Clinical Study Protocol	
Study Intervention	Osimertinib(TAGRISSO®)
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The Efficacy and Safety of Osimertinib with Platinum plus Pemetrexed Chemotherapy, as First-line Treatment in Recurrent or Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Patients with Uncommon Epidermal Growth Factor Receptor Mutations (EGFRm): A phase2, Open Label, Single Arm, Multicenter, Exploratory Study

Sponsor Name: China AstraZeneca Marketing Company

Legal Registered Address: AstraZeneca, [redacted], Shanghai, [redacted], China

Regulatory Agency Identifier Number(s) Not Applicable

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

Protocol Number:

Amendment Number: None

Study Intervention: osimertinib

Study Phase: Phase 2

Short Title: Osimertinib plus chemotherapy in uncommon EGFRm NSCLC

Acronym: MINAURA

Medical Monitor Name and Contact Information will be provided separately

National co-ordinating investigator: [redacted], Chengdu, China

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Original Protocol	30-Jul-2020

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: The Efficacy and Safety of Osimertinib with Platinum plus Pemetrexed Chemotherapy, as First-line Treatment in Recurrent or Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Patients with Uncommon Epidermal Growth Factor Receptor Mutations (EGFRm): A phase2, Open Label, Single Arm, Multicenter, Exploratory Study

Short Title: Osimertinib plus chemotherapy in uncommon EGFRm NSCLC

Rationale:

[redacted]

[redacted]

Objectives and Endpoints

Objectives	Endpoints
Primary	
To describe theefficacy signals of osimertinib with platinum plus pemetrexed as first-line treatment	● ORR (objective response rate) defined as the proportion of participants who achieved a complete response (CR) or partial response (PR) as their best overall response based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 as assessed by the investigator;
Secondary	

Objectives	Endpoints
To further describe the efficacy signals of osimertinib with platinum plus pemetrexed as first-line treatment	● PFS (progression free survival) defined as time from first dose of study intervention until progression (PD) per RECIST 1.1 as assessed by the investigator or death due to any cause prior to PDOS (overall survival) defined as the time from first dose of study intervention until the date of death due to any cause; ● DoR (duration of response), defined as time from first occurrence of a response to a documented PD per RECIST 1.1 as assessed by the investigator or death of any cause; ● Depth of response, defined as maximum response of target lesions per RECIST 1.1 as assessed by the investigator; ● DCR (disease control rate)), defined as the percentage of participants who achieved CR, PR or stable disease (SD) based on RECIST 1.1 as assessed by the investigator; ● Time to treatment failure (TTF), defined as the time from first dose of study intervention to earlier of the date of last study intervention administration or death due to any cause; ● Time to first subsequent treatment (TFST), defined as the time from first dose of study intervention to the earlier of the date of anti-cancer therapy start date following study intervention discontinuation or death due to any cause;
To describe the safety and tolerability of osimertinib with platinum plus pemetrexed as first-line treatment	● All Adverse events (AEs) graded by CTCAE v5 ● Incidence of ≥grade 3 AE/Serious AE (SAE); ● Incidence of all ADR; ● Discontinuation rate due to AEs; ● Clinical chemistry, haematology and urinalysis; ● Vital signs (pulse and blood pressure); physical examination; weight; LVEF; ECG parameters; ● ECOG/WHO Performance Status.

For exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design Disclosure Statement:

This is a Phase 2, open-label, single arm, multicentre study assessing the efficacy and safety of osimertinib plus platinum-based doublets chemotherapy in advanced NSCLC participants with uncommon EGFRm

Participant Population:

The target population in this study is participants with locally advanced or metastatic or recurrent NSCLC, about to start first-line treatment composed of platinum plus pemetrexed chemotherapy, harbouring uncommon EGFRm of G719X/L861Q/S768I/de novo T790M and without other EGFR mutations including ex19del/L858R.

Number of Participants:

Approximately 35 participants will be enrolled to study so that approximately 31 participants whom would be evaluable for PFS , assuming a 10% drop-out.

Note: "Enrolled" means a participant or their legally acceptable representative has given agreement to participate in the clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not enrolled in the study, are considered "screen failures", unless otherwise specified by the protocol.

Intervention Groups and Duration:

Participants successfully enrolled into the study will receive [redacted] until RECIST 1.1-defined radiological progression as judged by the investigator.

Efficacy Assessments

Tumour assessments will be performed as per RECISTv1.1 criteria, using computed tomography (CT)/magnetic resonance imaging (MRI). The baseline assessment is part of the screening procedures and should be performed before the start of study intervention. Imaging assessment performed according to local standard clinical practice within 28 days before the first dose of study intervention, but prior to signing the informed consent form (ICF), can be used for screening purposes if the patient consents to the use of those results. Efficacy for all patients will be assessed per investigator using objective tumour assessments according to RECIST v1.1 at week 6±1 week, week 12±1 week, week 18±1 week, week 24±1 week and every 9 weeks±1 week thereafter, until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping study intervention and/or initiation of subsequent therapy). The schedule of imaging radiological assessments should be followed regardless of any dose delays.

The date, procedure, and overall response at each follow-up visit time-point will be documented, as well as if the patient is receiving benefit from the study medication. In case of disease progression, the physician will assess, date, and document the progression and methods (eg CT scan) used as per standard definitions and routine institutional standard of care.

Follow-up of participants post discontinuation of study intervention:

After study intervention discontinuation, all participants will undergo an end-of-treatment visit (within 10 days of discontinuation) and will be followed up for safety assessments for 28 days after their last dose of study intervention (ie, the safety follow-up visit).

Participants who have discontinued study intervention in the absence of RECIST 1.1-defined radiological progression which is confirmed by investigator assessment will be followed up with tumour assessments according to the Schedule of Activities (SoA) until RECIST 1.1-defined progressive disease (PD) or death regardless of whether or not the participant start a subsequent anticancer therapy, unless they have withdrawn all consent of study-related assessments.

In addition, all participants will be followed up for survival status after intervention discontinuation every 12 weeks (±1 week) from the date of last dose until death, withdrawal of consent, or the end of the study (sufficient maturity achieves for OS events), as per the SoA.

See Section 6.6 for a detailed description of assessments following study cut−offs (DCOs).

Statistical methods

All statistical analyses will be completed using SAS version 9.4 or later. The efficacy analyses will be based on the Full Analysis Set (FAS), which includes all participants who have taken at least one dose of study intervention.

The Data Cut-off (DCO) date of the primary outcome endpoint, ORR, will be when all participants have completed at least two follow-up assessments based on Investigator assessment according to RECIST 1.1. In order to allow max time for response to be observed, the DCO date for primary analysis for ORR will be at 24 weeks after last subject in (LSI). Objective response is defined as a patient achieving a complete response (CR) or partial response (PR) as their best overall response based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 as assessed by the investigator. ORR is defined as the proportion of patients achieving an objective response and will be presented as a percentage with accompanying 95% Clopper-Pearson confidence interval. Participants who discontinue the intervention without progression or who, receive a subsequent anti-cancer therapy and then respond will not be considered as responders in the calculation of ORR.

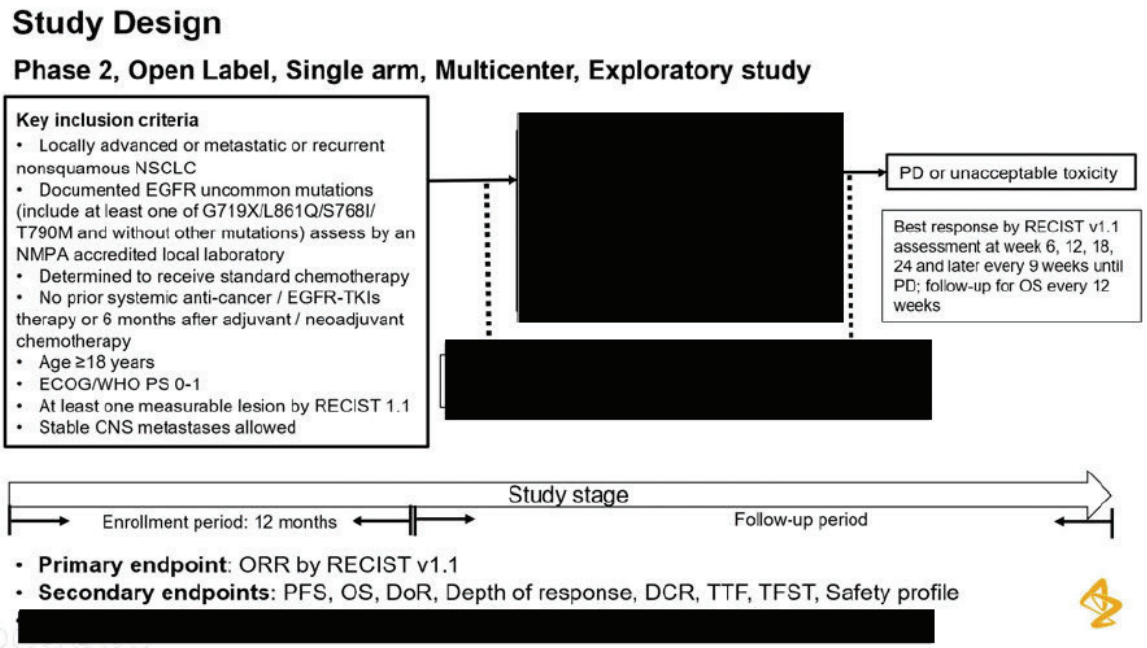
The secondary outcomes, PFS will be analysed when approximately 21 progression events have been achieved in the 35 participants (approximately 60% maturity). The Kaplan-Meier method will be used to estimate the median PFS (mPFS) and its 95% confidence interval. A KM curve will be provided as well. Other time-to-event endpoints (OS and DoR) will be summarized by same method.

Since this is a single-arm, exploratory study, the aim has been set to descriptive estimation of the primary endpoint, ORR. Thus, with the assumption of expected ORR is 60%, 35 enrolled participants (assuming a 10% drop-out rate) will provide the 95% confidence interval estimate of (42.2%, 78.2%), using Clopper-Pearson exact method.

Safety data will be summarized descriptively.

1.2 Schema

Figure 1 Study Design



RECIST 1.1=Response Evaluation Criteria in Solid Tumours, Version 1.1.
NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CNS, central nervous system; PD, progressive disease; ECOG, eastern cooperative oncology group; PS, performance score; OS, overall survival.

1.3 Schedule of Activities

The procedures for this study are presented in the SoA (Table 1).

Table 1 Schedule of Activities (SoA)

Procedure	**Screening**	**Intervention Period**							**Follow-up Period**				**For details see protocol section**
Visit	1	2	3	4	5	6	7	8+[a]	**Treatment discontinuation**	**Safety Follow-up (28 Days After Last Dose)** [b]	**Progression Follow-up** [c]	**Survival Follow-up** [d]	
Day (visit window ±days)	**-28 to -1**	**1**(+/-3)	**22**(+/-3)	**43**(+/-3)	**64**(+/-3)	**85**(+/-3)	**106**(+/-3)	**127+**(+/-3)	**+10**	+7	+/-7	+/-7	
Informed consent [e]	X												Section 5.1
Inclusion and exclusion criteria	X												Section 5.1 and 5.2
Diagnostic clinical procedures													
Record documented uncommon EGFR mutation results by an accredited laboratory through ARMS, Super-ARMS, and NGS testing [f]	X												Section 5.1 and 5.2
Optional provision of tumour sample (sufficient amount) allowed for central confirmation of the EGFR mutation status by Cobas® testing	X												Section 4.2.2
Routine clinical procedures [g]													
Demography and smoking history [h]	X												Section 5.1

Procedure	**Screening**	**Intervention Period**							**Follow-up Period**				**For details see protocol section**
Visit	1	2	3	4	5	6	7	8+[a]	**Treatment discontinuation**	**Safety Follow-up (28 Days After Last Dose)** [b]	**Progression Follow-up** [c]	**Survival Follow-up** [d]	
Physical examination and weight	X	X	X	X	X	X	X	X	X				Section 8.2.1
Height	X												Section 8.2.1
Medical history	X												Sections 5.1 and 5.2
ECOG/WHO performance status	X	X[i]	X	X	X	X	X	X	X		X		Section 8.2.6
Routine safety measurements [g]													
Serum or urine pregnancy test (WOCBP only)[j]	X	As clinically indicated. Serum pregnancy test performed at screening and urine pregnancy tests performed thereafter.											Sections 5.1, 5.2 and 8.2.4
Clinical safety laboratory assessments (clinical chemistry, haematology, urinalysis)	X	X[i]	X	X	X	X	X	X	X		X		Section 8.2.4
Creatinine clearance calculation	X	X[i]	X	X	X	X	X	X	X		X		Appendix G
12-lead ECG [k]	X	X[i]	X	X	X	X	X	X	X		X		Section 8.2.3
Echocardiogram/MUGA	X	At Week 12 (± 4 week), Week 24 (± 4 week) and then every 12 weeks (± 4 weeks) relative to first dose and as clinically indicated							X[l]				Section 8.2.5
Vital signs	X	X	X	X	X	X	X	X	X		X		Section 8.2.2

Procedure	**Screening**	**Intervention Period**							**Follow-up Period**				**For details see protocol section**
Visit	1	2	3	4	5	6	7	8+[a]	**Treatment discontinuation**	**Safety Follow-up (28 Days After Last Dose)** [b]	**Progression Follow-up** [c]	**Survival Follow-up** [d]	
AE	X	←═══ At every visit and may be conducted by phone if not tied to a visit. ═══→							X	X[m]	X[m]		Section 8.3
Concomitant medication	X	←═══ At every visit and may be conducted by phone if not tied to a visit ═══→							X	X	X		Section 6.4
Anti-cancer and surgical treatments [n]	X	←═══ All will be collected throughout the study ═══→											Sections **Error! Reference source not found.**, 5.1, and **Error! Reference source not found.**
Study treatment administration [g, o]													
Osimertinib treatment dispensed ([redacted])		X	X	X	X	X	X	X					Sections 6 and 7
Background treatment administration [o]													
Platinum plus pemetrexed followed by pemetrexed maintenance treatment stability		X	X	X	X	X[o]	X[o]	X					Sections 6 and 7
Efficacy measurements [g]													

Procedure	**Screening**	**Intervention Period**							**Follow-up Period**				**For details see protocol section**
Visit	1	2	3	4	5	6	7	8+[a]	**Treatment discontinuation**	**Safety Follow-up (28 Days After Last Dose)** [b]	**Progression Follow-up** [c]	**Survival Follow-up** [d]	
Tumour imaging (RECIST 1.1) [p,q]	X	After 6 weeks (±7 days), 12 weeks (±7 days), 18 weeks (±7 days), 24 weeks (±7 days) from first dose of intervention and then every 9 weeks (±7 days) until RECIST 1.1-defined radiological PD or PFS analysis / Per clinical practise after PD or PFS analysis											Section 8.1.1
Biomarker analyses													
[redacted]		X	[redacted]										Section 8.5

[a] Participants to attend visits every 9 weeks from visit 8 onwards until objective disease progression and then visits every 12 weeks until end of study.

[b] At a minimum telephone contact should be made with the participant.

[c] At the Investigator's discretion, study intervention may continue after progression if a participant continues to derive clinical benefit per guidelines Participants who continue on treatment following progression should maintain the schedule of assessments at each visit (ie, 21 days +/-3days) during progression follow-up period: routine safety measurements (AEs, safety laboratory assessments [clinical chemistry, hematology and urinalysis], and creatinine clearance calculation) and Routine clinical procedures (physical exam, ECOG/WHO PS, vital signs, ECGs, Echo/ MUGA and concomitant medications). In addition, participants will continue to be followed up for survival status every 12 weeks until end of study.. Details are provided in Section 7.2.

[d] Participants will be contacted for survival follow-up every 12 weeks up to the final OS analysis. Participants should be contacted in the week after DCO for each study analysis to establish survival status.

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

[f] Participants are eligible to be considered for inclusion on the basis of local pre-existing EGFR tumour tissue or plasma testing results by molecular testing whose method reviewed and approved by the regulatory authority in China.

[g] In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of intervention for each visit unless otherwise specified.

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

[i] If screening assessments have been performed within 14 days prior to starting study intervention, they do not have to be repeated at Day 1 if the participant's condition has not changed.

[j] Pregnancy test will be conducted in women of child-bearing potential only, within 14 days of the first dose of study intervention.

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

[l] If a participant had a MUGA or echocardiogram performed within 30 days prior to intervention discontinuation, the discontinuation visit Echo/MUGA scan is not required unless clinically indicated.

[m] AEs will be collected from time of signature of informed consent form until 28 days after last dose of study intervention or until the end of study, whichever occurs earlier. If the participant discontinues study intervention prior to disease progression, SAEs considered related to study intervention and/or study procedures will be collected until disease progression or end of study.

[n] All prior anti-cancer and surgical therapies will be collected at screening and throughout the study as indicated.

[o] Osimertinib and chemotherapy dosing should begin on the same day. Pemetrexed plus carboplatin or cisplatin should be used for 4-6 cycles followed by pemetrexed maintenance.

[p] The baseline radiological assessments should be performed during the 28-day screening period and preferably as close as possible to and prior to the date of enrolment. Baseline assessments include (i) CT (preferred) or MRI chest/abdomen (including liver and adrenal glands) plus any other sites where disease is suspected or known at baseline and (ii) Brain imaging - MRI is preferred unless contraindicated. Follow-up scans of anatomy imaged at baseline (as well as other sites where disease is suspected or known) are to be performed using the same modality as at baseline, after 6 weeks (±7 days), 12 weeks (±7 days), 18 weeks (±7 days), 24 weeks (±7 days) and then every 9 weeks (±1 week) subsequently, relative to first dose, until radiological disease progression as per RECIST 1.1, even if dose is delayed due to toxicity or a participant discontinues intervention prior to progression or receives other anti-cancer treatment. Following RECIST 1.1 defined progression, PFS assessment will be performed by the Investigator and defined according to local standard practice and may involve any of the following: objective radiological imaging (preferred), symptomatic progression, or death.

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

Note: All assessments on treatment days are to be performed prior to study intervention administration, unless otherwise indicated. Data collection following study analysis until the end of the study is described in Section 8.

AE=adverse event; C=cycle; CSP=Clinical Study Protocol; CTCAE=Common Terminology Criteria for Adverse Events; CV=cardiovascular; ECG=electrocardiogram; E/D=Early Study Intervention/Discontinuation; ICF=informed consent form; IV=intravenous; MUGA=multigated acquisition; PFS=time to progression or death; qXXw=every X weeks; RECIST 1.1=Response Evaluation Criteria in Solid Tumours, Version 1.1; SoC=standard of care; ECGO= eastern cooperative oncology group.

2 INTRODUCTION

Lung cancer is the most frequently occurring forms of malignancy worldwide (estimated at ~11.6% of all new cancer cases from GLOBOCAN 2018) [8, 9]. Non-small cell lung cancer (NSCLC) is the most common type in histology, which accounts for 80% to 90% of all lung cancers [1, 10]. NSCLC is also a leading cause of cancer related death in worldwide (~25.3% of all deaths from cancer) [9]. Among NSCLC, adenocarcinoma is the most common subtype and also additionally the most frequent histological type in female [11]. Chinese patients with lung cancer have increased rapidly in recent years. In China, the estimated new lung cancer cases and deaths were about 787,000 and 631,000 in 2015 from National Center Cancer Registry [12,13]. According to GLOBOCAN estimation, China accounted for 37.0% of annual lung cancer incidence and 39.2% of lung cancer mortality [9]. Consistent with global condition, NSCLC remains the predominant form of the lung cancer in China, with majority of patients being diagnosed as adenocarcinoma. Meanwhile, a retrospective analysis suggested that the percentage of adenocarcinomas increased significantly (from 36.4% to 53.5%; $P < 0.001$), with a decrease in squamous cell carcinomas (from 45.4% to 34.4%; $P < 0.001$) in recent years [14].

Lung cancer is a major disease burden in the whole world. And the financial burden appears to be mainly influenced by stage of disease, with healthcare costs increasing as the disease progresses. Despite a lot of new therapies were available in the several years, the prognosis of metastatic NSCLC patients remains poor with a mean 5-year survival rate of approximately 5% worldwide [10]. Similar to those in other countries, a majority of lung cancer in China are diagnosed at an advanced stage. A study from a tertiary hospital in east China showed that over half of lung cancer patients were diagnosed at an advanced stage [13]. A comprehensive analysis of several large-scale statistical results from 2000 to 2009 in China showed that the 5-year survival rate of stage I in NSCLC patients is about 70%, stage II is about 50%, stage III is about 15%, and stage IV is only about 5% [14]. The prognosis of lung cancer is still poor among most Chinese patients. Systemic treatment for NSCLC has advanced significantly with several new, effective agents available within recent years. Developing some more effective medication regimens to achieve long‐term declines in death rates was one of the strategies to further reduce the burden of disease.

Numerous gene mutations or alterations have been identified as molecular therapeutic targets that impact the choice of therapy. These mutations/alterations are generally not overlapping, although 1% to 3% of NSCLC tumours may harbor concurrent alterations [1]. Since it was identified in 1980s, EGFR aberrant activation has been shown to be prognostic in NSCLC, which provided a solid rationale for the development of EGFR-targeting strategies. Overall, the activating EGFRm have been found to be more frequent in never-smokers, in patients with the adenocarcinoma histological subtype and in women. Besides those, the prevalence of the EGFR mutations is also higher in East Asian patients than in Caucasian patients. Activating mutations in exons 18-21 of the kinase domain of EGFR are found in approximately 15% of patients with

lung cancer in the US [15], 10% of patients with lung cancer in the European Economic Area [16-19], and 30% to 50% of patients with lung cancer in Asia [20-23]. In Chinese NSCLC patients, genetic alterations are consistently more frequent than in western countries [24]. According to PIONEER (NCT01185314), a prospective genetic analysis of advanced lung adenocarcinoma, it suggested the prevalence of activating EGFRm in Chinese patients is 50.2% and is as large as 59.6% of people who have never smoked [21, 25].

Even though two major EGFR-activating mutations of ex19Del and L858R account for over 85% of all EGFRm, the remaining less than 15% patients acquire uncommon mutations of EGFR [26]. They are a heterogeneous group of molecular alterations and often detected as co-occurance with classic mutations which called complex or compound mutations in NSCLC [27]. It is estimated that over 75,000 worldwide and 28, 000 NSCLC patients in China have uncommon EGFRm. The largest study which investigated the epidemiology of common and uncommon EGFR mutations in a cohort of Chinese NSCLC patients reported that uncommon mutations comprised 11.9% of all EGFRm in this cohort, which is comparable with the prevalence reported in previous studies [28].

EGFR-TKIs have become the established first-line treatment in patients with advanced NSCLC harboring EGFR ex19del or L858R substitution mutations. Among them, osimertinib seemed to be the most effective and other candidates included erlotinib, afatinib, gefitinib, or dacomitinib [1]. Patients with advanced EGFRm NSCLC who receive EGFR-TKIs have a median OS of more than 2 years which in contrast to the survival of unselected NSCLC patients receiving platinum-based chemotherapy with approximately 1 year [29]. In NSCLC patients with activating EGFRm, response rates reached 50% to 80% under first-line EGFR-TKI treatment, compared with 15% to 34% in patients receiving platinum-doublet chemotherapy as first-line therapy [30-32].

[redacted]

2.1 Study Rationale

Uncommon EGFRm are defined as all mutations excluding ex19del and L858R in exons 18-21. The number of NSCLC patients with uncommon EGFRm is relatively small and they represent a heterogeneous group of molecular alterations. Due to the complicated genotypes and limited number of cases, few prospective clinical trials examined the clinical benefits of systemic therapy likes chemotherapy or EGFR-TKIs in patients with uncommon EGFRm.

The NCCN 2020 guidelines include pemetrexed in combination with cisplatin or carboplatin as category 1 first-line systemic therapy options for patients with adenocarcinoma of non-sensitizing EGFR mutation (**Error! Reference source not found.**). ESMO 2019 guidelines recommend pemetrexed in preference to gemcitabine or docetaxel for use in combination with platinum-based chemotherapy in patients with nonsquamous tumours (level II, Grade A) [33]. Per the ASCO guideline, platinum/pemetrexed combinations are acceptable options for patients with stage IV NSCLC [34]. Moreover, international guidelines recommend pemetrexed maintenance. ESMO 2019 guidelines recommend 4 cycles of platinum-based doublets followed by less toxic maintenance monotherapy as first-line treatment of NSCLC without actionable oncogenic driver regardless of programmed death ligand 1 (PD-L1) status [33]. It also appears that there are no prospective studies that have assessed whether pemetrexed maintenance is superior to no maintenance treatment (or placebo) specifically in patients with EGFRm disease who have been treated with 6 cycles of platinum-pemetrexed therapy. In hence, pemetrexed plus carboplatin or cisplatin for 4-6 cycles, followed by pemetrexed maintenance has been widely accepted as a standard of care or standard chemotherapy for nonsquamous NSCLC patients in current clinical practise.

[redacted]

[redacted]

2.2 Background

The accurate landscape and frequency of uncommon EGFRm in NSCLC are still controversial. A previous study of genomic signatures by target next-generation sequencing (NGS) in Chinese NSCLC patients showed that uncommon EGFRm sites include but not limited to several patterns likes G719X/S768I/L861X, exon 20 insertion, de novo T790M, complex ones and others [35]. A comprehensive view of uncommon EGFR mutations from five studies demonstrated that the G719X mutation in exon 18 was the most frequent point mutation, representing approximately 26% of uncommon EGFR mutations, followed by L861Q mutation in exon 21 (17%) and S768I mutation in exon 20 (9%). Then various exon 20 insertions accounted for 19% of uncommon EGFR mutations. In these data, complex mutations were not listed alone and were included as part of the other mutations [36]. Meanwhile, another study in Chinese patients reported the most frequent uncommon EGFRm was exon 20 insertion (30.7%), followed by G719X mutation (21.1%), compound L858R mutation (17.0%) and T790M mutation (13.8%) [28]. Compared with previous EGFR-TKIs, the improved efficacy of third generation EGFR-TKI, osimertinib in patients with acquired T790M has been confirmed. However, the efficacy of osimertinib in patients with de novo T790M-positive cases as the primary treatment is still under investigating through AZENT phase II trial (NCT02841579). It also appeared that around 40-50% of uncommon EGFRm were at least dual mutation positivity, which account for approximately 3–14% of all EGFRm NSCLC patients. And the clinical parameters analysis showed that uncommon EGFRm were more frequent in men, never-smokers, and adenocarcinomas[36, 37].

In addition, there was a significant heterogeneity in the response of these mutation sites to EGFR-TKIs. There are at least two subgroups such as major uncommon EGFRm or EGFR-TKIs sensitizing ones include G719X/L861Q/S768I, exon 19 insertion, A763_Y764insertion, as well as rare uncommon EGFRm include exon 20 insertion except A763_Y764insertion, pre-treatment de novo T790M and other uncommon mutations [1]. In a retrospective study in Asian patients where 28 NSCLC patients harbouring various uncommon EGFRm, first or second generation EGFR-TKIs therapy showed greater benefits for OS than platinum-doublet chemotherapy [38]. Another retrospective study from China suggested that in patients with

G719X mutations following EGFR-TKI monotherapy, positive efficacy was observed with a median PFS of 11.6 months (95% CI: 3.6-19.6) which was comparable to median PFS observed in patients with sensitizing EGFRm [39]. In contrast, T790 M and exon 20 insertion were associated with disease control deficiency, with median PFSs of 1.0 month (95% CI: 0.0-2.2) and 3.0 months (95% CI: 1.3-4.7) respectively [28]. In addition, compound mutations of uncommon EGFRm (G719X+ L861Q and G719X+ S768I) with or without co-occurring classical mutations may generally have the favourable survival outcomes [37, 39]. Controversy over the treatment of uncommon EGFRm NSCLC patients still remains despite some completed and ongoing clinical trials have been conducted.

A lot of clinical studies suggested that the majority of uncommon EGFRm in populations studied showed decreased sensitivity to EGFR-TKIs or chemotherapy when compared with common EGFRm [28]. In a post-hoc analysis of North East Japan Study Group (NEJ) 002 study, among the patients with uncommon EGFRm likes G719X/L861Q who were treated with 1st generation EGFR-TKI, gefitinib at any treatment line, the survival outcome of patients with uncommon EGFRm was greatly worse than that of patients with common EGFRm (11.9 months vs. 29.3 months, $p < 0.001$) [40]. Among 161 patients with stage IIIB/IV lung adenocarcinoma bearing G719X/S768I/L861Q mutations enrolled in a study from Taiwan, China, it also exhibited a significantly inferior tumour response rate than patients with common mutations in the controlled group (41.6% vs. 66.5%; $P<0.001$) and median PFS (7.7 vs. 11.4 months; $P<0.001$) after receiving EGFR-TKIs treatment [41]. Another retrospective analysis showed a significantly shorter mPFS in uncommon and complex EGFRm after EGFR-TKIs therapy when compared with ex19del and L858R mutations (4.0 (0.0-8.2) months and 8.6 (0.0-18.4) months vs. 14.0 (12.2-15.8) months and 13.0 (10.7-15.3) months) [42]. These results mainly indicated that single uncommon or complex EGFRm generally confers inferior efficacy of EGFR-TKIs treatment to the classic mutations. However, when comparing uncommon EGFRm with common EGFRm subgroups in patients receiving platinum doublet chemotherapy, slightly decrease but no significance of survival time was observed (22.8 vs. 28.0 months; $p= 0.358$) [40].

Several studies have preliminarily explored the efficacy of EGFR-TKIs in Chinese NSCLC patients with uncommon EGFRm. Zhang et al reported the ORR of 1st generation EGFR-TKIs was 20.0% and mPFS was 6.4 (95% CI: 4.8-7.9) months [43]. Consistently, Chen et al observed the ORR of 28.8% and a median PFS of 4.8 (95% CI: 3.5-6.1) months of uncommon EGFRm after EGFR-TKIs therapy [44]. For those treated with 1st generation EGFR-TKIs or platinum-based chemotherapy, Shi et al identified that median PFS was similar (7.1 vs. 6.1 months, $P=0.893$) in the uncommon EGFRm group [45]. Meanwhile, for the first-line treatment efficacy between 1st generation EGFR-TKIs and platinum-based chemotherapy, it showed no difference in ORR (33% vs. 27.1% $P=0.499$), but a superior median PFS of EGFR-TKIs therapy was measured in significance (7.2 months vs. 4.9 months, $P = 0.0088$) [44]. In terms of safety and improving the quality of life of patients, with fewer adverse reactions and better tolerance,

EGFR-TKIs show important signals of efficacy and safety in NSCLC patients with uncommon EGFRm.

With the development of molecular diagnostic techniques and detailed mutated gene profile, for the first-line treatment of NSCLC with uncommon EGFRm, EGFR-TKIs can be used in patients with sensitizing uncommon EGFRm likes G719X/L861Q/S768I, A763_Y764insertion, while others without sensitizing EGFRm should not be treated with EGFR-TKIs in any line of therapy and platinum-based chemotherapy remains the mainstream of treatment options [1]. Some data from Chinese patients also support the opinion. In patients with EGFR G719X/L861Q mutations, the longer median PFS was observed in the first-line EGFR-TKIs treatment group than in the chemotherapy group, but the difference was not statistically significant (G719X: 8.2 vs. 5.8 months, P=0.061; L861Q: 7.6 vs. 4.1 months, P=0.872) [46]. For more details, Xu et al ascertained that the EGFR-TKI therapy was effective in Chinese patients with G719X/L861Q mutations while less effective in patients with exon 20 insertion/T790M (median PFS: 8.90 months (95% CI: 4.47-13.34) / 5.98 months (95% CI: 1.53-10.42) vs. 2.00 months (95% CI: 0.00-5.41) / 1.94 months (95% CI: 0.00-4.43)) [39]. A real-world study conducted in patients with exon 20 insertion mutations showed better outcome in those received first-line platinum-based chemotherapy compared to a promising antitumor activity of 1st generation and all generation EGFR-TKIs (ORR 19.2% vs. 0% and 8.7%; mPFS 6.4m vs. 2.0m and 2.9m) [47].

Given the history of the first-line treatment options in common EGFRm NSCLC patients, a similar trend of promoted efficacy was observed especially in sensitizing uncommon EGFRm NSCLC patients. A previous retrospective study showed that the ORR and median PFS from platium-based doublet chemotherapy, and 1st generation EGFR-TKI, gefitinib were around 46.7% and 4.6 months, as well as 23.3% and 7.1 months in patients with G719X/S768I/L861Q EGFRm respectively [46]. Additionally, the second generation EGFR-TKI, afatinib has been approved to treat three uncommon EGFRm likes G719X/S768I/L861Q through FDA in 2018. The data from LUX-Lung 2,3,6 trials (NCT00525148, NCT00949650, NCT01121393) showed ORR and median PFS for afatinib treatment in G719X/L861Q/S768I were 71.1% and 10.7 months, but less effective in T790M, and exon 20 insertion mutations (ORR: 14.3%, 8.7%; mPFS: 2.9 months, 2.7 months) [2]. Osimertinib, as the first approved third generation EGFR-TKI in worldwide, there is a lack of comparable data from controlled trials currently. In China, Chinese Society of Clinical Oncology (CSCO) guidelines adopted the post-hoc analysis data to support the usage of afatinib in patients with G719X/L861Q/S768I mutations while chemotherapy as first-line treatment mainly for the rest NSCLC patients with other uncommon EGFRm [48].

Based on the FLAURA study, osimertinib has emerged as standard first-line treatment for patients with metastatic EGFRm NSCLC. The study assessed treatment with osimertinib compared to standard of care EGFR-TKI (erlotinib or gefitinib) and showed the clinically meaningful and statistically significant mPFS (18.9m vs. 10.2m, HR 0.46) and OS (38.6m vs.

31.8m, HR 0.799) benefit [6-7]. However, the study did not include those with simple uncommon EGFRm. A recent phase II, single arm study from Korea (NCT03424759) showed that the ORR and mPFS was 50% and 8.2 months of osimertinib in both first- and subsequent-line treatment of patients with G719X/L861Q/S768I EGFRm [3]. Interestingly, the latest research has indicated a promising antitumor activity of osimertinib with ORR 66.7% and mPFS 6.2m for 6 patients with certain exon 20 insertion mutation [49]. Moreover, in the phase II ECOG-ACRIN 5162 trial (NCT03191149), patients with exon 20 insertion of EGFRm receiving [redacted] showed ORR was 24%, and mPFS was 9.6 months (95% CI: 4.1-10.7) [50]. Compared with osimertinib as a first-line treatment for patients with common EGFRm, the therapeutic advantage from available data in major uncommon EGFRm population is limited. Therefore, there is a great unmet need in the treatment of NSCLC patients with uncommon EGFRm. As a highly mixed but small subpopulation of EGFR-positive NSCLC patients, it requires more optimal choices of therapy besides EGFR-TKIs monotherapy because of insufficient evidence to date from randomized clinical trials..

The hypothesis that the addition of platinum and pemetrexed chemotherapy to osimertinib could extend the benefit of osimertinib therapy is supported by NEJ 009 study. In this study 344 patients with newly diagnosed stage III/IV/ recurrent NSCLC harbouring an EGFR activating mutation (ex19del or L858R) were randomized 1:1 to receive gefitinib [redacted] in combination with carboplatin AUC5 and pemetrexed [redacted] followed by pemetrexed maintenance. Median PFS was statistically significantly longer in the gefitinib in combination with chemotherapy arm than that in the gefitinib monotherapy arm (20.9 months (95% CI: 18.0-24.2) vs. 11.2 months (95% CI: 9.0-13.4), respectively). The HR was 0.49 (95% CI: 0.390, 0.623; p<0.001). Second mPFS (the period from randomization to PD of the second-line therapy or death, whichever occurred first in the gefitinib monotherapy arm, but the same as the PFS in the combination group) was similar in both arms, with a median of 20.9 months (95% CI: 18.0, 24.2) in the gefitinib in combination with chemotherapy arm vs. 21.1 months (95% CI:1 7.9, 24.9) in the gefitinib monotherapy arm (HR= 0.891 (95% CI: 0.708, 1.122); p = 0.806). Overall survival was longer in the gefitinib in combination with chemotherapy arm than in the gefitinib monotherapy arm, with a median OS of 52.2 months (95% CI: 41.8, 62.5) vs. 38.8 months (95% CI: 31.1, 47.3), respectively (HR = 0.70 (95% CI: 0.58, 0.95); p = 0.013) [4, 5].

In addition, data from 5 prospective studies (3 randomized, 2 single arm) of gefitinib in combination with pemetrexed monotherapy or platinum/pemetrexed doublet therapy followed by pemetrexed maintenance and a retrospective study of erlotinib with chemotherapy (predominantly platinum/pemetrexed) further support the concept of adding chemotherapy to EGFR-TKI therapy in the first-line treatment for patients with advanced EGFRm NSCLC [51-56]. These results showed that for the patients with EGFRm, the combination strategy (EGFR-TKIs plus chemotherapy) could provide superior ORR (over 80%), mPFS and/or OS compared to those of 1st generation EGFR-TKI alone while the combination treatment was tolerable and

safe.

Considering the similar molecular pathogenesis of uncommon and common EGFRm in NSCLC, it is supposed a combination therapy may improve clinical responses and bring the improved clinical benefit of patients with uncommon EGFRm. The combination treatment strategy is promising due to its potential synergistic anti-cancer effect through induction of cellular apoptosis, suppressing mitogenic and anabolic signalling, as well as restricting the development of drug tolerance [57]. It is evident that heterogeneous mechanisms are responsible for acquired resistance to first-line osimertinib, and detailed mechanisms of acquired resistance to first-line osimertinib is limitedly understood. Platinum doublet chemotherapy is currently recommended following systemic progression on osimertinib. So concurrent treatment of osimertinib and chemotherapy may guarantee that patients can receive chemotherapy during their treatment journey. On the other hand, not all patients who progress on first-line EGFR-TKI therapy subsequently receive platinum doublet chemotherapy or single-agent chemotherapy as second- or later-line therapy because of poor physical condition. Given that patients in the proposed trial are required to have a PS of 0 or 1, all the participants will fit enough to receive platinum/pemetrexed chemotherapy.

A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of osimertinib is provided in the Investigator's Brochure (IB). A detailed description of the pharmacology, pharmacokinetics, efficacy, and safety of cisplatin or carboplatin and pemetrexed are provided in the respective prescribing information.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of osimertinib plus cisplatin or carboplatin and pemetrexed may be found in the IB, Patient Information Leaflet, Package Insert, Development Safety Update Report (DSUR).

2.3.1 Risk Assessment

2.3.1.1 Osimertinib

The tolerability profile of osimertinib when given as monotherapy is well characterized and suitable for long term dosing. In a pooled dataset that incorporated data from 1142 patients with EGFR mutation-positive NSCLC who received [redacted] osimertinib in all lines of therapy (first-, second-, and ≥third□line) in Phase I-III studies (FLAURA, AURA Phase I, AURA extension, AURA2, and AURA3), the median duration of osimertinib therapy was 12.9 months (mean, 13.9 months; range, <0.1 – 40.1 months). In the FLAURA trial based on a data cut-off of June 25th 2019, the median duration of treatment exposure was 20.7 months (range, 0.1 to 49.8) in the osimertinib group. The number of patients who were continuing to receive the assigned trial drug at the time of the data cutoff was 61 (22%) in the osimertinib group.

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

Interstitial Lung Disease (ILD) or ILD-like ADRs (eg, pneumonitis) were reported in 3.9% and were fatal in 0.4% (n=5) of the 1142 patients who received osimertinib [redacted] in the FLAURA and AURA studies. The incidence of ILD was 10.4% in patients of Japanese ethnicity, 1.8% in patients of non-Japanese Asian ethnicity and 2.8% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 2.8 months.

Of the 1142 patients in FLAURA and AURA studies treated with osimertinib [redacted], 0.9% were found to have a corrected QT interval (QTc) greater than 500 msec and 3.6% of patients had an increase from baseline QTc greater than 60 msec. No QTc-related arrhythmia events were reported in the FLAURA or AURA studies. A pharmacokinetic/pharmacodynamic analysis with osimertinib predicted a drug-related QTc interval prolongation at [redacted] of 14 msec with an upper bound of 16 msec (90% CI).

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

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

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

Across clinical trials, left ventricular ejection fraction (LVEF) decreases greater than or equal to 10% and a drop to less than 50% occurred in 3.9% of patients treated with osimertinib who had baseline and at least one follow-up LVEF assessment. Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established.

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

2.3.1.2 Chemotherapy

In this study, the background treatment included only pemetrexed plus cisplatin or carboplatin regimen. The safety profile of pemetrexed as monotherapy and in combination with cisplatin or carboplatin is well defined.

In a Phase III study of cisplatin and pemetrexed administered up to 6 cycles (but without pemetrexed maintenance), Grade 3 or 4 drug-related hematological toxicities occurred in the following: neutropenia (15% of patients), anemia (6%), and thrombocytopenia (4%). Drug-related Grade 3 or 4 non-haematological toxicities occurred in the following: nausea (7.2%), vomiting (6.1%), fatigue (6.7%), and febrile neutropenia (1.3%). In addition, alopecia of any grade was reported in 11.9% of patients and dehydration in 3.6% of patients [58].

In a placebo-controlled Phase III study of pemetrexed maintenance following completion of 4 cycles of cisplatin and pemetrexed in patients with EGFR unselected NSCLC, the most common Grade 3 or 4 ADRs included anemia (4.8% of patients), neutropenia (3.9%), fatigue (4.5%), nausea (0.3%)and mucositis/stomatitis (0.3%). In this study the median number of cycles of pemetrexed maintenance was 4; 47% of patients received ≥6 cycles and 28% received ≥10 cycles [59].

It should be noted that the present study of osimertinib with platinum/pemetrexed chemotherapy is estimated to explore an median PFS around 13 months. Assuming 5 months for the first 6 cycles of carboplatin/pemetrexed doublet therapy, this equates to a median duration of pemetrexed of 8 months (ie, approximately 11 cycles assuming patients receive pemetrexed maintenance and do not discontinue for reasons other than disease progression); thus, the average duration of pemetrexed treatment is anticipated to be shorter than has been observed in previous studies in which the median PFS was 18.3-20.9 months [60, 5]. Gefitinib in combination with platinum/pemetrexed with pemetrexed maintenance was generally well tolerated in these studies which provides reassurance for the present study.

There is evidence of cumulative nephrotoxicity in patients receiving pemetrexed therapy [61, 62]. With this in mind, in order to help maximize the potential to administer prolonged pemetrexed maintenance, patients will be required to have a screening creatinine clearance of ≥ 60 mL/min. Careful monitoring of renal function will be carried out during administration of

study medication plus background treatment in the present study. The background treatment may be interrupted by investigator if creatinine clearance is <45 mL/min and permanently discontinued .

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

2.3.1.3 Safety data from studies of chemotherapy with EGFR TKI therapies.

In Phase III studies of platinum-based chemotherapy (cisplatin/gemcitabine and carboplatin/paclitaxel) with or without EGFR-TKIs in patients with EGFR unselected NSCLC, there is no clear evidence that combination treatment increases the incidence of hematological toxicity or non-hematological toxicity other than the expected EGFR-TKI toxicities of rash and diarrhea [63-66].

In studies of EGFR-TKIs with or without pemetrexed-based chemotherapy in patients with EGFR mutation positive NSCLC, including the Phase III study of gefitinib with or without carboplatin/pemetrexed chemotherapy [5, 55], Phase III study of osimertinib with cisplatin/carboplatin and pemetrexed (FLAURA2) and Phase II studies [51-54, 56, 60], hematological toxicities were more common in patients receiving combination therapy compared with EGFR-TKI therapy alone. In safety run-in part of FLAURA2 study, no dose reductions due to a haematological AE were reported for any study treatment. In another study 2/127 (1.6%) patients receiving pemetrexed and gefitinib died as a result of AEs that were considered related to IP (pneumonitis and interstitial lung disease) [51]. However, across studies combination therapy was not clearly associated with a marked increased incidence of severe ILD. Overall, the safety profile of first-line EGFR-TKI therapy in combination with platinum/pemetrexed chemotherapy is manageable.

2.3.1.4 Potential for osimertinib and chemotherapy overlapping toxicity

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

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

The FLAURA and AURA studies suggested the incidence of CTCAE all grade shifts and CTCAE ≥Grade 3 shifts in laboratory values of patients treated with osimertinib [redacted] includes the following: leukocytes decreased all grades 68% and ≥Grade 3 1.5%; neutrophils decreased all grades 35% and ≥Grade 3 4.1%; lymphocytes decreased all grades 67% and ≥Grade 3 7.2%; and platelet count decreased, all grades 54% and ≥Grade 3 1.6%. Dose reductions due to AEs

of neutropenia and thrombocytopenia were reported in 0.4% and 0.3% of patients, respectively [6, 7].

Platinum agents and pemetrexed are associated with myelosuppression. Carboplatin is associated with a higher incidence of severe thrombocytopenia than cisplatin [67].

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

There is also the potential for overlapping toxicity with respect to effects on fertility. Based on studies in animals, male fertility and female fertility may be impaired by treatment with osimertinib. For further details see the osimertinib IB. Gonadal suppression resulting in amenorrhea or azoospermia may occur in patients receiving antineoplastic therapy and such effects may be irreversible. Moreover, chemotherapy can have genetically damaging effects. Guidance on contraception requirements and sperm donation is provided in Section 5.3 and Appendix E.

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

A Japanese Phase II open-label, randomized study of osimertinib alone vs. osimertinib plus carboplatin/pemetrexed for patients with locally-advanced or metastatic NSCLC whose disease has progressed with previous EGFR-TKI therapy and whose tumours harbour a T790M mutation within the EGFR gene is ongoing (TAKUMI Study LOGIK1604/NEJ032A; UMINCTR: UMIN). An interim safety review was conducted based on data from the first cycle in 24 patients (12 on monotherapy and 12 on combination therapy). One ≥Grade 3 AE was reported in the osimertinib arm (Grade 3 decreased neutrophil count); whereas, in the combination arm, 4 episodes each of Grade 3 or 4 decreased white blood cell count, decreased neutrophil count, decreased platelet count, and anemia; 2 episodes of Grade 3 skin rash, and 1 episode each of Grade 3 bronchial infection, oral mucositis, hypertension, and hypokalemia were reported. The authors stated that "The event frequency in the combination arm was similar to that in previous studies of carboplatin/pemetrexed. Exaggeration of AEs by osimertinib or previously unobserved events were not apparent in the combination arm." The authors concluded "The combination treatment was safe in the selected patient population" [68] and the Safety Review Committee for the study recommended that the study continue to enroll patients.

In a retrospective analysis of patients with advanced EGFRm NSCLC treated off-label with concurrent chemotherapy and osimertinib, 18 patients received 25 chemotherapy regimens in

combination with osimertinib, including 10 platinum doublets (8 on carboplatin/pemetrexed) and 15 monotherapy regimens (6 on pemetrexed) [50]. All patients had progressed on third-generation EGFR-TKI monotherapy before the addition of chemotherapy. One Grade 4 neutropenia (pemetrexed) and 5 Grade 3 neutropenia (1 carboplatin/pemetrexed; 2 pemetrexed; 1 gemcitabine; 1 carboplatin/nab-paclitaxel) were reported; 3 patients received support with granulocyte colony stimulating factors. Other Grade 3 toxicities were rare and all were reversible: 1 aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) elevation (carboplatin/pemetrexed), 1 thrombocytopenia (carboplatin/pemetrexed), and 1 anemia (carboplatin/pemetrexed). Adverse events led to treatment delay in 5 patients, osimertinib dose-reduction in 2 patients, and discontinuation of regimen in 2 patients. There were no cases of pneumonitis. The authors concluded that osimertinib does not appear to add significant toxicity to the various chemotherapy regimens.

The FLAURA2 study is currently underway, which is a global Phase III study of osimertinib, with cisplatin/carboplatin and pemetrexed in patients with locally-advanced or metastatic EGFRm NSCLC who have not received any prior therapy for advanced disease. Of the 43 patients enrolled in the safety run-in period, 13 patients did not receive treatment, resulting in 30 patients (15 patients in the osi-carbo-pem cohort and 15 patients in the osi-cis-pem cohort) who received at least one dose of study intervention.The overall incidence of SAEs and CTCAE Grade 3 or higher AEs were 20.0% (6/30 patients) and 36.7% (11/30 patients), respectively. The proportion of patients who were reported with an AE leading to death was low (1 patient; 3.3%), which was considered unrelated to study intervention (osi-carbo-pem) by the reporting investigator, and was also attributed to the disease under study. AEs infrequently led to the permanent discontinuation of any study treatment (7/30 patients overall [23.3%]). Dose modifications (interruption and/or reduction) of any study intervention due to AEs were reported in the minority of patients (4/15 patients [26.7%] in the osi-carbo-pem cohort, and 2/15 patients [13.3%] in the osi-cis-pem cohort).Following the review of all available data, the Safety Review Committee concluded that there were no new safety signals with osimertinib when used in combination with chemotherapy, and recommended that the FLAURA2 study progress to the randomised period with no additional safety measures required. The safety data from FLAURA2 safety run-in period provide sufficient confidence in the safety of osimertinib with carboplatin/pemetrexed treatment in this study.

2.3.2 Benefit Assessment

Although there can be no certainty of clinical benefit to patients, the positive efficacy data for osimertinib from FLAURA, supported by the Phase III NEJ 009 study and several other studies of 1st generation EGFR-TKIs in combination with pemetrexed or carboplatin/pemetrexed in patients with EGFR mutation-positive NSCLC, provide supportive evidence for evaluation of osimertinib with cisplatin/carboplatin plus pemetrexed as first-line treatment for locally advanced or metastatic or recurrent NSCLC patients with uncommon EGFRm.

2.3.3 Overall Benefit: Risk Conclusion

Based on a review of the potential benefits and risks, it is considered to be reasonable and appropriate to investigate the concurrent use of osimertinib and standard chemotherapy (platinum plus pemetrexed therapy followed by pemetrexed maintenance) in the first-line treatment for participants with locally-advanced or metastatic or recurrent uncommon EGFRm NSCLC.

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

Objectives	Endpoints/Variables
Primary	
To describe the efficacy signals of osimertinib with platinum plus pemetrexed as first-line treatment	● ORR (objective response rate) defined as participants who achieved a complete response(CR) or partial response (PR) as their best overall response based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 as assessed by the investigator;
Secondary	
To further describe the efficacy signals of osimertinib with platinum plus pemetrexed as first-line treatment	● PFS (progression free survival) defined as time from first dose of study intervention until progression (PD) per RECIST 1.1 as assessed by the investigator or death due to any cause prior to PD; ● OS (overall survival) defined as the time from first dose of study intervention until the date of death due to any cause; ● DoR (duration of response) defined as time from first occurrence of a response to a documented PD per RECIST 1.1 as assessed by the investigator or death of any cause; ● Depth of response defined as maximum response of target lesions per RECIST 1.1 as assessed by the investigator; ● DCR (disease control) defined as the percentage of participants who achieved CR, PR or stable disease (SD) based on RECIST 1.1 as assessed by the investigator; ● Time to treatment failure (TTF), defined as the time from first dose of study intervention to earlier of the date of last study intervention administration or death due to any cause; ● Time to first subsequent treatment (TFST), defined as the time from first dose of study intervention to the earlier of the date of anti-cancer therapy start date following study intervention discontinuation or death due to any cause;
Safety	

Objectives	**Endpoints/Variables**
To describe the safety and tolerability of osimertinib with platinum plus pemetrexed as first-line treatment	● All Adverse events (AEs) graded by CTCAE v5 ● Incidence of ≥grade 3 AE/Serious AE (SAE); ● Incidence of all ADR ; ● Discontinuation rate due to AEs; ● Clinical chemistry, hematology and urinalysis; ● Vital signs (pulse and blood pressure); physical examination; weight; LVEF; ECG parameters; ● ECOG/WHO Performance Status;
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a phase II, open-label, single-arm, multicenter, exploratory study to assess the efficacy and safety of osimertinib plus standard chemotherapy in locally advanced or metastatic or recurrent NSCLC participants with uncommon EGFRm (single or multiple mutations of G719X/L861Q/S768I/de novo T790M without other EGFR mutations including ex19del and L858R). The main assumption is that osimertinib plus chemotherapy could further enhance the ORR in these patients.

Locally advanced or metastatic or recurrent NSCLC patients with uncommon EGFRm who are untreated or received previous adjuvant/neoadjuvant chemotherapy that was completed at least 6 months prior to the development of recurrent disease will be enrolled into the study. Patients should have at least one lesion that can be accurately measured at baseline of study enrolment according to RECIST 1.1. Meanwhile, their mutation status must be confirmed through one of ARMS, Super-ARMS or NGS analysis, of which test method and product were reviewed and approved by the Chinese regulatory authority, to reduce waiting time.

Considering the low prevalence of uncommon EGFRm in Chinese newly diagnosed NSCLC patients, as well as other reasons for potential screen failure, participants with locally confirmed uncommon EGFRm report would be recruited so it's estimated that around 10% screen failure rate would be appropriate. Thus, a total of 40 patients across 10 sites will be screened over 12 months, with approximately 35 participants anticipated to be enrolled. Platinum based doublet chemotherapy as standard of care for the participants is considered as background treatment in this study. The participants will be treated with osimertinib ([redacted] plus standard chemotherapy which composed of cisplatin or carboplatin and pemetrexed i.v. for 4 to 6 cycles (dose , method and detail information, please see Section 6.1), followed by pemetrexed maintenance therapy. The osimertinib will be used to treat participants till treatment discontinuation criteria achieved such as inadequate cycles of platinum and pemetrexed treatment, or discontinuation of pemetrexed maintenance, unacceptable or irreversible toxicities, or confirmed objective disease progression as defined by RECIST 1.1, or symptomatic progression requiring urgent medical intervention (eg, CNS metastases, respiratory failure, spinal cord compression), or death, or study completion, or consent withdrawal.

Following treatment discontinuation, subsequent therapy will be at the discretion of the Investigator. Patients will be followed till death, or study completion after subsequent treatments for survival analysis.

Baseline evaluation consists of demography, physical examination, weight, height, medical history, smoking history, ECOG/WHO performance status, brain enhanced MRI, chest and

abdomen enhanced CT imaging, concomitant medication, ECG, echocardiogram/MUGA, as well as clinical chemistry, haematology, and urinalysis testing.

Patients will undergo the efficacy assessments based on RECIST 1.1 assessment criterion at week 6 , 12, 18, 24 and later every 9 weeks, until objective disease progression. The survival follow-up will be repeated every 12 weeks after disease progression until study complete.

There will be 3 analyses planned for this study. The data cut-off (DCO) date for primary analysis for ORR will be at 24 weeks after last subject in (LSI). The second analysis DCO for median PFS will be at the point when approximately 21 progression events (60% of maturity of PFS events) achieved. The final OS analysis will be performed when at approximately 21 death events (60% maturity of OS events) achieved.

What's more, participants will undergo the safety assessment in the whole treatment period and 28-day safety follow-up visit after discontinued osimertinib for any reason or study complete.

All adverse events and laboratory abnormalities will be graded according to NCI-CTCAE 5.0.

To evaluate the potential molecular resistance mechanism at disease progression after osimertinib plus chemotherapy treatment by plasma analysis, as well as the correlation between these genomic changes and clinical efficacy, plasma samples will be collected at the baseline and the disease progression in enrolled patients. And then the resistance profiling of molecular alterations including but not limited to mutations in, amplifications and expression of relevant pathway genes would be detected by NGS analysis.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for primary and secondary endpoint

The primary endpoint of this study is ORR, which on tumour imaging is one intuitive end point for single-arm trial design given its historical role in drug development. ORR is a rather convincing measure of anti-tumour activity more directly from treatment as for most tumours.

The secondary endpoints include PFS, which has been widely accepted as a surrogate endpoint for clinical benefit in studies of patients with advanced NSCLC. PFS also represents a direct effect of the efficacy of osimertinib with platinum plus pemetrexed chemotherapy as it is not confounded by the efficacy of different subsequent therapies used after disease progression. Other time to event measurements (Duration of response and overall survival) will be also evaluated as a secondary endpoint, as well as disease control rate, depth of response and OS.

4.2.2 Testing for uncommon EGFR mutations

Only participants with NSCLC with one or multiple EGFR mutations of G719X/L861Q/S768I/de novo T790M and without other EGFR mutations including ex19del

and L858R will be eligible for inclusion in the study.

A patient can be considered eligible for the study on the basis of documented before-mentioned uncommon EGFRm through any of ARMS, Super-ARMS, NGS analysis from accredited laboratories approved by the Chinese regulatory authority.

For patients eligible for inclusion in the study based on the pre-existing uncommon EGFRm plasma and/or tissue sample results, the local EGFR plasma and/or tissue testing laboratory methods will be recorded in the respective electronic case report forms (eCRF).

As an option, if a histological or cytological section of participant's disease is available, sufficient amount of sample per participant will be collected and used for confirmation of EGFRm status by the Cobas® EGFR Mutation Test v2 post-enrollment in the central lab.

4.3 Justification for Dose

4.3.1 Osimertinib

Osimertinib administered [redacted] is the approved dose for the first-line treatment of patients with metastatic NSCLC whose tumours have EGFR ex19del or exon 21 L858R substitution mutations, as detected by an approved test.

4.3.2 Platinum and pemetrexed regimen

In this study, the standard chemotherapy composed of pemetrexed in combination with cisplatin or carboplatin and pemetrexed maintenance is defined as background treatment. The chemotherapy part of the regimen is consistent with approved labels, national and international cancer guidelines, global clinical trials, and standard clinical practice. So the dose justification of platinum and pemetrexed will be made according to the drug instructions.

The administration of carboplatin or cisplatin at [redacted].
Meanwhile, The recommended dose of pemetrexed for maintenance treatment of NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m2 as an intravenous (IV) infusion over 10 minutes on [redacted] cycle until disease progression or unacceptable toxicity, to be administered [redacted] platinum-based first-line chemotherapy until disease progression or unacceptable toxicity.

4.4 End of Study Definition

The end of the study is defined as the date of 60% maturity of OS events achieve in the study.

The study is expected to start participant enrolment at Q3 2021 and to end by approximately Q4 2024.

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

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

The study may be stopped if, in the judgment of AstraZeneca, study participants are placed at undue risk because of clinically significant findings.

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

See Section 0 for details on participant management following the final OS analysis as well as following study completion.

5 STUDY POPULATION

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

Each subject should must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule. Participants who do not meet the entry requirements are screen failures, refer to Section 5.4.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed consent

1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Provision of signed and dated, written informed consent form prior to any mandatory study-specific procedures, sampling, and analyses.

The ICF process is described in Appendix A3.

Age

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

Type of participants and disease characteristics

4. Pathologically confirmed nonsquamous NSCLC
5. Newly diagnosed locally advanced (clinical stage IIIB, IIIC) or metastatic NSCLC (clinical stage IVA or IVB) or recurrent NSCLC (per Version 8 of the International Association for the Study of Lung Cancer [IASLC] Staging Manual in Thoracic Oncology), not amenable to curative surgery or radiotherapy.
6. The tumour harbors at least 1 of the 4 uncommon EGFR mutations (G719X/L861Q/S768I/ T790M), either alone or in combination, which not include other EGFR mutations including ex19del /L858R, assessed by one of ARMS, Super-ARMS or NGS analysis on the basis of tumour tissue or plasma testing from accredited laboratories approved by the Chinese regulatory authority.
7. Participants must be considered suitable by investigator and about to receive standard of care which composed of pemetrexed plus carboplatin or cisplatin for 4 to 6 cycles followed by pemetrexed maintenance.
8. Participants must have untreated advanced NSCLC not amenable to curative surgery or radiotherapy. Prior adjuvant and neo-adjuvant therapies (chemotherapy, radiotherapy, immunotherapy, biologic therapy, investigational agents), or definitive radiation/chemoradiation with or without regimens including immunotherapy, biologic therapy, investigational agents, are permitted as long as treatment was completed at least 6 months prior to the development of recurrent disease.
9. Stable CNS metastases participants will be allowed.
10. ECOG/WHO PS of 0 to 1 at screening with no clinically significant deterioration in the previous 2 weeks.
11. Life expectancy >12 weeks at Day 1.
12. At least 1 lesion, not previously irradiated that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis of ≥15 mm) with CT or MRI, and that is suitable for accurate repeated measurements. If only 1 measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously irradiated and as long as it has not been biopsied within 14 days of the baseline tumour assessment scans.

Reproduction

13. Female must be using highly effective contraceptive measures, must not be breast feeding, and must have a negative pregnancy test prior to first dose of study intervention or must have evidence of non-child-bearing potential by fulfilling 1 of the following criteria at screening:
    - Post-menopausal, defined as more than 50 years of age and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
    - Women under 50 years old would be considered as postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal

treatments and have luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the post-menopausal range for the institution

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

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

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

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

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

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

3 Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the participant to participate in the trial or which would jeopardize compliance with the protocol, or active infection including any patients receiving treatment for infection but not limited to hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.

4 Any of the following cardiac criteria:

- Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine-derived QTcF value;
- Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG; eg, complete left bundle branch block, third-degree heart block, second-degree heart block;
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as electrolyte abnormalities including serum/plasma potassium*, magnesium* and calcium* below the lower limit of normal (LLN), heart failure, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval and cause Torsades de Pointes. See Section 6.4 and Appendix F.

* correction of electrolyte abnormalities to within normal ranges can be performed during screening

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

- Absolute neutrophil count below the LLN *
- Platelet count below the LLN*
- Hemoglobin <90 g/L*

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

- ALT >2.5 x the upper limit of normal (ULN) if no demonstrable liver metastases or >5 x ULN in the presence of liver metastases
- AST >2.5 x ULN if no demonstrable liver metastases or >5 x ULN in the presence of liver metastases
- Total bilirubin >1.5 x ULN if no liver metastases or >3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases
- Creatinine clearance <60 mL/min calculated by Cockcroft and Gault equation (refer to Appendix G for appropriate calculation)

6 Any concurrent and/or other active malignancy that has required treatment within 2 years of first dose of study intervention (osimertinib, carboplatin and pemetrexed).

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

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

Prior/concomitant therapy

9 Prior treatment with any systemic anti-cancer therapy for advanced NSCLC not amenable to curative surgery or radiation including chemotherapy, biologic therapy, immunotherapy, or any investigational drug. Prior adjuvant and neo-adjuvant therapies (chemotherapy, radiotherapy, biologic therapy, investigational agents), or definitive radiation/chemoradiation with or without regimens including biologic therapies, investigational agents are permitted as long as treatment was completed at least 6 months prior to the development of recurrent disease.

10 Prior treatment with an EGFR-TKI or immune-oncology (IO) therapy.

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

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

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

Prior/concurrent clinical study experience

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

Other exclusions

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

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

17 Previously enrolled in the present study.

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

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

20 In addition, the following conditions are considered criteria for exclusion:

- Prior allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

5.3 Lifestyle Considerations

5.3.1 Pregnancy

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

1 Female participants of child-bearing potential must use highly effective methods of contraception from screening until at least 6 weeks after discontinuing study treatment. Acceptable methods are provided in Appendix E (Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods).

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

5.3.2 Meals and Dietary Restrictions

Once enrolled all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known to be strong inducers of CYP3A4 whenever feasible.

If medically feasible, participants taking regular medication, with the exception of strong inducers of CYP3A4, should be maintained on their regular medication throughout the study period. Participants may receive any medication that is clinically indicated for treatment of adverse events. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of osimertinib.

Participants taking concomitant medications whose disposition is dependent upon BCRP and/or P-glycoprotein (Pgp) with a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Appendix F).

Participants taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the participant experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.

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

5.4 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a single time. However, rescreening should be documented so that its effect on study

results, if any, can be assessed. All assessments must be repeated for rescreening unless they are within the 28-day screening period..

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

5.5 Procedures for handling incorrectly enrolled patients

Participants who fail to meet the eligibility criteria should not, under any circumstances, be enrolled to receive any study intervention. There can be no exceptions to this rule. Where a participant does not meet all the eligibility criteria but is incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the participant from treatment. The Study Physician should ensure all decisions are appropriately documented. The Investigator should make documentation in the medical record as appropriate.

6 STUDY INTERVENTION

Study intervention in this study refers to osimertinib. Participants would be given osimertinib as an add-on treatment to standard chemotherapy which was defined as background treatment. Osimertinib and standard chemotherapy dosing should begin on the same day.

6.1 Study Intervention Administered

6.1.1 Investigational Product

AstraZeneca will supply osimertinib. Dose modifications are described in Section 0.

Table 3 Investigational Products

ARM Name	**Osimertinib plus standard chemotherapy**
Intervention Name	osimertinib
Type	drug
Dose Formulation	osimertinib: tablet
Dosage Level(s)	[redacted]
Dosage formulation, dose reduction	[redacted]

Route of Administration	osimertinib: [redacted]
Use	experimental
IMP and NIMP	IMP
Sourcing	Osimertinib: AstraZeneca
Packaging and Labelling	Osimertinib will be provided in blisters packed in cartons containing. Each carton will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.

6.1.2 Dosing instructions

Osimertinib will be supplied as tablets for oral administration as [redacted] Each box will contain sufficient osimertinib treatment for 21 days. [redacted] will be supplied as needed upon request.

Osimertinib will be dispensed to participants at Cycle 1 Day 1 only after all study procedures and assessments have been performed and all eligibility criteria have been met. All the eligibility criteria are met as confirmed by the Investigator. It should be documented in the medical records in a proper manner.

Sufficient osimertinib treatment for 3 weeks will be distributed at each dispensing visit.

[redacted] Tablets should be taken whole with water, with or without food. The tablet should not be crushed, split or chewed.

If administration via nasogastric tube is required, the same process as above should be followed but using volumes of 15 mL for the initial dispersion and 10 mL for the residue rinses. The total liquid should be administered as per the nasogastric tube instructions with appropriate water flushes.

Every effort should be made to minimize the time between enrolment and starting study treatment. Pre-treatment should be started as soon as possible and will take place prior to the start of study intervention (osimertinib). It is recommended that participants commence study treatment, standard chemotherapy or chemotherapy pre-treatment as soon as possible after enrolment and whenever possible within 1 day.

To allow for management of study intervention-related toxicities, the initial dose of osimertinib [redacted] can be reduced to [redacted] (see Section 8.4). Once the dose of osimertinib

is reduced to [redacted], the participant will remain on the reduced dose until termination from study intervention. Re-challenge [redacted] not allowed in this study.

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

The reason for any missed dose and any change from dose interruptions, or dose reductions must be recorded in the medical record, the source document and the electronic Case Report Form (eCRF).

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

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

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

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

4 Used/unused study intervention will be disposed based on local procedures. The Investigator(s) is responsible for ensuring that the participant has returned all unused study intervention. **Study Intervention Compliance**

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the site will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Any change and the reason for changing the dose interruption, dose delay, dose reduction, dose discontinuation, overdosing or omission will also be recorded in the source document and eCRF.

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

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

6.4 Concomitant Therapy

Any concomitant treatment, procedure, or other medication considered necessary by the investigator for the participant's safety and wellbeing, or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest that the participant is receiving within 4 weeks prior to the first dose of study intervention or receives during the study including the 28-day follow-up period following the last dose of study intervention must be recorded in the eCRF along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

If any concomitant therapy is administered due to new or unresolved AE, it should be recorded.

Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Restricted, prohibited, and permitted concomitant medications/therapies are described in more detail in Appendix F 2.

Guidance regarding potential interactions with concomitant medications is provided in Appendix F 1.

6.4.1 Background medications

Standard chemotherapy defined as background medications in this study are described in the table below. The cisplatin or carboplatin plus pemetrexed regimen will be locally sourced. Full details on cisplatin, carboplatin and pemetrexed can be found in the local prescribing information for these products. Osimertinib and standard chemotherapy dosing should begin on the same day. Participants may receive pre-treatment and concomitant treatment (eg,

antiemetics) as recommended by the approved label for pemetrexed, cisplatin or carboplatin as clinically indicated by the Investigator.

Pemetrexed

Pemetrexed [redacted] will be administered as [redacted] as per local practice and labels until RECIST1.1-defined progression or another discontinuation criterion is met (see Section 7.1).

To reduce the severity of hematologic and gastrointestinal toxicity of pemetrexed toxicity, participants treated with pemetrexed may receive vitamin supplementation containing folic acid and vitamin B_{12}. Furthermore, a corticosteroid may be given to reduce the incidence and severity of skin reactions. All these pre-treatment can be implicated according to clinical practice.

Cisplatin

Cisplatin [redacted] will be administered as an IV infusion according to local practice and labels [redacted] and should be immediately preceded and followed by hydration.

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

Carboplatin

Carboplatin [redacted] will be administered [redacted] according to local clinical practice and labels.

Carboplatin dose is calculated using the Calvert formula. The carboplatin dose is not to exceed [redacted]

<u>Calvert Formula</u>

[redacted]

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

Table 4 Background Medications

Type	Background medications
Dose Formulation	pemetrexed: ampule cisplatin: ampule carboplatin: ampule
Dosage Level(s)	pemetrexed [redacted] plus carboplatin [redacted] or cisplatin [redacted]
Dosage formulation, dose reduction	Refer to the local drug instruction
Route of Administration	pemetrexed: IV infusion cisplatin/carboplatin: IV infusion
Use	Stand of care
IMP and NIMP	NIMP
Sourcing	Sourced locally
Packaging and Labelling	Sourced locally

6.4.2 Restricted and prohibited concomitant medications

Restricted and prohibited concomitant medications are described in the table below. For questions related to specific medications, contact the Study Physician of sponsor. Guidance on medications to avoid, medications that require close monitoring, and on washout periods are provided in Appendix F.

Table 5 Restricted, prohibited and allowed concomitant medications

Prohibited Medication/Class of drug:	**Usage:**
Other anti-cancer agents, investigational agents except cisplatin or carboplatin or pemetrexed and non-palliative radiotherapy	Should not be given while the participant is on study intervention.

Restricted Medication/Class of drug:	**Usage:**

Strong inducers of CYP3A4. See Appendix F for a list of drugs.	Once enrolled all participants must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known to be strong inducers of CYP3A4 whenever feasible. Such drugs must have been discontinued for an appropriate period before the patient enters screening and for a period of 3 months after the last dose of osimertinib. Patients may receive any medication that is clinically indicated for treatment of AEs.
Medications whose disposition is dependent upon the Breast Cancer Resistance Protein (BCRP) and/or P-glycoprotein (P-gp) with a narrow therapeutic index. See **Error! Reference source not found.** for a list of drugs. Rosuvastatin	Closely monitor for signs of changed tolerability as a result of increased exposure to the concomitant medication while receiving osimertinib. Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.
Nonsteroidal Anti-Inflammatory Drugs	Subjects taking nonsteroidal anti-inflammatory drugs (NSAIDs) or salicylates will not take the NSAID or salicylate (other than an aspirin dose ≤1.3 grams per day) for 2 days before, the day of, and 2 days after receiving pemetrexed. Subjects taking NSAIDs or salicylates with a long half-life (for example, naproxen, piroxicam, diflunisal, or nabumetone) will not take the NSAIDs or salicylates for 5 days before, the day of, and 2 days after pemetrexed.

Warfarin or other anticoagulant	Due to the possibility of an interaction between oral anticoagulants and anti-cancer chemotherapy, there is requirement to monitor International Normalized Ratio (INR) frequently, if it is decided to treat the patient with oral anti-coagulants. Participants taking warfarin or other anticoagulant with pemetrexed should be monitored regularly for changes in prothrombin time or INR.
Colony stimulating factors (CSFs)	Granulocyte colony stimulating factors (G-CSF) should not be used prophylactically during Cycle 1. Following first cycle chemotherapy, growth factors may be used in accordance with the American Society of Clinical Oncology Clinical Practice Guideline Update on the use of WBC Growth factors [69] or in accordance with local standards of care.
Antiemetic therapy	See Section 6.4.3
Drugs that prolong the QT interval	Detailed guidance is provided in Appendix F and additional specific guidance regarding anti-emetic drugs that can prolong the QT interval is provided in Section 6.4.3

Allowed Medication/Class of drug:	**Usage:**
Pre-medication will be allowed for subjects receiving osimertinib plus standard chemotherapy.	To be administered as directed by the Investigator. This includes management of diarrhoea, nausea and vomiting.
Calcium folinate/folinic acid	The use of calcium folinate/folinic acid in the management of pemetrexed overdose should be considered.

Leukocyte-depleted blood transfusions	Participants can have blood transfusions during the study treatment. However, patients aren't allowed to receive blood transfusions or platelet transfusions in order meet the inclusion criteria of the study.
Corticosteroids /bisphosphonates/Rank-ligand inhibitors	Please see Section 6.1.2 for details relating to corticosteroid pre-medication for subjects receiving standard chemotherapy. Corticosteroids can be used for the management of bone metastases. Regular, concomitant use of bisphosphonates and RANK-L inhibitors for management of bone metastases is permitted if therapy is initiated prior to first dose of study therapy. Initiation of therapy after enrollment is permitted in participants with no evidence of overall clinical or radiographic progression per RECIST 1.1. or in patients in survival follow-up.
Palliative local therapy-radiotherapy and surgical resection	Palliative local therapy, including radiation therapy and surgical resection for non-target lesions is permitted in participants with no evidence of overall clinical or radiographic progression per RECIST 1.1 or in patients in survival follow-up.
Vaccines	Vaccines can be administered in accordance with local labels.

6.4.3 Antiemetic therapy

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

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

Table 6 QT/TdP risk category for antiemetic therapies

QT/TdP risk Category	Definition	Antiemetic therapies
Known risk of TdP	These drugs prolong the QT interval **AND** are clearly associated with a known risk of TdP, even when taken as recommended	domperidone droperidol haloperidol levomepromazine levosulpiride ondansetron
Possible risk of TdP	These drugs can cause QT prolongation **BUT** currently lack evidence for a risk of TdP when taken as recommended.	**dolasetron** **granisetron** **palonosetron** **tropisetron**

QT/TdP risk Category	Definition	Antiemetic therapies
Conditional Risk of TdP	These drugs are associated with TdP **BUT** only under certain conditions of their use (eg, excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) **OR** by creating conditions that facilitate or induce TdP (eg, by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).	**metoclopramide**

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

In the light of this information, the following guidance is given:At screening participants are required to have serum electrolytes ≥LLN; ie, potassium, magnesium and calcium in the normal range. If during screening participants have electrolyte levels <LLN, measures can be taken to bring these into the normal range and retesting would be conducted. During study treatment, electrolyte levels should be maintained in the normal range.

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

In this study it is strongly recommended that antiemetic drugs from the known risk of TdP category are not given, ie, ondansetron, domperidone, droperidol, haloperidol, levomepromazine, or levosulpiride. If it is considered essential to give a 5-HT_3 receptor-antagonist, one of the following agents should be given if available: granisetron, dolasetron, tropisetron or palonosetron. However, as these drugs are categorized as having a possible risk of TdP, careful monitoring of ECGs and electrolytes is recommended. If it is essential to give a 5-HT_3 receptor- antagonist and ondansetron is the only available 5-HT_3 receptor- antagonist, careful monitoring with ECGs and electrolytes is recommended.

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

6.4.4 Other concomitant treatment

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

6.4.5 Prior immune-oncology therapy

Participants who were treated with immune oncology (IO) drug prior to study enrolment are prohibited to participate in this study. Immune-oncology therapies are prohibited during the study.

6.5 Dose Modification

Dose modifications are permitted in the management of study intervention-related toxicities as described in Section 8.4.

6.6 Intervention after the End of the Study

After the final OS analysis for this study, AstraZeneca will not provide any of the study intervention free of charge for participants even if the investigator judges that the participant can still benefit from that. All participants may continue on treatments which follow local clinical practice.

If a roll-over or safety extension study is available at the time of the final OS analysis and database closure, participants currently receiving treatment with osimertinib and standard chemotherapy may be transitioned to such a study, and the current study would reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would be proposed to move to such a study would be given a new informed consent, as applicable.

6.7 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Osimertinib will be relabelled to indicate "clinical use only", and also will include study number site number and subject number etc.

6.8 Storage

All study drugs should be kept in a secure place under appropriate storage conditions (sealed, below 30 ° C). The osimertinib label on the boxesspecify the appropriate storage.

As an investigational drug, the osimertinib must be stored appropriately and dispensed from a secure storage area (or site pharmacy). Study sites are required to maintain accountability logs for drug receipt, dispensation, destruction and return (as applicable per local regulations).

6.9 Accountability

The osimertinibd for this study will be used only as directed in the study protocol. The study personnel will account for all study drugs dispensed to and returned from the participant.

The study personnel at the investigational site will account for all treatments dispensed and for appropriate return or destruction. The site is required to maintain documentation of the delivery, return and destruction of study intervention.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention (osimertinib) for the situations listed below. If study intervention are permanently discontinued, regardless of the reason, the participant will be identified as having permanently discontinued treatment and continue in follow-up per the protocol. The investigator should instruct the participant to contact the site before or at the time if any study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

Participants who have permanently discontinued from further receipt of study intervention will need to return all study intervention at their next on-site study visit or unscheduled visit.

Participants may be discontinued from study intervention in the following situations.

- RECIST 1.1-defined radiological progression (refer to Appendix D) (notes: participants can still receive osimertinib at their own expenses if clinical benefits exists).
- Investigator determination that the participant is no longer benefiting from study intervention.
- Inadequate (less than 4 times totally) doublet chemotherapy cycles of platinum plus pemetrexed before pemetrexed maintenance.

- Permanently discontinuation of pemetrexed maintenance.
- An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets criteria for discontinuation defined in the dose modification guidelines for management of study intervention-related toxicities (see Section 8.4)
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment. A participant who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.2).
- Severe non-compliance with the CSP as judged by the investigator or AstraZeneca.
- Pregnancy or intent to become pregnant.
- Initiation of subsequent anticancer therapy, including another investigational agent.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

7.1.1 Follow-up of Participants Post Discontinuation of Study Intervention

All participants who discontinue the study intervention will be followed up for safety assessments 28 days (+7 days) after their last dose of study intervention. Additional assessments to be performed at the time of the discontinuation (+10 days) are detailed in the SoA.

Participants who have discontinued study intervention for the reason other than objective RECIST 1.1-defined radiological progression prior to the DCO for PFS analysis, regardless of whether or not they have commenced subsequent anticancer therapy, will be followed up with tumour assessments as indicated in the SoA until RECIST 1.1-defined PD or the DCO for PFS analysis, whichever occurs first, regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments. After PD or the DCO for PFS analysis, participants will continue to be followed for progression defined as per local clinical practice. Investigator assessment of response/progression will be collected up to disease progression or until the final OS analysis. SAEs considered related to study intervention and/or study procedures will be collected until disease progression or end of study, whichever occurs earlier.

7.1.2 Follow-up for Survival

Participants will be followed up for survival status as indicated in the SoA until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the participant or the participant's family, or by contact with the participant's current physician. Additional assessments to be performed at the time of survival follow-up are detailed in the SoA.

7.2 Intervention through progression

At the Investigator's discretion, study intervention may continue for as long as a patient continues to derive clinical benefit after RECIST 1.1 progression in the absence of any discontinuation criteria before the end of the study. However, if the patient is deemed to have clinically significant, unacceptable or irreversible toxicities, rapid tumor progression, or symptomatic progression requiring urgent medical intervention (eg, CNS metastases, respiratory failure, spinal cord compression) study intervention must be discontinued.

Participants who continue on study intervention following progression should maintain the schedule of assessments as shown below:

- Routine safety measurements (AEs, safety laboratory assessments [clinical chemistry, haematology and urinalysis], and creatinine clearance calculation);
- Routine clinical procedures (physical exam, ECOG/WHO PS, vital signs, ECGs, Echo/ MUGA [every 12 weeks relative to first dose], and concomitant medications).

In addition, patients who continue on treatment following progression will continue to be followed up for survival status every 12 weeks until death, withdrawal of consent, or the final OS analysis as per the survival follow-up column shown in the SoA (Table 1).

7.3 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options to ensure the collection of endpoints and safety information including new AEs and follow-up on any ongoing AEs and concomitant medications (eg, telephone contact at 28 days (+7 days) after study intervention is discontinued, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, it should be confirmed if he/she is still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Study Team.

7.4 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the participant's status at that time.

Participants who decline to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing participants throughout the study period. If contact with a missing participant is re-established, the participant should not be considered lost to follow-up and evaluations should resume according to the protocol.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record. Should the participant continue to be unreachable, he/she will be considered to have been lost to follow-up from the study and censored at the latest follow-up contact.
- Site personnel will attempt to collect the vital status of the participant during survival follow-up within legal and ethical boundaries for all participants. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1). Data collection following study analysis until the end of the study is described below.

- Protocol waivers or exemptions are not allowed.
- The Investigator ensures the accuracy and completeness of the eCRFs including legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRF and a copy will be archived at the study site.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

8.1.1 Imaging Tumour Assessments

Tumour assessments use images from CT (preferred) or MRI, with IV contrast, of the chest and abdomen, collected during screening/baseline and at 6 weeks (±1 week), 12 weeks (±1 week), 18 weeks (±1 week), 24 weeks (±1 week), and then every 9 weeks (±1 week) relative to first dose of study intervention until radiological disease progression. Any other areas of disease involvement should be additionally imaged at screening based on known metastasis sites or by the signs and symptoms of individual participants. Tumour assessments of the brain will be part of the RECIST 1.1 assessment for Investigators (recorded as non-target lesions), using images from contrast-enhanced T1 MRI (preferred over CT) that are collected at screening and at progression for all participants. In addition, participants with brain metastases or a history of brain metastases at screening should be followed up with repeated imaging assessments using the same frequency as the extracranial scans to allow whole-body RECIST assessments until progression. If brain metastases are not detected (within 28 days prior to enrolment), or if the participant does not have a history of brain metastases, the participant is not required to undergo further imaging of the brain unless metastases are suspected by the Investigator, or until

(extracranial) PD is assessed with RECIST 1.1 by the Investigator. Once PD is assessed in participants without brain metastases or without a history of brain metastases, a brain scan should be performed within 4 weeks, but preferably as soon as possible, to allow the assessment of new lesions in the brain.

If participants are contraindicated to CT contrast agents, a non-contrast CT otherwise MRI will be acceptable. In those participants who are contraindicated to contrast agents based on gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA), a non-contrast MRI would be sufficient. In those participants with a contraindication to MRI, a (contrast-enhanced) CT of the brain would be sufficient. The imaging modality used for baseline tumour assessment, CT/MRI for chest and abdomen and MRI for brain, should be kept the same consistently at each subsequent follow-up assessment throughout the study if possible. It is important to follow the tumour assessment schedule as closely as possible (refer to the SoA) relative to first dose. Screening/baseline imaging should be performed no more than 28 days before start of study intervention and ideally should be performed as close as possible to and prior to the start of study intervention. Treatment continues until RECIST 1.1-defined radiological progression (refer to Appendix D), and scanning/tumour assessments continue throughout treatment until RECIST 1.1-defined radiological progression by Investigator assessment. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit.

The baseline assessment is part of the screening procedures and ideally should be performed as close as possible to and prior to the first dose of treatment. Scans obtained prior to first dose of treatment do not need to be repeated and are acceptable to use as baseline evaluations, if the following criteria are met:

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

Participants with a CT scan of the brain obtained prior to the first dose of treatment will not be required to have an MRI brain scan during screening if the criteria above are met.

The RECIST 1.1 assessments of baseline images identify target lesions (TLs; defined as measurable) and non-target lesions (NTLs). On-study images are evaluated for TLs and NTLs

chosen at baseline, and for new lesions (NLs) when they appear. This allows determination of follow-up TL response, NTL lesion response, the presence of unequivocal NLs, and overall time point responses (complete response [CR], partial response [PR], stable disease [SD], PD, or not evaluable [NE]). Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Participants who discontinue study intervention without progression, receive a subsequent therapy, and then respond will not be included as responders in the analysis of ORR.

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

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

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

Height will be measured during screening only. Physical examination, and assessment of weight, will be performed at timelines as specified in the SoA; investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.3.6 for details.

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA.

Vital signs (to be taken before blood collection for laboratory tests) will be measured in a supine position after 5 minutes rest for the participant in a quiet setting without distractions (eg, television, cell phones) and will include systolic and diastolic blood pressure, temperature and pulse rate. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

Changes in vital signs as compared to baseline may qualify as an AE, see Section 8.3.

8.2.3 Electrocardiograms

Twelve-lead ECG will be performed at the visit indicated in the SoA (Table 1).

8.2.4 If there is a clinically significant abnormal ECG finding during the Treatment period, this should be recorded on the AE eCRF, according to standard adverse events collection and reporting processes. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the visits indicated in the SoA (Table 1).

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

Clinical chemistry, haematology, and urinalysis assessments that have been performed within 14 days prior to starting study treatment do not have to be repeated on Cycle 1 Day 1 if the participant's condition has not changed.

The clinical chemistry, haematology and urinalysis will be performed at a central laboratory.

Other safety laboratory tests include assessment for pregnancy (serum at screening and urine thereafter). Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following laboratory variables will be measured.

Table 7 Laboratory Safety Variables

Haematology/Haemostasis (Whole Blood)	Clinical Chemistry (Serum or Plasma)
Haemoglobin	Albumin
Leukocyte count	Alanine transaminase (ALT)
Leukocyte differential count (absolute count)	Aspartate transaminase (AST)
Platelet count	Alkaline phosphatase (ALP)
Absolute neutrophil count	Bilirubin, total
Absolute lymphocyte count	Calcium, total
Absolute monocytes count	Creatinine
Absolute basophils count	Glucose
Absolute eosinophils count	Lactate dehydrogenase (LDH) [a]
Total white blood cell count	Magnesium
Total red blood cell count	Potassium
Haematocrit	Sodium
Reticulocytes	Urea/Blood Urea Nitrogen
Urinalysis	
Haemoglobin/Erythrocytes/Blood	
Protein/Albumin	
Glucose	

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; INR=international normalised ratio; PTT=partial thromboplastin time.
a LDH is an additional variable collected during screening.
b The value is to be provided as percentage of the leukocyte count if the absolute leukocyte differential counts are not available.

The investigator should assess the available results with regard to clinically relevant abnormalities in documentation. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.6.

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

8.2.5 Echocardiogram/Multigated Acquisition Scan

An echocardiogram or MUGA scan to assess LVEF will be performed at the visits as shown in SoA (Table 1). The modality of the cardiac function assessments must be consistent for a given participant (ie, if echocardiogram is used for the screening assessment for a given participant, then echocardiogram should also be used for subsequent scans for that participant). The

participants should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken.

If a participant has had an echocardiogram or MUGA performed within 4 weeks prior to treatment discontinuation, the discontinuation visit echocardiogram/MUGA scan is not required unless clinically indicated. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study intervention, to confirm reversibility of the abnormality.

Situations in which echocardiogram or MUGA results should be reported as AEs are described in Section 8.3.6.

8.2.6 ECGO/WHO Performance Status

ECOG/WHO performance status will be assessed at the times specified in the SoA (Table 1) based on the following:

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

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

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

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

4 Completely disabled; unable to carry out any self-care and totally confined to bed or chair.

5 Dead.

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

8.3 Collection of Adverse Events and Serious Adverse Events

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

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

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

The investigator and any designees are responsible for detecting, documenting, recording, and reporting events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from time of signature of informed consent form until 28 days after last

dose of study intervention or until the end of study follow-up (death, loss of follow-up, withdrawal of consent, end of study), whichever occurs earlier.

If the patient discontinues study intervention prior to disease progression, SAEs considered related to study intervention and/or study procedures will be collected until disease progression or end of study, whichever occurs earlier. All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in **Error! Reference source not found.**. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of the data being available.

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

The methods of recording, evaluating, and assessing causality of AE and SAE are provided in **Error! Reference source not found.**.

If an Investigator learns of any SAEs, including death, at any time after a patient has discontinued study treatment (plus 28-day follow-up), and he/she considers there is a reasonable possibility that the event is causally related to osimertinib, the Investigator should notify AstraZeneca (see Section 8.4).

8.3.2 Follow-up of AEs and SAEs

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

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

8.3.3 Adverse event data collection

The following variables will be collected for each AE;

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

- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- AE caused participant's withdrawal from study (yes or no)
- Outcome

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

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

The grading scales found in the National Cancer Institute CTCAE v5 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.4 Causality Collection

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

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

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

8.3.5 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question

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

8.3.6 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests, vital signs, physical examinations, ECGs, and echocardiogram/MUGA scans will be summarised in the Clinical Study Report (CSR).

Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs ECG, or echocardiogram/MUGA scan should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or study intervention interruption).

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

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

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

8.3.7 Disease Progression

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

Progression of the malignancy under study, including signs and symptoms progression, should

not be reported as an SAE. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE.

8.3.8 Disease Under Study

Symptoms of the disease-under study are those that might be expected to occur as a direct result of locally advanced or metastatic or recurrent NSCLC. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study intervention.

8.3.9 New Cancers

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

8.3.10 Deaths

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

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

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

8.3.11 Safety Data to be Collected Following the Final Data Cut off of the Study

AEs and SAEs will be collected from time of signature of ICF until 28 days after last dose of study intervention or until the end of study, whichever occurs earlier. For participants continuing to receive osimertinib after the final OS analysis, AEs related to osimertinib spontaneously will be reported to the AstraZeneca-designated mailbox.

8.4 Safety reporting and medical management

8.4.1 Reporting of Serious Adverse Events

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

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

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

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

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone followed by completion of a investigator-signed paper SAE form whose scanned copy should be emailed to AZ Data Entry Site immediately but **no later than 24 hours** of awareness. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

Contact information of AZ Data Entry Site:

E-mail: [redacted].

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

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following the first date of

study intervention or within 6 weeks of the last dose of study intervention, including pregnancy in the partner of male participants, should be reported to AstraZeneca.

The investigator/site staff must inform the Study Representative immediately but **no later than 24 hours** after he/she becomes aware of a pregnancy. The Study Representative will ensure the pregnancy is reported to AZ Data Entry Site (DES) **within 30 calendar days** of awareness.

Pregnancy in itself is not considered to be an AE or SAE unless there is a suspicion that the IP may have interfered with the effectiveness of a contraceptive medication. However, events of congenital abnormality/birth defect, spontaneous miscarriage or ectopic pregnancy, or any complications in the subject which meet the criteria for serious should also be reported as SAEs. Elective abortions without complications are not considered to be SAEs.

Pregnancy occurring in study subjects will be reported via the Pregnancy Case Record Form (CRF) module. However, a Pregnancy Form may be used in situations where EDC system is not utilized or when the pregnancy CRF modules are not available/appropriate, for example, if the pregnancy occurred in the partner of the study subject.

8.4.2.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately.

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

If any pregnancy occurs during the study or within 6 weeks of the last dose of study intervention, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours**) of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.4.2.2 Paternal Exposure

Non-sterilised male participants who intend to be sexually active with a female partner of

childbearing potential should refrain from fathering a child or donating or banking sperm for the duration of the study and for at least 6 months after discontinuing chemotherapy or at least 4 months after discontinuing osimertinib.

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

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

8.4.3 Overdose

A maximum tolerated dose has not been established for osimertinib. An overdose is defined as any dose higher than the protocol-mandated dose.

The maximum dose of each study treatment is:

- Osimertinib [redacted]

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

Additional guidance regarding overdose for each study treatment is below:

- Osimertinib: There is no specific treatment in the event of osimertinib overdose. In case of suspected overdose, osimertinib should be withheld and symptomatic treatment initiated

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

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with an SAE (see Section 8.4) and within 30 days for all other overdoses.

For participants received standard chemotherapy over any dose higher than pemetrexed [redacted], or cisplatin [redacted], or carboplatin [redacted] (see Section 6.4), please refer to the local prescribing information for treatment of cases of overdose. If any overdose is associated with an AE or SAE please record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

8.4.4 Medication Error

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-threatening or follow-up Fatal/Life-threatening) or **5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3) and within 30 days for all other medication errors.

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

8.4.5 Management of study intervention-related toxicities

All adverse events will be managed per standard local practice.

8.4.5.1 General dose adjustments for adverse events

Osimertinib is the standard of care for participants with treatment-naïve sensitizing EGFR mutation NSCLC. And chemotherapy is the standard of care for participants without driver gene mutation NSCLC. In this study, osimertinib is considered as an investigational treatment and standard chemotherapy (cisplatin or carboplatin plus pemetrexed) as background treatment. As such, in order to maintain the dose intensity of the study intervention, it is recommended that if clinically appropriate, and where osimertinib interruption is not mandated, for the management of potential overlapping toxicities, dose interruption/dose reduction of chemotherapy in accordance with local practice/guidelines by the Investigating site is prioritized above dose interruption/dose reduction of osimertinib.

If appropriate, the Investigator may attribute each toxicity event to osimertinib alone, or to standard chemotherapy alone, or to a combination of osimertinib and standard chemotherapy and use a stepwise dose modification according to Table and **Error! Reference source not found.**. Dose modification can be implemented for the study treatment components depending upon the Investigator's assessment of causality. If, in the opinion of the Investigator, a toxicity is considered to be due predominantly to the study intervention (osimertinib) and the dose is delayed or modified in accordance with the guidelines below, the standard chemotherapy may

be administered if there is no contraindication. If a participant experiences several toxicities and there are conflicting recommendations for those toxicities, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Dose modifications for toxicities must be based on the maximum toxicity experienced during a cycle. Toxicity must resolve to CTCAE Grade ≤1 or baseline prior to resumption of study treatment.

Only 1 dose reduction is permitted for osimertinib treatment. If a participant experiences a toxicity associated with osimertinib that would cause a second dose reduction, osimertinib must be discontinued. If a dose reduction for toxicity occurs with osimertinib, the dose of osimertinib may not be re-escalated. Moreover, osimertinib may be interrupted for a maximum of 3 weeks. Participants may discontinue osimertinib and continue on standard chemotherapy alone if appropriate. The standard chemotherapy may be interrupted for a maximum of 3 weeks (ie, 6 weeks since the last dose of chemotherapy).

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

Table 8 Dose Modifications for Study Treatments

	Initial dose	**Dose reduction 1**	**Dose reduction 2**
Osimertinib	[redacted]	[redacted]	Discontinue

8.4.5.2 Dose adjustment information for osimertinib

If a participant experiences a CTCAE Grade 3 or higher and/or unacceptable toxicity not attributable to the disease or disease-related processes under investigation, not covered by the specific guidance below, where the investigator feels that there is a reasonable possibility of a causal relationship with osimertinib, dosing of osimertinib will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. If the toxicity does not resolve to ≤CTCAE grade 2 after 3 weeks of withholding osimertinib, osimertinib must be permanently discontinued. If the toxicity resolves or reverts to ≤CTCAE Grade 2 within 3 weeks of onset, treatment with osimertinib may be restarted at the same dose [redacted] or a lower dose (osimertinib [redacted]) using the rules below for dose modifications (Table 9) and at the discretion of the Investigator. Following restart of treatment, the participant should be closely monitored for recurrence. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption. Further guidance is provided in Table and text below.

Table 9 Osimertinib dose adjustment information for adverse reactions

Target Organ	**Adverse reaction***	**Dose modification**
Pulmonary	ILD/Pneumonitis	Permanently discontinue osimertinib

Target Organ	Adverse reaction*	Dose modification
Cardiac	QT interval >500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is <481 msec within 3 weeks of onset then restart [redacted] (at the discretion of the investigator).
	QT interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Other	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of osimertinib for up to 3 weeks	Osimertinib may be restarted at the [redacted]
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue osimertinib

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

Information on Specific Adverse Events

ILD/Pneumonitis-like toxicity

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of ILD is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca study team should be informed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema or pulmonary haemorrhage. The results of full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, haematological parameters) will be captured by eCRF. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and study treatment permanently discontinued.

QTc prolongation

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

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

Keratitis

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

Changes in cardiac contractility

.An Echocardiogram or MUGA scan to assess LVEF will be performed at screening (prior to first dose of osimertinib) and at least every 16 weeks throughout the treatment period. The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans. The patients should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study intervention, to confirm reversibility of the abnormality.

Erythema Multiforme and Stevens-Johnson syndrome

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

Permanent discontinuation due to toxicity

Patients experiencing Interstitial Lung Disease (ILD/pneumonitis) or QTc prolongation with signs/symptoms of serious arrhythmia will not be permitted to restart study treatment.

8.5 Biomarkers and exploratory research

8.5.1 Collection of samples

The subject's consent to the use of donated biological samples for research is mandatory during treatment period and at disease progression in the SoA (Table 1). Biological samples will be collected and may be used for central tesing of the EGFR mutation status resistance mechanisms analysis and biomarkers of response.

Blood samples (approx. 10 mL) will be taken at the baseline and disease progression or study intervention discontinuation whichever occurs earlier and are presented in the SoA (Table 1).

An unstained, archival tumour tissue or cellular sample from a fresh biopsy or surgical specimens in a quantity sufficient to allow for retrospective central confirmation of the EGFR mutation status with the cobas® EGFR Mutation Test v2 at the time of screening will be

collected as an option. Central confirmation will not be mandated before enrolment for participants with a positive tissue EGFR test result obtained from a locally accredited laboratory. The central testing of EGFR mutations will be used to assess concordance with local test results.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

8.5.2 Determination of exploratory analysis

Blood samples to generate plasma samples will be collected from all participants. These samples will be used for the extraction and analysis of circulating tumour deoxyribonucleic acid (ctDNA). Genetic profiles will be analysed by the central lab NGS testing, and then used to explore the relationship between changes in biomarkers and response to treatment. In addition, innate and acquired resistance mechanisms may be explored. The analytical method will be used is described in Section 9.4.2.3.

8.5.3 Storage and destruction of samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Sample storage and destruction will be performed according to the central labs' policy and China HGR regulations. DNA is a finite resource that may be used up during experiments. The results of any further analyses will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

All genetic testing and analysis in resistance mechanisms assessment and exploratory biomarker analysis will be performed after China HGR approved. Mutation testing residual plasma samples collected will be destroyed. The remaining tissue sections will be returned to the subjects.

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared with final amendments completed prior to database lock.

9.1 Statistical Hypotheses

There is no statistical hypothesis associated with the study objectives. As such, no statistical tests will be performed. The analyses of efficacy, safety and tolerability will primarily be descriptive.

9.2 Sample Size Determination

Approximately 40 participants will be screened to enrol 35 subjects into the study. With the

assumption of expected ORR as 60%, the sample size of 35 subjects will provide the 95% confidence interval estimation as [42.2%, 78.2%], assuming a potential dropout rate for loss to follow-up as 10%.

9.3 Populations for Analyses

The full analysis set (FAS) will include all enrolled participants who have received at least 1 dose of study intervention. The FAS will be used for all efficacy analyses and safety analyses unless specified otherwise.

9.4 Statistical Analyses

The SAP will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.4.1 General Considerations

All statistical analyses will be conducted using SAS version 9.4 or later. For continuous variables, the summarization will include number, mean, median, standard deviation, minimum and maximum. For categorical variables, this will include frequency counts and percentages at each category. Results of all statistical analyses will be summarized with descriptive statistics and presented with a 95% confidence interval estimate if applicable. Missing data will be assumed missing at random or missing completely at random. In general, no imputation will be applied unless otherwise specified.

9.4.2 Efficacy

Investigator RECIST 1.1-based assessments

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. All assessment results will be utilized to determine the endpoints of ORR, PFS and DoR. For detailed description of RECIST 1.1 please refer to section 8.1.1..

At each visit, participants will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, PD, or NE depending on the status of their disease compared with baseline and previous assessments. Baseline status will be assessed within the 28 days prior to the first dose of study intervention. The tumour response endpoints (PFS, ORR, and duration of response [DoR]) will then be derived from the baseline scan dates and overall visit responses dates.

9.4.2.1 Primary Endpoint(s)

Objective Response Rate

ORR (per RECIST 1.1 using Investigator assessments) is defined as the proportion of participants who achieved a complete or partial response as their best overall response based on

RECIST 1.1 as assessed by the investigator, where the response must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Participants who discontinue treatment without progression, or who receive a subsequent therapy and then respond will not be included as responders in the ORR calculation, where the denominator will always be the total number of participants in FAS.

ORR will be presented as s percentage, with the corresponding 95% confidence interval using the Clopper-Pearson (exact) method.

Subgroup Analysis
Subgroup analyses will be conducted using same method as described above, in the following subgroups of the FAS (but not limited to) as applicable:

- ECOG/WHO PS (0 vs. 1)

Other baseline variables may also be assessed if there is clinical justification. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors.

9.4.2.2 Secondary Endpoint(s)

9.4.2.2.1 Progression-Free Survival

PFS will be defined as the time from first dose of study intervention until progression per RECIST 1.1 as assessed by the investigator or death due to any cause prior to PD.

Participants who have not progressed or died at the time of analysis will have PFS right-censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the participant progresses or dies after 2 or more consecutive missed visits, PFS will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. (Note: NE visit is not considered as missed visit).

If the participant has no evaluable visits or does not have baseline data, PFS will be censored at Day 1, unless they die within 2 visits of baseline in which case their date of death will be used as an event.

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

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

- For investigator assessments, the date of progression will be determined based on the earliest RECIST assessment/scan dates of the component that indicates progression.

- When censoring PFS, right-censoring will be at the latest of the scan dates contributing to a particular overall visit assessment.

Analysis Methods

The analysis of secondary endpoint, PFS, (based on Investigator assessment) will occur when approximately 21 progression events have been observed in the 35 participants (approximately 60% PFS maturity). Kaplan-Meier method will be used to estimate the median PFS and its 95% confidence interval.

Kaplan-Meier plots of PFS will be presented. Summaries of the number and percentage of participants experiencing a PFS event and the type of event (RECIST 1.1 PD or death) will be provided.

9.4.2.2.2 Overall Survival

OS is defined as the time from the first dose of treatment to the date of death, regardless of the actual cause of the subject's death. For participants who are still alive at the time of data analysis or who are lost to follow up, OS will be right-censored at the last recorded date that the participant is known to be alive prior to or at the data cut-off date for the analysis.

The efficacy analysis of OS will be performed on the FAS.

The analysis of OS will occur when approximately 21 death events have been observed in the 35 participants (approximately 60% maturity). Results will be analysed with the same method as PFS.

9.4.2.2.3 Analysis of duration of response

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

The analysis of DoR will be based on the responding patients. Analysis method of DoR will be same as PFS.

9.4.2.2.4 Analysis of disease control rate

DCR is defined as the percentage of subjects who have a best overall response of CR or PR or SD by RECIST 1.1 as assessed by the Investigator. For participants with a best overall response of SD, a RECIST assessment of SD must have been observed at least 6 weeks following enrolment to be included in the numerator of the calculation for disease control rate. This is to

enable sufficient follow-up to establish SD.

Disease Control Rate will be summarized and presented as percentage, with 95% confidence interval estimated using Clopper-Pearson exact method.

9.4.2.2.5 Analysis of depth of response

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

9.4.2.2.6 Analysis of time to treatment failure or death

Time to treatment failure (TTF) or death is defined as defined as the time from first dose of study intervention (osimertinib) to earlier of the date of last study intervention administration or death due to any cause. Any participant not known to have permanently discontinued study intervention and not known to have died at the time of the analysis will be censored at the last known time on which the participant was known to be alive. Kaplan-Meier method will be used to estimate the median TTF and its 95% confidence interval.

9.4.2.2.7 Analysis of time to first subsequent therapy or death

Time to first subsequent therapy (TFST) or death is defined as the time from first dose of study intervention to the earlier of the date of anti-cancer therapy (except cisplatin or carboplatin or pemetrexed) start date following study intervention discontinuation or death due to any cause. Any participant not known to have had a subsequent therapy or not known to have died at the time of the analysis will be censored at the last known time to have not received subsequent therapy. Kaplan-Meier method will be used to estimate the median TFST and its 95% confidence interval.

9.4.2.3 Exploratory Endpoint

9.4.2.3.1 [redacted]

[redacted]

9.4.3 Safety

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs (pulse and BP), ECG, LVEF, and ECOG PS. These will be collected for all enrolled participants and will be summarized per descriptive analysis.

Adverse events (coded both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by participant. Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within 28 days of discontinuation of study intervention and prior to start of a new anti-cancer treatment will be included in the AE summaries. Any events in this period that occur after a participant has received further therapy for cancer (following discontinuation of study intervention) will be flagged in the data listings.

The AE/SAE incidence rate, ≥grade 3 AE/SAE incidence rate (AE/SAE graded by CTCAE v5), related AE incidence rate, and discontinuation rate due to AE will be summarized by MedDRA system organ class and preferred term.

The clinical chemistry, hematology, urinalysis results, vital signs (pulse and blood pressure); physical examination; weight; LVEF; ECG parameters and ECOG PS will be summarized by visit if applicable. The abnormalities with above measurement will be summarized by visit as well.

SAE reconciliation between AZ global safety database and clinical study database must be performed monthly, and a final reconciliation performed prior to database lock to ensure that all SAEs have been received by AZ global safety database. Data Management Manager is accountable for performing the reconciliation.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organisation but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [IB or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.

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

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

Participants who are rescreened are required to sign a new ICF.**Data Protection**

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Unless previously specified, the biomarker data will have unknown clinical significance and AstraZeneca will not provide biomarker assessment results to participants, their family members, any insurance company, any employer, a clinical study investigator, a general physician, or any other third party, unless required to do so by law.

The participant's samples will not be used for any purpose other than those described in the study protocol.

A 5 Committees Structure

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

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on the CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years from the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants. The first act of recruitment is the first site open.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any Contract Research Organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before

submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

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

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

B 2 Definitions of Serious Adverse Event

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

- Results in death.
- Is immediately life-threatening.
- Requires in-participant 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 participant or may require medical treatment to prevent one of the outcomes listed above.

Life threatening

"Life-threatening" means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

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

Important medical event or medical treatment

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

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

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

Adverse Events (AEs) for malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as Serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (i.e., it is not the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

Intensity rating scale:

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

Intensity is assessed according to the following scale:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a “reasonable possibility” that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as "not related".

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

B 4 Medication Error

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

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

Medication error includes situations where an error:

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

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

- Drug name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, for example, wrong route or wrong site of administration.
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature.
- Wrong participant received the medication.
- Wrong drug administered to participant.

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

- Participant accidentally missed drug dose(s) eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose).
- Participant failed to return unused medication or empty packaging.
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product.

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent specifically to the subsequent use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research. The participant will be presented with the option to opt out of the subsequent use of the donated samples during the withdrawal process. If the participant decides to opt out, then the donated samples will be disposed of. If the participant withdraws consent without opting out for the subsequent use of the donated samples, then the samples will be used as per protocol.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.

- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

Category A pathogens are infectious substances meeting these criteria which cause disease in humans or both in humans and animals. They must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

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

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

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

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

Appendix D Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

Introduction

This appendix details the implementation of RECIST 1.1 guidelines [1]. Investigator assessments will use the RECIST 1.1 guidelines described in this appendix.

Imaging modalities and acquisition specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumour assessment of TLs, NTLs and NLs is provided in **Table 10**.

Table 10 Summary of Imaging Modalities for Tumour Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT MRI	CT MRI Plain X-ray Chest X-ray	CT MRI Plain X-ray Chest X-ray Bone scan (Scintigraphy) ^{18}F-fluoro-deoxyglucose-PET/CT

CT=computed tomography; PET/CT=positron emission tomography/CT; MRI=magnetic resonance imaging.

Computed Tomography and Magnetic Resonance Imaging

CT with IV contrast is the preferred imaging modality (although MRI with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumour assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumour assessor (eg, radiologist), and method of tumour assessment (eg, RECIST 1.1) are used consistently for each participant throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumour assessment schedule as closely as possible (refer to the SoA), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artefacts (eg, heart, major blood vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal

resolutions; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

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

a. Anatomic coverage: Optimal anatomic coverage for most solid tumours is the chest-abdomen (-pelvis). Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual participants. Because a lesion later identified in a body part not scanned at baseline would be considered as a NL representing PD, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

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

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

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

1 Chest-abdomen (-pelvis) CT with IV CT contrast (most preferred).
2 Chest CT without IV-contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study.
3 Chest-abdomen (-pelvis) CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the participant has compromised renal function.

4 Chest-abdomen (-pelvis) MRI with IV MRI contrast, if CT cannot be performed at any time during the study.

b. IV contrast administration: Optimal visualisation and measurement of metastases in solid tumours require consistent administration (dose and rate) of IV contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumour lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given participant. Oral contrast is recommended to help visualise and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤5 mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses >5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

Chest X-ray

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

Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTLs and followed by the same method per baseline assessment (CT, MRI, or X-ray).

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. NLs may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that time point.

^{18}F-Fluoro-deoxyglucose-PET/CT

^{18}F-fluoro-deoxyglucose positron emission tomography(PET)/CT scans may be used as a method for identifying new extrahepatic lesions (but not intrahepatic lesions) for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[1] not present on baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the ^{18}F-fluoro-deoxyglucose-PET scan. The PET portion of the PET/CT introduces additional data that may bias an investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

At present, low-dose or attenuation correction CT portions of a combined ^{18}F-fluoro-deoxyglucose-PET/CT scan are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumour assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an investigator if it is not routinely or serially performed.

Ultrasound

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

Other tumour assessments

Clinical examination

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

Endoscopy and laparoscopy

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

1 A positive ^{18}F-fluoro-deoxyglucose-PET scan lesion should be reported only when an uptake (eg, standard uptake value) greater than twice that of the surrounding tissue or liver is observed.

Histology and cytology

Histology or tumour markers on tumour biopsy samples will not be used as part of the tumour response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumour response assessment as per RECIST 1.1.

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

Measurability of tumour lesions at baseline

RECIST 1.1 measurable lesions at baseline

A tumour lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis[2] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. Please see additional RECIST 1.1 guidance below on measurability of intrahepatic hepatocellular carcinoma lesions and porta hepatis lymph nodes.

Non-measurable lesions at baseline

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component).
  - Leptomeningeal disease.
  - Ascites, pleural effusion, or pericardial effusion.
  - Inflammatory breast disease.
  - Lymphangitic involvement of skin or lung.
- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline).[3]
- Previously irradiated lesions.[4]
- Brain metastasis.

Special considerations regarding lesion measurability at baseline

- Bone lesions:

[2] The short axis is defined as the longest in-plane axis perpendicular to the long axis.
[3] Lymph nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.
[4] Localised post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

  - Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability.
  - Blastic lesions are considered non-measurable.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same participant, these should be selected over cystic lesions as TLs.

RECIST 1.1 TL selection at baseline

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TLs at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

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

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases for TL assessment at baseline

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.

- Tumour lesions selected for newly acquired screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a NL.

RECIST 1.1 NTL selection at baseline

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

Evaluation of tumour response and progression

RECIST 1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumour visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimetres. The sum of the diameters for all TLs at each follow-up visit will be compared with the baseline sum of diameters (for response or SD) or to the smallest prior (nadir) sum of diameters (for progression) (Table 11).

Special cases for TL assessment at follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention (eg, definitive radiotherapy, embolisation, surgery, transarterial chemoembolisation, etc) during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 CRF for the current imaging visit and all subsequent visits. If a TL has been completely removed (surgery) or disappears, the longest diameter should be recorded as 0 mm.

Table 11 **RECIST 1.1 Evaluation of Target Lesions**

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.
PR	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
SD	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
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.
NE	Only relevant if any of the TLs at follow-up were not assessed or NE (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
Not applicable	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.

RECIST 1.1 NTL assessment at follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator (Table 12).

To achieve “unequivocal progression” on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit unequivocal progression by NTLs. A modest “increase” in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PD of target disease will therefore be extremely rare.

Table 12 **RECIST 1.1 Evaluation of Non-Target Lesions**

CR	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of 1 or more NTLs.
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
NE	Only relevant when 1 or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For participants 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	Only relevant if no NTLs present at baseline.

CR=complete response; NE=not evaluable; NTL=non-target lesion; PD=progression of disease; TL=target lesion.

RECIST 1.1 NL identification at follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the CRF. The presence of 1 or more NLs is assessed as progression. The finding of a NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumour. If a NL is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the previously (pre-existing) NL has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a NL and will indicate PD.

RECIST 1.1 evaluation of overall visit response at follow-up

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

Table 2 RECIST 1.1 Overall Visit Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Visit Response
CR	CR	No	CR
CR	NA	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE or NA	No	PR

Target Lesions	Non-Target Lesions	New Lesions	Overall Visit Response
SD	Non PD or NE or NA	No	SD
NE	Non PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Non-CR/Non-PD for overall response if only NTL (no TLs) are present at baseline.
Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.
CR=complete response; NA=not applicable (only relevant if there were no TLs or NTLs at baseline), NE=not evaluable; NTL=non-target lesion; PD=progression of disease; PR=partial response; SD=stable disease; TL=target lesion.

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

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

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Appendix E Contraception Requirements

Contraception requirements for this study are as follows.

E 1 Female Participants

Women of Childbearing Potential (WoCBP) are defined as women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.

Women not of childbearing potential are defined as those who are permanently or surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or who are post-menopausal.

Women who have undergone tubal occlusion should be managed on trials as if they are of WoCBP (eg, undergo pregnancy testing etc., as required by the study protocol).

Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy, or had radiation-induced menopause with last menses >1 year ago, or had chemotherapy-induced menopause with last menses >1 year ago.

Women of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a non-sterilised male partner must use at least 1 highly effective method of contraception (Table 3). They should have been stable on their chosen method of birth control for a minimum of 2 weeks before entering the study and continue to use it throughout the total duration of the drug treatment and the drug washout period (42 days after the last dose of study intervention).

Female participants should refrain from breastfeeding throughout this period.

E 2 Male Participants with a Female Partner of Childbearing Potential

Non-sterilised male participants (including males sterilised by a method other than bilateral

orchidectomy, eg, vasectomy) who intend to be sexually active with a female partner of childbearing potential must be using an acceptable method of contraception from the time of screening throughout the total duration of the treatment and the drug washout period (6 months after discontinuing chemotherapy or at least 4 months after discontinuing osimertinib) to prevent pregnancy in a partner.

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male participants should refrain from sperm donation or banking throughout this period.

Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period (Table 3).

E 3 Highly Effective Methods of Contraception

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in Table 3.

Table 3 Highly Effective Methods of Contraception (<1% Failure Rate)

Non-Hormonal Methods	Hormonal Methods
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) • Vasectomised sexual partner plus male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • Tubal occlusion plus male condom • Intrauterine device (provided coils are copper-banded) plus male condom	• Injection: Medroxyprogesterone injection (eg, Depo-Provera®)[a] plus male condom • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a] plus male condom • Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) plus male condom • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) plus male condom • Combined pill: Normal and low dose combined oral contraceptive pill plus male condom • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) plus male condom • Mini pill: Progesterone based oral contraceptive pill using desogestrel plus male condom. Cerazette® is currently the only highly effective progesterone-based pill

[a] Hormonal methods not prone to drug-drug interactions.

The following methods are considered not to be highly effective and are therefore not acceptable contraceptive methods in AstraZeneca clinical trials:

- Triphasic combined oral contraceptives (COCs)
- All progesterone only pills except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing Intra-Uterine Devices (IUDs)
- Fertility awareness methods
- Coitus interruptus

Appendix F Concomitant Medications

F 1 Guidance Regarding Potential Interactions with Concomitant Medications

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

DRUGS INDUCING OR INHIBITING CYTOCHROME P450 (CYP) 3A4/5 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMENDS ARE NOT COMBINED WITH STUDY INTERVENTION

Osimertinib is metabolised by CYP3A4 and CYP3A5 enzymes. Therefore, inhibitors or inducers of CYP3A4/5 may increase or decrease exposure, respectively, to osimertinib.

A drug-drug interaction study of osimertinib evaluated in patients showed that there is potential for osimertinib being a victim when co-administered with strong inducers of CYP3A4 (osimertinib concentrations are decreased when co-dosed with rifampicin).

The following potent inducers of CYP3A4 should not be used during this study for any participant receiving osimertinib.

Drugs inducing CYP3A4

Contraindicated drugs	**Withdrawal period prior to Study treatment start**
Carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentin St John's Wort	3 weeks
Phenobarbitone	5 weeks

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

Table 4 Drugs known to be inhibitors of CYP3A4/5

Strong CYP3A4/5 inhibitors (should not be combined)	**Moderate CYP3A4/5 inhibitors** (permitted with caution)
boceprevir	amprenavir
clarithromycin	aprepitant
conivaptan	atazanavir
elvitegravir/ritonavir	casopitant
fluconazole	cimetidine
grapefruit juice[a,b]	ciprofloxacin
indinavir	crizotinib
itraconazole	cyclosporine
ketoconazole	darunavir
lopinavir/RIT	diltiazem
mibefradil	dronedarone
nefazodone	erythromycin
nelfinavir	grapefruit juice[b]
posaconazole	imatinib
ritonavir	schisandra sphenanthera
saquinavir	tofisopam

Table 4 Drugs known to be inhibitors of CYP3A4/5

Strong CYP3A4/5 inhibitors (should not be combined)	**Moderate CYP3A4/5 inhibitors** (permitted with caution)
telaprevir telithromycin tipranavir/ritonavir troleandomycin voriconazole	verapamil

[a] Double-strength grapefruit juice

[b] Participants should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice [120 mL] or half a grapefruit or 1 to 2 teaspoons [15 g] of Seville orange marmalade daily)

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4/5 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

If the investigator feels that concomitant administration of medications or herbal supplements that strongly modulate CYP3A4/5 is essential (eg, to treat AEs), osimertinib treatment should be discontinued.

MEDICINES WHOSE EXPOSURES MAY BE AFFECTED BY OSIMERTINIB THAT ASTRAZENECA CONSIDERS MAY BE ALLOWED WITH CAUTION

Osimertinib may increase the concentration of sensitive BCRP and Pgp substrates (concentration of the sensitive BCRP substrate, rosuvastatin and sensitive Pgp substrate, fexofenadine, are increased).

Table 5 Exposure, Pharmacological Action, and Toxicity May be Increased by Osimertinib

Drug with Warning of Possible Interaction	Advice
Rosuvastatin	Drugs are permitted but caution should be exercised and participants monitored closely for possible drug interactions. Please refer to the full Prescribing Information for all drugs prior to co-administration with study intervention.
Sulfasalazine	
Doxorubicin	
Daunorubicin	
Topotecan	
Dabigatran	
Aliskiren	
Digoxin	

DRUGS THAT PROLONG QT INTERVAL

The drugs listed in this section are taken from information provided by the Arizona Centre for Education and Research on Therapeutics (ArizonaCert) website (https://www.crediblemeds.org/). The website categorises drugs based on the risk of inducing Torsades de Pointes (TdP).

During screening, the drugs that participants are currently using (prescription and non-prescription) should be checked opposite the ArizonaCert website. In addition, drugs intended for use during study intervention should be checked opposite the website.

Drugs with a known risk of Torsades de Pointes

The following drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended.

Before study intervention

These drugs **must** have been discontinued prior to the start of administration of study intervention in accordance with guidance provided in Table 6.

During study intervention

It is recommended that these drugs are not co-administered with study intervention considered essential for participant management to co-administer these drugs with study intervention, close monitoring with ECGs and electrolytes is recommended.

The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such, investigators are recommended to search the website to provide the most up to date information.

Table 6 Drugs with a Known Risk of Torsades de Pointes

Drug Name	**Withdrawal Period Prior to Study Intervention Start[b]**
Anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine, terlipressin	2 days
Cilostazol, cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days
Azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide[a], ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, probucol, vandetanib	4 months
Amiodarone, chloroquine	1 year

[a] Estimated value as pharmacokinetics of arsenic trioxide has not been studied.

[a] Check for the latest updates on this list of drugs on the ArizonaCert website to ensure accuracy.

Other TdP risk Categories

Participants receiving drugs that prolong QT interval or may increase the risk of TdP from other TdP risk categories can be enrolled, notwithstanding other exclusions and restrictions, if these drugs are considered essential for participant management, and the participant has been stable on therapy. Close monitoring with ECGs and electrolytes is recommended.

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

Guidance regardless of TdP risk category

During study intervention and for a period of 2 weeks after discontinuing study intervention, if it is considered essential for participant management to co-administer drugs known to prolong corrected QT interval, **regardless of TdP risk category**, close monitoring with ECGs and electrolytes is recommended.

F 2 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies

Restricted, prohibited, and permitted concomitant medications/therapies are described in Table 7, Table 8, and Table 9. Refer also to the dose modification guidelines for management of

study intervention-related toxicities in Section 0.

Table 7 Restricted medications/therapies

Medication/class of drug/therapy	Usage (including limits for duration permitted and special situations in which it's allowed)
Hormonal therapy	For non-cancer-related conditions (eg, hormone replacement therapy) only
Corticosteroids and/or bisphosphonates	For the treatment of bone metastases and for the treatment of specific adverse drug reactions (refer to Toxicity Management Guidelines document)
Foods or medications that are moderate inducers or inhibitors of CYP3A4/5.	See Appendix F 1

CYP3A4/5=Cytochrome P450 3A4/5.

Table 8 Prohibited medications/therapies

Prohibited medication/class of drug/therapy	Usage
Any anticancer therapy other than those under investigation in this study (including curative radiotherapy)	Must not be given concomitantly while the participant is on study intervention
Herbal and natural remedies that may interfere with interpretation of study results	Must not be given concomitantly unless agreed by the Sponsor
Foods or medications that are strong inducers or inhibitors of CYP3A4/5 , which are deemed to impact the pharmacokinetics of study medications	Must not be given concomitantly unless agreed by the Sponsor (See Appendix F 1)

CYP3A4/5=Cytochrome P450 3A4/5.

Table 9 Supportive medications/therapies

Supportive medication/class of drug/therapy	Usage
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate adverse event management, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator except for those medications identified as "prohibited," as listed in Table 8
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc]) except for those medications identified as "prohibited," as listed above	Should be used, when necessary, for all participants except for those medications identified as "prohibited," as listed in Table 8
Corticosteroids and/or bisphosphonates for the treatment of bone metastases and for the treatment of specific adverse drug reactions (refer to Toxicity Management Guidelines document)	Permitted

Supportive medication/class of drug/therapy	**Usage**
Inactivated viruses, such as those in the influenza vaccine	Permitted

Appendix G Calculated Creatinine Clearance

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Men

For serum creatinine concentration in mg/dL:

$$\textbf{CrCl} \text{ (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}^{b}) \times 1.0}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\textbf{CrCl} \text{ (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}^{b}) \times 1.0}{0.81 \times \text{serum creatinine (mg/dL)}}$$

[a] Age in years.
[b] Weight (wt) in kilograms.
Source: Cockcroft and Gault 1976.

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Women

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in µmol/L:

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

[a] Age in years.
[b] Weight (wt) in kilograms.
Source: Cockcroft and Gault 1976.

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

Appendix H Abbreviations

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse Event
eCRF	electronic Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DCO	Data cut off
ctDNA	Circulating tumour deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
EGFRm	Epidermal growth factor receptor mutations
FSI	First Subject In
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IP	Investigational Product
ITT	Intention To Treat
IV	Injection of vein
KM	Kaplan-Meier
LSI	Last Subject In
LSLV	Last Subject Last Visit
NGS	Next-generation sequencing technology
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PI	Principal Investigator
p.o.	Orally
RA	Research Agreement
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event

Abbreviation or special term	Explanation
TKI	Tyrosine kinase inhibitor
WoCBP	Women of childbearing potential

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