > 0 mg, date of death, date of DCO after 1st intracranial progression) – first dose date after 1st intracranial progression +1)

Actual exposure time (months) during the third line of osimertinib will be calculated as follows:

- Actual exposure = (Total exposure in days calculated from first dose after first intracranial progression-total duration of dose interruption from first dose after first intracranial progression (i.e. number of days with dose = 0)/30.4375

Missed or forgotten doses

Missed and forgotten doses should be recorded on the DOSE module as a dose interruption with the reason recorded as “Subject forgot to take dose”. These missed or forgotten doses will not be included as dose interruptions in the summary tables but the information will appear in the listing for dosing. However, these missed and forgotten doses will be considered in the derivation of actual exposure.

Patients who permanently discontinue during a dose interruption

If a patient permanently discontinues study treatment during a dose interruption, then the date of last administration of study medication recorded on DOSDISC will be used in the programming.

Safety Follow-up

Total Safety Follow-up = min((last dose date+28), date of withdrawal of consent, date of death, date of DCO)-first dose date+1

4.6.1.2 Presentation

The following summaries will be presented by actual treatment group:

- Total (or intended) exposure of osimertinib/placebo
- Actual exposure of osimertinib/placebo
- Total safety follow-up time
- Number of cycles received of cisplatin/carboplatin and pemtrexed.
- Number and reasons for dose reductions, dose interruptions, and dose modifications of osimertinib/placebo, cisplatin/carboplatin and pemetrexed.
- Total exposure of cisplatin/carboplatin and pemetrexed
- Total exposure of osimertinib during the third line treatment
- Actual exposure of osimertinib during the third line treatment

For patients on study treatment at the time of analysis, DCO date will be used to calculate exposure.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

A treatment emergent adverse event (TEAE) is an AE with an onset date or a pre-existing AE worsening on or after the first dose of study treatment through to 28 days after the treatment discontinuation and prior to start of a new anti-cancer treatment.

Adverse events and SAEs will be collected throughout the study, from informed consent throughout the treatment period and including the 28-day follow-up period (28 days after the last dose of IP). An adverse event (AE) is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any 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 considered related to the medicinal product. The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence.

AEs will be coded using the most recent version of MedDRA.

AEs will be graded according to the National Cancer Institute Common Terminology

Criteria for AEs.
An SAE is an AE occurring during any study phase (i.e. screening, treatment, follow-up), that fulfils one or more of the following criteria:

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

Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and 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 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 these could be marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

AEs of Special Interest

AEs of special interest (AESIs) represent pre-specified risks that are considered to be of importance to a clinical development program. These AESIs have been identified as a list of categories provided by the patient safety team.

Preferred terms used to identify adverse events of special interest will be listed before database lock and documented in the Study Master File. Groupings of certain MedDRA preferred terms will be based on preferred terms provided by the medical team and a listing of the preferred terms in each grouping will be produced. The grouped terms expected are ILD and pneumonitis, and cardiac effects (cardiac failure). Other categories may be added as necessary or existing terms may be merged.

An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which higher-level terms and which preferred terms contribute to each AESI. Further reviews may take place prior to database

lock (DBL) to ensure any further terms not already included are captured within the categories.

4.6.2.2 Presentation

All AEs, both in terms of MedDRA PT and Common Terminology Criteria for Adverse Events (CTCAE) grade, will be listed and summarized descriptively by count (n) and percentage (%) for each actual treatment group.

Any AE occurring before start of study treatment (i.e. before Dose Day 1) will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'.

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.

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

Summary information (the number and percent of patients by treatment) by SOC and PT will be tabulated for:

- All AEs
- All AEs causally related to osimertinib/placebo
- All AEs causally related to cisplatin/carboplatin
- All AEs causally related to pemetrexed
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, causally related to osimertinib/placebo
- AEs with CTCAE grade 3 or higher, causally related to cisplatin/carboplatin
- AEs with CTCAE grade 3 or higher, causally related to pemetrexed
- AEs leading to osimertinib/placebo dose reduction
- AEs leading to osimertinib/placebo dose interruption
- AEs leading to cisplatin/carboplatin dose reduction
- AEs leading to cisplatin/carboplatin dose interruption
- AEs leading to pemetrexed dose reduction
- AEs leading to pemetrexed dose interruption
- All SAEs
- All SAEs causally related to osimertinib/placebo

- All SAEs casually related to cisplatin/carboplatin
- All SAEs casually related to pemetrexed.
- AEs leading to discontinuation of osimertinib/placebo
- AEs leading to discontinuation of cisplatin/carboplatin
- AEs leading to discontinuation of pemetrexed
- AEs leading to discontinuation of osimertinib/placebo, causally related to osimertinib/placebo
- AEs leading to discontinuation of cisplatin/carboplatin, causally related to cisplatin/carboplatin
- AEs leading to discontinuation of pemetrexed, causally related to pemetrexed
- OAEs
- OAEs causally related to osimertinib/placebo
- OAEs casually related to cisplatin/carboplatin
- OAEs causally related to pemetrexed.

An overall summary of the number and percentage of patients in each category will be presented, as well as an overall summary of the number of events in each category. In addition, a truncated AE table of most common AEs, showing all events that occur in at least 5% of patients overall will be summarized by PT, by decreasing frequency. This cut-off may be modified after review of the data.

AEs will be assigned CTCAE grades and summaries of the number and percentage of patients will be provided by maximum reported CTCAE grade, SOC, PT and actual treatment group.

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

Any SAE occurring before study treatment will be included in the data listings but will not be included in the summary tables of AEs.

Any SAE occurring within 28 days of discontinuation of IP (i.e. the last dose of study randomized) will be included in the relevant SAE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

Listings

By patient listings will be produced as follows:

- A by patient listing of AEs
- A by patient listing of AEs causally related to osimertinib/placebo
- A by patient listing of SAEs

- A by patient listing of AEs with CTCAE grade 3 or higher (separately for causally related to osimertinib)
- A by patient listing of AEs leading to dose reduction or dose interruption
- A by patient listing of AEs presenting any event that occur prior to dosing or starting more than 28 days after discontinuing therapy.

Deaths

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

- Related to disease under investigation,
- AE outcome=death,
- Both related to disease under investigation and with AE outcome=death,
- AE with outcome=death ≥28 days after last treatment dose,
- Deaths ≥28 days after last treatment dose, unrelated to AE or disease under investigation, and
- Patients with unknown reason for death.

The following summary tables of AEs with an outcome of death will be prepared and presented by actual treatment group.

- By SOC and PT
- Causally related to osimertinib/placebo by SOC and PT
- Causally related to cisplatin/carboplatin by SOC and PT
- Casually related to pemetrexed by SOC and PT

A corresponding death listing will also be produced.

Adverse events of Special Interest

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

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

- At least one AESI presented by event outcome
- At least one AESI causally related to study medication

- At least one AESI leading to discontinuation of study medication

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

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

Summary of AEs for crossover patients

Summary tables from the AEs described above, including casually related AEs, AEs leading to death, AEs leading to dose interruption/reduction, serious AEs, AESIs will be repeated for cross over subjects only. The AE summary tables for crossover subjects will include all AEs that occurred after the start of crossover treatment up until the end of 28 day follow-up period. The 28 day follow-up period will be defined as 28 days following treatment discontinuation.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

The following laboratory variables will be collected:

Table 7 Laboratory safety variables

tHematology/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)
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
	S/P-Urea/Blood urea nitrogen
	Creatinine clearance [c]
	Blood creatine phosphokinase

[a] The value is to be provided as percentage of the leukocyte count if the absolute leukocyte differential counts are not available.
[b] LDH is an additional variable collected during screening.
[c] Refer to Appendix H of clinical study protocol.

All values will be classified as low (below range), normal (within range) and high (above range) based on AstraZeneca specific reference ranges. As applicable, values will be converted to standard units and will be graded using latest version of CTCAE.

Hy's Law incidents are those cases where a patient shows an AST or ALT ≥ 3xULN or total bilirubin ≥ 2xULN.

4.6.3.2 Presentations

For all continuous laboratory assessments, absolute value, change from baseline and percentage change from baseline will be summarized using descriptive statistics at each scheduled assessment time by actual treatment group.

Shift tables for laboratory values from baseline to worst value on-treatment categorized using the common toxicity criteria (CTC) will be produced.

For parameters with no CTC grading, shift tables from baseline to worst value on-treatment will be provided using normal ranges for categorization.

Box-plots of absolute values for continuous laboratory assessments will be presented, with AZ project defined reference ranges indicated.

A scatter plot of ALT versus total bilirubin, both expressed as multiples of the upper limit of normal (ULN), will be produced with reference lines at 3×ULN for ALT, and 2×ULN for total bilirubin. The scatter plot will be repeated for AST versus total bilirubin with reference lines at 3×ULN for AST, and 2×ULN for total bilirubin. In each plot, total bilirubin will be in the vertical axis.

Liver biochemistry test results over time for patients who show elevated ALT or AST (≥3xULN) and elevated total bilirubin (≥ 2xULN) (elevated results
do not need to be present at the same visit), or a total bilirubin of ≥ 5xULN will be tabulated and plotted.

All laboratory summaries and listings will be presented by actual treatment group.

By-patient listings of laboratory assessments will be provided showing at least: laboratory parameters, actual time point, measurements/results, CTC grade (if available), and the change from baseline value (for continuous data) (if appropriate). In addition, a flag will indicate if the value was out of normal range, if appropriate.

The following listings will be provided:

- Laboratory reference ranges
- Hematology
- Serum chemistry
- Urinalysis
- Individual patient data with elevated ALT or AST plus total bilirubin

Summaries of clinical laboratory parameters will be repeated for crossover subjects.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

The following urinalysis variables will be summarized:

Table 8 Urinalysis variables

Urinalysis (dipstick)
Urine-Glucose
Urine-Protein
Urine-Blood

Creatinine clearance will be derived based on the appendix H of CSP.

4.6.4.2 Presentations

Shift tables for urinalysis values ("Negative", "Trace", "Positive", "0", "+", "++", "+++") from baseline to worst grade on-treatment will be produced by actual treatment group. Absolute value and change from baseline for creatinine clearance will be summarized by actual treatment group using the safety analysis set.

4.6.5 Other Laboratory Evaluations

4.6.5.1 Definitions and Derivations

Serum and urine pregnancy test and COVID-19 test is performed according to SoA.

4.6.5.2 Presentations

Serum pregnancy and COVID-19 data will be listed.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

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.

4.6.6.2 Presentations

Absolute values and change from baseline for pulse (bpm), BP (mmHg) and weight (kg) will be summarized by actual treatment group and visit.

A shift table comparing baseline to maximum value on treatment will be summarized for systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate by actual treatment group, using the following normal ranges: SBP = 100 - 160 mmHg; DBP = 60 - 95 mmHg; pulse rate = 55 – 95 bpm.

Box plots for absolute values in SBP, DBP, pulse rate, and weight will be presented by actual treatment group.

Vital signs data will be listed.

Summaries of vital signs will be repeated for crossover subjects.

4.6.7 Electrocardiogram and Echocardiogram

4.6.7.1 Definitions and Derivations

The ECG parameters which are of interest are:

- Mean heart rate
- PR interval
- RR interval
- QTcF interval
- QRS
- QTC interval

Fridericia QTc correction (QTcF) will be calculated as:

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

QTc outliers are defined as QTcF values following dosing that are greater than 450 ms or are increases from baseline greater than 30 ms. QTcF outliers will be highlighted in the data listings and summarised using the following categories:

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

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 of CSP) until completion of chemotherapy and pemetrexed maintenance treatment.

LVEF outliers are defined as LVEF values following dosing that are

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

4.6.7.2 Presentations

All ECG data received will be presented in data listings. ECG summaries will be presented for patients in the safety analysis set.

The absolute values and change from baseline of ECG parameters will be summarized by visit and actual treatment group.

Box plots for observed ECG parameters and change from baseline in ECG parameters over time will be presented by actual treatment group. Shift plots of the value corresponding to the maximum absolute change from baseline versus the baseline value for QTcF, with reference lines for 450 ms, ±30 ms and ±60 ms change, will be presented.

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

A summary of ECG assessment (normal/abnormal (clinically significant, not clinically significant)), baseline versus last observation on treatment will be presented.

Summaries of ECG data will be repeated for crossover subjects.

Left ventricular ejection fraction (LVEF)

LVEF parameter (absolute values and change from baseline) will be summarized by visit and actual treatment group.

Box plots of absolute LVEF values and change from baseline in LVEF values over time will be presented.

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

- LVEF increase

  - ≥30%
  - ≥20 - <30%
  - ≥10 - <20%
- LVEF change <10%
- LVEF decrease
  - ≥10 - <20% and absolute value <50%
  - ≥10 - <20% and absolute value ≥50%
  - ≥20 - <30% and absolute value <50%
  - ≥20 - <30% and absolute value ≥50%
  - ≥30% and absolute value <50%
  - ≥30% and absolute value ≥50%

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

4.6.8 Other Safety Assessments

4.6.8.1 Definitions and Derivations

WHO PS

WHO PS will be assessed at the times specified in the SoA (Table 1 and Table 2 of CSP) based on the following:

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

1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work)

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

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

4. Completely disabled, cannot carry out any self-care and totally confined to bed or chair.

Physical Examination

Physical examination will be assessed at the times specified in the SoA (Table 1 and Table 2 of CSP).

4.6.8.2 Presentations

WHO PS

A shift table will be produced comparing baseline value to maximum WHO PS on-treatment value in the safety analysis set.

Physical examination

Abnormalities identified from physical examination will be listed.

Ophthalmologic assessments

Ophthalmologic data will be listed.

5 INTERIM ANALYSIS

No interim analysis is planned for this study.

6 REFERENCES

Berry et al 1991
Berry G, Kitchin RM, Mock PA. A comparison of two simple hazard ratio estimators based on the logrank test. Statistics in Medicine 1991;10:749-55.

Robins and Tsiatis 1991
Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank-preserving structural failure time models. Commun Stat Theory Methods 1991;20(8):2609-31.

Robins 1993
Robins JM. Information recovery and bias adjustment in proportional hazards regression analysis of randomized trials using surrogate markers. ASA Proceedings of Biopharmaceutical Section 1993:24-33.

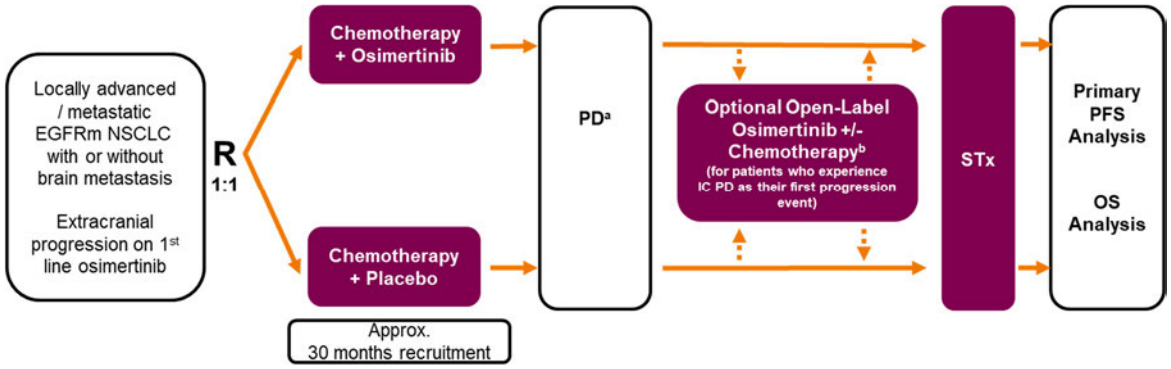
Selke and Siegmund 1983
Selke T, Siegmund D. Sequential analysis of the proportional hazards model. Biometrika 1983;70:315-26.

Sun and Chen 2010
Sun X, Chen C. Comparison of Finkelstein's method with the conventional approach for interval-censored data analysis. Stat Biopharm Res 2010; 2:97-108.

7 APPENDIX

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.

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