A Single Arm Phase II Study: Osimertinib in Patients with Stage 4 Non-small Cell Lung Cancer with Uncommon *EGFR* Mutations
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Statement of Compliance and Signature Page

STUDY TITLE: A Single Arm Phase II Study: Osimertinib in Patients with Stage 4 Non-small Cell Lung Cancer with Uncommon EGFR Mutations

This study will be conducted in compliance with the protocol approved by the Institutional Review Boards of Duke University Health System and The Ohio State University, according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible. The signature below constitutes the approval (by the PI) of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local and state legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
AUC	Area Under the Curve
BIRC	Blinded Independent Central Review
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMax	Peak Concentration
CMin	Trough Concentration
CR	Complete Response
CRF	Case Report Form (sometimes referred to as Clinical Report Form). A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CMP	Comprehensive Metabolic Panel
CRT	Chemotherapy-Radiation Therapy
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events; National Cancer Institute, Version 4.0
CYP34A	Cytochrome P450 3A4
CTQA	Clinical Trials Quality Assurance
DCI	Duke Cancer Institute
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DSMB	Data and Safety Monitoring Board
DUHS/DUMC	Duke University Health System/Duke University Medical Center
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
FDA	Food and Drug Administration
H&P	History & Physical Exam
HRPP	Human Research Protections Program
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
IV (or iv)	Intravenously
IRB	Institutional Review Board

NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PI	Principal Investigator
PK	Pharmacokinetic
p.o.	per os/by mouth/orally
PR	Partial Response
PRO	Patient Reported Outcomes
PS	Performance status
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
SOC	Safety Oversight Committee
TKI	Tyrosine Kinase Inhibitor
ULN	Upper Limit of Normal
WBC	White Blood Cells

STUDY SCHEMA

1. Histologically confirmed Stage 4 NSCLC
2. TKI Treatment naive
3. *EGFR* mutation testing by CLIA certified laboratory with exon 18 G719X, exon 20 S768I, or exon 21 L861Q
4. PS of 0-1
5. Adequate organ function
6. Ejection fraction ≥ 45%
7. Measurable Disease per RECIST 1.1

Osimertinib until disease progression, unacceptable toxicity or withdraw of consent

1.0 PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

1.1 Protocol Synopsis

This is a single arm phase 2 study to investigate the activity of osimertinib in patients with stage 4 non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation exon 18 G719X, exon 20 S7681, or exon 21 L861Q. Patients will be epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment naïve. The study will use RECIST 1.1 for assessment of efficacy and Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. [1]

Primary Objective: Objective response rate (ORR) as assessed by investigator using RECIST 1.1

Secondary Objectives:

1. Progression free survival (PFS) using RECIST as assessed by the investigator
2. Safety
3. Overall survival (OS)

Exploratory objectives:

1. Estimate the response rate and PFS in the specific mutation subsets of exon 18 G719X, exon 20 S7681, exon 21 L861Q or compound mutations

Hypotheses: Osimertinib has demonstrated activity in patients with *EGFR* exon 19 or exon 21 L858R mutations, and with the resistance mutation exon 20 T790M and is currently approved by the United Sates Food and Drug Administration for this patient population. There no approved targeted therapies for patients with *EGFR* mutations of exon 18 G719X, exon 20 S7681, or exon 21 L861Q. This study will investigate the activity of osimertinib in patients with these *EGFR* mutations to determine if a larger prospective clinical trial should be pursued.

1.2 Research Summary

For patients with advanced NSCLC which harbor activating *EGFR* exon 19 deletion and exon 21 L858R mutations first-line therapy with EGFR tyrosine kinase inhibitor (TKI) (e.g. erlotinib, gefitinib, or afatinib) is the standard first-line therapy.[2-5] *EGFR* exon 19 deletion and exon 21 L858R mutations are the majority of *EGFR* mutations.[6,7] The United States Food and Drug Administration (FDA) approval for epidermal tyrosine kinase inhibitors is restricted to these specific mutations. In addition to these exquisitely sensitive mutations, there are other *EGFR* mutations identified present in 4% of NSCLC with adenocarcinoma. Several of the less common

EGFR mutations have demonstrated sensitivity to EGFR TKI such as exon 18 G719A, G719C, and G719S (approximately 6% of *EGFR* mutations), exon 20 S768I (approximately 1.5% of *EGFR* mutations) and exon 21 L861Q (approximately 3% of EGFR mutations).[8] EGFR TKIs have demonstrated activity in patients with uncommon *EGFR* mutations (defined as exon 18 G719X, exon 20 S768I, or exon 21 L861Q) but the ORR and PFS are lower. A subset analysis of phase 3 trials demonstrated activity of afatinib demonstrated activity, but 40% of patient required dose reduction related EGFR-associated adverse events.[9,10] The standard first-line therapies for patients with NSCLC which harbor these mutations is pembrolizumab alone or in combination with chemotherapy, and at the time of disease progression is single agent chemotherapy or single agent immunotherapy.[11-15] There is not a targeted therapy approved for this patient population.

For patients with an EGFR exon 19 or exon 21 L858R mutation who have progressed on first-line EGFR TKI and have an exon 20 T790M mutation osimertinib is the standard and the FDA approved therapy.[16-18] Osimertinib retains the activity against the activating *EGFR* mutation, with activity against the resistance T790M resistance mutation, and less EGFR associated adverse events since there is relative sparing of the EGFR wild-type receptor. The FDA approved dose of osimertinib is 80 mg daily.

This single arm study will investigate the activity of osimertinib in patients with *EGFR* exon 18 G719X, exon 20 S768I, or exon 21 L861Q mutations to determine if it has sufficient activity and an acceptable safety profile for further investigation.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Disease Background

The rate of epidermal growth factor (EGFR) mutations in non-small cell lung cancer (NSCLC) with adenocarcinoma histology is approximately 15%.[6,7] For patients with NSCLC with EGFR exon 19 deletion and exon 21 L858R point mutations first-line therapy with a EGFR tyrosine kinase inhibitor (TKI) (e.g. gefitinib, erlotinib or afatinib) is the standard of care. The current FDA approval for these three agents is specifically for these activating mutations. EGFR TKI activity in *EGFR* mutant NSCLC with these activating mutations is due to the increased binding of the TKI compared to the binding of ATP leading to inhibition of the EGFR pathway and upregulation of pro-apoptotic pathway.[19]

In addition to these exquisitely sensitive mutations, there are other EGFR mutations identified present in 4% of NSCLC with adenocarcinoma.[20] Several of the uncommon mutations have demonstrated sensitivity to EGFR TKI such as exon 18 G719A, G719C, and G719S (approximately 6% of EGFR mutations), exon 20 S768I (approximately 1.5% of EGFR mutations) and exon 21 L861Q (approximately 3% of EGFR mutations).[8] These mutations have activation of the EGFR pathway without the increased affinity for the EGFR TKI observed in the EGFR exon 19 deletion and exon 21 L858R mutation.[19] The inhibitory concentration of first generation EGFR TKI required is higher in these mutations compared to EGFR exon 19 deletion,

and the response rate to first generation reversible EGFR TKIs rarely exceed 55%.[8] Patients with uncommon EGFR mutations were enrolled in two phase 3 trials of afatinib, an irreversible EGFR TKI, compared to platinum-based chemotherapy.[4,5] In a retrospective analysis of the two phase 3 trials, afatinib is associated with a response rate of greater 55%, especially in NSCLC EGFR mutations G719X, L861Q, and S768I.[4,5,9] However, the subset of patients with G719X, L861Q and S768I EGFR mutations were 18 patients, 16 patients, and 8 patients, respectively. This study reveals activity of EGFR TKI's in patients with these mutations. However, approximately 40% of patients treated with afatinib 40 mg daily require a dose reduction, largely related to EGFR-related adverse events, which raises concerns about the tolerability of this agent.[10] A post-hoc analysis of the patients assigned to afatinib in two phase 3 trials did not reveal a difference in progression-free survival (PFS) between patients who underwent dose reduction in the first 6 months and those who did not.[21] However, patients with uncommon mutations represent a small subset of patients (approximately 10% of patients, n=52), and efficacy data are not available from this subset.

The fundamental problems with assessment of EGFR TKI activity in this uncommon mutation subtypes has been that most of the data are retrospective and consisted of small subsets.[22] The definition of "uncommon" mutation has varied from study to study which further complicates the assessment of the efficacy. There is concern that the first generation EGFR TKIs (gefitinib, erlotinib) do not achieve the necessary inhibitory concentration, and afatinib has issues with tolerability and the frequent need for dose reduction. Collectively these mutations represent a significant proportion the *EGFR* mutant patient population.

Current therapy

The current standard first-line therapy is a platinum doublet for patients with stage 4 disease and uncommon *EGFR* mutations. Platinum and pemetrexed has an objective response rate (ORR) of approximately 30% and a median PFS 4 to 5 months in patients with an *EGFR* mutation.[18,23] The standard second-line therapies are immunotherapy and docetaxel. A response rate of approximately 5-10% and median PFS of approximately 3 months are observed with docetaxel, and with immunotherapy a response rate of 20% is observed in the intent-to-treat patient population. The response rate is estimated to be lower in the *EGFR* mutant patient population.[13-15,24] In subset analyses of phase 3 trials of immunotherapy compared to docetaxel a survival benefit was not observed with immunotherapy in the *EGFR* mutation subset.[13-15]A higher mutational burden and a history of smoking is associated with benefit from immunotherapy, and patients with *EGFR* mutant NSCLC have lower mutational burden and frequently a history of never smoking or light smoking.[25] These clinical and biomarker data have raised questions about the activity of immunotherapy in patients with *EGFR* mutant NSCLC.

Recently the second and third-line approval of erlotinib was rescinded by the FDA. Afatinib is approved in the second-line setting only for squamous histology NSCLC. This limits the availability of EGFR TKIs in the second-line setting for patients with *EGFR* mutations besides the exon 19 deletions and exon 21 L858R mutation. Thus, there are limited effective options for patients with uncommon *EGFR* mutations.

2.2 Study Agent

The T790M gatekeeper resistance mutation is located in the hinge region of the ATP-binding pocket of the EGFR kinase domain where the bulky methionine side chain prevents binding of first-line EGFR TKI.[26] In contrast to first-generation inhibitors, osimertinib (AZD9291, TAGRISSO) is a potent irreversible inhibitor of both the single *EGFR* mutant (TKI-sensitivity-conferring mutations) and dual EGFR mutant/T790M (TKI resistance-conferring mutation) forms of EGFR. As a result, osimertinib has the potential to provide clinical benefit to patients with advanced NSCLC harboring both the single sensitivity mutations and the T790M resistance mutation following prior therapy with an EGFR TKI.

In vitro studies have shown osimertinib (AZD9291, Tagrisso) to be a potent and selective irreversible inhibitor of isolated wild-type and mutant EGFRs (IC50s <10 nm). Cell line EGFR phosphorylation assays demonstrated potent inhibition of single-activated (EGFR mutant) and double-T790M mutant (EGFR mutant/T790M) assays, with much weaker inhibition towards wild-type EGFR. *In vitro* washout and time-dependent cellular kinetic studies demonstrated an irreversible mechanism of action of osimertinib. Oral treatment of mice bearing *EGFR* mutant and *EGFR* mutant/T790M exograft tumors leads to profound tumor growth regression. In contrast, higher doses of osimertinib were required to achieve significant tumor growth inhibition in wild-type *EGFR* xenograft models. Xenograft growth regression with osimertinib was accompanied by dose-and time-dependent pharmacodynamic inhibition of phospho-EGFR and the key downstream biomarkers phospho-AKt and phospho-ERK across mutant and wild-type EGFR disease models *in vivo*. Furthermore, chronic longer term oral treatment with osimertinib led to complete and sustained macroscopic disappearance of an EGFR mutant xenograft tumor. In support of this hypothesis, the *EGFR* mutant cell line showed greater time to resistance in response to the osimertinib treatment *in vitro* compared to earlier generation EGFR inhibitors. The active metabolites of AZD9291, AZD5104 and AZ7550, showed similar pharmacological selectivity and activity profiles to parent, although AZ5104 showed a smaller margin of selectivity against wild-type EGFR in vitro.

2.3 Preclinical and Clinical Trial Data

Non-clinical pharmacology

Non-clinical in vitro studies have demonstrated potent inhibition of mutant EGFR activity in biochemical enzyme assays and across NSCLC cell lines harbouring clinically relevant EGFR mutations (T790M, L858R and exon 19 deletion), with lower activity against wild-type EGFR. Moreover, osimertinib has caused profound tumour regression across representative mutant EGFR xenograft and transgenic disease models in vivo at clinically relevant concentrations, which was accompanied by dose and time dependent pharmacodynamic target effects.

Taken together, in vitro and in vivo non-clinical studies have provided strong support that osimertinib is more potent towards mutant EGFR compared with wild-type EGFR.

Osimertinib has two active metabolites, AZ5104 and AZ7550. The geometric mean exposure area under the plasma concentration time curve (AUC) of each metabolite (AZ5104 and AZ7550) was approximately 10% of the exposure of osimertinib at steady-state. AZ7550 displays near identical pharmacology properties in vitro to osimertinib. In contrast, AZ5104 has greater potency against mutant and wild-type EGFR in vitro than osimertinib, which suggests this metabolite may have a smaller selectivity margin compared with mutant EGFR than osimertinib.

Osimertinib is a highly selective inhibitor of mutant EGFR, showing minimal off-target kinase activity when tested in a broad biochemical kinome panel, only showing significant potency against 18 other kinases (including ACK1, BLK, ErbB2, ErbB4, BRK, MLK1, MNK2), although the clinical significance of this biochemical activity remains unclear.

Osimertinib, AZ5104 and AZ7550 inhibited the hERG-encoded potassium channel with IC50 values of 0.69 μM, 17.48 μM and >33 μM, respectively.

There were no notable effects on the respiratory, visual, central nervous or cardiovascular systems in safety pharmacology studies. Reductions in gastric emptying and small intestinal transit were observed in rats.

Pharmacokinetics and drug metabolism in animals

Osimertinib is a moderately permeable compound in Caco-2 cells and has good absorption properties in rats and dogs. Osimertinib plasma protein binding is high (>94%) across mouse, rat, dog, monkey and in human plasma (94.7%). [14C]Osimertinib related material was shown to distribute to all tissues in a rat quantitative whole-body autoradiography (QWBA) study and there was also evidence that [11C]osimertinib and its active metabolite [11C]AZ5104 penetrated the blood-brain barrier (BBB) in a cynomolgus monkey PET study. In mouse, rat, dog and human hepatocytes, osimertinib metabolism was primarily to hydroxylated and dealkylated products with conjugation to a range of glutathione, cysteineglycine, glucuronide and sulphate conjugates with all human metabolites also produced by rat and dog hepatocytes.

The major route of osimertinib excretion in rats and dogs was via the feces with only minor elimination observed in urine. In vitro data supports CYP3A4/5 as the major enzyme responsible for the metabolism of osimertinib and its two active metabolites AZ5104 and AZ7550. These data led to the conduct of clinical drug-drug interaction (DDI) studies with itraconazole (strong CYP3A4 inhibitor) and rifampicin (strong CYP3A4 inducer). In vitro, osimertinib showed potential to inhibit intestinal breast cancer resistance protein (BCRP) and CYP3A4 that led to the conduct of clinical DDI studies with rosuvastatin (BCRP substrate) and simvastatin (CYP3A4 substrate).

Toxicology

The principal histopathological findings following daily oral dosing of osimertinib in rats and dogs were consistent with inhibition of wild-type EGFR. In a rat female fertility study osimertinib was associated with a reversible increase in post-implantation loss. Osimertinib had marked adverse effects on embryonic survival plus early postnatal viability and growth when administered to pregnant or lactating rats. Osimertinib has shown no genotoxic or phototoxic potential. The integrated non-clinical safety data supports the continued clinical development of osimertinib in the patient populations studied in the ongoing clinical studies.

Clinical data

At the data cut-off date (DCO) of 12 November 2016, 2777 subjects have been exposed to study treatment (osimertinib alone, osimertinib in combination with another treatment, or comparator) in AstraZeneca-sponsored clinical studies. Of these, 2141 NSCLC patients and 118 healthy volunteers have been exposed to osimertinib (osimertinib alone [2080] or osimertinib in combination with another treatment [179]) in the ongoing osimertinib AstraZeneca-sponsored clinical program, and an additional 4188 NSCLC patients have participated in the osimertinib Expanded Access Program. The key findings from the clinical program to date are summarized below.

Clinical pharmacokinetics

Osimertinib pharmacokinetic parameters have been characterized in healthy subjects and NSCLC patients. Based on population pharmacokinetic analysis, osimertinib apparent plasma clearance is 14.2 L/h, apparent volume of distribution is 997 L and terminal half-life is approximately 48 hours. The area under the plasma concentration-time curve (AUC) and maximal plasma concentration (Cmax) of osimertinib increased dose proportionally over 20 mg to 240 mg dose range (i.e, 0.25 to 3 times the recommended dosage) after oral administration and exhibited linear pharmacokinetics (PK). Administration of osimertinib orally once daily resulted in approximately 3-fold accumulation with steady state exposures achieved after15 days of dosing. At steady state, the Cmax to Cmin (minimal concentration) ratio was 1.6-fold.

The median time to Cmax of osimertinib was 6 hours (range 3 to 24 hours). The absolute bioavailability of TAGRISSO is 70% (90% CI 67, 73). Neither food nor gastric pH affects the exposure of osimertinib.

In vitro, plasma protein binding of osimertinib is 94.7% (5.3% free). Osimertinib has also been demonstrated to bind covalently to rat and human plasma proteins, human serum albumin and rat and human hepatocytes.

In vitro studies indicate that osimertinib is metabolized predominantly by CYP3A4/5. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in the plasma after oral administration. The geometric mean exposure (AUC) of each metabolite (AZ5104 and AZ7550) was approximately 10% of the exposure of osimertinib at steady-state.

Osimertinib is primarily eliminated in the feces (67.8%) and to a lesser extent in the urine (14.2%). Unchanged osimertinib accounted for approximately 2% of the elimination.

Based on in vitro studies, osimertinib is a competitive inhibitor of CYP 3A4/5 but not CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at clinically relevant concentrations.

In vitro, osimertinib is not a substrate of OATP1B1 and OATP1B3 and does not inhibit P-gp, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2K at clinically relevant concentrations. Based on in vitro studies, osimertinib is a substrate of P-glycoprotein and BCRP, but is unlikely to result in clinically relevant drug interactions

Based on clinical DDI studies, interactions with strong CYP3A4 inhibitors are unlikely but strong CYP3A4 inducers can decrease the exposure of osimertinib. Osimertinib may also increase the exposure of co-administered BCRP substrates. Clinical PK interactions with co-administered CYP3A4 substrates are unlikely.

No clinically significant differences in the pharmacokinetics of osimertinib were observed based on age, sex, ethnicity, body weight, smoking status, mild or moderate or severe renal impairment (creatinine clearance [CLcr] >15 mL/min by Cockcroft-Gault) or mild or moderate hepatic impairment (mild: total bilirubin less than or equal to the upper limit of normal [ULN] and aspartate aminotransferase [AST] greater than ULN or total bilirubin between 1 to 1.5 times ULN and any AST; moderate: total bilirubin between 1.5 to 3 times ULN and any AST). As patients with CLcr less than 15 mL/min, patients on dialysis, or patients with severe hepatic dysfunction were not included in the clinical trials, the appropriate dose of osimertinib has not been established in these patients.

Based on an analysis of dose-exposure response relationships over the dose range of 20 mg (0.25 times the recommended dose) to 240 mg (3 times the recommended dose), no apparent relationship between osimertinib exposure and objective response rate, duration of response and progression-free survival was identified. Over the same dose range, increased exposure led to increased probability of adverse reactions, specifically rash, diarrhea and interstitial lung disease (ILD). A pharmacokinetic/pharmacodynamic analysis in AURA2 suggested a concentration-dependent QTc interval prolongation of 14 msec (upper bound of two-sided 90% confidence interval [CI]: 16 msec) at a dose of 80 mg orally (PO).

In summary, the clinical pharmacology package provides characterization of the key PK and ADME characteristics of osimertinib and provides confirmatory data in support of the 80 mg dose and adequate labelling for special populations. From a clinical PK perspective, these data support a once daily fixed 80 mg PO dose for this advanced NSCLC population.

Renal Impairment

A formal clinical study to investigate the impact of severe renal impairment on osimertinib PK is planned. In Study 11 (14C-ADME) osimertinib, AZ5104 and AZ7550 were shown to undergo negligible renal clearance; however, as renal impairment can adversely affect some pathways of hepatic / gut metabolism, the impact of renal impairment was assessed in the population PK analysis.

In the population PK analysis, there was no impact of creatinine clearance on the PK of osimertinib (N=1086, median (min-max) baseline creatinine clearance of 82 [20.5 to 196] mL/min). Based on a population pharmacokinetic analysis of 471 patients with mild renal impairment (CLcr 60 to <90 mL/min), 208 patients with moderate renal impairment (CLcr 30 to <60 mL/min), 5 patients with severe renal impairment (CLcr 15 to <30 mL/min) and 402 patients with normal renal function (≥90 mL/min), osimertinib apparent clearance (and exposure) were similar. Osimertinib can be administered to patients with mild, moderate and severe renal impairment (CLcr ≥15 mL/min) without any dose adjustments. Caution should be exercised when treating patients with end stage renal impairment (CLcr <15 mL/min)

Hepatic impairment

In Study 11, osimertinib was shown to undergo significant metabolism mediated clearance presumably with the liver as a major site of biotransformation and hence, hepatic impairment might be expected to lead to increased exposure of osimertinib

A clinical study investigating the impact of mild and moderate hepatic impairment (as assessed by Child-Pugh criteria) on osimertinib pharmacokinetics is ongoing (Study 08). In AURA Phase I, AURA extension and AURA2 patients were excluded if they had:

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

No clinical studies have been conducted to specifically evaluate the effect of hepatic impairment on the pharmacokinetics of osimertinib. Population PK analysis of 104 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST), 8 patients with moderate hepatic impairment (total bilirubin between 1.5

times to 3.0 times ULN and any AST) and 972 patients with normal hepatic function (total bilirubin ≤ULN and AST ≤ULN), osimertinib apparent clearance (and exposures) were similar. Hence, no dose adjustment is necessary for mild or moderate hepatic impairment. Due to no patients with severe hepatic dysfunction being evaluated in the clinical trials, dose recommendation is not available for subjects with severely impaired hepatic function.

Food

The impact of food on the bioavailability of osimertinib was evaluated in NSCLC patients in a definitive study (Study 09) at the 80 mg dose with the film-coated tablet (the proposed commercial formulation). The geometric least square (LS) mean ratios comparing fed to fasted treatments for osimertinib Cmax and AUC0–72 were 92.75% (81.40, 105.68) and 106.05% (94.82, 118.60), respectively and were contained within the predefined equivalence limits of 70% to 143%. Administration of the tablet with a high-fat meal did not affect median osimertinib tmax when compared with fasted conditions.

An exploratory earlier assessment of the impact of food was also conducted in healthy volunteers in Study 05 (Part B) at 20 mg dose using the Phase 1 tablet formulation. Although this study was not powered to meet the criteria of a formal food effect study and used a fixed-sequence, 2-period design, point estimates and 90% CIs of the ratios comparing fed to fasted treatments for osimertinib Cmax and AUC were also contained within the limits of 70% to 143.

Based on the results from the definitive food effect study (Study 09) and supporting results from the exploratory study (Study 05, Part B) it is recommended that osimertinib can be taken with or without food.

Clinical efficacy

First-line locally advanced or metastatic NSCLC patient population

In first-line (treatment-naïve) NSCLC patients, a total of 60 patients received PO treatment with osimertinib in the AURA Phase I study (30 patients each at 80 mg and 160 mg respectively). The overall ORR was 77% (95% CI: 64, 87) and the overall disease control rate (DCR) was 98% (95% CI: 89, 100). The median PFS was 19.3 months, with maximum duration of response (DoR) at 22.1 months. The percentage of patients remaining progression-free at 12 months was 72% (95% CI: 59, 82) and at 18 months 55% (95% CI: 41, 67).

2nd line or greater, T790M mutation positive, advanced NSCLC patient population

The AURA3 study demonstrated superior efficacy of osimertinib compared to chemotherapy in patients with advanced EGFR T790M mutation positive NSCLC, whose disease has progressed on or after EGFR TKI therapy:

- For the primary objective of progression free survival (PFS) by Investigator assessment, at 59.7% maturity, there was a statistically significant and clinically meaningful improvement in PFS for patients on osimertinib 80 mg PO once-daily vs. those on chemotherapy based on investigator assessment (hazard ratio [HR]: 0.30, 95% CI: 0.23, 0.41; p-value: <0.001), indicating a 70% reduction in risk of disease progression or death (in the absence of a Response Evaluation Criteria In Solid Tumours [RECIST] progression) in the osimertinib arm. Treatment with osimertinib resulted in a 5.7-month improvement in median PFS compared to chemotherapy (10.1 months [95% CI: 8.3, 12.3] vs. 4.4 months [95% CI: 4.2, 5.6]).

  The superiority of osimertinib over chemotherapy for PFS was independent of chemotherapy regimen used in the study, and was maintained across all predefined demographic or disease subgroups.

  The median PFS by Blinded Independent Central Review (BICR) assessment was 11.0 months (95% CI: 9.4, not calculable [NC]) in the osimertinib arm and 4.2 months (95% CI: 4.1, 5.6) in the chemotherapy arm, (HR: 0.28, 95% CI: 0.20, 0.38; p<0.001).

- The objective response rate (ORR; unadjusted) by investigator assessment was 70.6% (95% CI: 64.9, 75.9) in the osimertinib arm vs. 31.4% (95% CI: 23.9, 39.8) in the chemotherapy arm. There was a clinically meaningful and statistically significant improvement in ORR in the osimertinib arm compared with the chemotherapy arm, with an odds ratio (OR) of 5.39 (95% CI: 3.47, 8.48) (p-value: <0.001).

- The median DoR (51.9% maturity) based on the investigator assessment was 9.7 months (95% CI: 8.3, 11.6) in the osimertinib arm vs. 4.1 months (95% CI: 3.0, 5.6) in the chemotherapy arm. There was a statistically significant improvement in expected DoR (EDoR) for patients on osimertinib compared with those on chemotherapy (ratio of EDoR: 6.22; 95% CI: 4.04, 9.57; p-value: <0.001).

- The analysis of overall survival (OS) was performed at 26.0% overall maturity. The HR of OS was 0.72 (99.96% CI: 0.34, 1.52). A numerical advantage in OS for patients on osimertinib compared to patients on chemotherapy was observed, which did not reach statistical significance (p-value 0.121). The median OS was not calculable in either arm, the lower limit of the 95% CI was 20.53 months in the osimertinib arm and 20.47 months in the chemotherapy arm

- Analysis of patient-reported outcomes (PRO) findings demonstrated a statistically significant difference (p≤0.001) in mean change from baseline between osimertinib and chemotherapy during the overall time period from randomisation until 6 months, for all 5 pre-specified key lung cancer symptoms (cough, dyspnoea, pain in chest, fatigue, and appetite loss); with prolonged time to deterioriation for dyspnea and cough.

- The CNS metastases efficacy analysis results in AURA3 demonstrate the superior efficacy of osimertinib compared to chemotherapy in patients with CNS metastases. A BICR assessment of CNS efficacy in patients with CNS metastases at baseline showed a clinically meaningful improvement for patients randomised to receive osimertinib vs. chemotherapy. The improvements in CNS efficacy outcomes were consistent across multiple analyses (ORR of 70% vs 31.3%, OR of 5.13 with a p-value of 0.015; DoR 8.9 months vs 5.7 months; PFS 11.7 months vs 5.6 months, for osimertinib vs. chemotherapy, respectively). Efficacy findings in the osimertinib arm of the AURA3 study were consistent with those in the pooled Phase II studies. The pooled single arm Phase II studies (AURA extension and AURA2) support the consistency and durability of effect of osimertinib 80 mg PO once-daily in a broader population of patients (including second [2nd] line and ≥third [3rd] line therapy) with advanced EGFR T790M mutation positive NSCLC with longer follow up.

- The pooled confirmed ORR in the evaluable-for-response analysis set based on blinded independent central review (BICR; primary analysis) was 66.0% (95% CI: 61.1, 70.7).

- The durability of response was confirmed with a longer follow-up: the BICR assessed median DoR for the pooled analysis (44.3% maturity) was 12.5 months (95% CI: 11.1, NC). Based on a KM analysis, the estimated percentage of patients remaining in response at 9 months was 65.0% (95% CI: 58.5, 70.6) and 52.9% (95% CI: 45.9, 59.4) at 12 months.

- The median PFS in the full analysis set (FAS) was 11.0 months (95% CI: 9.6, 12.4) based on BICR assessment.

- The median follow-up for OS was 13.4 months, however OS data were still immature. The median OS and upper limit were not calculable but the lower limit was 16.4 months

- Overall, the efficacy variables determined by both BICR and investigator assessment showed similar results.

- A BICR assessment of CNS efficacy in a subgroup of patients with CNS metastases from the pooled Phase II studies showed consistent results with the AURA3 analysis. ORR in patients was 54.0% (95% CI: 39.32, 68.19); 80.4% of patients remained in response at 6 months and 75.4% at 9 months. The Kaplan-Meier (KM) estimated percentage of patients alive and CNS progression-free at 6 and 12 months was 72.1% (95% CI: 56.8, 82.8) and 56.3% (95% CI: 39.9, 69.9), respectively.

In summary, the Phase III AURA3 study demonstrated clear evidence of overall favorable efficacy of osimertinib compared with the standard of care, chemotherapy. The CNS metastases efficacy analysis results in AURA3 also demonstrated the superior efficacy of osimertinib compared to chemotherapy in patients with CNS metastases. The overall efficacy and CNS

efficacy findings from the pooled single arm Phase II studies support the consistency and durability of effect of osimertinib in a broader population of patients (including 2nd-line and ≥3rd-line therapy) with advanced EGFR T790M mutation-positive NSCLC with longer follow-up and are consistent with the efficacy observed with osimertinib in AURA3

2.4 Clinical safety and Rationale for Dose Selection, Regimen, and Treatment Duration

Osimertinib 80 mg PO once-daily dose, approved by the FDA, has an acceptable safety profile for the intended advanced NSCLC population. The standard clinical practice is to continue targeted therapies until disease progression or unacceptable toxicity.

In the AURA3 study:

The overall incidence of all causality AEs was 97.8% for the osimertinib arm and 99.3% for the chemotherapy arm. Regardless of causality, the majority of all adverse events (AEs) reported with osimertinib were mild or moderate in severity. Adverse events of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 were reported for a lower proportion of patients in the osimertinib arm than in the chemotherapy arm: 63 (22.6%) vs. 64 (47.1%) patients, with 16 (5.7%) and 46 (33.8%)% of CTCAE Grade ≥3 considered related treatment by the investigator for osimertinib and chemotherapy respectively. A number of serious adverse events (SAEs) were reported for patients in the osimertinib arm than the chemotherapy arm: 50 [17.9%] vs. 35 [25.7%] patients. SAEs considered to be possibly related to study drug were less common in the osimertinib arm (8 [2.9%] patients) than the chemotherapy arm (17 [12.5%] patients)

During the treatment period or 28-day follow-up period, death was due to disease under investigation plus a fatal AE in 0.7% of patients in each treatment arm; death due to a fatal AE only occurred in 0.7% osimertinib vs. no chemotherapy patients. All other deaths were due to disease under investigation only.

Osimertinib is well tolerated. Adverse events leading to discontinuation (6.8% osimertinib arm vs 10.3% chemotherapy arm), dose reduction (2.9% osimertinib arm vs 12.5% pemetrexed, 28.6% cisplatin, 10.6% carboplatin of the chemotherapy arm), or dose interruption/delay (12.9% osimertinib arm vs 20.6% pemetrexed, 11.9% cisplatin, and 16.0% carboplatin) were low and less common in the osimertinib arm than in the chemotherapy arm.

The most commonly reported AEs (ie, >15%) in the osimertinib arm vs the chemotherapy arm, respectively were: diarrhea (40.5% vs. 11.0%), rash ([grouped terms] 33.7% vs. 5.9%), dry skin (18.6% vs. 4.4%), decreased appetite (17.9% vs. 36.0%), paronychia (16.5% vs. 1.5%), cough (16.5% vs.14.0%), nausea (16.1% vs. 49.3%), and fatigue (15.8% vs. 27.9%).

In the osimertinib clinical program:

ILD or ILD-like adverse reactions (eg, pneumonitis) were reported in 3.5% and were fatal in 0.6% (5 patients) of the 833 patients who received osimertinib in AURA studies (who received at least one dose of 80 mg in the 2nd-line or later setting). The incidence of ILD was 8.2% in patients of Japanese ethnicity, 1.9% in patients of non-Japanese Asian ethnicity and 2.9% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 2.7 months.

Osimertinib leads to a predicted drug-related QTc interval prolongation at the 80 mg dose of 14.2 msec with an upper bound (90% CI) of 15.8 msec, but with no evidence that this is associated with an increased risk of cardiac arrhythmias or Torsades de Point (TdP). In safety dataset of 833 patients in AURA studies treated with osimertinib 80 mg, 0.7% (n=6) were found to have a QTc greater than 500 msec, and 2.9% (n=24) had an increase from baseline QTc greater than 60 msec.

Based on the available clinical trial data, a causal relationship between changes in cardiac contractility and osimertinib has not been established.

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

AstraZeneca considers there to be a reasonable possibility of a causal relationship between osimertinib, keratitis and related corneal disorders.

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.

Evaluation for potential liver toxicity has shown no apparent association of osimertinib with drug induced liver injury. In the Phase II studies approximately 5% of patients reported AEs of elevations in alanine aminotransferase (ALT) or AST and the vast majority of these elevations were Grade 1 or 2 changes.

There is no apparent association of osimertinib with renal toxicity.

Safety findings in the pooled single-arm Phase II studies were generally consistent with those observed in the osimertinib arm of AURA3. The most commonly reported AEs with osimertinib were low-grade gastrointestinal (GI) disturbances (primarily diarrhea) and skin effects (mainly rashes and acnes, paronychia, and dry skin).

An increased incidence in the ILD reporting rate has been reported for the combination of durvalumab and osimertinib in Study D5160C00006 (the TATTON study). This study showed an incidence rate of 29.4% for pneumonitis/ILD-like events, at a data cut-off of 12 July 2016,

compared with an overall frequency of pneumonitis (including both non serious and serious cases) of around 2% for durvalumab monotherapy across all doses and indications and an overall frequency of pneumonitis/ILD of 2.4% for osimertinib monotherapy.

In Phase I Clinical Pharmacology studies in healthy volunteers osimertinib was generally well tolerated without any significant safety concerns. The healthy volunteer dose limit is set to 80 mg as a single oral dose. Further details are provided in the osimertinib IB version 8.

Clinical experience: Osimertinib Adverse Events

Gastrointestinal tract effects

Osimertinib can cause gastrointestinal tract side effects. Osimertinib has not been associated with gastrointestinal perforations or hemorrhagic diarrhea. No events leading to dehydration or renal failure have been reported. Investigators are advised to follow the general toxicity management guidelines regarding dose interruption and reduction as detailed in Section 9.

Dermatological effects

Osimertinib can cause dermatological side effects (diarrhea, rashes, acnes, paronychia and dry skin). No severe bullous, blistering or exfoliative skin conditions have been reported. Investigators are advised to follow the general toxicity management guidelines regarding dose interruption and reduction as detailed in Section 9.

Ocular surface effects

Keratitis and related corneal disorders have been reported with Osimertinib use. Investigators are advised to follow the general toxicity management guidelines regarding dose interruption and reduction as detailed in Section 9.

Cardiovascular effects

Osimertinib leads to a predicted drug-related QTc interval prolongation at the 80 mg dose, but with no evidence that this is associated with an increased risk of cardiac arrhythmias or Torsades de Point (TdP). Based on available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. Investigators are advised to follow the general toxicity management guidelines regarding dose interruption and reduction as detailed in Section 9.

Respiratory effects

ILD or ILD-like adverse reactions (eg, pneumonitis) have been reported in in patients who received Osimertinib who received at least one dose of 80mg in the 2nd line or later setting. An

increased incidence in the ILD reporting rate has been reported for the combination of durvalumab and osimertinb study (TATTON). Investigators are advised to follow the general toxicity management guidelines regarding dose interruption and reduction as detailed in Section 9.

Liver effects

In the Phase II studies, approximately 5% of patients reported AEs of elevations in alanine aminotransferase (ALT) or AST. The vast majority of these elevations were Grade 1 or 2 changes.

Hematopoietic effects

Osimertinib is known to have hematopoietic side effects. Decreases from baseline in median values for platelets, neutrophils and leukocytes 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 the CTCAE grade. Investigators are advised to follow the general toxicity management guidelines regarding dose interruption and reduction as detailed in Section 9.

Reproductive organ effects

No reproductive toxicology or teratogenicity studies have been conducted with osimertinib to date, although the male and female reproductive tracts have been assessed as part of the 1-month toxicology studies.

Renal effects

There is no apparent association of osimertinib with renal toxicity.

3.0 STUDY RATIONALE

3.1 Trial Summary

Abbreviated Title	TOP 1703
Trial Phase	II
Clinical Indication	Stage IV NSCLC (TKI naïve with EGFR mutations: exon 18 G719X, exon 20 S7681 or exon 21 L861Q
Trial Type	Therapeutic treatment
Type of control	Open Label
Route of administration	Tablet(s) taken P.O. (by mouth)
Trial Blinding	Unblinded, open-label
Study Treatment Group	Single Arm Single daily dose of Osimertinib 80mg on days 1-28 of each study cycle.
Number of trial subjects	37
Estimated enrollment period	Approximately 3 years; first patient in First Quarter 2018.
Estimated duration of trial	Estimated at 5 years from the first patient in to last subject's final 2 year follow-up
Duration of Participation	Active study treatment until progression or study treatment not tolerated followed for a maximum of 2 years after completion of study therapy.

3.2 Design and Procedure

This is an open label single arm phase 2 trial of osimertinib with the primary end-point of objective response rate (ORR) as assessed by the investigator, and uses Simon's optimal 2-stage design. All patients will receive the FDA approved dose of osimertinib of 80 mg daily.

3.3 Selection of Subjects

Patients with stage 4 non-small cell lung cancer who have undergone testing for EGFR mutations in a CLIA certified lab will be screened for study participation. Patients are required to demonstrate one of the following EGFR mutations: exon 18 G719X, exon 20 S7681 or exon 21 L861Q. Additional details or the eligibility criteria are in section 5.0

3.4 Duration of Study

At a rate of 1 to 2 patients per month, we expect that trial will take approximately 19~37 months to reach its target accrual if it will not be terminated earlier due to lack of efficacy according to the two-stage design. Patients will continue study therapy until disease progression, unacceptable

toxicity or withdraw of consent. Patients who discontinue therapy for reasons other than disease progression will be followed for disease progression. After discontinuing study therapy patients will be followed for overall survival every 3 months by telephone or review of medical records until death or a maximum of 2 years from discontinuation of study therapy.

4.0 OBJECTIVES AND ENDPOINTS

Table 1

	Objective	Endpoint	Analysis
Primary	Objective response rate	Patients experiencing a confirmed partial or complete response using RECIST 1.1 (appendix 4)	See Section 22
Key Secondary	Progression-free survival	Time from starting study therapy until disease progression using RECIST 1.1 or death (whichever occurs first) (appendix 4)	See Section 22
Key Secondary	Safety	Common Terminology Criteria for Adverse Events (CTCAE) to assess adverse events	See Section 22
Key Secondary	Overall survival	Time from starting study therapy until death	See Section 22
Exploratory secondary	ORR and PFS in the specific mutation subsets of exon 18 G719X, exon 20 S7681, exon 21 L861Q or compound mutations	RECIST 1.1 (appendix 4)	See section 22

5.0 SUBJECT ELIGIBILITY

The following guidelines are to assist physicians in selecting patients from whom protocol therapy is safe and appropriate. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this study treatment is appropriate. For entry into the study, the following criteria MUST be met.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria. For time limits on imaging and blood tests please refer to on-study Tests and Procedures Table.

1. EGFR mutations as performed on a CLIA certified laboratory demonstrating EGFR exon 18 G719X, exon 20 S768I, or exon 21 L861Q. Patients with compound (also referred to as multiple mutations) will be eligible provided the NSCLC demonstrates one of these mutations).
2. Histological or cytological confirmation diagnosis of Stage 4 NSCLC per AJCC v7.
3. Measurable disease by RECIST 1.1 (please refer to appendix 4)
4. The following laboratory values obtained ≤ 14 days prior to study initiation.
   a. Hematology: ANC ≥ 1, 500 / ml, platelet count, ≥ 100,000 / ml, hemoglobin ≥ 9.0 g / dl

   Hepatic:
   b. ALT or ALT < 2.5 times ULN if no demonstrable liver metastases or <5 times ULN in the presence of liver metastases
   c. Total bilirubin < 1.5 times ULN if no liver metastases or < 3 times ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or liver metastases

   Renal: Cockcroft-Gault calculated creatinine clearance of ≥ 45 ml/min or creatinine ≤1.5 x ULN
5. Have normal QT interval on ECG evaluation QT corrected of ≤ 450 ms in males or ≤ 470 ms in females obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine-derived QTc value
6. Cardiac ejection fraction of ≥ 45%
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or1
8. Negative pregnancy test done ≤7 days (or per institutional policy) prior to treatment, for women of childbearing potential only. Female must use highly effective contraceptive measures, and must have a negative pregnancy test or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:
   a. Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments.
   b. Women under 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous

hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution

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

9. Male subjects must be willing to use barrier contraception
10. Age ≥ 18 years
11. Provision of written informed consent prior to any study-specific procedures

5.2 Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

1. Prior therapy with EGFR TKI therapy
2. Greater than 2 lines of prior systemic therapy for metastatic non-small cell lung cancer.
3. Any cytotoxic chemotherapy or other anticancer drugs from previous treatment regimen or clinical study within 14 days of first dose of study drug.
4. Treatment with an investigational drug within 5 half-lives of the compound
5. Other active malignancy ≤ 2 years prior to study enrollment. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. NOTE: If there is a history of prior malignancy, patients must **not** be receiving other specific treatment (i.e. hormonal therapy) for their cancer
6. Prior radiotherapy ≤ 14 days
7. Untreated symptomatic brain metastases (treated brain metastases are allowed provided > 14 days have elapsed from completion of radiotherapy and patient is neurologically stable as assessed by treating physician).
8. Malabsorption syndrome, 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
9. Detection of concurrent *EGFR* mutation with exon 20 T790M, exon 19 deletion, exon 21 L858R mutation or exon 20 insertion. Patients with compound (also referred to as multiple mutations) will be excluded if the molecular testing includes one of these mutations
10. Active pregnancy or breast-feeding: Pregnant women are excluded from this study because the effects of osimertinib on the development of the fetus are unknown, and there is potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with osimertinib, breastfeeding should be discontinued if the mother is treated with these agents.
11. Grade ≥ 2 blurred vision, conjunctivitis, corneal ulcer, dry eye, or keratitis
12. Men who intend to father children during the study or within 4 months afterward are excluded
13. Major surgery within 4 weeks of first dose of study drug.

14. Any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of starting study treatment, with the exception of alopecia or neuropathy
15. Currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inducers of CYP3A4 (at least 3 weeks prior) (Appendix 2).
16. Significant medical history or unstable medical comorbidities, including but not limited to:
    a. Heart disease including congestive heart failure (NYHA Grade II or greater); unstable angina; prior myocardial infarction (NSTEMI or STEMI) within 6 months prior to study enrollment; hypertension with a systolic blood pressure of >150 mm Hg **or** diastolic blood pressure of >100 mm Hg while on antihypertensive medication
    b. Any clinically significant abnormalities in rhythm, conduction or morphology of resting ECG e.g. complete left bundle branch block, third degree heart block and second degree heart block.
    c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as 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
    d. Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease
    e. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses
    f. Active infection or ongoing antiviral medication for viral infections including hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). Screening for chronic conditions is not required. HIV-positive participants on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with osimertinib.
    g. Ongoing use of warfarin (injectable low-molecular weight heparins are permitted). Patients must be off warfarin for > 7 days prior to enrollment

5.2 Protocol Eligibility Waivers

No waivers of inclusion or exclusion criteria will be granted. All prospective patients must meet all entry criteria prior to enrollment in the study. If there are any questions regarding the interpretation of an eligibility criterion for a potential patient, contact the principal investigator to discuss the potential patient to confirm eligibility.

6.0 INCLUSION of WOMEN and MINORITIES

There are no exclusions based on gender, race or ethnicity in this trial.

7.0 REGISTRATION PROCEDURE

Patient registration for all patients signing informed consent will be completed through the Duke Cancer Institute (DCI) Clinical Research Unit (CRU) into EPIC and ONCORE systems within 1 business day of obtaining consent. Patients will be enrolled only after all pre-treatment evaluations are completed and all eligibility criteria are met.

7.1 Registration for Outside Sites

All patients signing informed consent at outside sites must be registered with Duke (including screen failures- indicate screen failure status on last page of eligibility checklist). The following documents are to be completed by the investigator and/or designee and faxed to (919)-684-8926 or scanned/emailed to the Thoracic Oncology Protocol Office (Thoracic-multisite@dm.duke.edu): All supporting documents should be sent de-identified.

- TOP 1703 Eligibility Checklist with supporting source documents
- Signed Informed Consent

8.0 STUDY PERIODS (Visit Requirements):

The Schedule of Events (Table 4) summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

For the purpose of scheduling evaluations and to allow for patient and investigator schedules, holidays and weather or other emergencies requiring clinical facilities to be closed, a window of 7 days will be applied to all study visits unless otherwise noted.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and or AstraZeneca for reasons related to subject safety.

TABLE 4: Schedule of Events

Assessment	Screening[1] Days -28 to 0	D1 of every Cycle[1,2,13]	End of Study Treatment (EOT)[3]	Follow-up [2,4,9]
Informed consent	X			
Inclusion/exclusion Criteria	X			
Demography Baseline Characteristics, Smoking Hx	X			
Medical History[5]	X	X	X	
Prior NSCLC therapies	X			
Physical exam & vital signs[5]	X	X	X	
Height	X			
ECOG Performance Status	X	X	X	
CBC with differential[6]	X	X	X	
Serum Chemistries[7]	X	X	X	
Serum pregnancy test[8]	X	X		
CT scan chest/abdomen[9]	X	X[9]		
Brain MRI[9]	X	X[9]		
Echocardiogram /MUGA[12]	X			
EKG[10]	X			
Tumor Histology	X			
EGFR mutation status	X			
Adverse event assessment	X	X	X	
Study drug and diary[11]		Provide & Review	X	
Concomitant Meds	X	X	X	
Subsequent Therapy and Survival Status				X

[1]Within 28 days prior to Day 1 of study therapy unless otherwise noted. If screening (baseline) hematology and serum chemistries performed within 14 days of D1 of cycle 1, these do not need to be repeated.
[2] Unless otherwise noted, a window of 7 days will be applied to all study visits.
[3]This visit should occur 30 days (+/- 3 days) after study therapy stops for whatever reason (adverse event, progression, or at discretion of the investigator). Patients who have an ongoing grade 4 AE or SAE at the time of discontinuation from study treatment will be contacted every 2 weeks until the event is resolved, determined to be irreversible by the investigator, or until the patient begins an alternate form of treatment. If patient is unable to make appointment due to health reasons (e.g. patient admitted to hospice) or the visit would place an undue burden on the patient in the assessment of the treating physician this visit may be omitted.
[4] Long-term follow up will occur every 3 months from the last administration of protocol-directed therapy for a maximum of 2 years or until death, whichever occurs first. Subsequent therapy and survival status will be documented. If molecular testing performed (e.g. molecular testing of tumor biopsy or circulating tumor DNA) the results of the testing will be recorded if available. NOTE: follow-up may occur via phone or review of medical records, on-site visits are not required.
[5]Complete history at baseline only, thereafter focused history on symptoms/adverse event. Patients will need baseline evaluation for unexplained eye symptoms to exclude corneal ulceration. Any eye symptoms on study should be referred for full ophthalmologic exam. Vital sign assessment should include B/P, pulse temperature and oxygen saturation. Weight will be taken at screening and Day 1 of every cycle.
[6]This includes CBC with differential (auto or manual) and platelet count
[7]Serum chemistries include blood urea nitrogen (BUN), creatinine, bilirubin, ALT (SGPT), AST (SGOT), alkaline phosphatase. Additional laboratory tests can be ordered if clinically indicated or at the discretion of the investigator but are not required by the protocol
[8]Within 7 days of D1 (or institutional policy) of treatment with study therapy in women of childbearing potential
[9] CT scan chest and abdomen. MRI of the brain should be performed at baseline on all subjects and with every disease assessment in patients with known brain metastases to assess for intracranial disease progression. Patients without brain metastases will undergo repeat brain imaging as clinically indicated, and patients with brain metastases will undergo repeat imaging every 3 cycles starting with cycle 4 (i.e., cycle 4, 7, 10, 13 etc). CT scan are done on day 1 of cycle 3, and then on cycles 5, 7, 9, 11, and 13 (every 2 cycles for the first year of study therapy), then every 3 cycles (i.e. 16, 19, 22) until disease progression. Patients who discontinue therapy for reasons other than disease progression will be followed for disease progression. The imaging schedule is at the discretion of the treating physician, but the recommended interval is every 6 to 12 weeks. Tumor imaging starting with D1 of cycle 5 may take place within 7 days prior to the study visit to accommodate holiday, weekends, and transportation issues.
[10] EKGs to be obtained in triplicate. EKGs consist of 12-lead studies performed within a 5 minute window after at least 10 minutes rest in supine position. Repeat EKGs may be performed at the discretion of the investigator or per institutional standard.
[11] On C1D1 provide the patient medication diary for use. D1 of all subsequent cycles patient diary is to be collected from previous cycle, reviewed with the patient, and a new diary provided. Collect at EOT if not returned earlier.
[12] Echocardiogram or MUGA scan to assess LVEF, testing to be repeated if clinically indicated based on assessment of the investigator or per institutional standard.
[13]To be completed prior to dispensing next cycle.

8.1 Screening

The following procedures and tests are to be performed within **28** days (unless otherwise specified) of study enrollment to confirm eligibility. Baseline and Cycle 1 Day 1 procedures may be completed on the same day, however, screening assessments to confirm eligibility **MUST** have already been determined. Refer to Table 4 for details.

1. Informed consent
2. Review of past medical history and previous therapies for NSCLC
3. Eligibility criteria review (Inclusion/exclusion)
4. Demography/Baseline characteristics, smoking history
5. A directed physical examination will be performed at the visit with vital signs including pulse, blood pressure, temperature, oxygen saturation, weight
6. Height
7. ECOG Performance status
8. Routine blood work (CBC, chemistries)
9. EKG in triplicate
10. Echocardiogram/Muga to assess LVEF
11. Pregnancy test if applicable
12. Tumor Histology
13. EGFR mutation status
14. Review of baseline sign/symptoms
15. Review of concomitant medications
16. Staging Disease assessment: Brain MRI, CT scan of chest and abdomen

8.2 On-Study Treatment Period: Day 1 of each cycle or as noted in Table 4

1. Review of interval medical history, concomitant medications and assessment of performance status
2. A directed physical examination will be performed at the visit with vital signs including pulse, blood pressure, temperature, oxygen saturation, weight
3. Laboratory: chemistry, and hematology
4. A repeat ECG may be performed at the discretion of the investigator or per institutional standard.
5. Echocardiogram/MUGA will be repeated if clinically indicated based on assessment of the investigator or per institutional standard
6. MRI of the brain to be performed with every 3 cycles starting with cycle 4 (cycles 4, 7, 10, 13 etc…) in patients with known brain metastases to assess for intracranial disease progression. Patients without brain metastases will undergo repeat brain imaging as clinically indicated.
7. Adverse event assessment
8. Review of study drug and diary
9. Pregnancy test (if applicable)

10. CT Chest/abdomen are done on day 1 of cycle 3, and then on cycles 5, 7, 9, 11, and 13 (every 2 cycles for the first year of study therapy). Then every 3 cycles (i.e. 16, 19, 22).

8.3 End of Study Treatment (30 days (+/- 3 days) after study therapy stops)

1. Review of interval medical history since the last visit and assessment of performance status
2. A directed physical examination will be performed at the visit with vital signs including pulse, blood pressure, temperature, oxygen saturation, weight
3. Laboratory: chemistry and hematology

8.4 Follow-up Period

1. After discontinuing study therapy patients will be followed for overall survival every 3 months by telephone or review of medical records until death or a maximum of 2 years. **Subsequent therapy and survival status will be documented.** If molecular testing performed (e.g. molecular testing of tumor biopsy or circulating tumor DNA) the results of the testing will be recorded if available. Patients who discontinue therapy for reasons other than disease progression will be followed for disease progression. The imaging schedule is at the discretion of the treating physician, but the recommended interval is every 6 to 12 weeks.

8.5 End of Study

The end of study will be defined as the time at which all patients have discontinued study therapy and study report is accepted for publication.

8.6 Study Assessments

8.6.1 Medical History

The history will be reviewed, with the patient, using the health care provider notes (i.e. the investigator's and/or designees note).

8.6.2 Physical Exam

A directed physical examination will be performed at the visits as indicated in the time and events table. Performance status will be assessed at screening, prior to the first dose of study treatment, at the beginning of each cycle, and at discontinuation according to ECOG criteria as discussed in Appendix 1.

9.0 INVESTIGATIONAL THERAPY

9.1 Study Therapy

AstraZeneca will supply osimertinib tablets for oral administration as a single daily dose of 80 mg. Tablets can be taken whole with approximately 240 ml water, with or without regard to food Study drugs will be taken by patients at home after they have received administration instructions. Doses should be taken approximately 24 hours apart at the same time-point each day.

Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking osimertinib, they should not make up for this dose, but should take the next scheduled dose. The missed doses and reason should be recorded in the patient diary.

A study cycle is defined as 28 consecutive days and patients will take their study drug on days 1-28 of each cycle. Study drug may be interrupted up to 21 days. Additional information about the investigational product may be found in the IB for each agent.

Investigational product	Dosage form and strength	Manufacturer
Osimertinib	40 mg tablet	AstraZeneca
Osimertinib	80 mg tablet	AstraZeneca

Reported adverse events and potential risks are described in Section 2. No investigational or commercial agents or therapies other than those described in this study may be administered with the intent to treat the patient's malignancy. All patients will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle.

9.1.1 Dose Modification

Dose delays and modifications will be made as indicated below. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

1. If any patient experiences a CTCAE grade 3 or intolerable grade 2 adverse event related to osimertinib, dosing will be interrupted and supportive therapy administered as per institutional standard. Patients will not be permitted to restart osimertinib until toxicities have resolved to CTCAE grade ≤1.
2. If grade 3 or intolerable adverse event does not resolve with 21 days, patient should permanently discontinue study therapy
3. If first grade 3 or intolerable grade 2 adverse event which resolves within 21 days patient may restart at 80 mg dose level or 40 mg dose delay (at the discretion of the treating physician)
4. If second grade 3 or intolerable grade 2 adverse event which resolves within 21 days patent must have dose reduced to 40 mg daily
5. If patient is on 40 mg dose level and experiences a grade 3 or intolerable grade 2 adverse event patient must discontinue study therapy
6. Patients experiencing corneal ulceration (any grade), interstitial lung disease (ILD), and QT_c interval prolongation with signs/symptoms of serious arrhythmia will permanently discontinue the osimertinib.
7. For patients with grade 3 QT_c prolongation dose reduction to 40 mg daily is mandatory

Patients who are unable to remain on study therapy because of toxicity should be considered for treatment, as per institutional standard.

Dose reduction schema for grade 3 or intolerable grade 2 adverse events.
For specific management other than pulmonary, QT_c prolongation, and corneal ulceration or grade 3 ophthalmologic adverse events please refer to table and text

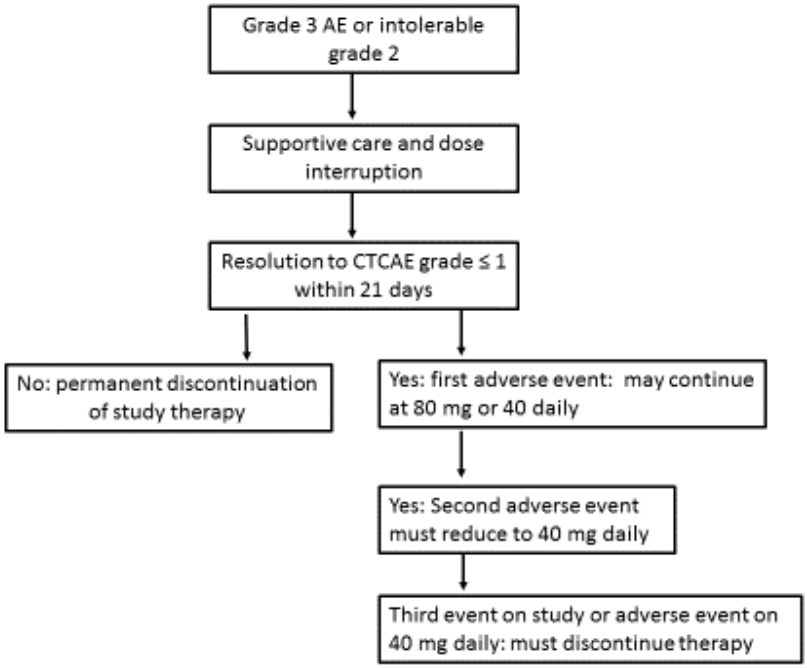

TABLE 2: DOSE REDUCTION

Dose level	Osimertinib dose	Schedule
"0"	80 mg	Daily
"-1"	40 mg	Daily

9.1.2 Management of adverse effects

Symptom-specific toxicity management

Guidance for toxicity management will be as indicated below for patients enrolled, and investigators should manage toxicities per institutional standards and the specific clinical circumstances. Other toxicities should be managed as per institutional standards or at the discretion of the investigator.

For additional details, please refer to the table and text below:

TABLE 3 DOSE MODIFCATION GUIDELINES

NCI-CTCAE (v4.03) Grade	Dose Modification	Guideline for Management
Diarrhea		
Grade 1	None	Consider loperamide (4 mg at first onset, followed by 2 mg q2-4 hours until free of diarrhea for 12 hours, maximum daily dose of 16 mg/day).
Grade 2	None	Loperamide (4 mg at first onset, followed by 2 mg every 2-4 hours until free of diarrhea for 12 hours, maximum daily dose of 16 mg/day).
Grade 3 or intolerable grade 2	Hold study treatment for up to 21 days	Dose modification as noted, with supportive care per PI discretion.
Grade 4	Discontinue study treatment.	Supportive care as per intuitional standard
Rash		
Grade 1 and 2 tolerable rash	None	Any of the following, at the discretion of the investigator: 1. Oral antibiotics (tetracycline, minocycline, doxycycline) 2. Topical clindamycin, diphenhydramine, topical corticosteroids or emollient cream
Grade 2 intolerable or grade 3 rash	Study treatment interruption for up to 21 days	Manage as described above with both oral antibiotics and topical agent. Oral corticosteroids may be considered at the discretion of the investigator.
Grade 4	Discontinue study treatment	Manage as described above with both oral antibiotics and topical agent. Oral corticosteroids may be considered at the discretion of the investigator.
Paronychia		
Grade 1	None	Topical antibiotic bid and vinegar soaks (soaking finger or toes in a 1:1 solution of white vinegar in water for 15 minutes every day)
Grade 2	May continue at current dose or dose reduce at the discretion investigator	Topical antibiotic BID and vinegar soaks as outline above Topical silver nitrate weekly

Grade 2 intolerable or grade 3	Study treatment interruption for up to 21 days	Topical antibiotic bid and vinegar soaks as outline above Topical silver nitrate weekly Consider nail avulsion or removal
Grade 4	Discontinue study treatment	
Hepatic Transaminases and/or total bilirubin: please refer criteria for Hy's law provided in appendix 3		
Grade 1	None	Observation
Grade 2	None	Observation
Grade 3	Study treatment interruption for up to 21 days	Observation until laboratory values return to Grade 1
Grade 4	Discontinue study treatment	
Pulmonary Events if possibly Interstitial Lung Disease (ILD)		
All Grades	Temporarily interrupt study treatment pending the diagnostic evaluation. If the pulmonary adverse event is felt to be related to osimertinib, then permanently discontinue osimertinib.	Unexplained dyspnea, either new or progressive, should be thoroughly evaluated. Where ILD is suspected, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper.
Cardiac		
Grade 3	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
Grade 4	QTc interval greater than 500 msec or > 60 msecs from baseline and with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Management of elevated creatine kinase: please check for drug-drug interactions and refer to appendix 2 for potential drug-drug interactions		
Grade 1	None	Observation (assess for drug-drug interactions contributing to elevation. Please refer to appendix 2)
Grade 2	None	Observation (assess for drug-drug interactions contributing to elevation. Please refer to appendix 2)

Grade 3	Study treatment interruption for up to 21 days	Observation until laboratory values return to Grade 1 (assess for drug-drug interactions contributing to elevation. Please refer to appendix 2)
Grade 4	Discontinue study treatment	Discontinue study treatment
Ocular		
	Corneal ulceration	Permanently discontinue osimertinib
Grade > 3 or eye symptoms that are clinically significant and/or persistent (>7 days)	Referral to ophthalmologist	Permanently discontinue osimertinib
Grade 4	Referral to ophthalmologist	Permanently discontinue osimertinib
Other		
Grade ≥3 adverse event	If Grade 3 or higher adverse reaction improves to grade ≤ 1 after withholding of osimertinib for up to 21 days	Osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg) at the discretion of the investigator
	If grade 3 or higher adverse reaction that does not improve to grade ≤ 1 after withholding for up to 21 days.	Permanently discontinue osimertinib

9.1.3 Definition of Evaluable Subjects, On Study, and End of Study

All patients who receive a dose of the study medication (osimertinib) will be considered evaluable. Patients who withdraw consent before starting study medication, sign informed consent document and are subsequently found ineligible, or do not start study medication will not be a considered evaluable. Patients who start study medication and do not have a radiographic assessment due to clinical progression will be considered as having disease progression. Patients who have progressive disease, unacceptable toxicity, or withdraw consent will be considered as coming off study and the date of the most recent clinic visit or imaging will be considered the end of the study.

9.1.4 Early Study Termination

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 13, which describes procedures and process for prematurely withdrawn patients.

10.0 BLINDING

This is an open-label study, therefore, each patient will be aware of his or her assigned study treatment. All staff involved in treating and caring for study patients will have full knowledge of study treatment assignment for those patients under their care.

11.0 CONCOMITANT MEDICATIONS

The site PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix 2 presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the counter (OTC), herbal supplements, and IV medications and fluids.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment are to be records.

12.0 OTHER CONSIDERATIONS

12.1 Contraception

Female
Being a part of this study while pregnant may expose the unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be excluded from the study. Females of childbearing potential, if sexually active, must agree to use two forms of appropriate contraceptive measures from the time of screening, for the entire duration of the study and **at least 6 weeks** after discontinuing the study drug. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections) that are not prone to drug-to-drug interactions (IUS Levonorgetrel Intra Uterine System (Mirena)

Medroxyprogresterone injections (Depro-Provera), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If you do become pregnant during this study or if you have unprotected sex, you must inform your study physician immediately.

Male
Must agree to use a medically acceptable form of birth control in order to be in this study and for **6** months afterward. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. Men should refrain from donating sperm from the start of dosing until 6 months after discontinuing study drug. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should promptly notify her doctor.

12.1 Use in Pregnancy

There are no or limited amount of data from the use of osimertinib in pregnant women. Studies in animals have shown reproductive toxicity. Based on its mechanism of action and preclinical data, osimertinib may cause fetal harm when administered to a pregnant woman. Administration of osimertinib to pregnant rats was associated with embryolethality, reduced fetal growth and neonatal death at exposures similar to what is expected in humans. Osimertinib is not recommended during pregnancy and in women of childbearing potential not using contraception.

12.3 Use in Nursing Women

It is not known whether osimertinib or its metabolites are excreted in human milk. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death. There is insufficient information on the excretion of osimertinib or its metabolites in animal milk. A risk to the suckling child cannot be excluded. Breast-feeding should discontinue during study treatment with osimertinib.

12.4 Fertility

There are no data on the effect of osimertinib on human fertility. Results from animal studies have shown that osimertinib has effects on male and female reproductive organs and could impair fertility.

13.0 SUBJECT WITHDRAWAL/DISCONTINUATION CRITERIA

13.1 Criteria for Early Withdrawal

A subject may be discontinued from the study for any of the following reasons. The PI may also withdraw a subject from the study at any time based on his/her discretion

- Subject or legal representative withdraws consent
- Confirmed radiographic disease progression
- There is toxicity deemed by the investigator or subject to be unacceptable
- Concurrent illness that prevents further administration of treatment
- The subject, for any reason, reason requires treatment with another systemic agent potentially effective for treatment of the study indication. In this case, discontinuation from the study occurs immediately upon introduction of the new agent
- Noncompliance with trial treatment or procedure requirements
- Abnormal laboratory values
- Abnormal test procedure results
- Protocol deviation
- Administrative issues
- Pregnancy
- Subject is lost to follow-up
- The investigator for any reason, stops the study
- Termination of the study by AstraZeneca

13.2 Follow-up Requirements for patients who discontinue therapy prior to disease progression

Patients who do not start study drug will not have any study follow-up requirements. Patients who discontinue therapy for reasons other than disease progression will be followed for disease progression every 6-12 weeks at the discretion of the treating physician until disease progression and once patient stop study therapy they will be followed for overall survival every 3 months by telephone or by review medical records for a maximum of 2 years.

13.3 Replacement of Early Withdrawal(s)

Patients who do not start study drug will be replaced and will be considered non-evaluable. They will be classified as “consented but not treated.”

13.4 Clinical Criteria for Early Trial Termination

- Quality of quantity of data recording is inaccurate or incomplete
- Poor adherence to protocol and regulatory requirements
- Incidence of severity of adverse drug reaction in this or other studies indicate a potential health hazard to subjects.
- Plans to modify or discontinue the development of the study drug

13.5 Discontinuation of the Study

This study can be terminated at any time for any reason by the PI-sponsor, Astrazenca or the IRB. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow-up should occur in accordance with Table 4.

14.0 STUDY DRUG

14.1 Names, Classification, and Mechanism of Action

Osimertinib (AZD9291, Tagrisso) is a third generation EGFR TKI. It is potent irreversible inhibitor of both single *EGFR* activating mutations (TKI sensitivity-conferring mutations) and EGFR T790M mutations (TKI resistance mutations). As a result, osimertinib has the potential to provide clinical benefit to patients with advanced NSCLC harboring both the single sensitivity mutations and the T790M resistance mutation following prior therapy with an EGFR TKI. The molecular formula is C28H33N7O2. The molecular weight is 499.6 g/mol.

14.2 Packaging and labeling

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The labels will fulfill Good Manufacturing Practice Annex 13 requirements for labeling. The label will include the Name of the Sponsor, Study Code, For Clinical trial use only and /or any other market specific requirements. All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the pack specifies the appropriate storage.

14.3 Supply, Receipt, and Storage

Osimertinib should be stored at temperatures of 15°C and 30°C (59°F and 86°F). There are no special handling precautions or special equipment needed for handling or administration of this agent. Osimertinib will be provided by AstraZeneca free of charge and will be ordered through the research pharmacy.

14.4 Dispensing and Preparation

Osimertinib tablets will be supplied to the research pharmacy in white, high-density polyethylene (HDPE) bottles with child-resistant closures and should be stored at temperatures of 15°C and 30°C (59°F and 86°F). Each bottle will contain 30 tablets but it is permissible for the research pharmacy to open stock bottles and dispense 30 tablets of either 40 or 80 mg to patients in standard amber prescription vials.

14.5 Compliance and Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

14.6 Disposal and Destruction

Unused osimertinib will be returned to the clinic study nurse at the indicated clinic visit and returned to the research pharmacy for disposal.

15.0 COSTS TO THE SUBJECT

There will be no additional cost to subjects as a result of being in this study. AstraZeneca will provide the study drug, osimertinib, free of charge.

Routine medical care given for the disease under study (which is care a subject would receive whether or not they were in this study), such as blood draws, will be charged to subject's insurance company.

16.0 SAFETY MONITORING AND REPORTING

The PI at each institution is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred. Adverse events that are judged to be Serious Adverse Events by the institutional PI should be reported to the Duke Cancer Institute Safety Desk to their local Institutional IRBs in accordance with the reporting requirements.

16.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject receiving study drug and which does not necessarily have a causal relationship with this study treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to use of the study drug. Abnormal laboratory, physical exam or vital sign findings without clinical significance (based on the PI's judgment) should not be recorded as AEs

From the time that the subject signs the informed consent form through the End of Study Treatment visit (as defined in Section 8.3), all AEs must be recorded in the subject medical record and adverse events case report form.

AEs will be assessed according to the CTCAE version 4.03. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study drug
- Probably: The AE is likely related to the study drug
- Possible: The AE may be related to the study drug
- Unlikely: The AE is doubtfully related to the study drug
- Unrelated: The AE is clearly NOT related to the study drug

16.1.1. Reporting of AEs

All Adverse Events must be reported in routine study data submissions to the Overall PI on the toxicity case report forms. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

Abnormal laboratory results are to be records as AEs if any of the following conditions are met:

- The abnormal laboratory value leads to a therapeutic intervention (e.g. corrective therapy).
- The abnormal laboratory value is considered to be clinically significant by the Investigator.
- Any lab test result that is clinically significant or meets the definition of an SAE.
- Any laboratory test result abnormality that required the subject to have study treatment discontinued or interrupted

16.2 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Astrazeneca's product. An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Results in death
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.

16.2.1 Serious Adverse Event Reporting

Life-threatening (grade 4 or 5) SAEs, deaths, and unknown reactions or unexpected events that occur in the course of any patient's treatment on study (from the time of enrollment) or within 30 days following cessation of study treatment are reportable. All sites will complete DCI SAE Report Form and Page 1 of the DCI Safety Review Form.

Sub-sites will submit both forms to the DCI Safety Desk (Fax #: 919-681-9357 or email to dcccsafe@dm.duke.edu) and to the Lead PI, Dr. Stinchcombe (Fax: 919-684-8926 and scanned/emailed to the Thoracic Oncology Protocol Office Thoracic-multisite@dm.duke.edu).

Note: It is imperative that initial SAE reports are submitted as soon as possible (within 24 hours of knowledge of the event) with available information to the DCI Safety Desk. Missing and/or clarified event information may be provided in a follow-up report.

If the safety desk cannot be reached within 24 hours, the Duke PI, Dr. Thomas Stinchcombe, should be contacted (thomas.stinchcombe@duke.edu, Pager (919) 970- 2829, Office: (919) 681-9509.

The initial report for each SAE or death should include at minimum the following information:

- protocol # and title
- patient initials, study identification number, sex, age
- date the event occurred
- description of the SAE
- dose level and cycle number at the time the SAE occurred
- description of the patient's condition
- indication whether the patient remains on study
- causality or causal relationship

De-identified source documentation (i.e. admission notes, discharge notes, applicable laboratory results, radiology/diagnostic testing results, etc.) must be sent with the SAE Report Form. Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to Duke as soon as possible using the same forms mentioned above.

The Lead PI or designee will complete Page 2 of the DCI Safety Review Form and promptly submit it to the DCI Safety Desk. The DCI Safety Desk will forward the information from the SAE report and the PI's Assessment of the SAE to the Duke University IRB if it meets reporting requirements.

Reporting to the FDA

Duke as the lead center is responsible for reporting the serious adverse event to the FDA in accordance with 21CFR 312.32. Any SAE that is possibly related and unexpected must be submitted to the FDA attached to the IND. This will be done by DCI Safety Desk and/or coordinate with study team regulatory coordinator.

Reporting SAEs at participating institutions

Each site is responsible for reporting unexpected and/or serious adverse events to their individual IRB.

Expedited Reporting Procedure for Duke Cancer Institute (Coordinating Center):

Duke Cancer Institute as the coordinating center for this study is responsible for reporting SAEs to the FDA in accordance with 21CFR 312.32. Any SAE that is possibly related and unexpected must be submitted to the FDA attached to the IND. If the SAE meets criteria for reporting to the FDA, the DCI Safety Desk will complete the Form FDA 3500A (MedWatch) and send to the

Principal Investigator and the Sponsor that are noted above. This submission of the Form FDA 3500A to the FDA attached to the IND will be completed by the designee.

- All unexpected, drug related SAEs that are fatal or life-threatening will be reported to the FDA by phone or fax within 7 calendar days of initial receipt of the information and will provide a complete report within 8 days of the initial report submission (by calendar day 15).
- All unexpected, study treatment-related SAEs that are not fatal or life-threatening will be reported in a written report to the FDA within 15 days of initial receipt of the information

Reporting of SAEs

Process for Reporting of SAEs to Duke:

When an SAE or pregnancy/lactation occurs at a participating site, the responsible coordinator will report the event to the Duke Cancer Institute Safety Desk within 24 hours using the DCI SAE Notification and Report Form. Adverse events (non-serious) are to be appropriately recorded in the case report forms, but are not reported to the DCI Safety Desk.

The Duke Safety Desk will conduct a preliminary review of the information to confirm expectedness and reporting to the Duke IRB. The Duke PI is responsible for causality assessment and final determination of reportability. The Duke PI will complete Page 2 of the DCI Safety Review Form and promptly submit it to the DCI Safety Desk.

The DCI Safety Desk will forward the information from the SAE report and the PI's Assessment of the SAE to the Duke University IRB, if it meets reporting requirements. **Each institution is responsible for reporting SAEs to their local institutional IRBs in accordance with reporting requirements.**

In addition to the DCI Safety Notification form and the SAE PI Assessment Review form (page 1), the initial report for each SAE or death should include at a minimum the following information:

- Protocol number (TOP 1703, Pro00088376)
- Patient initials, study identification number, sex, age
- Date the event occurred
- Description of the SAE
- Dose level and cycle number at the time the SAE occurred
- Description of the patient's condition.

- Indication whether the patient remains on study
- Causality or causal relationship

De-identified source documentation (admission notes, discharge notes, applicable laboratory results, radiology/diagnostic testing results, etc.) must be sent with the SAE Report Form. Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to Duke as soon as possible using the same forms mentioned above.

REPORTING SAEs to ASTRAZENECA and the FDA:

The Duke Safety Desk will be responsible for reporting SAEs and reports of pregnancy/lactation to AstraZeneca within 2 working days (provider of investigational compound) and for any follow-up information requested by AstraZeneca.

The Duke Safety Desk will complete Form 3500A (21CFR 312.32) as needed.

16.2.2 Protocol Specific Exceptions to Serious Adverse Event Reporting

Events which are unequivocally due to disease progression should not be reported as an AE during the study

Hospitalization related to convenience (e.g. transportation issues etc.) will not be considered an SAE.

16.3 Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see Section 17.1 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator greater-than-minimal-risk intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

17.0 QUALITY CONTROL AND QUALITY ASSURANCE

17.1 Monitoring

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1 – 3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the sponsor, the PI, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

Please refer to the study specific external site monitoring plan for monitoring sites external to the Duke University Heath System.

17.2 Audits

The Duke School of Medicine Office of Audit, Risk and Compliance (OARC) may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the OARC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the OARC auditor(s) in order to discuss findings and any relevant issues.

OARC audits are designed to protect the rights and well-being of human research subjects. OARC audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

OARC audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB.

The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize "best practices" in the research/clinical trials environment.

18 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

18.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

18.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the PI has received written and dated approval from the CPC and IRB.

The PI must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The PI must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The PI must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

18.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The PI or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential

subjects will have the opportunity to contact the PI or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the PI must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject. The PI is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

18.4 Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan (DSMP). For a more detailed description of the DSMP for this protocol, refer to Sections 16.3 and Section 17.1.

18.5 Protocol Amendments

All protocol amendments must be initiated by the PI and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the PI must inform the IRB and all other applicable regulatory agencies of such action immediately.

Though not yet required, the CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, etc.).

18.6 Publication Plan

The results will be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. A report is planned to be published in a peer-reviewed journal, thus the initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes is planned to be made public no later than three (3) years after the end of the study.

19 Privacy, Confidentiality, and Data Storage

The PI will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Site Based Research group.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated database (MediData RAVE) which is housed in an encrypted and password-protected, DCI file server. Access to electronic databases will be limited to authorized key personnel only. Subject data may be stored temporarily on encrypted and password-protected portable memory devices such as flash drives and external hard drives, but only when absolutely necessary. Data stored on portable memory devices will be de-identified. Subject data will be deleted from the portable memory device at the earliest opportunity. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

20 Data Collection and Maintenance

20.1 Study Documentation

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with PI-sponsor or regulatory bodies/committees, regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications and clinical supplies receipts and distribution records (if applicable).

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification of being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible and exact duplication of the original document.

The research nurse, research coordinator, data manager and PI are responsible for ensuring that data extraction (information required by the protocol) is completed in a timely manner for every patient enrolled on study. The following forms are an integral part of the study data and will be maintained in the patients' clinical or research chart in accordance with the institutions practice. Any errors on the forms should be lined through, but not obliterated with the correction inserted, initialed and date by the person making the correction

- Eligibility checklist
- Serious and non-serious adverse evert forms (if applicable)
- Protocol Deviation Form (if applicable)

20.2 Case Report Forms (CRFs)

The electronic CRF will be the primary data collection document for the study. The CRFs will be updated within two weeks of acquisition of new source data. The electronic records of subject data will be maintained using a dedicated database (Medidata Rave and/or Redcap) which is housed in an encrypted and password protected DCI file server. Access to electronic databases will be limited to the PI and designated stud staff listed on key personnel. Subject data may be stored temporarily on encrypted and password-protected portable memory devices such as flash drives and external hard drives, but only when absolutely necessary. Data stored on portable memory deviced will be de-identified. Subject data will be deleted from the portable memory device at the earliest opportunity. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine. Only approved study staff, are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management system (Medidata Rave and/or Redcap). Designated personnel will complete user training, as required or appropriate per regulations

20.3 Data Management Procedures and Data Verification

Designated personnel using the electronic CRF will have access based on their specific roles in the protocol.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data manager and will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

21 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories

Upon completion of the study, research records will be archived and handled per DUHS (or participating Institution's) HRPP policy.

21.1 Records Retention

The Principal Investigator will maintain study-related records for the longer period of:

- At least two years after the date on which a New Drug Application is approved by the FDA (if an IND is involved).
- At least two years after formal withdrawal of the IND associated with this protocol (if an IND is involved).
- At least six years after study completion (Duke policy).

22 STATISTICAL METHODS AND DATA ANALYSIS

22.1 Analysis Sets

The efficacy and safety analysis set consists of all patients who receive at least one dose of osimertinib and it will be used to analyze safety and efficacy endpoints, including objective response rate, progression-free survival and overall survival. Patients who withdraw prior to study treatment or fail to receive study treatment for various reasons, will not be included in the efficacy and safety analysis.

22.2 Patient Demographics and Other Baseline Characteristics

Standard demographic information (age, gender, etc.) and prior therapies, smoking history and specific mutation type will be collected.

22.3 Study Treatments

Osimertinib 80 mg daily until disease progression, unacceptable toxicity or withdraw of consent.

22.4 Primary Objective

Objective response rate, defined as all patients with a confirmed partial or complete response as assessed by investigator using RECIST 1.1

22.4.1 Variable

The primary outcome will be objective response rate as assessed by the investigator using RECIST 1.1 (appendix 3). Patients with confirmed partial or complete responses will be considered responders and patients without a partial or complete response will be considered non-responders.

22.4.2 Statistical Hypothesis, Model, and Method of Analysis

The single-arm phase II trial is designed to test the following hypothesis about the anti-tumor activity of the experimental therapy:

$$H0: ORR <= 20\% \text{ versus } H1: ORR >= 40\%,$$

where ORR is the true ORR for the experimental therapy. We will use Simon's optimal 2-stage design to evaluate the ORR.[27] The 2-stage design allow a futility test after stage

I patients has been evaluated for tumor response. The specific design described below is also the design that yields the smallest expected sample size under the null hypothesis (optimal) among all designs satisfying type I error of 0.10 and type II error of 0.10.

Specifically, the first stage will enroll 17 patients. If there are 3 or fewer patients confirmed responders (complete or partial response) among the 17 patients, the trial will be terminated; otherwise, the trial will move forward to enroll additional 20 patients. If 10 or fewer patients among the total of 37 patients are confirmed responders, the experimental therapy will be concluded as not worthy of further investigation; otherwise it will be conducted that the experimental therapy has sufficient activity worthy of further investigation. The above design has expected sample size 26 under the null hypothesis. The early stopping probability at stage I is 0.5489 under the null hypothesis. The actual type I and type II errors are 0.0948 and 0.0967, respectively.

Patient characteristics at baseline will be summarized in tables and graphs. Categorical data will be summarized using frequency tables while summary statistics such as means, medians, standard deviation, range, etc. will be provided for continuous data.

All enrolled patients, except for those withdrawn prior to study treatment or fail to receive study treatment for various reasons, will be included in the efficacy analysis. The primary endpoint will be objective response rate (ORR) per RECIST 1.1. Patients with confirmed partial or complete responses will be considered responders and patients without a confirmed partial or complete response will be considered non-responders. Patients who stop therapy prior to confirmation of response per RECIST will be considered non-responders. Patients who are not able to get radiographic assessment for all reasons will be considered non-responders. At the end of the trial, the ORR will be estimated using the UMVUE method, and the p-value and 95% confidence interval will calculated.[28,29]

22.4.3 Handling of missing values, censoring, and discontinuations

Ineligible subjects and subjects who cancel registration before receiving any therapy will not be included in the efficacy analyses. Patients who receive at least one dose of the experimental therapy will be included in the safety analysis.

22.5 Secondary Objectives

22.5.1 Key Secondary Objectives

1. Progression free survival using RECIST 1.1 as assessed by the investigator. Progression will be defined as time from start of study therapy to disease progression or death (whichever occurs first)
2. Safety using CTCAE version 4.03
3. Overall survival from start of study therapy to death (any cause)

22.5.2 Exploratory Objectives

1. Estimate the response rate and PFS in the specific mutation subsets of exon 18 G719X, exon 20 S7681, exon 21 L861Q or compound mutations

22.5.3 Statistical Analysis for Secondary Objectives

Patients who are not able to get radiographic assessment for all reasons will be considered disease progression at the time they discontinue protocol therapy for the PFS analysis. Patients who stop therapy for reasons other than disease progression will be followed for disease progression. Patients who have not experienced an event of interest by the time of analysis will be censored at the date they are last known to be alive and progression-free. Overall survival is defined as the time from start of study therapy to death from any cause, and patients who are alive at the time of analysis will be censored at the last date of contact. Time to event endpoints will be summarized using the method of Kaplan and Meier as well as by Cox regression in the presence of covariates. Potential co-variates including smoking history, mutation subtype, gender, and performance status.

An exploratory subset analysis will estimate the objective response rate, PFS and OS in the specific mutation subsets of exon 18 G719X, exon 20 S7681, exon 21 L861Q or compound mutations.

The evaluation of safety using the AE using NCI CTCAE version 4.03. All patients who receive at least one dose of study treatment will be included in the safety analysis.

22.6 Interim Analysis

An interim analysis will be performed for efficacy part of the 2-stage design as outlined in section 22.4.2

22.7 Accrual and Follow-Up

Taking into 5% ineligibility/cancelation rate, we will enroll approximately 39 patients to have 37 evaluable patients for the efficacy analysis of the trial. At a rate of 1 to 2 patients per month, we expect that trial will take approximately 19-37 months to reach its target of 37 evaluable patients if it will not be terminated earlier based on the planned interim analysis. All patients will be followed for disease progression and mortality from the date that the subjects were registered on study. Once patients are no longer on study therapy, they will be followed for overall survival for a maximum 2 years from discontinuation of study therapy.

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24 LIST OF APPENDICES

Appendix 1 Performance Status Criteria: ECOG
Appendix 2 Information on Possible Drug Interactions Osimertinib
Appendix 3 Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law.
Appendix 4 Measurement of Effect
Appendix 5 Standard Cockcroft and Gault Formula for Calculated Creatinine Clearance

24.1 APPENDIX 1: Performance Status Criteria: ECOG

Grade	Description
0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50 percent of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50 percent or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20)
5	Dead

24.2 APPENDIX 2: Information on Possible Drug Interactions Osimertinib

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 electronic case report form (eCRF).

1. Drugs Inducing CYP3A4 Metabolism That AstraZeneca Strongly Recommend Are Not Combined With Osimertinib

Osimertinib is metabolised by CYP3A4 and CYP3A5 enzymes.

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

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

Table 1: Drugs Inducing CYP3A4

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

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

2. Medicines Whose Exposures May be Affected by Osimertinib That AstraZeneca Considers May be Allowed With Caution

Osimertinib may increase the concentration of sensitive breast cancer resistance protein (BCRP) substrates (concentration of the sensitive BCRP substrate, rosuvastatin, is increased).

Table 2: Exposure, Pharmacological Action and Toxicity May be Increased by Osimertinib

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

3. Drugs That May Prolong QT Interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: http://www.arizonacert.org/medical-pros/drug-lists/drug lists.htm.

3.1 Drugs known to prolong QT interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with osimertinib. Recommended withdrawal periods following cessation of treatment with these agents are provided in the table.

Table 3: Drugs Prolonging QT Interval

Contraindicated drug	Withdrawal period prior to osimertinib start
Clarithromycin, droperidol, erythromycin, procainamide	2 days
Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide	6 weeks [a]
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

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

3.2 Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Table 4: Drugs That May Prolong QT Interval

Drug	Minimum treatment period on medication prior to osimertinib start
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isridipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprin-sulfa, trimipramine, voriconazole	7 days
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 weeks

24.3 APPENDIX 3: Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

A Potential Hy's Law (PHL) case is defined as a study subject with an increase in serum Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN irrespective of serum Alkaline Phosphatase (ALP), at any point during the study following the start of study medication.

Hy's Law (HL)

A Hy's Law (HL) case is defined as a study subject with an increase in serum AST or ALT ≥ 3x ULN together with TBL ≥ 2xULN, where no other reason can be found to explain the combination of increases, e.g. elevated serum ALP indicating cholestasis, viral hepatitis, another drug.
For PHL and HL to be met the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

- ALT ≥ 3xULN
- AST ≥ 3xULN

- TBL ≥ 2xULN

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

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

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (See Section 6).
- Notify the AstraZeneca representative who will then inform the central Study Team
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:
- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available.
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

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

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

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

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

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

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

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to subjects who meet PHL criteria on study treatment (including the 28 day follow-up period post discontinuation of study treatment) having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the subjects' condition compared with the last visit where PHL criteria were met
- If there is no significant change no action is required

- If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section 4.2 of this Appendix.

A 'significant' change in the patient's condition refers to a subsequent clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, eosinophilia. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment (including the 28-day follow-up period) and has already met PHL criteria at a previous on study treatment visit.

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

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

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6?

If No: Follow the process described in Section 4.2 of this Appendix

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

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 6 of this Appendix

A 'significant' change in the patient's condition refers to a subsequent clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms, such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, eosinophilia. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

8. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation': http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

24.4 APPENDIX 4: Measure of Effect

Although response is the primary endpoint of this trial, participants with measurable disease will be assessed by standard criteria. For the purposes of this study, participants should be re-evaluated every as per time and events table in section 8.

Antitumor Effect – Solid Tumors
Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[1]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one dose of study therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one dose of study therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are considered measurable if the lesion is not in bone.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis),

are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being

followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, 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. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent

fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or PI).

Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first

date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

25.5 APPENDIX 5: Standard Cockcroft and Gault Formula for Calculated Creatinine Clearance

Standard Cockcroft and Gault Formula for Calculated Creatinine Clearance
For serum creatinine concentration in mg/dL:
Creatinine clearance (CrCl) will be calculated using the Cockroft-Gault equation as follows:

$$\text{CrCl (ml/min)} = \frac{(140\text{-age}) \times (\text{actual weight in kg})}{72 \times \text{serum creatinine (mg/dl)}} \times 0.85 \text{ for females}$$

For serum creatinine concentration in □mol/L:
CrCl = [(140 - age) x (wt in kg)] / [0.81 x serum creatinine (mol/L)]
Females: Multiply the result x 0.85
Units: age in years, weight in kilograms.

Source: Cockcroft DW, Gault MH. 1976. Prediction of creatinine clearance from serum creatinine.
Nephron 16:31-4.