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Phase II trial of Osimertinib in combination with Stereotactic Ablative Radiation (SABR) in *EGFR* mutant advanced non-small cell lung cancer (NSCLC)

**Principal investigator:**

Sawsan Rashdan, MD  
UT Southwestern Medical Center-Oncology  
5323 Harry Hines Boulevard, Dallas, TX 75390  
Telephone: (214) 648-4180. Fax: (214) 648-1955  
Email: [Sawsan.rashdan@utsouthwestern.edu](mailto:Sawsan.rashdan@utsouthwestern.edu)

**Medical oncology co-chair**

David Gerber, MD  
UT Southwestern Medical Center-Oncology  
5323 Harry Hines Boulevard, Dallas, TX 75390  
Telephone: (214) 648-4180. Fax: (214) 648-1955  
Email: [David.Gerber@UTSouthwestern.edu](mailto:David.Gerber@UTSouthwestern.edu)

**Radiation Oncology co-chair**

Puneeth Iyengar, MD  
UT Southwestern Medical Center-Oncology  
5323 Harry Hines Boulevard, Dallas, TX 75390  
Telephone: (214) 648-4180. Fax: (214) 648-1955  
Email: [Puneeth.Iyengar@UTSouthwestern.edu](mailto:Puneeth.Iyengar@UTSouthwestern.edu)

**Biostatistician:**

Hong Zhu, PhD  
University of Texas, Southwestern Medical Center  
Department of Clinical Science  
5323 Harry Hines Boulevard, Dallas, TX 75390  
Phone: (214) 648-7438. Fax: (214) 648-5120  
Email: [Hong.Zhu@UTSouthwestern.edu](mailto:Hong.Zhu@UTSouthwestern.edu)

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**UT Southwestern Medical Center (UTSW)  
Harold C. Simmons Cancer Center  
Attn: Clinical Research Office  
5323 Harry Hines Blvd. MC 9179  
Dallas, Texas 75390-9179**

## Signature Page

The signature below constitutes the approval 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 legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Phase II trial of Osimertinib in combination with Stereotactic Ablative Radiation (SABR) in *EGFR* mutant advanced non-small cell lung cancer (NSCLC)

**Protocol Version 2.0      31 JUL 2018**

**Principal Investigator (PI) Name:** \_\_\_\_\_

**PI Signature:** \_\_\_\_\_

**Date:** \_\_\_\_\_

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## LIST OF ABBREVIATIONS

AE	Adverse Event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BCRP	multidrug transporter ABCG2
b.i.d.	bis in diem/twice a day
CBR	Clinical benefit rate
CNS	Central nervous system
CR	Complete Response
CrCl	creatinine clearance
CRO	Contract Research Organization
DLT	Dose Limiting Toxicity
DoR	Duration of response
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
EIAED	enzyme inducing anti-epileptic medication
EGFR	epidermal growth factor receptor
EGFRm	EGFR mutated
EOT	End of treatment
FAS	Full Analysis Set
GI	Gastric intestinal
hERG	human Ether-à-go-go-Related Gene
IUD	intrauterine device
IUS	intrauterine system
i.v.	intravenous (ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IRB	Institutional Review Board
LLN	Lower limit of normal
LLNA	local lymph node assay
MUGA	Multigated acquisition
MTD	Maximum Tolerated Dose
NSCLC	non-small cell lung cancer
o.d.	omnia die/once a day
ORR	Objective response rate
OS	Overall survival
OTC	over-the counter
QD	once daily
PD	Progressive disease
p.o.	per os/by mouth/orally
PFS	Progression free survival
PHI	Protected Health Information
PK	Pharmacokinetics
PPI	proton pump inhibitors
PR	Partial response



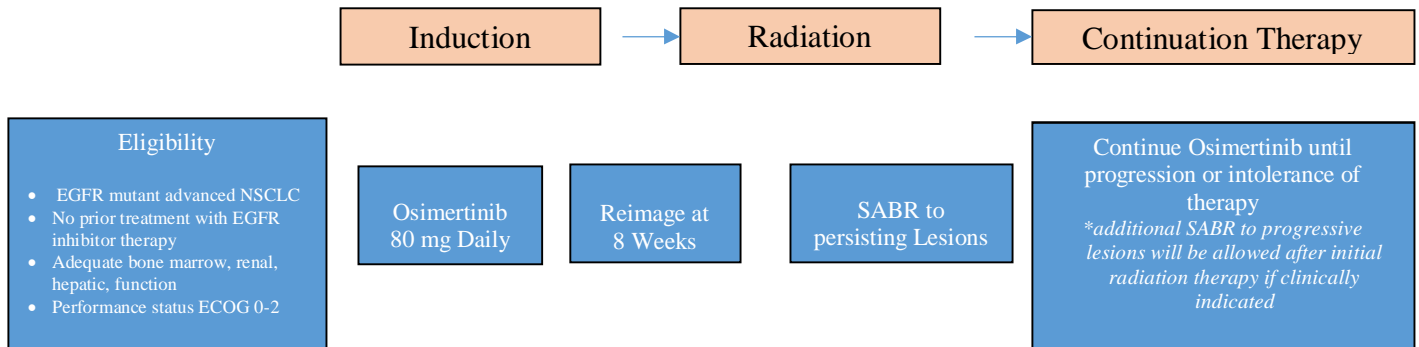
Racc	accumulation ratio
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RDE	Recommended dose for expansion
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response Rate
SABR	Stereotactic Ablative Radiation
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TDI	time-dependent inhibition
TKI	tyrosine kinase inhibitors
ULN	upper limit of normal
UV	Ultraviolet radiation
VATS	Video-assisted thoracic surgery
VEGF	vascular endothelial growth factor
WHO	World Health Organization

**STUDY SUMMARY**

Title	Phase II trial of Osimertinib in combination with Stereotactic Ablative Radiation (SABR) in <i>EGFR</i> mutant advanced non-small cell lung cancer (NSCLC)
Short Title	Osimertinib and SABR in <i>EGFR</i> mutant NSCLC
Protocol Number	SCCC-02518
Phase	II
Methodology	Open label, single arm
Study Duration	4 years
Study Center(s)	Multicenter
Objectives	<p><u>Primary endpoint:</u> To determine if osimertinib and SABR can increase PFS in patients with <i>EGFR</i>m NSCLC.</p> <p><u>Secondary endpoints:</u> Safety/toxicity, duration of response (DoR), objective response rate (ORR), overall survival (OS), time to subsequent SABR or death, time to osimertinib discontinuation or death.</p> <p><u>Exploratory endpoints:</u> predictive and pharmacodynamic biomarkers, molecular mechanisms of resistance</p>
Number of Subjects	42
Diagnosis and Main Inclusion Criteria	<ol style="list-style-type: none"> <li>1. <i>EGFR</i> mutant (exon 19 and 21) advanced NSCLC</li> <li>2. No prior treatment with <i>EGFR</i> inhibitor therapy</li> <li>3. Adequate bone marrow, renal, hepatic, function</li> <li>4. Performance status ECOG 0-2</li> </ol>
Study Product(s), Dose, Route, Regimen	Osimertinib 80 mg orally daily
Duration of administration	Until progression or intolerance of therapy.
Reference therapy	Expansion cohort of the AURA trial presented at ESMO LBA1_PR, 2016 (S. Ramalingam)
Statistical Methodology	Kaplan Meier Methods will be used to estimate progression-free survival and overall survival. A sample size of 42 patients achieves 80% power to detect the difference between the null hypothesis of median PFS of 19.3 months and the alternative hypothesis of median PFS of 30 months at one-sided significance level of 0.1. We assume the patient accrual period of 36 months and the follow-up period of 12 months, and assume that the survival time follows an exponential distribution.

## Protocol summary

Figure 1.1



## 1 Background and Rationale

### 1.1 Overview of lung cancer pathology, epidemiology and current treatment

#### 1.1.1 Epidemiology of lung cancer targetable molecular alterations

Lung cancer is the most common cancer worldwide. There are over 1.5 million cases annually, leading to more than 1 million deaths every year [1]. In the US, 160,000 deaths occur from lung cancer annually [2].

Lung cancer is classified broadly into small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC is further classified into squamous cell cancer, adenocarcinoma, large cell, and NSCLC NOS. Treatment for each classification varies, as well as their clinical behavior and molecular/genetic profile.

Non-squamous NSCLC, in particular adenocarcinoma, has been found to harbor mutations that can be targeted with specific anti-cancer agents. These have dramatically improved the outlook for the minority of patients with tumors that do harbor an actionable mutation. These drugs are much better tolerated than traditional chemotherapies, with fewer side effects and also easier to take. However, the duration of response to these targeted therapies is limited by the development of clinical resistance.

#### 1.1.2 Treatment for *EGFR* mutant (EGFRm) NSCLC

Patients with lung adenocarcinoma now routinely have molecular/genetic testing performed on their tumor. EGFRm NSCLC accounts for 10%–15% of NSCLC patients in Europe and the United States, it is more frequently observed in women and non-smokers. In Asia, however, the incidence of EGFR mutations ranged from 22-62%. Although this was more common in non-smokers, the incidence in smokers was still high at 37%. [3]. Due to the large number of lung cancer cases annually, this small percentage in North America represents thousands of patients every year in the US. *EGFR* mutations are rarely found in squamous cell cancer.

Most of the *EGFR* mutations have been found in between exon 18 and exon 21. The most common mutations are in-frame deletions in exon 19, and the L858R point mutation in exon 21. Together, the exon 19 and 21 mutations account for about 90% of all EGFRms [4]

EGFR TKIs has dramatically transformed the treatment of EGFR mutated lung cancer with an objective response rate (ORR) of ~70%–80% and a median progression-free survival (PFS) of 10–12 months. [5]

To date, there are three generations of TKIs. Erlotinib and gefitinib are the first-generation agents; afatinib, dacomitinib, and neratinib are the second-generation agents; and osimertinib, rociletinib, HM61713, and ASP8273 are the recently developed third-generation agents.

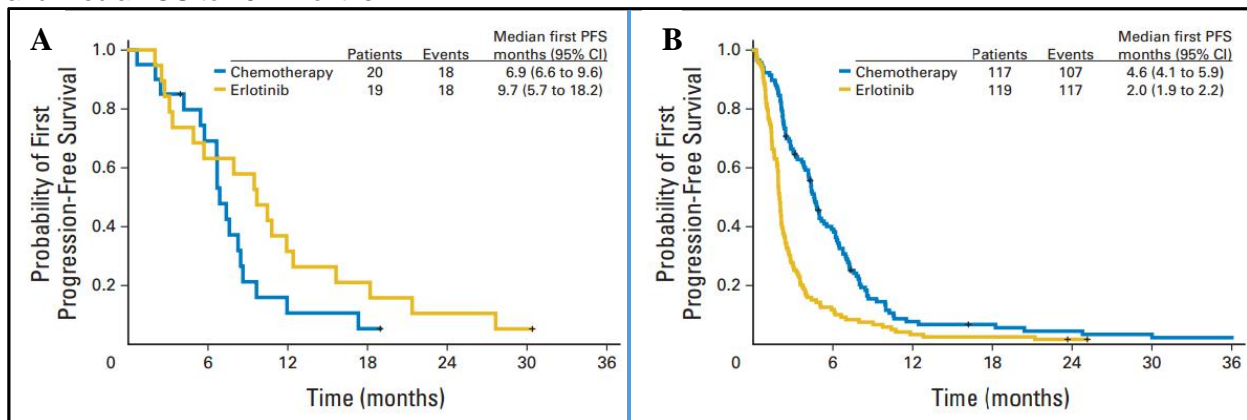
Osimertinib is FDA approved for patients with advanced *EGFR* mutant, T790M mutation positive NSCLC, whose disease has progressed on or after *EGFR* TKI therapy. It has also showed significant activity when used as a first-line treatment for patients with *EGFR* mutant NSCLC. A Phase I/II, open-label, multicenter study recently reported by Ramalingam et al[6], patients were treated with either osimertinib 80 mg orally once daily (n=30) or 160 mg orally once daily (n=30). Objective response rate was 77% (80-mg dosing, 67%; 160-mg dosing: 87%). PFS was 19.3 months with the 160 mg dosing and was not reached with the 80 mg dosing. It is expected that osimertinib will outperform first generation *EGFR* inhibitors in the currently ongoing phase III trial in which it is compared with erlotinib and gefitinib in the first-line setting (Clinicaltrials.gov NCT02296125)

Despite these encouraging results, it is clear that—as the case for all other molecularly targeted therapies for lung cancer—patients treated with osimertinib inevitably progress. In some instances of so-termed oligo-progression, patients may be successfully treated with local therapy (most commonly stereotactic radiation) and continue to receive the same systemic therapy for several more months. This approach is most effective for intracranial progression, which is more likely to represent pharmacologic limitation (ie, drug delivery) than molecular evolution[7, 8]. Indeed, secondary resistance mutations to osimertinib have already been identified [9].

### 1.1.3 Combination of targeted therapy with stereotactic radiation

Stereotactic ablative body radiation (SABR) is a technique of delivering precisely targeted radiation to tumors while minimizing the dose given to adjacent normal tissue. Large doses of radiation are delivered in a small of number of treatments. Due to the radio-biological response to this type of radiation, there can be dramatic tumor responses leading to the ablative terminology.

SABR has an increasing role in advanced NSCLC, as demonstrated by a Phase II trial of targeted therapy with SABR [10]. This trial was conducted at UT Southwestern and enrolled 24 patients with advanced NSCLC that had progressed on standard chemotherapy. These patients were treated with the erlotinib plus stereotactic ablative radiation to sites of visible disease. As a historical control, in a previous trial, patients with advanced NSCLC who had progressed after one line of chemotherapy and were then treated with erlotinib had a progression free survival (PFS) of 2.3 months and overall survival (OS) of 6.7 months [11]. In our trial, combining SABR with erlotinib trial prolonged the median PFS to 14.7 months and median OS to 20.7 months.



**Fig 3.** Kaplan-Meier curves for Progression Free-Survival.

Panel A: Patients with *EGFR* mutations, PFS with erlotinib=9.7 months. Panel B: Patients with *EGFR* wild-type, PFS with erlotinib =2 months.

This combination of SABR with targeted therapy greatly prolonged the duration of time that targeted therapy was beneficial for patients. The combination was well tolerated, and completion of study enrollment in a period of several months demonstrated our site's ability to carry out such trials efficiently and successfully.

Accordingly, we propose to administer local therapy in conjunction with osimertinib not at the time of progression—when radiographically evident changes likely represent only a fraction of biological disease worsening—but at the time of anticipated best response. Specifically, we believe that tumor sites that remain radiographically evident after 8-10 weeks of osimertinib monotherapy may harbor weakly sensitive or resistant clones. This is suggested by (1) the observation that disease progression usually occurs at sites of known disease; and (2) the Goldie-Coldman hypothesis of tumor resistance, [12] which suggests that any detectable tumor will contain some resistant clones. According to this hypothesis, the probability of resistance developing in a tumor depends on (a) the number of cancer cells and (b) the mutation rate of the constituent cells [13]. Therefore, targeting known and visible disease may delay progression that requires a change in systemic therapy.

#### 1.1.4 Patterns of failure in non-small cell lung cancer

Reasons for discontinuing anti-cancer therapy include ineffective control of existing lesions or the development of new lesions. The patterns of failure in non-small lung cancer were evaluated in 64 patients with advanced non-small lung cancer [14]. 64% of patients in this study demonstrated progression in already known sites of disease. This suggests that enhanced control of existing lesions will result in prolongation of the benefit from systemic therapy.

#### 1.1.5 Concept

The proposed study is designed to prolong the clinical benefit of EGFR targeted therapy in patients with EGFR mutant lung cancer. This will evaluate the combination of two well-tolerated therapies, osimertinib and SABR. This dual therapy is expected to be more effective than either alone in destroying sensitive tumor cells and also in preventing the development of resistant cells.

Based on current studies, patients derive benefit from first generation EGFR inhibitors for less than a year before they need to be switched to another treatment, usually osimertinib if the tumor harbors the *EGFR* T790M mutation. Osimertinib alone is active therapy. However, resistance and progression will develop as with all EGFR TKIs. Tumors that remain after 8 weeks of osimertinib monotherapy may harbor weakly sensitive or resistant clones. While on systemic therapy, progression usually occurs at sites of known disease. Therefore, targeting known and visible disease may delay progression that requires a change in systemic therapy.

This study will treat lesions that persist after 8 weeks of osimertinib with stereotactic ablative radiation. Limited progression after that period will also be considered for repeat SABR if possible, rather than discontinuing the osimertinib. This accurately reflects current clinical practice and recommendations from expert groups such as the NCCN, which recommend continuing targeted therapy after progression in some cases.

### 1.2 Introduction to investigational treatment(s) and other study treatment(s)

#### 1.2.1 Overview of osimertinib (osimertinib):

Osimertinib is an oral, potent, irreversible EGFR TKI selective for sensitizing (EGFR<sub>m</sub>) and T790M resistance mutations with a significant selectivity margin against wild-type *EGFR*. As a result, osimertinib can effectively block EGFR signaling both in *EGFR* single mutant cells with activating *EGFR* mutations and in double mutant cells bearing the resistance T790M mutation. Osimertinib is currently FDA approved as a treatment option in Patients with advanced T790M positive NSCLC who have previously failed an EGFR-TKI. It is under investigation in patients with advanced EGFR<sub>m</sub> NSCLC who are treatment naïve; and In combination with novel agents for patients with EGFR TKI resistant NSCLC.

### 1.2.1.1 Non-clinical experience

#### 1.2.1.1.1 Pharmacology

Osimertinib is a kinase inhibitor for oral administration. The molecular formula for osimertinib mesylate is  $C_{28}H_{33}N_7O_2 \cdot CH_4O_3S$ , and the molecular weight is 596 g/mol. The chemical name is N-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-[[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide mesylate salt. Osimertinib binds irreversibly, via the C797 amino acid covalent bond, and potently inhibits EGFR phosphorylation to certain mutant forms of EGFR (L858R, exon 19 deletion, and double mutants containing T790M). But it is less potent at inhibiting phosphorylation of EGFR in wild-type cell lines. IC<sub>50</sub> (50% inhibiting concentration) values for exon 19 deletion and L858R/T790M are 12.92 nM and 11.44 nM, respectively, while IC<sub>50</sub> for wild-type EGFR is ~493.8 nM. [16]

This inhibits the downstream pathways such as RAS/ RAF/MAPK and PI3K/AKT, that regulate DNA synthesis and proliferation. There are two main products of the metabolism of osimertinib: AZ5104 and AZ7550. AZ7550 has similar profile to the parent molecule, while AZ5104 exhibits less selectivity against WT EGFR compared with osimertinib[16]

The tablets contain 40 or 80 mg of osimertinib, equivalent to 47.7 and 95.4 mg of osimertinib mesylate, respectively. Inactive ingredients in the tablet core are mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose and sodium stearyl fumarate. The tablet coating consists of polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, ferric oxide yellow, ferric oxide red and ferric oxide black.

#### 1.2.1.1.2 Pharmacodynamics:

In vitro studies showed that osimertinib potently inhibits cellular growth in both EGFRm+ and EGFRm+/T790M mutant cell line, with 9 folds lower activity against wild-type EGFR lines. It also inhibits the activity of ERBB2, ERBB3, ERBB4, ACK1, and BLK at clinically relevant concentrations. In vivo studies showed that osimertinib caused significant and sustained tumor shrinkage in tumor xenograft and transgenic mouse models harboring activating EGFR mutations and EGFR T790M after 14 days of 2.5 mg/kg/day dose.[17]

Osimertinib showed higher activity in patients with detectable plasma levels of EGFR T790M DNA compared with patients without detectable plasma (85% vs 33%) when used as the second-line treatment for patients with EGFRm+ NSCLC.[18]

#### 1.2.1.1.3 Pharmacokinetics

The area under the plasma concentration-time curve (AUC) and maximal plasma concentration (C<sub>max</sub>) of osimertinib increased dose proportionally over 20 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 after 15 days of dosing. At steady state, the C<sub>max</sub> to C<sub>min</sub> (minimal concentration) ratio was 1.6-fold.

**Absorption** The median time to C<sub>max</sub> of osimertinib was 6 hours (range 3-24 hours). Following administration of a 20 mg osimertinib tablets with a high-fat, high-calorie meal (containing approximately 58 grams of fat and 1000 calories), the C<sub>max</sub> and AUC of osimertinib increased by 14% and 19% respectively, compared to fasting conditions.

**Distribution** The mean volume of distribution at steady-state (V<sub>ss/F</sub>) of osimertinib was 986 L. Plasma protein binding of osimertinib is likely high based on its physiochemical properties.

**Elimination** Osimertinib plasma concentrations decreased with time and a population estimated mean half-life of osimertinib was 48 hours, and oral clearance (CL/F) was 14.2 (L/h).

**Metabolism** The main metabolic pathways of osimertinib were oxidation (predominantly CYP3A) and dealkylation in vitro. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in the plasma after osimertinib oral administration. The geometric mean exposure (AUC) of each metabolite (AZ5104 and AZ7550) was approximately 10% of the exposure of osimertinib at steady-state.

**Excretion** Osimertinib is primarily eliminated in the feces (68%) and to a lesser extent in the urine (14%). Unchanged osimertinib accounted for approximately 2% of the elimination.

**Specific Populations** No clinically significant differences in the pharmacokinetics of osimertinib were observed based on age, sex, ethnicity, body weight, smoking status, mild (CL<sub>cr</sub> 60-89 mL/min) or moderate (CL<sub>cr</sub> 30-59 mL/min) renal impairment, or mild hepatic impairment (total bilirubin <ULN and AST between 1 to 1.5x ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST). There are no data on the pharmacokinetics of osimertinib in patients with severe renal impairment (CL<sub>cr</sub> less than 30 mL/min) or with moderate to severe hepatic impairment (moderate: total bilirubin between 1.5 to 3.0 times ULN and any AST, and severe: total bilirubin between 3.0-10 times ULN and any AST).

#### 1.2.1.1.4 PK drug-drug interactions

As CYP3A4/5 is the principal P450 protein responsible for the metabolism of osimertinib, AZ5104 and AZ7550, co-administration with a potent CYP3A4 inhibitor or inducer may affect their exposure. Osimertinib, AZ5104 and AZ7550 are substrates for P-gp and BCRP but are not substrates for OATP1B1 and OATP1B3.

No restrictions on co-administration of osimertinib with CYP3A4/5 inhibitors or substrates are required; however, it is recommended that potent inducers of CYP3A4/5 be only co-administered with osimertinib if no other alternative exists and patients be closely monitored for reduction in efficacy.

The likelihood of a clinically meaningful DDI with osimertinib and drug transporters suggests that an 80 mg dose of osimertinib may result in a DDI via inhibition of intestinal BCRP. It is recommended that patients taking concomitant medications where the disposition is dependent upon BCRP and with narrow therapeutic index (eg, rosuvastatin) should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib.

#### 1.2.1.1.5 Safety pharmacology and toxicology

The toxicology of osimertinib has been evaluated in repeat dose oral toxicity studies of up to 6 months in rats and 9 months in dogs (1 month studies included an assessment of recovery), genetic toxicology studies, reproductive toxicology studies (assessing male and female fertility and effects on embryofetal development and early post-natal survival/growth in rats) and in an in vitro phototoxicity assay. Lung findings identified in the 3 month rat study were further characterised by electron microscopy.

The nonclinical toxicology profile of osimertinib largely reflects the pharmacological action of this compound. Osimertinib is a potent inhibitor of the mutant forms of the EGFR, but also shows less



potent inhibition of the wild-type EGFR and other members of the ErbB receptor family (eg.HER2), which are expressed in normal tissues (Yano et al 2003; Wieduwilt and Moasser, 2008). Osimertinib has demonstrated a margin of selectivity over these closely related receptors in in vitro pharmacology models; however, it is not unexpected that toxicities associated with inhibition of these receptors would be seen when doses up to the maximum tolerated are evaluated in the toxicology studies.

The principal histopathological findings observed in the repeat dose toxicity studies comprised atrophic, inflammatory and/or degenerative changes affecting the epithelia of the eye (cornea), GI tract (including tongue), skin and female reproductive tract with secondary changes in the spleen, bone marrow and lymph nodes. Similar findings have been reported in animal studies with other EGFR TKIs including gefitinib, erlotinib, afatinib (a pan irreversible inhibitor of EGFR, HER2 and HER4) and lapatinib (dual EGFR and HER2 selective inhibitor). There were additional histopathological findings in the male reproductive tract, male mammary gland, lymph nodes, Harderian gland, lung, bone marrow, thymus, lacrimal gland, tarsal gland, kidney, liver and adrenal gland. These target organ findings are briefly discussed below:

#### **1.2.1.2 Clinical efficacy safety and tolerability:**

Please refer to the osimertinib Investigator's Brochure (IB) for details of the clinical programme for osimertinib.

In the phase 1 dose escalation study of osimertinib (D5160C00001, AURA), no dose-limiting toxicities were reported in any of the dose escalation cohorts (20, 40, 80, 160, and 240mg) and a non-tolerated dose has not been defined. Based on the totality of the safety, pharmacokinetic and preliminary efficacy data, 80 mg once daily was selected as the recommended phase II dose.

Data from the ongoing phase I AURA study (D5160C00001) in patients with T790M positive NSCLC who were previously treated with EGFR TKI, have achieved promising efficacy with osimertinib; 54.2% 95% CI (40.8%, 67.3%) of subjects achieved a response, 91.5% 95% CI (81.3%, 97.2%) achieved disease control, median duration of response of 12.4 months 95% CI (8.3, NC) and median PFS based on 38% maturity of data was 13.5 months 95% CI (8.3, NC), as assessed by blinded independent central review[15]. Promising evidence of efficacy has also observed in patients with EGFRm treatment naïve NSCLC treated with osimertinib as first line EGFR TKI[6] .

Across the clinical development programme, osimertinib has demonstrated a manageable safety profile [15]

#### **1.2.2 Rationale of continuing systemic therapy after oligoprogression**

This continuation of erlotinib beyond progression is recommended by the NCCN guidelines for the following benefits; delayed symptoms, reduction in tumor size and FDG avidity on PET [19, 20]. In a Japanese study, 64 out of 186 EGFR mutated patients treated with an EGFR TKI with radiological PD on first- or second-line treatment with an EGFR TKI either continued TKI or chemotherapy upon PD. Survival advantage (32.2 months versus 23.0 months) was achieved with the continuation of EGFR TKI treatment versus the switch to chemotherapy, respectively [21-23] These data suggest that for a carefully selected group of patients, continuing *EGFR* inhibitors even in the setting of limited progressive disease results in clinically meaningful benefit.

However the optimal therapy to combine with targeted therapy beyond progression is ill-defined as adding systemic chemotherapy is often too toxic.

The decision to continue osimertinib at the time of oligoprogression will be at the discretion of treating oncologist in line with standard clinical practice. If, in the opinion of the treating oncologist, the patient would benefit from continued osimertinib this will be allowed even after documented oligoprogression.



### 1.2.3 Rationale of adding stereotactic ablative radiation therapy after targeted therapy

Stereotactic ablative body radiation (SABR) is a technique of delivering precisely targeted radiation to tumors while minimizing the dose given to adjacent normal tissue. Large doses of radiation are delivered in a small number of treatments. Due to the radio-biological response to this type of radiation, there can be dramatic tumor responses leading to the ablative terminology.

In this study, SABR will be added as a cytoreductive agent after major cancer cell killing is achieved with osimertinib administered for 8 weeks. Following the Goldie-Coldman hypothesis, it seems plausible that the resulting cancer debulking will then result in a smaller chance of resistant clones developing according to the Goldie-Coldman hypothesis. Accordingly, this approach may prolong the overall duration of osimertinib efficacy, delaying the development of clinically significant resistance that necessitates a switch from osimertinib to another systemic therapy.

In the trial, subsequent post-SABR limited progression will be considered for repeat SABR if clinically feasible, with ongoing osimertinib administration. This strategy accurately reflects current clinical practice and recommendations from the national authorities such as the NCCN, which recommend continuing targeted therapy after progression in some cases.

#### At study entry:

Patients on this trial who have lesions requiring radiation prior to initiation of systemic therapy in the view of the treating physician will be allowed to get such radiation. This will not limit their trial participation, though the lesion will be noted as having been radiated.

#### After 8 weeks of osimertinib monotherapy:

Lesions that persist after osimertinib monotherapy will receive stereotactic radiation. These include lesions that may have progressed during osimertinib monotherapy alone. As long as no change in systemic therapy is indicated, these patients will continue on the trial. Up to 6 sites or organs will receive stereotactic radiation, at the discretion of the treating physician. All sites of gross tumor (typically defined by CT and PET) should be treated for patients to continue on study.

#### Subsequent areas of progression:

As long as the study participant is on osimertinib as the sole systemic therapy, further stereotactic radiation may be delivered to up to 6 sites or organs at a time. Lesions in close proximity to one another amenable to treatment with a single SABR field are considered a single site. When osimertinib is no longer the systemic agent or when new progressive sites cannot feasibly be treated with stereotactic radiation (e.g., malignant pleural effusion or site previously irradiated), study participation will end. The primary endpoint of progression-free survival will be calculated from the start of treatment to the first episode of progression.

#### Osimertinib during stereotactic radiation:

Currently there are limited data about the safety of concurrent osimertinib and stereotactic radiation, though studies are ongoing. In this trial, osimertinib will be held for 3 days prior to and 3 days after the stereotactic radiation. The total expected duration of the stereotactic radiation is expected to range between 1-5 treatments, generally not exceeding 21 days from first to last radiation therapy.

#### CNS metastases:

Stereotactic radiation to CNS lesions that require therapy will be allowed. At study entry the presence of CNS lesions or their treatment with radiation will not constitute a restriction to study participation. Subsequently, progression in the CNS will not terminate study participation, and patients may receive stereotactic radiation to those areas.

Evaluation of CNS metastases will consist of an MRI or contrast enhanced CT performed at baseline and then as clinically indicated, but at least every 3 months. Patients without CNS involvement will not be required to have mandatory CNS imaging. All patients with new symptoms suspicious of CNS involvement will have urgent CNS imaging performed.

### 1.3 Study rationale and purpose

Patients with *EGFR* mutant non-small cell lung cancer will receive the current optimal therapy with osimertinib. After 8 weeks of targeted therapy, there will likely be some persisting lesions that would not have completely regressed. These persisting lesions would likely consist of cells that are less sensitive to targeted therapy. From the data summarized above [14], these persisting lesions are most to subsequently develop resistance and demonstrate progression.

To delay the onset of clinical progression, lesions that persist after 8 weeks of osimertinib therapy and are amenable to stereotactic ablative radiation will be radiated. Osimertinib will be held for 3 days before the first dose of radiation and resumed 3 days after the last dose.

After radiation, all patients will continue osimertinib therapy. If subsequently there is any evidence of progression, there will be an assessment of whether a repeat course of radiation is feasible. If it is feasible to repeat SABR to sites of progression, this will be performed and osimertinib resumed. If SABR is not possible, then a change in systemic therapy will be required.

### 1.4 Rationale for the protocol design

The purpose of the trial is to determine if the addition of SABR to osimertinib can prolong the clinical benefit of targeted therapy. This will be an open-label, non-randomized, single arm trial in *EGFR* mutant lung adenocarcinoma. The protocol will also report the safety of treating with SABR and osimertinib, though both are widely used in clinical practice.

### 1.5 Rationale for dose and regimen selection

In the AURA phase I study, the recommended dose for the expansion cohorts and future trials was determined to be 80 mg daily (QD). The dose-escalation cohort with 31 patients and the dose-expansion cohort with 222 patients who received oral osimertinib at five dosages of 20 mg/d, 40 mg/d, 80 mg/d, 160 mg/d, or 240 mg/d. No dose-limiting toxic effects were observed in the dose escalation cohort (31 patients). Tumor response rates were similar across all osimertinib dose levels, with increasing toxicities at the 160 mg and 240 mg daily doses; thus, a dose of 80 mg daily was adopted for future studies.

The most common adverse events were diarrhea (47% of patients), rash (40%), nausea (22%), and decreased appetite (21%). Adverse events of diarrhea and rash increased in frequency in a dose-dependent manner. Any event of grade 3 or higher was observed in 32% of the patients. Adverse events leading to dose reduction or drug discount inuation were observed in 7% and 6%, respectively, of all patients. Serious adverse events were observed in 22% of the patients;

The package insert for osimertinib recommends a starting dose of 80 mg daily. There are recommendations for holding/discontinuation for toxicity however no dosing adjustments are needed for renal/hepatic impairment.

## 2 Hypothesis and Study Objectives

### 2.1 Hypothesis

Our proposed study is designed to prolong the clinical benefit of osimertinib therapy in patients with *EGFR* mutant lung cancer. We will evaluate the combination of two well-tolerated therapies: osimertinib and SABR. This dual therapy is expected to be more effective than either alone in destroying sensitive tumor cells and also in preventing the development of resistant cells. Published experience suggests that median PFS for patients who have previously been treated with *EGFR* TKI is less with osimertinib than those who have never been treated with an *EGFR* TKI (10.1 months vs 19.3 months). In this study, the patients enrolled will have no prior treatment with *EGFR* inhibitors.

## 2.2 Objectives:

### Primary Objective

- The primary objective of this study will be to determine the efficacy of osimertinib plus SABR in patients with EGFR mutant lung cancer. The measure for this outcome will be: Progression-Free Survival (PFS); defined as time from first dose of osimertinib to date of objective progression (as determined by the investigator according to RECIST 1.1) or death (in the absence of progression). Patients will still be followed for progression even if they stop due to toxicity or start a subsequent therapy prior to progression.

There may be progression in a specific localized region that is amenable to stereotactic radiation. If all existing lesions that enlarge and any new lesions that develop can still be effectively treated with stereotactic radiation, patients will be evaluated for repeat SABR therapy and osimertinib resumed. This will be at the recommendation of the treating physician according to standard practice. This will be defined as Time to 2<sup>nd</sup> SABR therapy and will be one of the study secondary endpoints. Similarly, if 3<sup>rd</sup> round of SABR can be safely provided with subsequent resumption of osimertinib, that will be defined as the Time to 3<sup>rd</sup> SABR therapy.

### Secondary Objectives

Secondary objectives include the following:

Objective	Endpoint	Definition of endpoint
To determine the impact of osimertinib plus SABR on survival	Overall survival	Defined as: Time from the date of initiation of osimertinib until death of any cause.
To determine the impact of osimertinib plus SABR on length of response	Duration of response (DoR)	Defined as the time from documentation of tumor response to disease progression.
To determine the impact of osimertinib plus SABR on the length of time until next therapy needed.	Time to subsequent SABR (2 <sup>nd</sup> , 3 <sup>rd</sup> , etc) or death.	Defined as the duration of time from when measurement criteria are met for CR or PR (whichever is first recorded) until the first date that: recurrent or progressive disease is objectively documented AND is amenable to SABR.
To determine the impact of osimertinib plus SABR on tumor response.	Objective response rate (ORR)	Defined as the proportion of patients with measurable disease who had a response per the definitions stated in section (6.1.4) After receiving at least one cycle of therapy.
To determine the impact of osimertinib plus SABR on the duration of time while on osimertinib.	Time until discontinuation of osimertinib or death	Defined as time from initiation of osimertinib to evidence of disease progression by RECIST 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason.
Demonstrate safety of osimertinib followed by SABR	Safety and tolerability	Safety: Defined as the risk to patients by using osimertinib plus SABR Tolerability: Defined as and the degree to which overt adverse

		events of the osimertinib plus SABR can be tolerated.
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#### Translational and exploratory objectives

Biopsy of progressive sites will be encouraged per standard of care practice. After 8 weeks of osimertinib, treatment will be transiently held and SABR will be delivered to persisting lesions. These patients will then resume osimertinib monotherapy and continue clinical and radiographic monitoring. During this time if progressive lesions are found after resumption of osimertinib they will be biopsied if feasible. These research biopsies will be performed after informed consent is obtained and only if biopsies can be done safely. Research biopsies will not be required for patients on this study. We will collect blood at the time of progression for circulating tumor DNA (ctDNA) mutation analysis.

This trial will offer the opportunity to improve our understanding of the molecular changes that occur during the process of osimertinib resistance. Collected tissue and blood samples will be tested for molecular mechanisms of resistance, which may include C797S resistant mutation[24], MET and HER2 amplifications [25], and small cell transformation, all of which have been reported as resistance mechanisms to osimertinib .

### **2.3 Description of protocol design**

This is an, open-label, single arm protocol designed to evaluate the activity of targeted therapy and SABR in EGFR+ lung adenocarcinoma. Study participants will have to be eligible for both radiation and targeted therapy with osimertinib.

#### **2.3.1 Treatment phase and duration of treatment**

Patients eligible for treatment will receive 80 mg daily of osimertinib as part of a 28-day cycle. The first dose of each cycle will be administered after evaluation at the study center. Patients will remain on study and take osimertinib until there is evidence of disease progression by RECIST 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason. In case of oligoprogression amenable to repeat courses of SABR, the treating oncologist may resume osimertinib if it is indicated per standard clinical practice. Patients must continue to be followed for safety and efficacy assessments as per the schedule of assessments.

At 8 weeks from initiation of osimertinib, persisting lesions will be treated with a course of SABR. Osimertinib will be held 3 days before the start of radiation. Patients will resume osimertinib 3 days after completion of the SABR. Regular surveillance will follow and any new or enlarging lesions that develop will be assessed for repeat SABR.

#### **2.3.2 Definition of end of the Study**

The study will end when all 42 patients have evidence of disease progression by RECIST1.1, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason.

At the completion or discontinuation of study medication, all patients will be seen within 30 days for an end of therapy evaluation. This will include a safety assessment for AE's SAE's. Any unused medication will be returned.

#### **2.3.3 Early Termination**

Treatment on protocol may be terminated early if the Principal investigator or institution assess that the safety of the enrolled subjects will be compromised by continuation of the trial. The procedure followed will be that of the premature withdrawal patient and any patients on treatment will be seen as soon as possible.

### 3 Subject eligibility

#### 3.1 Patient population

Subjects for this study will be selected from those with *EGFR* mutant NSCLC. *EGFR* mutations may be demonstrated by standard, clinically accepted methods, including direct gene sequencing, PCR, and NextGen sequencing.

Patients will be informed about their potential eligibility status for this trial. None of these patients will be given any therapy or undergo any study related assessments/procedures until they have successfully screened and enrolled on to the therapeutic portion of the study.

Patients enrolled to the therapeutic portion of the study will have histologically proven lung adenocarcinoma with *EGFR* mutation detected by polymerase chain reaction or gene sequencing assays as described above.

#### 3.2 Inclusion criteria

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

1. Written informed consent in accordance with federal, local, and institutional guidelines. The patient must provide informed consent prior to the first screening procedure. However, the Investigator should not repeat procedures that are performed as part of standard of care (SOC), if they are within the screening window and are done prior to signing the ICF.
2. Age  $\geq$  18 years
3. Advanced *EGFR* exon 19 or 21 mutant NSCLC, not amenable to curative surgery or radiotherapy. *EGFR* mutations may be demonstrated by standard, clinically accepted methods, including direct gene sequencing, PCR, and NextGen sequencing.
4. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
5. Patients must have a life expectancy  $\geq$  12 weeks.
6. Females should be using adequate contraceptive measures, should not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:
  - Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments
  - Women under 50 years old would be consider 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
  - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
7. Male patients should be willing to use barrier contraception (see Restrictions, Section 3.3)
8. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
9. At least one lesion, not previously irradiated, that can be accurately assessed at baseline with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.
10. Adequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

- Absolute neutrophil count  $>1.5 \times 10^9/L$
- Platelet count  $>100 \times 10^9/L$
- Haemoglobin  $>9.0$  g/dL (transfusion is permitted to achieve Hgb  $\geq 9.0$  g/dL)
- Alanine aminotransferase  $<2.5$  times the upper limit of normal (ULN) if no demonstrable liver metastases or  $<5$  times ULN in the presence of liver metastases
- Aspartate aminotransferase  $<2.5$  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 hyperbilirubinemia) or liver metastases
- Serum Creatinine  $<1.5$  times ULN concurrent with creatinine clearance  $>50$  ml/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is  $>1.5$  times ULN.

### 3.3 Exclusion criteria

1. Involvement in the planning and/or conduct of the study (applies to both sponsor staff and/or staff at the study site)
2. Previous treatment with osimertinib or any EGFR TKI.
3. Previous treatment with immunotherapy or any check point inhibitors.
4. Treatment with an investigational drug within five half-lives of the compound
5. Patients 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 week prior) (Appendix A). All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4.
6. Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 1 at the time of starting study treatment with the exception of alopecia and grade 2, prior platinum-therapy related neuropathy.
7. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.
8. Patients with symptomatic CNS metastases who are neurologically unstable
9. Past medical history of ILD, drug-induced ILD, radiation pneumonitis requiring steroid treatment, or any evidence of clinically active ILD
10. Any of the following cardiac criteria:
  - a. Mean resting corrected QT interval (QTc using Fredericia's formula)  $> 470$  msec
  - b. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block)
  - c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, 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

11. 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
12. History of hypersensitivity to osimertinib (or drugs with a similar chemical structure or class to osimertinib) or any excipients of these agents
13. Males and females of reproductive potential who are not using an effective method of birth control and females who are pregnant or breastfeeding or have a positive (urine or serum) pregnancy test prior to study entry
14. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements

In addition, the following is considered a criterion for exclusion from the exploratory genetic research:

15. Previous allogeneic bone marrow transplant.
16. Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

### **Restrictions:**

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

1. Females of child-bearing potential should use reliable methods of contraception from the time of screening (at least 2 weeks prior to first dose) until 6 weeks after discontinuing osimertinib. Acceptable methods of contraception include total and true sexual abstinence, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions (IUS Levonorgestrel Intra Uterine System (Mirena), Medroxyprogesterone injections (Depo-Provera)), copper-banded intra-uterine devices, and vasectomized partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse.
2. Male patients should be asked to use barrier contraceptives (i.e., by use of condoms) during sex with all of their female partners during the trial and for a washout period of 4 months. Patients should not father a child for 4 months after completion of osimertinib treatment. Patients should refrain from donating sperm from the start of dosing until 4 months after discontinuing osimertinib treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of osimertinib treatment.
3. If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see above), should be maintained on it throughout the access program period (30 days post-last dose). Patients taking concomitant medications whose disposition is dependent upon breast cancer resistance protein (BCRP) and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Appendix A).

Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of

muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.

Patients taking warfarin should be monitored regularly for changes in prothrombin time or international normalized ratio (INR).

## 4 Treatment Plan

### 4.1 Treatment Dosage and Administration

For this protocol, the term “treatment” refers to osimertinib. The dose and schedule are listed under table 4-1.

Each cycle of therapy will be 28 days long. A completed cycle will be 28 days of once daily continuous treatment. Day 1 will be the first day that osimertinib is taken, and the last day of a completed treatment cycle will be day 28.

Table 4-1:

Investigational product	Dosage form and strength	Manufacturer
osimertinib	40mg Tablets	AstraZeneca
	80mg Tablets	

AstraZeneca will supply osimertinib as tablets for oral administration as a single daily dose of 80 mg. osimertinib will usually be supplied as either bulk or unlabelled bottles for ISS/ESR studies.

Additional information about the Investigational product may be found in the Investigators' Brochure.

#### Administration guidance

Osimertinib is administered as 80 mg once daily. Osimertinib may be taken without regard to food.

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 their osimertinib, they should not make up for this dose, but should take the next scheduled dose.

The dose of 80 mg osimertinib daily can be reduced to 40 mg osimertinib once daily under circumstances described in Section [4.7]. Further dose reductions are not possible. Once a dose has been reduced, it should not be re-escalated at future cycles.

Patients will self-administer the doses of osimertinib for the cycle. A dosing diary will be given to the patient to record doses and missed doses. The dosing diary will be reviewed by the study team at each visit for dosing compliance.

#### **Patients who have difficulty swallowing solids:**

Disperse tablet in 4 tablespoons (approximately 60 mL) of non-carbonated water only. Stir until tablet is completely dispersed and swallow or administer through naso-gastric tube immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 4 to 8 ounces of water and immediately drink or administer through the naso-gastric tube.



Any change from dosing schedule, dose interruptions, or dose reductions should be recorded

#### 4.2 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling.

#### 4.3 Storage:

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and the Investigator Brochure specifies the appropriate storage.

#### 4.4 Treatment duration

Patients will continue osimertinib treatment until they experience any of the following:

- Disease progression not amenable to SABR and necessitating change in systemic therapy determined by the treating physician.
- Unacceptable toxicity that precludes further treatment.
- Start of a new anti-cancer therapy.
- Pregnancy.
- Treatment is discontinued at the discretion of the investigator or patient.
- Lost to follow-up.
- Death.

#### 4.5 Dose escalation guidelines

No doses escalation will be permitted on this study.

#### 4.6 Dose modifications

Dose adjustment for adverse events should be in accordance with the following table:

**Table 4.6 Osimertinib dose adjustment information for adverse reactions**

Target Organ	Adverse Reaction <sup>a</sup>	Dose Modification
Pulmonary	ILD/Pneumonitis	Permanently discontinue osimertinib
Cardiac	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).
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Other	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of osimertinib for up to 3 weeks	osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue osimertinib

<sup>a</sup> Note: The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade), where the clinician considers the event of concern to be specifically associated with osimertinib (and not attributable to the disease or disease-related processes for which patient is being treated), dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. Detailed information on the clinical management of events may be found in Appendix B, "Guidance for the Management of Adverse Events in Studies using 80 mg osimertinib."

Patients with QTc prolongation (i.e., confirmed QTc prolongation to >500 msec absolute on at least 2 separate ECGs) should have osimertinib treatment interrupted and regular ECGs performed until resolution to baseline.

If the toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset, treatment with osimertinib may be restarted at the same dose (80 mg, daily) or a lower dose (40 mg, daily) using the rules below for dose modifications (Table 1). There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption.

If the toxicity does not resolve to ≤CTCAE grade 2 after 3 weeks, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

#### 4.7 Dose Interventions

Intervention	Osimertinib Dose
Starting Dose	80 mg daily
Reduced Dose	40 mg daily

On resolution of toxicity within 3 weeks:

If an event subsequently requires dose interruption, osimertinib may restart at the same dose or the reduced dose, on resolution/improvement of the event at the discretion of the clinician.

##### 4.7.1 Pulmonary Symptoms

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in osimertinib dosing is recommended, and the Sponsor study team should be informed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued.

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.

In the absence of a diagnosis of interstitial lung disease osimertinib may be restarted.

##### 4.7.2 QTc Prolongation

Patients with QTcF prolongation fulfilling the following criteria (i.e., confirmed QTcF prolongation to > 500 msec absolute) should have osimertinib interrupted and regular ECGs performed until resolution to <481 msec or baseline QTcF if baseline QTcF is >481 msec, and then restarted at a reduced dose of 40 mg. If the toxicity does not resolve to ≤ grade 1 within 3 weeks the patient will be permanently withdrawn from osimertinib treatment. For QTc prolongation with signs/symptoms of serious arrhythmia, osimertinib treatment will not be reinitiated.

##### 4.7.3 Keratitis

Keratitis was reported in 0.7% (n=6) of the 833 patients treated with osimertinib in the AURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

##### 4.7.4 Changes in cardiac contractility

Across clinical trials, LVEF decreases greater than or equal to 10% and a drop to less than 50% occurred in 4.0% (26/655) of patients treated with osimertinib who had baseline and at least one follow-up LVEF assessment. Based on the available clinical trial data, a causal relationship between effects on changes

in cardiac contractility and osimertinib has not been established. Echocardiogram/MUGA to assess LVEF should be performed at screening in patients with pre-existing cardiac disease that does not meet the criteria for study exclusion but may worsen on treatment with osimertinib. Subsequent assessment of LVEF should be performed as clinically indicated. In patients who develop cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

#### 4.7.4 Liver abnormalities

**NOTE:** In case a subject shows an AST or ALT  $\geq 3 \times \text{ULN}$  or total bilirubin  $\geq 2 \times \text{ULN}$  please refer to Appendix C 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

#### 4.8 Concomitant medications

Once enrolled, all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known to be potent inducers of CYP3A4 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of adverse events. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of osimertinib. All concomitant medications should be captured on the CRF. Guidance on medicines to avoid, medications that require close monitoring and on washout periods is provided (see Appendix A).

If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see above), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon BCRP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib.

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

Guidance on medications to avoid, medications that require close monitoring and on washout periods should be provided (see Appendix A).

Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

#### 4.9 Patient numbering, treatment assignment or randomization

##### 4.9.1 Patient numbering

Each patient will be assigned a subject number at the time of screening which shall be the primary identifier for the patient throughout the entire trial. This number will not be reassigned if a patient is not enrolled on to the therapeutic portion of the trial. Once assigned a number, the patient will not be given a new number if enrollment is delayed behind other patients.

##### 4.9.2 Treatment assignment

Before the first dose of osimertinib, the investigator will confirm that the patient meets all eligibility criteria. The patient will be assigned to the treatment arm and the Investigator or delegate will update the trial record accordingly.

#### 4.9.3 Treatment blinding

Not applicable.

#### 4.10 Study drug compliance

At each visit, the patient's compliance in study medication according to protocol will be assessed by the investigator and/or study personnel. This information will be entered into the Drug Accountability Form and captured into the source document at each visit, in their medication diary.

### 5 Visit schedule and assessments

#### 5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for therapy on this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

##### 5.1.1 Informed Consent

Screening assessments to confirm eligibility will be performed as per the schedule of assessments. Documented Informed consent must be obtained before any study specific procedure will be performed.

For treatment on the trial, the patient must have a documented *EGFR mutation* either by sequencing or assay and meet the remainder of the eligibility criteria. This must be done at the treating center and all study required testing must be completed within the 30 day period prior to day of initiating therapy.

Re-screening of patients will be allowed, if all entry criteria are met during the re-screening phase time period (-30 days to -1 day).

##### 5.1.2 Medical history

Complete medical and surgical history, including history of infections.

##### 5.1.3 Demographics

Data to be collected on patient characteristics at screening include:

- Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)

- Lung adenocarcinoma diagnosis and extent of disease, including:

- Date of diagnosis

- Site of active disease

- Prior antineoplastic therapies (medications, radiation, surgeries)

- Prior and Concomitant Medications, surgical and medical procedures

All other medications taken within 30 days before the first dose of osimertinib treatment is administered will be noted in the clinical trial medication record and updated on a continual basis if there is new change to the medication.

##### 5.1.4 Review subject eligibility criteria

According to section 3

### 5.1.5 Review previous and concomitant medications

### 5.1.6 Physical exam including vital signs, height and weight

A physical examination will be performed prior to receiving first dose of study drug on day 1 of every cycle and at the EoT Visit. Vital signs (temperature, pulse, respirations, blood pressure, and weight) will be obtained and recorded with any clinically relevant findings notated as such.

### 5.1.7 Performance status

Performance status evaluated prior to study entry.

### 5.1.8 Adverse event assessment

Baseline adverse events will be assessed. See section 7.1 for Adverse Event monitoring and reporting.

### 5.1.9 Hematology

Hgb, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute)).

### 5.1.10 Serum chemistries and coagulation

Albumin, ALT, AST, calcium, creatinine, total bilirubin, direct bilirubin (only if total bilirubin is  $\geq$  grade 2), blood urea nitrogen (BUN) or urea, magnesium, potassium, sodium, glucose, phosphate (inorganic phosphorus), alkaline phosphatase. Creatinine clearance will be calculated using the serum creatinine value. Coagulation tests will be Prothrombin Time (PT) and Partial Thromboplastin Time.

### 5.1.11 Urinalysis

Macroscopic panel (dipstick)(color, total bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)

### 5.1.12 ECG

Patients should be monitored for ECG changes at every cycle. ECGs should be reviewed and any abnormalities noted.

Resting 12 lead ECG:

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. For each time point three ECG recordings should be taken at about 5 minute intervals. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

The investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, ECG intervals and an overall evaluation will be recorded.

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

Cross reference QTc standards.

#### **5.1.13 Echocardiogram:**

Echocardiogram to assess LVEF should be performed at screening in patients with pre-existing cardiac disease that does not meet the criteria for study exclusion but may worsen on treatment with osimertinib. Subsequent assessment of LVEF should be performed as clinically indicated. In patients who develop cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

#### **5.1.14 Ophthalmologic exam:**

Full ophthalmic assessment, including slit lamp examination, should be performed at screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Ophthalmology examination results should be collected in the eCRF. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings. These photographs should be available for submission to AstraZeneca representatives if necessary.

#### **5.1.15 Pregnancy test (for females of child bearing potential)**

At screening visit, serum pregnancy test will be performed. Following the screening assessment, urine or serum pregnancy tests should be performed.

#### **5.1.16 Tumor assessment**

To be performed using radiographic imaging according to section 5.3.1.

#### **5.1.17 Follow-up after Treatment**

The study team will attempt to collect survival status and new therapy information for patients who are enrolled. Public sources may be searched for survival status information.

### **5.2 Protocol flow and visit schedule**

Table 5-1 lists the protocol schedule and assessments and indicates when particular assessments will be performed with an "X". The cycle length is fixed at 28 days, and will be maintained regardless of whether there were dose modifications or interruptions in therapy. If treatment with osimertinib is interrupted, future visits and assessments will continue as listed from cycle 1 day as Day#1 for the purpose of scheduling. Screening procedures may overlap with Cycle 1 Day 1 procedures only if all eligibility criteria is met and confirmed prior to dosing. A physician visit is not needed on C1D1 if performed within 7 days prior to starting treatment. In this case, delegated study personnel may assess performance status (WHO) on Cycle 1 Day 1. There will be variation of up to +/- 3 days allowed in visits and assessments.

<b>Table 5-1 Visit evaluation Schedule</b>	<b>Protocol Section</b>	<b>EGFR status</b>	<b>Screening / Baseline</b>	<b>Day 1 of Cycle 1</b>	<b>Day 15 of Cycle 1 (28d) ± 3</b>	<b>Day 1 of Cycle 2 (28d) ± 3</b>	<b>Day 1 of Subsequent cycles (28d) ± 3</b>	<b>End of study treatment (EoT)</b>	<b>Long Term Follow up Q3 mo following EOT</b>
<b>Visit Number</b>			<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5, 6..</b>	<b>Last</b>	
<b>Day of cycle</b>		<b>-180 to -1</b>	<b>-30 to -1</b>	<b>D1</b>	<b>D15</b>	<b>D29</b>	<b>D57, D85..</b>	<b>Last</b>	
Obtain Informed Consent	ICF	X	X						
Inclusion/exclusion criteria	3.2 & 3.3		X						
Documentation of EGFR positivity by PCR or sequencing.	5.1.1	X	X						
Diagnosis and extent of cancer	5.1.2		X						
Demography	5.1.3		X						
Ophthalmologic evaluation *			X						
Relevant medical history/ current medical conditions	5.1.4		X						
Prior antineoplastic therapy (meds, surgery, radiation)	5.1.5		X						
Prior/concomitant medications	5.1.5		X	Continuous					
Surgical and Medical Procedures	4.4		X	Continuous					
Eligibility Screening	5.1.4		X						
End of Phase Disposition	5.1.3		X Screening Phase Disposition					X End of Treatment Phase	
<b>Physical examination</b>	<b>5.1.6</b>		<b>X</b>	<b>X***</b>		<b>X</b>	<b>X</b>	<b>X</b>	
Performance status (WHO)	5.1.7		X	X			X	X	
Height	5.1.6		X						
Weight	5.1.6		X	X		X	X	X	
Vital signs	5.1.6		X	X		X	X	X	

<b>Table 5-1. Visit evaluation Schedule (continued)</b>	<b>Protocol Section</b>	<b>EGFR status</b>	<b>Screening / Baseline</b>	<b>Day 1 of Cycle 1 (28d) ± 3</b>	<b>Day 15 of Cycle 1 (28d) ± 3</b>	<b>Day 1 of Cycle 2 (28d) ± 3</b>	<b>Day 1 of Subsequent cycles (28d) ± 3</b>	<b>End of study treatment (EoT) (at last visit, or up to 30 days from last dose)</b>	<b>Long Term Follow Up Q3 mo following EOT</b>
<b>Visit Number</b>			<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5, 6,...</b>	<b>Last</b>	
<b>Day of cycle</b>		<b>-180 to</b>	<b>-30 to-1</b>	<b>1</b>	<b>D15</b>	<b>D29</b>	<b>D57, D85..</b>	<b>Last</b>	
<b>Lab assessments</b>			X	X **	X	X	X	X	
CBC	5.1.9		X	X	X	X	X	X	
Chemistry	5.1.10		X	X	X	X	X	X	
Creatinine clearance	5.1.10		X		X				
Coagulation (PT/PTT)	5.1.10		X						
Urinalysis (dipstick) with microscopic analysis	5.1.11		X		X			X	
Pregnancy test	5.1.15		X			X	X	X	
Standard of care imaging of neck/chest/abdomen (CT, MRI) as indicated to areas of known/	5.2.1		X				X (Every 8 weeks or 2 cycles +/- 7 days)		
Standard of Care Imaging of the brain as clinically indicated (MRI/CT)	5.2.1		X (if known or suspected brain metastases)				X Every 12 weeks or 3 cycles		
Adverse events	7.1		X	Continuous					
EKG	5.1.12		X	X		X	X	X	
Echocardiogram	5.1.13		X****						
Drug administration	4.1			Continuous					
Survival Assessment	5.1.17								X

\*Ophthalmologic will also be performed if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated.

\*\* Laboratory assessments must be performed on Cycle 1 Day 1 or within 24 hours prior to dosing.\*\*\* Cycle 1 day 1 Physical exam does not need to be repeated if screening PE was performed within 7 days of C1D1

\*\*\*\* Echo should be performed at screening in patients with pre-existing cardiac disease that may worsen on treatment with osimertinib, and as clinically indicated throughout study participation



### **5.2.1 Screening/Baseline**

Screening assessments to confirm eligibility will be performed as per the schedule of assessments. Documented Informed consent must be obtained before any study specific procedure will be performed.

The patient must have a documented *EGFR mutation* either by sequencing or assay and meet the remainder of the eligibility criteria. All study required testing must be completed within the 30 day period prior to day of initiating therapy.

Re-screening of patients will be allowed, if all entry criteria are met during the re-screening phase time period (-30 days to -1 day).

#### **5.2.1.1 Biomarker required for Eligibility on this trial arm**

Patient eligibility will be checked once all screening procedures are completed.

##### **5.2.1.1.1 *EGFR* mutation**

Histologically or cytologically confirmed diagnosis of lung adenocarcinoma with *EGFR mutation* will be required to be considered eligible for the therapeutic portion of the trial. *EGFR* testing will be via, standard clinically accepted methods such as:

- i. Polymerase chain reaction
- ii. Gene sequencing
- iii. NextGeneration sequencing

Documentation of *EGFR mutation* using one of the above tests is required.

#### **5.2.1.2 Patient demographics and other baseline characteristics**

Data to be collected on patient characteristics at screening include:

-Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)

-Relevant medical history

-NSCLC diagnosis and extent of disease, including:

Date of diagnosis

Site of active disease

Prior antineoplastic therapies (medications, radiation, surgeries)

Prior and Concomitant Medications, surgical and medical procedures

All other medications taken within 30 days before the first dose of osimertinib treatment is administered will be noted in the clinical trial medication record and updated on a continual basis if there is new change to the medication.

#### **5.2.1.3 Information to be collected on screening failures**

A patient who signs an informed consent but fails to satisfy all eligibility criteria for any reason will be considered a screen failure. The reason for not entering the treatment protocol will be recorded. The demographic information, informed consent, and Inclusion/Exclusion pages will be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 7 for SAE reporting details).

Subjects who signed ICF but are considered ineligible after signing the study consent will be considered as screening failures, and data will be handled in the same manner.

The following information will be recorded for screening failure patients:

- Screening Phase Disposition page (including reason for not satisfying eligibility criteria and being started on treatment).
- Informed consent.
- Demography.
- Adverse Events (only if an SAE occurs).
- Inclusion/Exclusion Criteria.

### **5.2.2 Treatment period**

Following completion of screening procedures and verifying patient eligibility, the patient will be approved for treatment per protocol.

The study treatment phase begins on Cycle 1, Day 1 with the first administration of osimertinib and will continue to receive osimertinib treatment until disease progression by RECIST1.1 not amenable to SABR necessitating a change in systemic therapy, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason whichever occurs first. Patients who have RECIST-defined PD as assessed by the investigator but who, in the opinion of the investigator, have evidence of continued clinical benefit from osimertinib may continue to receive the study medication upon approval by the principal investigator. In such cases, these patients must continue to be followed for safety and efficacy assessments as per the schedule of assessments. Patients will be assessed as per visit schedule in Table 5-1.

There is a visit window of  $\pm 3$  days for scheduled study assessments.

As some patients might have symptomatic metastases, they may need palliative radiotherapy during the treatment period:

- Palliative radiotherapy to control symptoms (including gamma knife technique), e.g. to control brain disease, is permitted during osimertinib studies.
- For brain and thoracic radiotherapy (only to control symptoms), a 7-10 day washout period before the procedure and one week period after procedure before restarting osimertinib is advised.
- All radiotherapy related toxicities should be managed and ideally resolved before restarting osimertinib.
- Investigators should consider the radiotherapy when assessing causality if there are any localised AEs following the procedure.
- If any lesions (including brain or thoracic disease) are asymptomatic then radiation would not be permitted

(This would not apply to the planned on-study SBRT)

### **5.2.3 End of treatment visit including study completion and premature withdrawal**

#### **5.2.3.1 End of Treatment Disposition**

Patients will be evaluated upon discontinuation of the osimertinib by a clinic visit. At that time all assessments listed for End of Treatment will be performed. A note will be entered into the clinical trial record will be completed, giving the date and reason for stopping the osimertinib treatment.

At a minimum, all patients who discontinue osimertinib treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of treatment.

#### **5.2.3.2 Criteria for patient withdrawal**

Patients may voluntarily withdraw from the study (no further study data to be collected) at any time.

Patient death will be considered as a withdrawal from the study. Patients may also be withdrawn (the physician may decide to remove the patient from any further study activity) if any of the following occur. Note, data will continue to be collected in a number of the following scenarios; see the applicable sections of the protocol for further information.

- Adverse events (see [Section 7.1](#))
- Disease progression
- Major protocol deviation
- Technical problems
- Physician decision
- Non-compliance with study treatment.
- Death
- Completed

Patients must be withdrawn if any of the following occur:

- Lost to follow-up
- Subject/guardian decision
- Pregnancy (Pregnancy will be followed for outcome, but pregnant women will undergo no other study procedures, including any end-of-treatment visits)

Patients lost to follow up should be recorded as such in the clinical trial record. For patients who are lost to follow-up, the investigator will record the attempts at “due diligence” by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

#### **5.2.3.3 Replacement policy**

If an eligible patient is unable to start therapy with osimertinib, they may be replaced with another eligible patient if they have not received any study drug.

Apart from the above, patients will not be replaced on this study.

### **5.3 Assessment types**

#### **5.3.1 Efficacy assessments**

Efficacy evaluations will be via revised RECIST 1.1 criteria on imaging performed at the conclusion of every 2 cycles. Target lesions will be identified prior to initiation of therapy on imaging and will be followed on subsequent imaging.

Physical exam findings of progressive disease will be considered as sufficient for documented progression if the record records biopsy proven tumor measurements in 2 dimensions and shows an increase in both dimensions of 20%. If the progression is amenable to SABR, the patient will receive SABR and be maintained on osimertinib. If the progression is not amenable to SABR and a change in systemic therapy is needed, the patient will be considered to have progressed and have reached the end of the study.

Imaging exams will be according to standard of care guidelines to areas of known/suspected disease. These will include CT of the neck, chest, abdomen and pelvis as well as MRI of the brain. Other tests may be clinically indicated, these will be ordered according to disease and patient specific guidelines. Imaging of the brain will be performed at baseline by CT or MRI per standard of care for lung adenocarcinoma.

Subjects with known CNS metastases must have an MRI of the brain performed every 3 cycles while on study. If an MRI cannot be performed, CT of the brain would be an acceptable alternative. Subjects without documented CNS metastases will not have mandated CNS imaging requirements.

### 5.3.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. For details on AE collection and reporting, refer to Section 7. Significant findings that were present prior to the signing of informed consent must be included in the relevant medical history/current medical conditions in the clinical trial record. Significant new findings that begin or worsen after informed consent must be recorded in the clinical trial record.

#### 5.3.2.1 Physical examination

A physical examination will be performed and include an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems. Significant findings that were present prior to the signing of informed consent must be included in the clinical trial record. Significant new findings that begin or worsen after informed consent must be recorded in the clinical trial record.

#### 5.3.2.2 Vital signs

Vital signs include body temperature, blood pressure and pulse measurements. Blood pressure (systolic and diastolic) and pulse should be measured.

For the assessment schedule refer to Table 5-1.

#### 5.3.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Height will be measured at screening only.

For the assessment schedule for weight refer to Table 5-1.

#### 5.3.2.4 Performance status

WHO performance status will be assessed as per the assessment schedule (refer to Table 5-1).

Assessment of WHO performance status (Table 5-2) will be performed within the time windows described above of the scheduled assessment, even if osimertinib medication is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

**Table 5-2 WHO/ECOG Performance status scale**

Score	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
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
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

#### 5.3.2.5 Laboratory evaluations

Local site laboratories will be used for the analysis of scheduled hematology, biochemistry, urine, and other blood specimens collected as part of safety monitoring. All unscheduled blood testing will be performed locally, with exceptions for emergency conditions. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 5.1).

Laboratory abnormalities that are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in osimertinib treatment constitute an adverse event (AE) and must be reported as an AE in the clinical trial record.

Laboratory values obtained at the screening visit will be used to assess eligibility to meet inclusion criteria. In addition, eligible patients must have baseline laboratory assessments performed on Cycle 1 Day 1 or within 24 hours prior to dosing.

#### 5.3.2.5.1 Hematology

Hematology assessments of the parameters listed in Table 5-3 will be tested as per the schedule of assessments (Table 5-1).

**Table 5-3 Local Clinical laboratory parameters collection plan**

<b>Test Category</b>	<b>Test Name</b>
Hematology	Hgb, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute))
Chemistry	Albumin, ALT, AST, calcium, creatinine, total bilirubin, direct bilirubin (only if total bilirubin is $\geq$ grade 2), blood urea nitrogen (BUN) or urea, magnesium, potassium, sodium, glucose, phosphate (inorganic phosphorus), alkaline phosphatase, GGT, lipase, amylase
Coagulation	PT/PTT
Creatinine clearance	Creatinine clearance
Urinalysis	Macroscopic panel (dipstick)(color, total bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)
Pregnancy test	For women of childbearing potential : At screening visit, serum pregnancy test At subsequent cycles, urine or serum pregnancy test. If local requirements dictate otherwise, local regulations should be followed

#### 5.3.2.5.2 Clinical chemistry and Creatinine clearance

Clinical chemistry and Creatinine clearance assessments of the parameters listed in Table 5-3 will be tested as per the schedule of assessments (Table 5-1).

#### 5.3.2.5.3 Urinalysis

Dipstick measurements will be performed as per Table 5-3 and according to the schedule of assessments (Table 5-1). Any significant findings on dipstick will be followed up with microscopic evaluation as per Table 5-3.

#### 5.3.2.5.4 Pregnancy and assessments of fertility

During screening, a serum pregnancy test will be completed. Starting on day 1 of Cycle 2, and at EOT, urinary pregnancy test (dipstick) will be performed. The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit. If local requirements dictate otherwise, local regulations should be followed.

Women who are determined not to be of child bearing potential before the study will only be tested at screening. When non-child bearing potential status is determined during the study, further pregnancy testing will not be continued. Women are considered post-menopausal if they have had 12 months of

natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), and otherwise not of child bearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If a positive pregnancy test is performed in between study visits, the patients must immediately notify the investigator.

### **5.3.2.6 Cardiac assessments**

#### **5.3.2.6.1 Electrocardiogram (ECG)**

Patients should be monitored for ECG changes at every cycle. ECGs should be reviewed and any abnormalities noted. Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. For each time point three ECG recordings should be taken at about 5 minute intervals. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study if possible. The investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, ECG intervals and an overall evaluation will be recorded.

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

#### **5.3.2.6.2 Echocardiogram:**

Assess LVEF by echocardiogram before initiation of osimertinib and then at 3 month intervals while on treatment. Withhold treatment with osimertinib if ejection fraction decreases by 10% from pretreatment values and is less than 50%. For symptomatic congestive heart failure or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue osimertinib

### **5.3.2.7 Ophthalmologic exam**

Full ophthalmic assessment, including slit lamp examination, should be performed at screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Ophthalmology examination results should be collected in the eCRF. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings. These photographs should be available for submission to AstraZeneca representatives if necessary.

## **6 Measurement of Effect**

### **6.1 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) Committee [JNCI 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

#### **6.1.1 Definitions**

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study therapy.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-

evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

### 6.1.2 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  $\geq 20$  mm with conventional techniques (CT, MRI, x-ray) or as  $\geq 10$  mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter  $< 20$  mm with conventional techniques or  $< 10$  mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 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 or absence of each should be noted throughout follow-up.

### 6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days 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 when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI. These should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

CT scans of the neck, chest, abdomen and pelvis will be performed at baseline and every two cycles according to standard of care. Other imaging of these areas such as PET/MRI will be allowed if CT cannot be performed.

MRI of the brain will be performed at baseline and as clinically indicated. Wherever it can be safely given, radiographic contrast agents should be given for the imaging studies.

## 6.1.4 Response Criteria

### 6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

### 6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): 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

### 6.1.4.3 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 subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	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	
* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.				
Note: Subjects with a global deterioration of health status requiring				



discontinuation of treatment without objective evidence of disease progression at that time should be reported as “ <i>symptomatic deterioration</i> ”. Every effort should be made to document the objective progression even after discontinuation of treatment.
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Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

#### **6.1.5 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) AND is amenable to SABR. This will be defined as time to subsequent SABR.
- recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started) and is NOT amenable to SABR. This will be defined as progression on systemic therapy.

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

#### **6.1.6 Progression-Free Survival**

Progression Free Survival will be the primary endpoint for this study. If oligoprogression occurs that is amenable to repeat treatment with SABR, the osimertinib will be held and SABR therapy delivered. If the treating oncologist then feels the patient would benefit from continuing the osimertinib that will be permitted. The patient will however be deemed as having progressed even if osimertinib is resumed.

After the initial SABR to persisting lesions if new lesions appear or if existing lesions enlarge but are NOT amenable to SABR (necessitating a change in systemic therapy), the patient will have completed the therapeutic portion of the study.

Time to 2<sup>nd</sup> SABR is defined as the duration of time from the start of treatment to the time of development of new or enlarging lesions that are amenable to SABR and the progression does not require a discontinuation of osimertinib.

Time to 3<sup>rd</sup> SABR is defined in patients who have already received two rounds of SABR while on this study as the duration of time from the start of treatment to the time of development of new or enlarging lesions that are amenable to SABR and the progression does not require a discontinuation of osimertinib.

### **7 Adverse events**

#### **7.1 Definition of adverse events**

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

#### **7.2 Definitions of serious adverse event**

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.
- Based upon appropriate medical judgment, may jeopardize the patient's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca in accordance with the agreed process.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 7.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 7.2.

### **7.3 Contraindications:**

Osimertinib is contraindicated in individuals who are hypersensitive to any component of the finished dosage forms. No other contraindications are listed in the package insert.

### **7.4 Special Warnings and Precautions for Use:**

#### **7.4.1 Interstitial Lung Disease/Pneumonitis:**

Across clinical trials, interstitial lung disease (ILD)/pneumonitis occurred in 3.3% (n=27) of osimertinib treated patients (n=813); 0.5% (n=4) were fatal. Withhold osimertinib and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue osimertinib if ILD is confirmed

#### **7.4.2 QTc Interval Prolongation:**

The heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with osimertinib. Of the 411 patients in Study 1 and Study 2, one patient (0.2%) was found to have a QTc greater than 500 msec, and 11 patients (2.7%) had an increase from baseline QTc greater than 60 msec [see Clinical Pharmacology (12.2)]. In Study 1 and 2, patients with baseline QTc of 470 msec or greater were excluded. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue osimertinib in patients who develop QTc interval prolongation with signs/symptoms of life threatening arrhythmia

#### **7.4.3 Cardiomyopathy**

Across clinical trials, cardiomyopathy (defined as cardiac failure, pulmonary edema, ejection fraction decreased or stress cardiomyopathy) occurred in 1.4% (n=11) of osimertinib treated patients (n=813);

0.2% (n=2) were fatal. In Study 1 and Study 2, Left Ventricular Ejection Fraction (LVEF) decline >10% and a drop to <50% occurred in 2.4% (9/375) of patients who had baseline and at least one follow up LVEF assessment. Assess LVEF by echocardiogram before initiation of osimertinib and then at 3 month intervals while on treatment. Withhold treatment with osimertinib if ejection fraction decreases by 10% from pretreatment values and is less than 50%. For symptomatic congestive heart failure or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue osimertinib

#### **7.4.4 Embryo-Fetal Toxicity:**

Based on data from animal studies and its mechanism of action, osimertinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended human dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5-times those observed in patients at the 80 mg dose level. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with osimertinib and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose.

### **7.5 Adverse Reactions**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to osimertinib (80 mg daily) in 411 patients with EGFR T790M mutation-positive non-small cell lung cancer who received prior EGFR TKI therapy, in two single arm studies, AURA 1 and AURA 2. Patients with a past medical history of ILD or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 ms were excluded from AURA 1 and AURA 2. Baseline patient and disease characteristics were: median age 63 years, 13% of patients were ≥75 years old, female (68%); White (36%), Asian (60%); metastatic disease (96%), history of brain metastases (39%); World Health Organization (WHO) performance status of 0 (37%) or 1 (63%); 1 prior line of therapy [EGFR-TKI treatment only, second line, chemotherapy-naïve (31%)], 2 or more prior lines of therapy (69%). Of the 411 patients, 333 patients were exposed to osimertinib for at least 6 months; 97 patients were exposed for at least 9 months; however, no patient was exposed to osimertinib for 12 months.

In AURA1 and AURA2 studies, the most common (>20%) adverse reactions (all grades) observed in osimertinib-treated patients were diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%). Dose reductions occurred in 4.4% of patients treated with osimertinib. The most frequent adverse reactions that led to dose reductions or interruptions were: electrocardiogram QTc prolonged (2.2%) and neutropenia (1.9%). Serious adverse reactions reported in 2% or more patients were pneumonia and pulmonary embolus. There were 4 patients (1%) treated with osimertinib who developed fatal adverse reactions of ILD/pneumonitis. Other fatal adverse reactions occurring in more than 1 patient included pneumonia (4 patients) and CVA/cerebral hemorrhage (2 patients). Discontinuation of therapy due to adverse reactions occurred in 5.6% of patients treated with osimertinib. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis and cerebrovascular accidents/infarctions.

Tables 2 and 3 summarize the common adverse reactions and laboratory abnormalities observed in osimertinib-treated patients.

**Table 7.6.1, Adverse Reactions (>10% for all NCI CTCAE\* Grades or >2% for Grades 3-4) in AURA1 and AURA2**

Adverse Reaction	Osimertinib N=411	
	All Grades	Grade 3-4
	%	%
<b>Gastrointestinal disorders</b>		
Diarrhea	42	1.0
Nausea	17	0.5
Decreased appetite	16	0.7
Constipation	15	0.2
Stomatitis	12	0
<b>Skin disorders</b>		
Rash <sup>a</sup>	41	0.5
Dry skin <sup>b</sup>	31	0
Nail toxicity <sup>c</sup>	25	0
Pruritus	14	0
<b>Eye Disorders<sup>d</sup></b>	18	0.2
<b>Respiratory</b>		
Cough	14	0.2
<b>General</b>		
Fatigue	14	0.5
<b>Musculoskeletal</b>		
Back pain	13	0.7
<b>Central Nervous System</b>		
Headache	10	0.2
<b>Infections</b>		
Pneumonia	4	2.2
<b>Vascular events</b>		
Venous thromboembolism <sup>e</sup>	7	2.4

\* NCI CTCAE v4.0.

<sup>a</sup>Includes cases reported within the clustered terms for rash adverse events: Rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis and acneform dermatitis.

<sup>b</sup>Includes dry skin, eczema, skin fissures, xerosis.

<sup>c</sup>Includes nail disorders, nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, onychoclasia, onycholysis, onychomadesis, paronychia.

<sup>d</sup>Includes dry eye, vision blurred, keratitis, cataract, eye irritation, blepharitis, eye pain, lacrimation increased, vitreous floaters. Other ocular toxicities occurred in <1% of patients.

<sup>e</sup>Includes deep vein thrombosis, jugular venous thrombosis, and pulmonary embolism.

<sup>f</sup>No grade 4 events have been reported.

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with osimertinib included cerebrovascular accident (2.7%).

**Table 7.6.2, Common Laboratory Abnormalities ( $\geq 20\%$  for all NCI CTCAE Grades) in AURA1 and AURA2.**

Laboratory Abnormality	Osimertinib N=411	
	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4
<b>Clinical Chemistry</b>		
Hyponatremia	26	3.4
Hypermagnesemia	20	0.7
<b>Hematologic</b>		
Lymphopenia	63	3.3
Thrombocytopenia	54	1.2
Anemia	44	0.2
Neutropenia	33	3.4

<sup>a</sup>The only grade 4 laboratory abnormality was 1 patient with grade 4 thrombocytopenia.

All Adverse Drug Reactions (ADRs) are considered unexpected if the outcome is fatal, except ILD/pneumonitis, which is considered expected for all severity grades, including ILD/pneumonitis with fatal outcome.

## 7.6 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the patient's participation in the research, whether or not it is considered related to the patient's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death

### Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol.

Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

#### Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the patient's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets any of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study

#### Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

The term "unanticipated problem" is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets **each** of the following criteria:

- Unexpected (in terms of nature, severity or frequency) **AND**
- Definitely or probably related to participation in the research **AND**
- Serious or a possible unexpected problem in that the research places subjects or others at greater risk of harm than was previously known or recognized. Note: Any serious adverse event would always suggest a greater risk of harm.

#### Follow-up

All adverse events will be followed up according to good medical practices.

### **7.6.1 Disease progression**

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

### **7.6.2 New cancers**

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

### **7.6.3 Lack of efficacy**

When there is deterioration in the condition for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

### **7.6.4 Deaths**

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 6.6.4 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.
- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca within the usual timeframes.

## **7.7 Reporting adverse events**

The UTSW IRB requires reporting of all UPIRSOs according to the guidance below. For participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events. All SAEs occurring during the protocol-specified monitoring period should be submitted to the UTSW study team within 2 business days of the center learning of the event.

UPIRSOs occurring on the study require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB by the UTSW study team and to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the UTSW study team and will be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent documentation that is available are also submitted to the DSMC Chair who determines if further action is required.

All serious adverse events which occur on research patients on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Written reports to:

Sawsan Rashdan, MD  
Sawsan.Rashdan@utsouthwestern.edu  
c/o Lung DOT Manager  
5323 Harry Hines Blvd, NB2.402  
Fax: 214-648-1578

UTSW SCCC Data Safety Monitoring Committee Coordinator

Email: SCCDSMC@utsouthwestern.edu  
Fax: 214-648-5949 or deliver to BLB.306

UTSW Institutional Review Board (IRB)

Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

### SAEs

Serious adverse events (SAEs) for studies where the SCCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 2 working days of PI awareness, or as described in the protocol.

### Adverse event reporting to AstraZeneca.

The investigator/Lead coordinator shall inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch/AdEERs report must be faxed or **email** to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

\* A **cover page** should accompany the **MedWatch/AdEERs** form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number

\* Investigative site must also indicate, either in the SAE report or the cover page, the **causality** of events **in relation to all study medications** and if the SAE is **related to disease progression**, as determined by the principal investigator.

SAE report and accompanying cover page to AstraZeneca will be sent by email to AE Mailbox Clinical Trial (TCS) <AEMailboxClinicalTrialTCS@astrazeneca.com> or by fax to 1-302-886-4114 (US Fax number). Email is the preferred method.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.



Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

For all studies of osimertinib, the Sponsor should continue sending SUSARs to AstraZeneca in parallel to regulatory authorities as defined per AZ standard minimum requirements for safety data collection; all other SAEs should be sent to AZ on a monthly basis.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Non-serious adverse events and SAEs will be collected from the time consent is given, throughout the treatment period and up to and including the *30 day follow-up period*. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for *30 calendar days after the last dose of trial drug and/or until event resolution*. All new AEs occurring during that period must be recorded (if SAEs, then they must be reported to the FDA and AstraZeneca). All study-related toxicities/ SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

Recording of adverse events:

Variables:

- AE (verbatim)
- The date <<and time>> when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no), comparator/combination drug (yes/no)
- Action taken with regard to investigational product/ comparator/combination agent
- AE caused subject's withdrawal from study (yes or no)
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- <<Causality assessment in relation to Additional Study Drug>>
- Description of AE.

### 7.7.1 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

Local Serious Adverse Event UPIRSOs require reporting to the UTSW IRB within 48 hours of PI awareness of the event (life threatening or fatal events experienced by patients enrolled by the investigator(s) under UTSW IRB jurisdiction).

Local UPIRSOs (non-serious events experienced by patients enrolled by the investigator(s) under UTSW IRB jurisdiction) require reporting to the UTSW IRB within 5 business days of PI awareness.

External UPIRSOs including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document:<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351>

### 7.7.2 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy  
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.  
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

### 7.7.3 Adverse events based on signs and symptoms

All AEs spontaneously reported by the care provider or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

### 7.7.4 Adverse events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, physical examination, performance status and imaging should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s). Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

## **7.8 Warnings and precautions**

Additional safety information collected between IB updates will be noted and added to the protocol. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. The package insert for osimertinib does not contain any specific contraindication.

## **8 Investigational product and other Treatments**

### **8.1 Identity of investigational product(s)**

#### **8.1.1 Agent:**

- Other names for the drug(s): AZD9291, Osimertinib or Tagrisso™
- Classification - type of agent: Targeted cancer therapy
- Mode of action: *EGFR TKI*.

Storage and stability: Store osimertinib bottles at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F)

- Protocol dose: 80 mg
- Preparation: 40mg or 80mg film coated tablets
- Route of administration for this study: Oral
- Incompatibilities: none
- Availability: FDA-approved
- Side effects: Please refer to the osimertinib package insert for a comprehensive list of adverse events.

#### **8.1.2 Return and Retention of Study Drug**

The study drug osimertinib will be destroyed by the UT Southwestern designated investigational drug service pharmacy in accordance with institutional protocols. No patient returned drug will be re-assigned to other patients or diverted to another person.

#### **8.1.3 Study Drug compliance**

The patient will be asked to keep a diary of taking the medication, as well as bringing pill bottles to each clinic visit.

## 8.2 Therapy: Stereotactic Ablation Body Radiation (SABR)

### 8.2.1 SABR DOSE AND TECHNIQUES

SABR (also termed stereotactic body radiation therapy [SBRT]) will begin at least 8 weeks after initiation of osimertinib for consolidation of residual disease sites. There is not a window for radiation initiation, however it should be started as soon as possible following 8 weeks of osimertinib. Additional SABR treatments will be delivered to new distinct areas of disease that develop after that period at the discretion of the treating medical oncology/radiation oncology teams. PFS will at that point already been established, but patients will be followed for OS.

Stereotactic treatment is the targeting, planning, and directing of treatment fields guided to a target based on known 3-D coordinates related to reliable fiducial markers. This differs from conventional radiation therapy in which treatment is guided by skin or bony landmarks assumed to correlate to the target volume based on the initial simulation. SABR in this study will be delivered with an ablative range of dose per fraction. Treatment will account for inter/intra-fractional errors with careful dosimetry that delivers an ablative dose to the metastatic lesion(s) while respecting normal tissue constraints.

#### 8.2.1.1 Osimertinib during SABR

It is not expected osimertinib and SABR would have significant toxicity if given concurrently. However to minimize risk to the patient, osimertinib will be held for 72 hours before the first radiation treatment and resumed 72 hours after the last radiation dose. While radiation is being delivered, concurrent treatment with osimertinib is not allowed.

#### 8.2.1.2 SABR Prescription

Patients randomized to the SABR arm will be evaluated by the treating Radiation Oncologist. Based on location of the metastatic lesion(s), dose fractionation will be determined by clinical appropriateness that balances ablation of the lesion(s) while respecting normal tissue constraints.

##### Prescription Dose

Number of Fractions	Total Cumulative Dose Encompassing 95% of Planning Target Volume		
	Protocol Compliant	Variation Acceptable	Deviation Unacceptable
1	21-27 Gy	<21 Gy but $\geq$ 16 Gy	<16 Gy or >27 Gy
3	26.5-33 Gy	<26.5 Gy but $\geq$ 24.5 Gy	<24.5 Gy or >33 Gy,
5	30-37.5 Gy	$\geq$ 28 Gy, <30 Gy	<28 Gy or >37.5 Gy,

Treatment may be delivered on consecutive days with 18 hours between fraction or every other day as deemed appropriate by the treating Radiation Oncologist.

If there is residual disease not amenable to SABR fractionation schemes proposed in the study, especially for bulky hilar or mediastinal disease, a fractionation schema of 45 Gy in 15 fractions may be employed, with adherence to standard normal tissue constraints outlined in the trial. This treatment will be delivered daily for three weeks.

#### 8.2.1.3 Planning Constraints and Concerns

The tolerance dose of SABR to the gastrointestinal tract is not established, and patients with metastatic disease involving the esophagus, stomach, intestines, or mesenteric lymph nodes will not be eligible. Patients with renal or adrenal metastases are potentially eligible if normal tissue constraints are otherwise met.

Cutaneous metastases are an uncommon manifestation of non-small cell lung cancer that are typically associated with poor prognosis [26]. Patients with cutaneous metastases will be ineligible. As this may

represent a group of patients with particularly poor prognosis, again this will be considered within any comparison with historical controls.

It is well established that for palliative effect for a painful bone metastasis, a single dose of 8 Gy is usually as effective as 30 Gy. Long term survival after bone metastasectomy has been reported [27]. Irradiation of non-spinal skeletal sites does not generally require specialized techniques of treatment. Metastases in major lower extremity weight-bearing bones should undergo surgical stabilization if there is plain film evidence of cortical erosion.

Corticosteroid premedication will not be mandated, although it can be used at the discretion of the treating oncologist. Analgesic premedication to avoid general discomfort during long treatment durations is recommended when appropriate.

## **8.2.2 Technical Factors**

### **8.2.2.1 Physical Factors**

Only photon (x-ray) beams produced by linear accelerators with photon energies of 4-15 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Restriction of photon beam energies > 10 MV but less than 15 MV will be based on clinical appropriateness taking into account distance the beam must travel to the target.

### **8.2.3 Dose Verification at Treatment**

*In-vivo* dosimeter measurements (e.g., diode, TLD) may be obtained for surface dose verification for accessible beams. This information is not required by the protocol.

### **8.2.4 Treatment Platforms**

The trial allows most commercially available photon producing treatment units except the exclusion of units described in Section 4.3.1 (e.g., cobalt units and charge particle accelerators). Conventional linear accelerators and specialized linear accelerators with image guidance (e.g., Novalis, Trilogy, Synergy, Artiste) are allowed. These units can be used with conformal dose delivery or IMRT. Other specialized accelerators (e.g., the CyberKnife® or Tomotherapy) are allowed as long as they meet the technical specifications of the protocol.

## **8.2.5 Simulation/Image Guidance**

### **8.2.5.1 Patient Positioning**

Patients will be positioned in a stable position that allows accurate reproducibility of the target between treatments. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be utilized including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients external contours) with reference to the stereotactic coordinate system. Patient immobilization must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) with any significant probability (i.e., < 5%).

At the time of simulation for patients who will receive SABR to the lung and/or liver, the movement of the dome of the diaphragm (superior portion of the liver) is to be observed under fluoroscopy or other acceptable means to estimate respiratory movement during treatment if no breathing control device is used. Patients will be assessed for suitability for tolerance of a respiratory control device using a breath-hold technique, respiratory gating, or abdominal compression to limit diaphragmatic excursion during respiration. Patients with severe lung disease and patients who cannot tolerate diaphragmatic or breathing control devices for other reasons will be treated without them. A larger margin to account for breathing related intra-fractional organ movement is required.

### **8.2.5.2 Image Guidance**

Isocenter or reference point port localization images should be obtained on the treatment unit

immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. These IGRT images can be obtained with planar kV imaging devices or cone-beam CT equipment. For treatment systems that use kV imaging but also allow EPID imaging using the treatment beam, orthogonal images verifying the isocenter also should be obtained.

### **8.3 Treatment Planning/Target volumes**

#### **8.3.1 Image Acquisition**

Computed tomography will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting. CT scan with IV contrast is recommended unless the patient has allergy to contrast or renal insufficiency. Oral GI contrast to highlight the stomach and duodenum is recommended for patients with medial liver lesions or lesions of the caudate lobe. Axial acquisitions will be required with spacing  $\leq 3.0$  mm between scans. Images will be transferred to the treatment planning computers.

#### **8.3.2 Target Volumes**

The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume (GTV). The target will generally be drawn using appropriate windowing based on location of the metastatic lesion(s). 4-dimensional CT image guided GTV delineation to take tumor motion into consideration will be allowed.

For treatment to the lung, the target will generally be drawn using CT pulmonary windows; however, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. This target will not be enlarged whatsoever for prophylactic treatment (including no “margin” for presumed microscopic extension); rather, include only abnormal CT signal consistent with gross tumor (i.e., the GTV and the clinical target volume [CTV] are identical). An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane (craniocaudal) will be added to the GTV to constitute the PTV.

For treatment to the liver, the following structures are contoured: entire liver, each individual liver gross tumor volume (GTV), each kidney, and the spinal cord. The planning target volume (PTV) is constructed to account for the positional uncertainty of the GTV during treatment. The PTV for each contoured GTV should be at least 5mm larger than the GTV in the axial plane and 1.0 cm larger than the GTV in the craniocaudal plane. Larger margins may be used in cases where greater motion of the hemidiaphragm is observed in simulation despite standard maneuvers to diminish motion.

Treatment to skeletal and paraspinal lesions may be accomplished with any 3D conformal radiotherapy or intensity-modulated radiotherapy technique suitable for this application with performance specifications adequate to provide proper tumor dose distribution and normal tissue sparing.

### **8.4 Dosimetry**

#### **8.4.1 3D-Conformal Planning**

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Generally, more beams are used for larger lesion sizes. For this protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The isocenter in stereotactic coordinates will be determined from system fiducials (or directly from the tumor in the case of volumetric imaging) and translated to the treatment record.

The treatment dose plan will be made up of multiple static beams or arcs as described above. The plan should be normalized to a defined point corresponding closely to the center of mass of the PTV

(COMPTV). Typically, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. Regardless, the point identified as COMPTV must have defined stereotactic coordinates and receive 100% of the normalized dose. Because the beam apertures coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning typically around 80% but ranging from 60-90%. The prescription dose will be delivered to the margin of the PTV. As such, a “hotspot” will exist within the PTV centrally at the COMPTV with a magnitude of prescribed dose times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

#### 8.4.2 Intensity Modulated Radiation Therapy (IMRT)

IMRT is allowed in this study. The use of IMRT in this study is at the discretion of the treating physician. However, IMRT should be considered only when target coverage, OAR dose limits, or dose spillage are not achievable with 3D conformal planning. In addition, IMRT plans should follow the same planning principles as discussed above for 3D conformal planning. The number of segments (control points) and the area of each segment should be optimized to ensure deliverability and avoid complex beam fluences. Ideally, the number of segments should be minimized (2-3 segments per beam should be adequate), and the area of each segment should be maximized (the aperture of one segment from each beam should correspond to the projection of the PTV along a beam’s eye view).

#### 8.4.3 Dose Calculations

For purposes of dose planning and calculation of monitor units for actual treatment, this protocol will require tissue density heterogeneity correction.

Successful treatment planning will require accomplishment of all of the following criteria:

Maximum dose: The treatment plan should be created such that 100% corresponds to the maximum dose delivered to the patient. This point must exist within the PTV.

Prescription isodose: The prescription isodose surface must be  $\geq 60\%$  and  $< 90\%$  of the maximum dose.

Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface (PTV V95%RX = 100%) and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (PTV V90%RX  $> 99\%$ ).

#### 8.4.4 Normal Tissue Dose Constraints

In accordance with the prior Phase I studies [7, 8], certain normal tissue dose constraints must be respected.

The possibility that SABR-induced fibrosis might cause occlusion of large central airways, thus impeding ventilation distal to the occlusion has been well considered. An adjustment to the fractionation scheme may be made if, in the opinion of the treating radiation oncologist, the following conditions apply: (1) the location of a lung lesion is close enough to a large proximal bronchial airway such that occlusion might occur, and (2) compromised ventilation to the segment(s) of lung potentially affected would cause clinically significant adverse consequences.

The same special condition applies in the setting of a patient whose primary lung disease has not been irradiated previously but is present as a PET-positive site of disease, often in proximity to mediastinal structures which is a dose-limiting concern. These patients will be considered by the PI on a case-by-case basis.

The following table lists the specific organ and dose fractionation constraints on normal tissues.

##### One Fraction

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint ( $\geq$ Grade 3)
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Spinal Cord and medulla	<0.35 cc <1.2 cc	10 Gy 8 Gy	14 Gy	myelitis
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	10 Gy	14 Gy	myelitis
Cauda Equina	<5 cc	14 Gy	16 Gy	neuritis
Sacral Plexus	<5 cc	14.4 Gy	16 Gy	neuropathy
Esophagus*	<5 cc	11.9 Gy	15.4 Gy	stenosis/fistula
Brachial Plexus	<3 cc	13.6 Gy	16.4 Gy	neuropathy
Heart/Pericardium	<15 cc	16 Gy	22 Gy	pericarditis
Great vessels	<10 cc	31 Gy	37 Gy	aneurysm
Trachea and Large Bronchus*	<4 cc	17.4 Gy	20.2 Gy	stenosis/fistula
Bronchus- smaller airways	<0.5 cc	12.4 Gy	13.3 Gy	stenosis with atelectasis
Rib	<5 cc	28 Gy	33 Gy	Pain or fracture
Skin	<10 cc	25.5 Gy	27.5 Gy	ulceration
Stomach	<5 cc	17.4 Gy	22 Gy	ulceration/fistula
Bile duct			30 Gy	stenosis
Duodenum*	<5 cc <10 cc	11.2 Gy 9 Gy	17 Gy	ulceration
Jejunum/Ileum*	<30 cc	12.5 Gy	22 Gy	enteritis/obstruction
Colon*	<20 cc	18 Gy	29.2 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	39 Gy 22 Gy	44.2 Gy	proctitis/fistula
Ureter			35 Gy	stenosis
Bladder wall	<15 cc	12 Gy	25 Gy	cystitis/fistula
Penile bulb	<3 cc	16 Gy		impotence
Femoral Heads	<10 cc	15 Gy		necrosis
Renal hilum/vascular trunk	15 cc	14 Gy		malignant hypertension
<b>Parallel Tissue</b>	<b>Critical Volume (cc)</b>	<b>Critical Volume Dose Max (Gy)</b>		<b>Endpoint (≥Grade 3)</b>
Lung (Right & Left)	1500 cc	7 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	7.6 Gy	V-8Gy <37%	Pneumonitis
Liver	700 cc	11 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	9.5 Gy		Basic renal function

\*Avoid circumferential irradiation

\*\* "point" defined as 0.035cc or less

### Three Fractions

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)
Spinal Cord and medulla	<0.35 cc <1.2 cc	15.9 Gy 13 Gy	22.5 Gy	myelitis
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	18 Gy	22.5 Gy	myelitis
Cauda Equina	<5 cc	21.9 Gy	25.5 Gy	neuritis
Sacral Plexus	<5 cc	22.5 Gy	24 Gy	neuropathy



Esophagus*	<5 cc	17.7 Gy	25.2 Gy	stenosis/fistula
Brachial Plexus	<3 cc	22 Gy	26 Gy	neuropathy
Heart/Pericardium	<15 cc	24 Gy	30 Gy	pericarditis
Great vessels	<10 cc	39 Gy	45 Gy	aneurysm
Trachea and Large Bronchus*	<5 cc	25.8 Gy	30 Gy	stenosis/fistula
Bronchus- smaller airways	<0.5 cc	18.9 Gy	23.1 Gy	stenosis with atelectasis
Rib	<5 cc	40 Gy	50 Gy	Pain or fracture
Skin	<10 cc	31 Gy	33 Gy	ulceration
Stomach	<5 cc	22.5 Gy	30 Gy	ulceration/fistula
Bile duct			36 Gy	stenosis
Duodenum*	<5 cc <10 cc	15.6 Gy 12.9 Gy	22.2 Gy	ulceration
Jejunum/Ileum*	<30 cc	17.4 Gy	27 Gy	enteritis/obstruction
Colon*	<20 cc	24 Gy	34.5 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	45 Gy 27.5 Gy	49.5 Gy	proctitis/fistula
Ureter			40 Gy	stenosis
Bladder wall	<15 cc	17 Gy	33 Gy	cystitis/fistula
Penile bulb	<3 cc	25 Gy		impotence
Femoral Heads	<10 cc	24 Gy		necrosis
Renal hilum/vascular trunk	15 cc	19.5 Gy		malignant hypertension
<b>Parallel Tissue</b>	<b>Critical Volume (cc)</b>	<b>Critical Volume Dose Max (Gy)</b>		<b>Endpoint (≥Grade 3)</b>
Lung (Right & Left)	1500 cc	10.5 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	11.4 Gy	V-11Gy<37%	Pneumonitis
Liver	700 cc	17.1 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	15 Gy		Basic renal function

\*Avoid circumferential irradiation

\*\* “point” defined as 0.035cc or less

#### Five Fractions

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)
Spinal Cord and medulla	<0.35 cc <1.2 cc	22 Gy 15.6 Gy	28 Gy	myelitis
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	22 Gy	28 Gy	myelitis
Cauda Equina	<5 cc	30 Gy	31.5 Gy	neuritis
Sacral Plexus	<5 cc	30 Gy	32 Gy	neuropathy
Esophagus*	<5 cc	19.5 Gy	35 Gy	stenosis/fistula
Brachial Plexus	<3 cc	27 Gy	32.5 Gy	neuropathy
Heart/Pericardium	<15 cc	32 Gy	38 Gy	pericarditis
Great vessels	<10 cc	47 Gy	53 Gy	aneurysm
Trachea and Large Bronchus*	<5 cc	32 Gy	40 Gy	stenosis/fistula
Bronchus- smaller airways	<0.5 cc	21 Gy	33 Gy	stenosis with atelectasis

Rib	<5 cc	45 Gy	57 Gy	Pain or fracture
Skin	<10 cc	36.5 Gy	38.5 Gy	ulceration
Stomach	<5cc	26.5 Gy	35 Gy	ulceration/fistula
Bile duct			41 Gy	stenosis
Duodenum*	<5 cc <10 cc	18.5 Gy 14.5 Gy	26 Gy	ulceration
Jejunum/Ileum*	<30 cc	20 Gy	32 Gy	enteritis/obstruction
Colon*	<20 cc	28.5 Gy	40 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	50 Gy 32.5 Gy	55 Gy	proctitis/fistula
Ureter			45 Gy	stenosis
Bladder wall	<15 cc	20 Gy	38 Gy	cystitis/fistula
Penile Bulb	<3 cc	30 Gy		impotence
Femoral Heads	<10 cc	30 Gy		necrosis
Renal hilum/vascular trunk	15 cc	23 Gy		malignant hypertension
<b>Parallel Tissue</b>	<b>Critical Volume (cc)</b>	<b>Critical Volume Dose Max (Gy)</b>		<b>Endpoint (≥Grade 3)</b>
Lung (Right & Left)	1500 cc	12.5 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	13.5 Gy	V-13.5Gy<37%	Pneumonitis
Liver	700 cc	21 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	18 Gy		Basic renal function

\*Avoid circumferential irradiation

\*\* “point” defined as 0.035cc or less

Exceeding these dose tolerances by more than 2.5% constitutes a minor protocol violation. Exceeding these dose tolerances by more than 5% constitutes a major protocol violation.

## 8.5 Intracranial Stereotactic Radiosurgery Dose (SRS) for and Technique

Patients with up to 10 brain metastases with the maximal size  $\leq 4$ cm will be treated by SRS in a single fraction. If there are more than 10 intracranial lesions or the size of the largest lesion is  $>4$ cm, such patients will be ineligible.

### 8.5.1 SRS Dose

All supratentorial lesions are treated to the prescribed dose below.

	SRS Dose by lesion diameter		
Diameter (cm)	$\leq 2.0$ cm	$>2.0 - 3.0$ cm	$>3.0 - 4.0$ cm
Dose (Gy)	20-24	18	15

For lesions within the brainstem (pons, medulla, and midbrain), the prescription dose will be 10-13 Gy in a single fraction.

Multiple SRS sessions are allowed, as long as all intracranial lesions are treated within 14 days.

### 8.5.2 SRS Technique, Pre-SRS Image acquisition and target planning with Conformality Index

Protocol SRS will be administered with a linear accelerator (LINAC), Vero® (BrainLab, Feldkirchen, Germany), CyberKnife® (Accuray, Sunnyvale, CA) or Gamma Knife®

Perfixion (Elektra Instruments, Inc., Atlanta, GA). Fixed-frame stereotactic localization and planning will be used for SRS.

Pre-SRS Image Acquisition: MRI with gadolinium contrast is the recommended imaging method for stereotactic localization. In the case of LINAC, Vero or CyberKnife, MRI with contrast has to be obtained within 14 days of SRS with an acquisition of  $\leq 1.5$  mm slice thickness. The stereotactic target is the contrast-enhancing tumor as defined on MRI with contrast.

In patients who cannot tolerate the contrast, other MR sequences may be utilized without the contrast, as long as the target lesion can be clearly demarcated for treatment and follow up.

Conformality Index (CI) is derived from dividing the volume encompassed by the prescription isodose line by the target volume.

$$CI = Rx \text{ Isodose Vol} / (\text{Target Vol})$$

The target lesion in the SRS planning MRI will be contoured, and its volume will be calculated. Planning should achieve a conformity index specified below.

Size of Target	Prescription Isodose	Conformality Index
<u><math>\leq 1\text{cm}</math></u>	<u>35-100%</u>	$\leq 2$
<u>1-2cm</u>		$\leq 2$
<u>2-3cm</u>		$\leq 1.5$
<u>3-4cm</u>		$\leq 1.25$

At least 95% of the target volume must receive the prescription dose; the plan should be adjusted to achieve such coverage by the isodose line between 40-100%. No part of the target should receive less than 90% of the prescription dose.

### 8.5.3 Normal Tissue Dose Constraints

The following table lists maximum dose limits, in one fraction, to a point or volume within several critical structures of the cranium. These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation.

Critical Structure and margin	Volume	Volume Max (Gy)	Max Point Dose (Gy)*	Endpoint ( $\geq$ Grade 3)
Optic Pathway	<0.2 cc	8 Gy	10 Gy	neuritis
Brainstem (not medulla)	<0.5 cc	10 Gy	15 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35cc <1.2 cc	10 Gy 8 Gy	14 Gy	myelitis

\* "point" defined as 0.035cc or less

Patients with lesions within or near the above structures and the dose constraints cannot be satisfied, will be deemed ineligible.

## 8.6 Radiation Therapy Quality Assurance

The radiation oncologist will perform an RT Quality Assurance Review after complete data for the first half of cases (18) enrolled at the University of Texas Southwestern Medical Center. They will perform the final review after complete data for the subsequent 19 cases at the University of Texas Southwestern Medical Center are completed. These cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received, whichever occurs first.

## 9 STATISTICAL CONSIDERATIONS

### 9.1 Study Design/Study Endpoints

This is an, open-label, single arm protocol designed to evaluate the activity of targeted therapy and SABR in advanced *EGFR* mutant NSCLC who have not been treated previously with *EGFR* targeted therapy.

Osimertinib will be administered to the patient until disease progression by RECIST 1.1 (The investigator may continue osimertinib post-progression if deemed to still be clinically beneficial), unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason including death.

#### Study Design:

**Purpose:** of this prospective, multi-center, single arm, non-randomized trial is to evaluate the impact of the combination of osimertinib and stereotactic radiation delivered to patients with *EGFR mutated* adenocarcinoma of the lung. The enhanced efficacy of this combination is to be evaluated specifically with regards to prolongation of clinical benefit of osimertinib. We will also evaluate the safety of this combination of targeted therapy and radiation.

For patients started on osimertinib and treated with SABR to persisting lesions: PFS compared to published historical results with osimertinib alone PFS=19.3 months for no previous osimertinib therapy [6] PFS will be defined as time from first dose of osimertinib to date of objective progression (as determined by the investigator according to RECIST 1.1) or death (in the absence of progression).

As secondary objectives, please refer to section 2.2 we will report, duration of response (DoR), objective response rate (ORR), overall survival (OS), time to subsequent SABR or death, time to osimertinib discontinuation or death. We will also be describing toxicity and AEs and then evaluating them in the context of historical controls

### 9.2 Sample Size and Accrual

The results of a Phase I trial of osimertinib in advanced *EGFR* mutant NSCLC were presented at the ESMO 2016 conference by Ramalingam et al. Osimertinib demonstrated activity in patients with an overall response rate of 77% at doses of 80 mg or 160 mg daily. Median progression free survival (PFS) was 19.3 months for the 160 mg dose and was not reached for the 80 mg dose.

The sample size calculation is based on the primary endpoint, progression-free survival, and the assumption that patients are enrolled until the end of accrual.

A sample size of 42 patients achieves 80% power to detect the difference between the null hypothesis of median PFS of 19.3 months and the alternative hypothesis of median PFS of 30 months at one-sided significance level of 0.1. We assume the patient accrual period of 36 months and the follow-up period of 12 months. The assumption is that patients are enrolled until the end of accrual. The sample size was estimated using SWOG ([https://www.swogstat.org/stat/public/one\\_survival.htm](https://www.swogstat.org/stat/public/one_survival.htm)) sample size calculator.

### **9.3 Data Analyses Plans**

We will use Kaplan-Meier methods to estimate the progression-free survival, time to subsequent SABR and overall survival, clinical benefit rate, time to treatment discontinuation duration of response and time to new metastases.

Duration of response (defined in 6.1.5) duration will be summarized for patients who responded. Descriptive summary statistics like median, 25% and 75% percentiles will be used.

Toxicities are dichotomized as none versus any, or none and mild versus moderate to severe (based on CTCAE grades).

The rates of overall response, toxicity and adverse events as well as their 95% confidence intervals will be estimated using exact binomial method. We will compare the rates of toxicity and adverse events in this study with those of historical controls from the previously referenced trial by Ramalingam et al, by the Fisher's exact test.

### **9.4 Analysis sets**

#### **9.4.1 Full Analysis Set**

The Full Analysis Set (FAS) comprises all enrolled patients.

#### **9.4.2 Safety Set**

The Safety Set includes all patients who received at least one dose of osimertinib medication.

#### **9.4.3 Patient demographics/other baseline characteristics**

Demographic, disease characteristics and other baseline data will be summarized descriptively for the FAS.

#### **9.4.4 Treatments (osimertinib treatment, concomitant therapies, compliance)**

All analyses from this section will be performed on all patients from the safety set. Duration of osimertinib treatment exposure will be summarized.

#### **9.4.5 Handling of missing values/censoring/discontinuations**

All attempts will be made to ensure that the database contains full information for the safety set.

#### **9.4.6 Safety objectives**

The safety objective is to describe toxicities in patients treated with osimertinib.

#### **9.4.7 Analysis set and grouping for the analyses**

For all safety analyses, the safety set will be used. Toxicities will be dichotomized as none versus any adverse event, or none and mild versus moderate to severe adverse event.

The safety summary tables will include assessments from the on-treatment period, unless otherwise specified.

All safety data collected in the study will be listed regardless of the study period with data collected during the pre-treatment and post-treatment period flagged.

#### **9.4.8 Adverse events (AEs)**

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified category, number and percentage of patients with at least one event per category will be summarized.

#### **9.4.9 Other safety data**

Other safety data (including ECGs, vital signs and weight) will be summarized and listed, notable values will be flagged, and any other information collected will be listed as appropriate.

#### **9.4.10 Treatment phase and duration of treatment**

Patients eligible for treatment will receive 80 mg daily of osimertinib as part of a 28-day cycle. The first dose of each cycle will be administered after evaluation at the study center. Patients will remain on study and take osimertinib until there is evidence of disease progression by RECIST, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason.

Continuation of osimertinib will be permitted if the treating oncologist feels the patient would benefit. If there is oligoprogression amenable to SABR, resumption of osimertinib after SABR will be permitted also if the treating oncologist feels the patient would benefit.

### **9.5 Definition of end of the Study**

The study will be continued until all 42 patients have evidence of disease progression by RECIST not amenable to SABR requiring discontinuation of osimertinib, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason to a maximum of 10 years.

At the completion or discontinuation of study medication, all patients will be seen within 30 days for an end of therapy evaluation. This will include a safety assessment for AE's SAE's. Any unused medication will be returned. Patients will be followed post study to collect survival data every 3 months for a maximum of 10 years.

### **9.6 Early Termination**

Treatment on protocol may be terminated early if the Principal investigator or institution assess that the safety of the enrolled subjects will be compromised by continuation of the trial. The procedure followed will be that of the premature withdrawal patient and any patients on treatment will be seen as soon as possible.

## **9.7 Data confidentiality**

Information about protocol subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this protocol
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled protocol treatment period.

## **10 Ethical considerations and administrative procedures**

### **10.1 Regulatory and ethical compliance**

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

### **10.2 Informed consent procedures**

Eligible patients will only be included on this after providing written IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any protocol-specific procedures (i.e. all of the procedures described in the protocol). However, the Investigator should not repeat procedures that are performed as part of standard of care (SOC), if they are within the screening window and are done prior to signing the ICF. The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in the clinical trial record. The informed consent document will be approved by the IRB.

### **10.3 Discontinuation of the study**

This study will discontinue if terminated by the Institutional Review Board or at the discretion of the Principal Investigator.

### **10.4 Publication of the study and results**

The results of this study will be updated and posted per regulatory requirements, including (but not limited) to databases such as [clinicaltrials.gov](http://clinicaltrials.gov).

#### **10.4.1 Communication and Publication of Clinical Trial Results**

All submitted manuscripts will comply with institutional guidelines and with authorship guidelines of the International Committee of Medical Journal Editors.

### **10.5 Study documentation, record keeping and retention of documents**

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

## **10.6 Confidentiality of study documents and patient records**

The investigator must ensure anonymity of the patients; patients must not be identified by names in any trial documents. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification.

## **10.7 Audits and inspections**

Source data/documents must be available to inspections by Health Authorities.

# **11 STUDY MANAGEMENT**

## **11.1 Conflict of Interest (COI)**

Any investigator who has a conflict of interest (COI) with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

## **11.2 Institutional Review Board (IRB) Approval and Consent**

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

## **11.3 Registration Procedures**

For UT Southwestern Medical Center:

The coordinating center for the trial will be UT Southwestern. Patients who are candidates for registration into the study will be evaluated for eligibility by the Investigator once consent has been obtained to ensure that the inclusion and exclusion criteria have been satisfied and that the patient is eligible for participation in this clinical study. The site should maintain a log of all patients who are consented. This log will include patients who are enrolled and patients who are consented but do not qualify for the study or who do not receive study drug. The reason for disqualification should be documented on the log.

For Sub-Site Management:

The coordinating center for the trial will be UT Southwestern. Patients who are candidates for registration into the study will be approved by UTSW after confirmation of eligibility of the inclusion and exclusion criteria have been satisfied. UTSW will confirm eligibility for all patients prior to receipt of the first dose of study drug.

For patients who pass screening the following items will be required for registration:

- copy of the signed patient treatment consent
- completed patient eligibility verification registration form



- completed inclusion/exclusion checklist
- source documentation (which includes, but not limited to, pathology, labs, progress notes, etc) that confirms all eligibility items on the inclusion-exclusion checklist has been met

This information will be provided no later than 48 hours prior to the planned cycle 1 day 1 treatment to allow adequate time for review. These items can be faxed or emailed to:

**Jessica Saltarski**  
**UT Southwestern**  
**fax 214-648-1906**

or scanned then emailed to [jessica.saltarski@utsouthwestern.edu](mailto:jessica.saltarski@utsouthwestern.edu). The Lung DOT manager will complete the patient ID assignment on the patient eligibility verification registration form and provide this completed form back within 48 hours of receipt of the package.

The site should maintain a log of all patients who are consented but do not qualify for the study or who do not receive study drug. The reason for disqualification should be documented on the log.

#### **11.4 Data Management and Monitoring/Auditing**

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for this and all SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements.

Other institutions participating in this trial as sub-sites will be expected to enter data into REDCap and upload de-identified source materials when instructed by the Simmons Comprehensive Cancer Center study team to facilitate remote source to case report form verification.

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT, which includes but is not limited to accuracy of case report forms, protocol compliance, timeliness and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

##### **11.4.1 Adherence to the Protocol**

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

##### **11.4.2 Emergency Modifications**

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

#### **11.4.3 Other Protocol Deviations/Violations**

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

**Protocol Deviations:** Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

**Protocol Violations:** Study personnel should report violations within two (2) weeks of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

#### **11.5 Amendments to the Protocol**

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

#### **11.6 Record Retention**

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In

all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

### **11.7 Obligations of Investigators**

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

#### **11.7.1 Source data**

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients.

Source data include all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The study CRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRFs, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained.

#### **11.7.2 Study agreements**

Agreements between AstraZeneca and the Investigator Sponsor should be in place before any study-related procedures can take place, or subjects are enrolled.

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## 13 Appendices

### Appendix A Guidance Regarding Potential Interactions with Concomitant Medications

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

#### D1 Drugs Inducing CYP3A4

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

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. 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).

#### D2 Exposure, Pharmacological Action and Toxicity May be Increased by Osimertinib

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine Doxorubicin Daunorubicin Topotecan	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.

#### 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.

#### D3 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 <sup>a</sup>
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

<sup>a</sup> 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.

#### D4 Drugs That May Prolong QT Interval

Drug	Minimum treatment period on medication prior to osimertinib start
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isradipine, 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, trimethoprim-sulfa, trimipramine, voriconazole	7 days
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 weeks

## Appendix B Guidance for the management of Adverse Events

AZD9291 is a potent irreversible small molecule inhibitor of both the single EGFRm (tyrosine kinase inhibitor (TKI) sensitivity conferring mutations) and dual EGFRm/T790M (TKI resistance conferring mutation) receptor forms of EGFR, with weaker inhibition towards wild type EGFR.

Clinical experience with 80mg AZD9291 has shown an association with the occurrence of dermatological adverse events (particularly rash and dry skin) and diarrhea. The considerable majority of these events have been mild, transient events that have not always required treatment.

Based on experience with other EGFR and HER2 inhibitors, decreases in LVEF, anterior ocular effects and ILD/pneumonitis should be monitored for.

Some guidance is provided in this document regarding these events.

The purpose of these treatment guidelines is:

- To prevent tolerable adverse events becoming intolerable for the patient and leading to discontinuation of treatment.
- To promote consistency of treatment for specific adverse events across the AZD9291 clinical program.

All SAEs, deaths, overdose and pregnancy are reportable per protocol. Any events leading to the modification or discontinuation of drug are also reportable per protocol.

You can request additional expert advice regarding the AZD9291 toxicities or the clinical management thereof, by contacting [\*\*AZD9291Safety@ubc.com\*\*](mailto:AZD9291Safety@ubc.com).

- ➔ Especially if a patient has not responded to intervention and permanent discontinuation of AZD9291 is being considered:
  - Please provide anonymised description of reaction: time to onset, associated symptoms, interventions already implemented, patient age, comorbidities and concomitant medications

## **1. SKIN EVENTS – RASHES & ACNES, DRY SKIN / XEROSIS, PARONYCHIA**

**Patients may consider applying over-the-counter moisturising cream to face, hands and feet twice daily from the start of treatment with AZD9291.**

Skin effects may occur at any time, but most likely to start within 2 weeks of starting treatment.



## Rashes and Acne

<b>CTCAE(v4) Grade 1</b>	
<ul style="list-style-type: none"> <li>• <b>&lt;10% body surface area (BSA)</b> papules/pustules</li> <li>• with or without symptoms of pruritus or tenderness</li> </ul>	<p><b>Emollient cream application</b> and/or <b>Topical steroid moderate strength bid</b> and/or <b>Topical antibiotic bid</b></p>
<b>CTCAE(v4) Grade 2</b>	
<ul style="list-style-type: none"> <li>• <b>10 to 30% BSA</b> papules/pustules with or without symptoms of pruritus or tenderness</li> <li>• <b>psychosocial impact</b></li> <li>• <b>limiting instrumental activities of daily living (ADL)</b></li> </ul>	<ul style="list-style-type: none"> <li>• Treatment same as Grade 1</li> <li>• Consider using oral antibiotic for 6 weeks</li> </ul>
<b>CTCAE(v4) Grade ≥3</b>	
<ul style="list-style-type: none"> <li>• <b>&gt;30% BSA</b> papules/pustules with or without symptoms of pruritus or tenderness</li> <li>• <b>limiting self-care ADL</b></li> <li>• <b>associated with local superinfection</b></li> </ul>	<p><b>Topical steroid moderate strength bid</b> and <b>Oral antibiotic for 6 weeks</b> Switch to broad spectrum/gram negative coverage if infection suspected (yellow crusts, purulent discharge, painful skin / nares). Consider skin swab for bacterial culture</p>

## Dry Skin / Xerosis

### **CTCAE(v4) Grade 1**

- <10% body surface area (BSA)
- No associated erythema or pruritus
- Face/Hands/Feet: over-the-counter moisturising cream or ointment bid
- Body: ammonium lactate 12% cream bid or salicylic acid 6% cream bid

### **CTCAE(v4) Grade 2**

- 10 to 30% BSA
- Associated with erythema or pruritus
- Limiting instrumental activities of daily living (ADL)
- Treatment same as Grade 1

### **CTCAE(v4) Grade $\geq 3$**

- >30% BSA
- Associated with erythema or pruritus
- Limiting self-care ADL
- Treatment same as Grade 1/2, plus:
- Eczematous areas of body: topical steroid moderate strength bid

## Pruritis

CTCAE(v4) Grade 1	
<ul style="list-style-type: none"><li>• Mild or localised</li><li>• Topical intervention indicated</li></ul>	<ul style="list-style-type: none"><li>• Topical steroid moderate strength bid or topical antipruritic bid</li></ul>
CTCAE(v4) Grade 2	
<ul style="list-style-type: none"><li>• Intense or widespread</li><li>• Intermittent</li><li>• Skin changes from scratching (e.g. oedema, papulation, excoriation, lichenification, oozing/crusts)</li><li>• Oral intervention indicated</li><li>• Limiting instrumental ADL</li></ul>	<ul style="list-style-type: none"><li>• Topical steroid moderate strength bid or topical antipruritic bid</li><li>• Oral antihistamine</li></ul>
CTCAE(v4) Grade ≥3	
<ul style="list-style-type: none"><li>• Intense or widespread</li><li>• Limiting self-care ADL or sleep</li><li>• Oral corticosteroid or immunosuppressive therapy indicated</li></ul>	<ul style="list-style-type: none"><li>• Oral antihistamine</li><li>• GABA agonist (gabapentin 300 mg or pregabalin 50-75 mg every 8 hours)</li></ul>



## Paronychia

CTCAE(v4) Grade 1	
<ul style="list-style-type: none"><li>• Nail fold oedema or erythema</li><li>• Disruption of the cuticle</li></ul>	<ul style="list-style-type: none"><li>• Topical antibiotic bid and vinegar soaks<sup>#</sup></li></ul>
CTCAE(v4) Grade 2	
<ul style="list-style-type: none"><li>• Localised intervention indicated</li><li>• Nail fold oedema or erythema with pain</li><li>• Associated with discharge or nail plate separation</li><li>• Limiting instrumental activities of daily living (ADL)</li></ul>	<ul style="list-style-type: none"><li>• Topical antibiotic bid and vinegar soaks<sup>#</sup></li><li>• Topical silver nitrate weekly</li></ul>
CTCAE(v4) Grade ≥3	
<ul style="list-style-type: none"><li>• Surgical intervention or IV antibiotics indicated</li><li>• Limiting self-care ADL</li></ul>	<ul style="list-style-type: none"><li>• Topical antibiotic bid and vinegar soaks<sup>#</sup></li><li>• Topical silver nitrate weekly</li><li>• Consider nail avulsion / removal</li></ul>

<sup>#</sup> Soaking fingers or toes in a 1:1 solution of white vinegar in water for 15 minutes every day

## Dermatologic Guidance Summary:

- Patients may consider applying over-the-counter moisturising cream to face, hands and feet bid from the start of treatment.
- Physicians may consider issuing a prescription for topical treatment to patients. However, topical steroids and topical or oral antibiotics should not be implemented prophylactically and treatment should only be started when confirmed by the treating physician.
- As soon as an acneiform / papulopustular rash occurs, treatment with moderate strength topical steroids and antibiotics should be implemented.
- The occurrence of non-papulopustular skin reactions should be treated appropriately, as defined by the treating physician, and in consultation with a dermatologist where necessary

- Use of topical benzoyl peroxides and other irritating anti-acne agents should be avoided.
- Patients should be fully informed regarding skin reactions
  - may occur during treatment with AZD9291
    - skin reactions are not contagious, and
    - do not result from allergy to treatment
  - may consider applying over-the-counter moisturising cream to face, hands and feet bid from the start of treatment
  - to contact the site to report any instances of skin reaction as soon as they arise so that appropriate treatment can be promptly initiated
    - and, especially if the skin reaction changes (e.g. if it spreads or becomes painful)
  - It may be beneficial to avoid irritating skin products (e.g. irritating soaps, products containing retinol or retinoic acid)
  - Camouflage make-up (non-comedogenic or non-pore blocking) can be used during treatment

## 2. DIARRHEA TREATMENT GUIDANCE

<b>Uncomplicated CTCAE (v4) Grade <math>\leq 2</math> diarrhea</b>	
<b><u>Dietetic measures:</u></b> <ul style="list-style-type: none"> <li>• Stop all lactose-containing products</li> <li>• Drink 8 to 10 large glasses of clear liquids per day</li> <li>• Eat frequent small meals</li> <li>• Recommend low fat regimen enriched with rice, bananas, and apple sauce</li> </ul>	<b><u>Pharmacological treatment:</u></b> <ul style="list-style-type: none"> <li>• Administer loperamide: initial dose 4mg, followed by 2mg every 4 hours or after every unformed stool.</li> <li>• Grade 1 intermittent diarrhea may not require treatment</li> <li>• Consider continuation of loperamide until diarrhea-free for 12h</li> <li>• Consider electrolyte replacement, as appropriate</li> </ul>
<b>CTCAE (v4) Grade <math>\geq 3</math> or any Grade with complications (dehydration, fever and/or Grade <math>\geq 3</math> neutropenia)</b>	
<b><u>Dietetic measures:</u></b>  As per Grade $\leq 2$ diarrhea	<b><u>Pharmacological treatment:</u></b> As per Grade $\leq 2$ diarrhea <ul style="list-style-type: none"> <li>• If dehydration is severe, administer octreotide and use IV fluids as appropriate</li> <li>• Consider prophylactic antibiotics, especially if diarrhea is persistent beyond 24h or there is fever or Grade 3-4 neutropenia</li> <li>• Consider electrolyte replacement, as appropriate, and consider more frequent measurement of electrolytes until AE resolves</li> </ul>

### **Diarrhea Guidance Summary:**

- Patients should be fully informed regarding diarrhea
  - May occur during treatment with AZD9291
    - diarrhea is not contagious, and
    - does not result from allergy to treatment
  - Contact the site to report any instances of diarrhea as soon as they arise so that appropriate treatment can be promptly initiated

### 3. OPHTHALMIC GUIDANCE

There is a known association between the use EGFR TKIs and the occurrence of ophthalmic adverse events.

Patients on EGFR TKIs, including AZD9291, should be

- Fully informed that ophthalmic events may occur during treatment with AZD9291
- Monitored periodically for these events
- AZD9291 should not be administered on the first scheduled day if the patient has any clinically significant eye symptoms.
- Encouraged to report any instances of ophthalmic symptoms and/or vision changes to allow the appropriate treatment to be initiated. Symptoms may include:
  - Burning / itching / irritation / smarting
  - Redness with / without discharge
  - Blurred vision
  - Light sensitivity

Patients who wear contact lenses must discontinue wearing them if

- They have any mild to moderate eye symptoms (CTCAE grade  $\leq 2$ ) until at least one week after symptoms have resolved.
- Patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade  $\geq 3$ ) ocular events until at least one week after treatment with AZD9291 is permanently discontinued.

Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by treating physician, at any time during the study until 1 week after AZD9291 has been permanently discontinued.

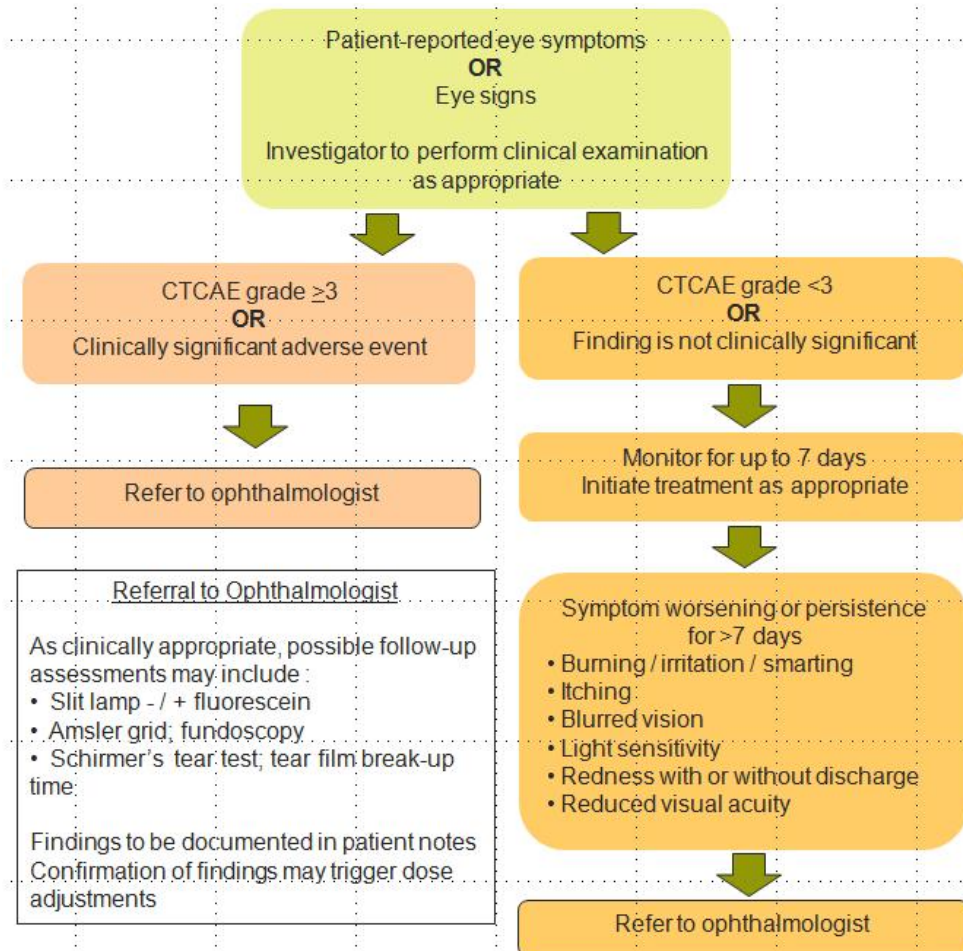
#### **Assessments During Treatment**

- If the patient reports any eye symptoms during treatment with AZD9291 or if signs are observed during a study visit, the Investigator should perform a clinical examination including a best corrected near and distant visual acuity assessment as appropriate
- Findings should be documented in the patient's notes

#### **Referral to Ophthalmologist**

Patients with ophthalmic AEs of CTCAE Grade  $> 3$  or eye symptoms that are clinically significant and/or persistent ( $>7$  days) should be referred to the ophthalmologist. For example:

- Deterioration in near or distant visual acuity by more than one level
- Persistence or worsening of:
  - Burning/ irritation/ smarting
  - Light sensitivity (photophobia)
  - Itching
  - Blurred vision
  - Redness with or without discharge



### **Ophthalmic Dose Adjustments**

Confirmed CTCAE Grade  $\geq 3$

**OR**

Clinically significant or persistent  
(present for >7 days) event

**AND**

Considered causally related to AZD9291



Initiate ophthalmic treatment as appropriate and withhold dose for up to 3 weeks

- If event improves to CTCAE Grade  $\leq 1$  within 3 weeks, reinstate AZD9291 at the current dose maintaining ophthalmic treatment as appropriate
- If event improves to CTCAE Grade 2 within 3 weeks, consider reinstating AZD9291 at reduced dose of 40 mg daily, maintaining ophthalmic treatment as appropriate
- Permanently discontinue AZD9291 and maintain ophthalmic treatment as appropriate, where
  - CTCAE Grade  $\geq 3$  or clinically significant or persistent adverse event does not improve to a lower CTCAE Grade within 3 weeks of AZD9291 interruption, OR
  - Any ulcerative event

#### **Ophthalmic Guidance Summary**

- It is important that patients are fully informed that ophthalmic events may occur during treatment with AZD9291.
- AZD9291 should not be administered on the first scheduled day if the patient has any clinically significant eye symptoms.
- Patients should be encouraged to report any instances of ophthalmic symptoms and/or vision changes to allow the appropriate treatment to be initiated (or ophthalmic referral).
- Patients who wear contact lenses must discontinue wearing them if
  - They have any mild to moderate eye symptoms (CTCAE grade  $\leq 2$ ) until at least one week after symptoms have resolved.
  - Patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade  $\geq 3$ ) ocular events until at least one week after treatment with AZD9291 is permanently discontinued.
- Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by a study doctor, at any time during the study until 1 week after AZD9291 has been permanently discontinued
- AZD9291 dose should be interrupted, modified or permanently discontinued as appropriate for any ophthalmic events

#### **4. LEFT VENTRICULAR EJECTION FRACTION (LVEF)**

AZD9291 and its active metabolite may also inhibit HER2. For this reason:

- Measurement of LVEF should be performed if the investigator has clinical suspicion of new onset impaired cardiac function

- Consult cardiologist or AstraZeneca for abnormal LVEF results, at the Investigator's discretion
- Patients are to be managed clinically according to standard of care

## 5. INTERSTITIAL LUNG DISEASE (ILD) / PNEUMONITIS GUIDANCE

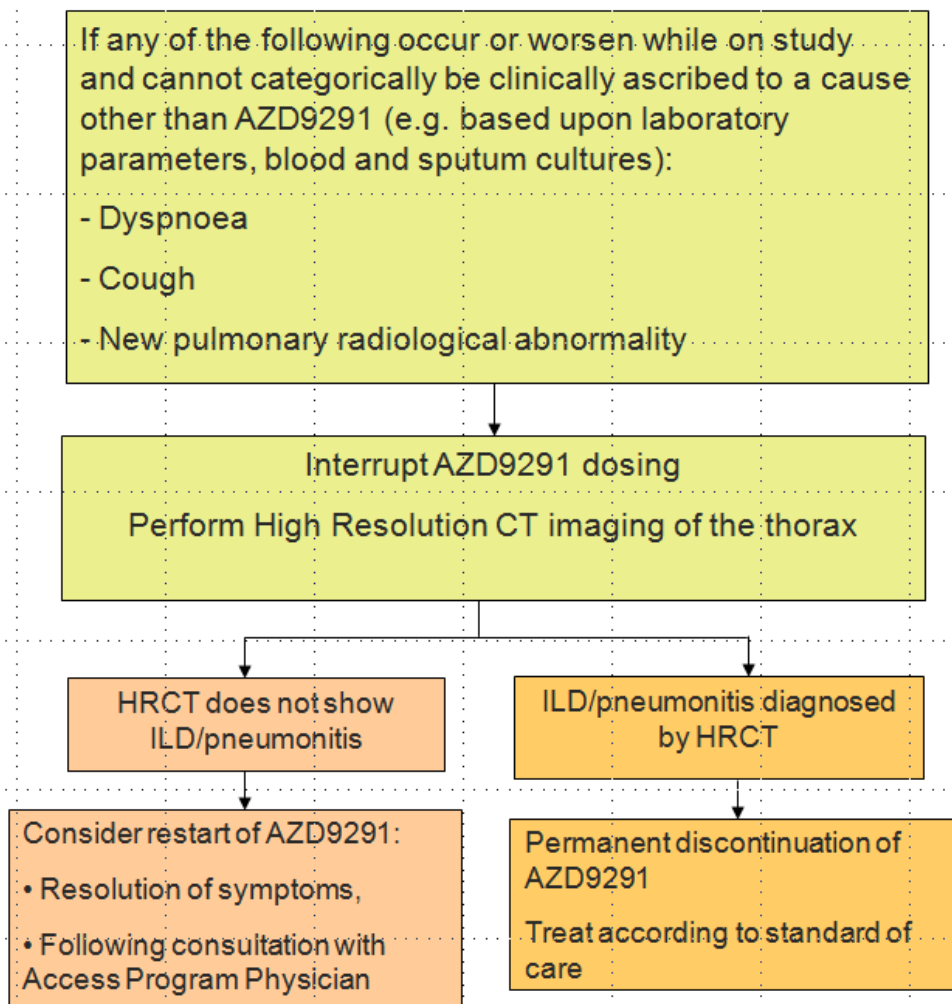
If you have clinical suspicion of interstitial lung disease (ILD), dosing with AZD9291 should be interrupted while further investigations are performed.

Please contact the Access Program team ([AZD9291Safety@ubc.com](mailto:AZD9291Safety@ubc.com)) as soon as a potential pneumonitis event is identified. A pneumonitis questionnaire will be sent to you, in order to collect more information about the event for full review and reporting.

The questionnaire and all imaging conducted throughout the access program, (including High Resolution CTs (HRCT), at time of pneumonitis diagnosis and follow up) will be requested to be sent to AstraZeneca for independent review.

A diagnostic workup (including HRCT, blood and sputum culture, laboratory parameters) should be performed, to exclude conditions such as lymphangitic carcinomatosis, infection, allergy or pulmonary haemorrhage.

In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued.



### **ILD / Pneumonitis Guidance Summary**

- Interrupt AZD9291 dosing, if you have clinical suspicion of interstitial lung disease (ILD), while further investigations are performed.
- Perform full diagnostic workup (including HRCT, blood and sputum culture, laboratory parameters to exclude conditions such as lymphangitic carcinomatosis, infection, allergy or pulmonary haemorrhage)
- Contact the Access Program team as soon as a potential pneumonitis event is identified.
- Complete and submit pneumonitis questionnaire
- Resume AZD9291 dosing as appropriate

## Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

### 1 Introduction

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

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 Sponsor 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

#### 2A Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT)  $\geq 3x$  Upper Limit of Normal (ULN) **together with** total bilirubin (TBL)  $\geq 2x$ ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

#### 2B Hy's Law (HL)

AST or ALT  $\geq 3x$  ULN **together with** TBL  $\geq 2x$ ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (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  $\geq 3x$ ULN
- AST  $\geq 3x$ ULN
- TBL  $\geq 2x$ ULN

The Investigator will remain vigilant for any local laboratory reports where the identification criteria are met; where this is the case the Investigator will:

- Notify the Sponsor representative
- Request a repeat of the test (new blood draw) by the local laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.

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

- Notify the Sponsor representative
- Determine whether the patient meets PHL criteria (see 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

#### 4 Follow-up

##### 4A Potential Hy's Law Criteria not met

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

- Inform the Sponsor representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

##### 4B Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- Notify the Sponsor/Company

The Sponsor contacts the Investigator, to provide guidance, discuss and agree on approach for the study patients' 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 Company.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Sponsor) 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 Company 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 Sponsor 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

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 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, amending the reported term if an alternative explanation for the liver biochemistry elevations is determined

## 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients << *with liver metastases*>> who meet PHL criteria on 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 patients' condition<sup>#</sup> compared with the last visit where PHL criteria were met<sup>#</sup>
  - If there is no significant change no action is required
  - If there is a significant change notify the Sponsor representative, who will inform the Company, then follow the subsequent process described in 4B Potential Hy's Law Criteria met of this Appendix

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

## Actions Required for Repeat Episodes of Potential Hy's Law

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

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

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

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, << or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in 6      Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment >>?

If No: follow the process described in 4B Potential Hy's Law Criteria met 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 4.2 of this Appendix

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

## 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>

## Appendix D      Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods

### 1      Definition of Women of Childbearing Potential

#### Women of Childbearing Potential (WoCBP):

Women between menarche and menopause who have not been permanently or surgically sterilised and are capable of procreation.

#### Women NOT of Childbearing Potential:

Women who are permanently or surgically sterilised or postmenopausal (definitions below):

Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).

- Women who have undergone tubal occlusion should be managed on trials as if they are of WoCBP (e.g. undergo pregnancy testing etc., as required by the study protocol)
- Women will be considered postmenopausal if they are amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:
  - Women under 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle-stimulating hormone levels in the postmenopausal range
  - Women over 50 years of age will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments

### 2      Acceptable Contraception Methods

Highly effective method of birth control is defined in Note 3 in International Conference on Harmonisation Guidance M3 (Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals) as one that results in a low failure rate (e.g., less than 1 percent per year) when used consistently and correctly.

Note that women should have been stable on their chosen method of birth control for a minimum of 2 weeks before entering the trial. Generic names and examples of trade names are given. As trade names may vary, Investigators should check the generic name of any contraception to ensure suitability.

Acceptable contraception methods are:

- Total sexual abstinence (abstinence must be for the total duration of the trial and the follow-up period)
- Vasectomised sexual partner plus male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
- Tubal occlusion plus male condom
- Intra-uterine device – provided coils are copper-banded, plus male condom
- Intra-uterine system (IUS) levonorgestrel IUS (e.g., Mirena), plus male condom
- Medroxyprogesterone injections (Depo-Provera) plus male condom



- Etonogestrel implants (e.g., Implanon, Norplan) plus male condom
- Normal and low dose combined oral contraceptive pills, plus male condom
- Norelgestromin / ethinylestradiol transdermal system plus male condom
- Intravaginal device (e.g., ethinylestradiol and etonogestrel) plus male condom
- Cerazette (desogestrel) plus male condom (Cerazette is currently the only highly efficacious progesterone based pill)

### 3 Unacceptable Contraception Methods

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

- Triphasic combined oral contraceptives
- All progesterone only pills except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing intra-uterine devices
- Fertility awareness methods
- Coitus interruptus