UCSF Helen Diller Family Comprehensive Cancer Center

NCT# 03433469

A phase II study to evaluate neoadjuvant osimertinib therapy in patients with surgically resectable, EGFR-mutant non-small cell lung cancer

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Protocol Signature Page

Protocol No.: 17658 **Version Date:**04/12/2022

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

UCSF Principal Investigator

_____

Printed Name

_____ _____

Signature Date

Protocol Signature Page – Participating Sites

Protocol No.: 17658 **Version Date:** 04/12/2022

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Principal Investigator	**Site**
Printed Name	Institution Name
Signature	Date

Abstract

Title	A phase II study to evaluate neoadjuvant osimertinib therapy in patients with surgically resectable, EGFR-mutant non-small cell lung cancer
Patient population	Patients with stage I-IIIA, EGFR-mutant lung adenocarcinoma population
Rationale for Study	Somatic activating mutations in epidermal growth factor receptor (EGFR) are present in 15-20% of non-small cell lung cancer (NSCLC) patients [2, 3]. The EGFR tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib, and afatinib have each demonstrated significant improvement in progression-free survival compared to standard platinum doublet-based chemotherapy when used in the first line setting for advanced EGFR-mutant NSCLC [4-6]. Despite this clinical advance, tumor resistance to EGFR TKI treatment is a major clinical challenge. Approximately 20-30% of patients exhibit innate resistance and fail to respond to initial treatment; moreover, 98% of patients who respond to initial EGFR TKI treatment exhibit an incomplete response [4-6]. To date, efforts to understand the basis of EGFR TKI resistance have largely focused on uncovering mechanisms of acquired resistance. A second site T790M resistance mutation in EGFR accounts for over 50% of acquired resistance to first- and second-generation EGFR TKIs [7-17]. The third-generation EGFR TKI osimertinib has shown efficacy against lung cancers harboring the EGFRT790M mutation [18, 19]. However, even in patients whose tumors harbor EGFRT790M, the objective response rate is only 60-70% and complete responses (CRs) are rare [20]. Further, all patients treated with osimertinib eventually develop disease progression (PD) and succumb to their cancer [18, 19]. While mechanisms of acquired resistance to osimertinib are being explored [21, 22], the basis of incomplete response and residual disease that occurs after initial third-generation EGFR TKI therapy is poorly understood. We hypothesize that neoadjuvant treatment with osimertinib in stage I-IIIa EGFR-mutant lung cancers will result in significant tumor reduction and major pathological responses (MPRs). Furthermore, the neoadjuvant design of this trial will permit comprehensive molecular analyses on tumor specimens pre-treatment and after initial response to osimertinib. This will allow us to define mechanisms of incomplete initial response to osimertinib and identify rational companion therapies that when combined with osimertinib in the first line setting could result in more durable and CRs for patients.
Primary Objective	To evaluate the efficacy of osimertinib as neoadjuvant therapy in patients with surgically resectable EGFR-mutant NSCLC. The primary endpoint of the study will be MPR rate defined as ≤10% viable tumor present histologically in the resected tumor specimen.

Secondary Objectives	1. To evaluate the safety of osimertinib given as neoadjuvant therapy in early stage EGFR-mutant NSCLC patients 2. To evaluate whether neoadjuvant osimertinib treatment increases the frequency of tumors that are unresectable due to adverse events (AEs) or PD. 3. To evaluate secondary measures of clinical efficacy in early stage EGFR-mutant NSCLC patients treated with osimertinib induction therapy. Secondary endpoints of efficacy will include radiographic decrease in maximum tumor diameter, complete pathologic response rate, 5-year disease-free survival (DFS), and 5-year overall survival (OS).
Study Design	This is a phase II multi-institution (UCSF and participating sites), single-arm, open-label clinical trial of neoadjuvant osimertinib in Stage I-IIIa EGFR-mutant lung cancer patients who are planning to undergo surgical resection of their lung cancer. A total of 27 evaluable subjects will be enrolled in the study. This will provide 87% power to detect a MPR rate of 50% among patients receiving osimertinib induction therapy as compared to a null hypothesis response rate of 22%, which has been observed for neoadjuvant chemotherapy in unselected NSCLC populations [23, 24], at the 5% significance level. Patients will receive the study drug for a minimum of 1 cycle prior to surgery (28 days). ORR will be determined by CT scan prior to surgery. Investigators will have the option to give a second cycle of study drug prior to surgery if clinically indicated.
Number of patients	27 patients will be enrolled.
Duration of Therapy	Patients may continue treatment for up to 70 days from the time of study entry.
Duration of Follow-up	Follow-up for individual participants will be up to 5 years.
Duration of study	The study will reach completion 48 months from the time the study opens to accrual.
Study Drugs	Osimertinib 80 mg *per os* (PO) daily
Safety Assessments	Analyses will be performed for all patients who have received at least one dose of study drug. The study will use the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 for reporting of non- hematologic AEs and modified criteria for hematologic AEs. The number of patients whose surgery is not performed as planned will also be reported.

Efficacy Assessments	The primary measure of efficacy will be MPR as determined by central review. Secondary measures of efficacy will be radiographic decrease in maximum tumor diameter, 5-year DFS, 5-year OS, pathological response rate (pCR), and depth of response (DpR).
Unique Aspects of this Study	This is the first study to evaluate the safety and efficacy of a 3rd generation EGFR TKI in the neoadjuvant setting.

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CITI	Collaborative Institute Training Initiative
CLIA	Clinical Laboratory Improvement Amendments
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CRO	Contract research organization
CT	computerized tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
ctDNA	circulating tumor DNA
DFS	disease-free survival
DpR	Depth of Response
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HBV	hepatitis B virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
ILD	interstitial lung disease
IND	investigational new drug
IP	investigational product
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MPR	Major Pathological Response
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells

NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	Overall survival
PD	progressive disease/disease progression
PDX	patient-derived xenograft
PD-1	programed cell death protein 1
PI	Principal investigator
PK	Pharmacokinetic
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
SAE	serious adverse event
SD	stable disease
SIV	Site initiation visit
SOP	Standard operating procedure
SPE	Single patient exception
TAM	tumor-associated macrophage
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal

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1 Introduction

1.1 Background on Indication

Lung cancer is the leading cause of cancer-related mortality in the United States. Molecular profiling of NSCLC has identified multiple driver mutations responsive to targeted therapy. The most common of these targetable somatic activating mutations is in the EGFR, present in 15-20% of patients [2, 26], leading to constitutive activation of EGFR signaling. The vast majority of patients with tumors harboring these mutations will respond to treatment with first or second-generation EGFR TKIs such as erlotinib, gefitinib, and afatinib. In this patient population, response rates from 56-80% have been reported [4, 27, 28].

Despite this high initial response rate, less than 2% of patients will experience a CR to initial EGFR TKI therapy and on average patients will progress within the first year of treatment [4, 27, 28]. The EGFR T790M “gatekeeper” mutation is the most common mechanism of acquired resistance to EGFR TKIs. The third generation EGFR TKI osimertinib is Food and Drug Administration (FDA)-approved for T790M-mutated NSCLC progressive after prior EGFR TKI therapy, with a 71% overall response rate (ORR) in a phase three study. However, as with treatment with earlier generation TKIs, the CR rate was low at only 1% and responses were not durable, with a median progression-free survival of 10.1 months [20].

While mechanisms of acquired resistance to osimertinib are being explored [21, 22], the molecular basis of incomplete response and residual disease that occurs after initial 3rd generation EGFR TKI therapy is poorly understood.

1.1.1 Treatment of early stage Non-Small Cell Lung Cancer

In patients with resectable stage I and II NSCLC, the standard of care is surgical resection, followed by consideration for adjuvant chemotherapy depending on pathologic staging. Adjuvant chemotherapy (with a platinum doublet) is recommended in patients with T3 or node positive disease, and should be considered in patients with T2 node negative disease in which there are other high risk features (such as poor differentiation, vascular invasion, size >4 cm, visceral pleural involvement, and wedge resection or unknown lymph node pathologic status). Concurrent or sequential chemoradiation should be considered in patients with positive margins after resection.

In patients with resectable stage IIIA disease, standard of care is to proceed with surgical resection followed by adjuvant chemotherapy, with radiation therapy if with positive margins or if found to have N2 nodal involvement upon pathologic staging. Patients with N2 positive stage IIIA disease are generally not felt to have upfront resectable disease and will instead undergo a course of neoadjuvant therapy (chemotherapy with or without radiation therapy) prior to reconsideration for surgical resection or upfront definitive chemoradiation therapy (National Comprehensive Cancer Network Guidelines – Non-Small Cell Lung Cancer, Version 7, 2017).

1.1.2 Use of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Early Stage, EGFR-mutant Non-Small Cell Lung Cancers

Induction therapy with platinum-based chemotherapy given prior to surgical resection for patients with resectable lymph node-positive NSCLC is a safe and acceptable practice [29], as discussed above. The role of EGFR TKI therapy as induction therapy for patients with EGFR-mutant NSCLC remains incompletely explored. In an unselected study of 50 patients with stage I or II NSCLC treated with gefitinib, 17 of 21 patients found to have activating EGFR mutations in their resected tumor specimens had a radiographic response to treatment [30]. In a separate study of an enriched population of 60 patients non-squamous patients with early stage lung cancer treated with erlotinib for 21 days prior to surgery, patients with EGFR-activating

mutations (n=7), 40% (3 of 7) had a pathological response with >50% tumor necrosis at the time of resection. In contrast, only 20% (8 of 35 patients) with WT EGFR exhibited >50% necrosis in their tumors at the time of resection [25]. While these results suggest that neoadjuvant therapy may be beneficial to patients with EGFR-activating mutations prior to surgery, a prospective trial in pre-selected EGFR-mutant lung cancer patients has not been performed.

It has been reported that up to 60% of patients harbor pre-existing EGFR T790M resistance mutations within their lung cancers prior to initiating EGFR TKI, which correlates with worse clinical outcomes for patients treated with erlotinib therapy [31]. The contribution of pre-existing EGFR T790M expressing cells to incomplete initial response to therapy is unknown.

1.2 Background on the Compounds

1.2.1 Osimertinib

Investigators should be familiar with the current osimertinib Investigator's Brochure.

Osimertinib (AZD9291, AstraZeneca) is an oral, potent, irreversible EGFR TKI selective for EGFR-activating mutations and the T790M resistance mutation 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 for treatment of EGFR T790M mutated NSCLC after progression on prior EGFR TKI therapy.

In the phase 1 dose escalation study of osimertinib (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 (PK) and preliminary efficacy data, 80 mg once daily was selected as the recommended phase II dose.

Osimertinib has been studied in NSCLC patients with EGFR T790M positive tumors following progression on prior EGFR TKI therapy in the AURA studies, including the AURA phase 1 extension component and the AURA2 phase 2 study. Of 398 patients in these pooled studies, the ORR was 66.1% (95% CI: 61.2, 70.7). This included 0.5% patients with a CR and 65.6% with a partial response (PR). The estimated progression-free survival was 9.7 months (95% CI: 8.3, NC) [32]. Osimertinib is also efficacious for first-line treatment of patients with EGFR-mutated NSCLC, with a 77% ORR and median PFS that was not yet reached after a median of 16.6 months of follow up in phase 1 extension cohorts. [33]

Osimertinib has also been studied in the first line setting for patients with metastatic EGFR mutations (exon 19 deletion, or L858R) in comparison to erlotinib or gefitinib (FLAURA study) [34]. The median progression-free survival was significantly longer with osimertinib than with standard EGFR TKIs (18.9 months vs. 10.2 months; hazard ratio for PD or death, 0.46; 95% CI [0.37 to 0.57]; P<0.001). The objective response rate was similar in the two groups: 80% with osimertinib and 76% with standard EGFR TKIs (odds ratio, 1.27; 95% CI, 0.85 to 1.90; P=0.24). The median duration of response was 17.2 months (95% CI, 13.8 to 22.0) with osimertinib versus 8.5 months (95% CI, 7.3 to 9.8) with standard EGFR TKIs. Data on OS were immature at the interim analysis (25% maturity). The survival rate at 18 months was 83% (95% CI, 78 to 87) with osimertinib and 71% (95% CI, 65 to 76) with standard EGFR TKIs (hazard ratio for death, 0.63; 95% CI [0.45 to 0.88], P=0.007 [nonsignificant in the interim analysis]). AEs of grade 3 or higher were less frequent with osimertinib than with standard EGFR TKIs (34% vs. 45%).

Osimertinib has an overall 9-fold selectivity over wild-type EGFR towards EGFR bearing traditional activating mutations and towards T790M-mutated EGFR. There was minimal off-target kinase activity, including minor activity against ACK1, BLK, ErbB2, ErbB4, BRK, MLK1, and MNK2. Metabolism is primarily via CYP3A4/5, with strong CYP 3A4inhibitors found to

increase net osimertinib exposure. Osimertinib and its major metabolites are also substrates for P-gp and BCRP and may increase exposure to co-administered BCRP substrates.

Oral absorption is greater than 80% with a median Tmax of 6-8 hours. Absorption was not affected by food intake or by gastric pH. The major route of excretion is fecal, with minor urinary excretion. Less than 1% of overall clearance is accounted for by renal clearance, with clearance not affected by mild to moderate renal dysfunction in population PK analyses. Given limited data in patients with several renal dysfunction, osimertinib should be used with caution in this population. Osimertinib showed similar steady state clearance in patients with normal hepatic function and mild hepatic dysfunction; however, appropriate dosing has not been established in moderate and severe hepatic dysfunction.

Common adverse effects include rash (45.7%), low-grade diarrhea (45.5%), dry skin (25.5%), and paronychia (21.7%). AEs of Grade 3 or higher were reported in 36.3% of patients in phase II studies and serious AEs (SAEs) were reported in 26.0% of patients. There was a very low rate of AEs leading to dose reduction (3.9%) and high mean dose intensity (97.7%) consistent with good overall tolerability. Potential AEs of note include risk of interstitial lung disease (ILD)/pneumonitis, which occurs in 3.3% of treated patients. QTc prolongation is seen, with a predicted increase of 14.2 ms. An association between osimertinib and CHF/reduction in LVEF has been reported.

In this study, patients will be treated at the FDA-approved dose of osimertinib 80 mg PO daily.

Please see the osimertinib investigator's brochure and package insert for full details.

1.3 Rationale for the Proposed Study

Despite high initial response rates to EGFR TKIs, patients with EGFR-mutant NSCLC treated with these agents will ultimately develop PD, on average in less than one year. Much of the research into EGFR TKI resistance has focused on mechanisms of acquired resistance present at the time of PD. For patients who received first and second generation EGFR TKIs, the most common of these mechanisms is the T790M gatekeeper mutation, occurring in 50-60% of patients who progress on these agents, with less commonly occurring mechanisms including amplification of alternative signaling pathways such as MET and HER2 [35]. The third generation EGFR TKI osimertinib has activity against T790M mutant NSCLC and is FDA approved in this setting; however, resistance will ultimately develop leading to progression of disease. Specific EGFR mutations, such as the EGFR C797S mutation [21, 22] have been identified as contributing to acquired resistance to osimertinib.

Less is known about the phenomenon of persistent disease, which is the most common outcome in patients treated with all generations of EGFR TKIs, with CR rates less than 2% with these agents. The persistence of disease in the face of EGFR TKI therapy may contribute to selection for resistant subclones and ultimately to PD.

1.3.1 Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) tumor cell survival is induced by epidermal growth factor receptor tyrosine kinase inhibitor treatment

Prior work has uncovered a cancer cell population termed ‘drug tolerant persisters’ that withstood initial treatment via an IGF1R-mediated epigenetic program that could be pharmacologically reversed with chromatin-directed or IGF1R targeted therapy [36]. Subsequent clinical trials did not show a significant effect of either chromatin-directed or IGF1R targeted therapy on response to concurrent EGFR kinase inhibitor treatment in lung cancer patients [37, 38]. Although this hypothesis remains promising, additional studies are required. Other work exploring initial response to targeted therapy in cancer cells showed that EGFR inhibition provokes STAT3 survival signaling [39]. We further investigated signaling events that occur in response to EGFR oncogene inhibition in lung adenocarcinoma cells to enable their adaptation and survival during initial therapy. We found that NF-kB signaling is rapidly engaged upon initial EGFR inhibitor treatment to promote tumor cell survival and residual disease. EGFR oncogene inhibition induced an EGFR-TRAF2-RIP1-IKK complex that stimulated an NF-kB-mediated transcriptional survival program **(Fig. 1)** [1]. Validation of these findings in patients could unveil NF-kB activation as a critical adaptive survival mechanism engaged by EGFR oncogene inhibition and provide rationale for EGFR and NF- kB co-inhibition to eliminate residual disease and enhance patient responses. Beyond adaptive NF-kB activation, pre-treatment tumor heterogeneity may in part explain incomplete responses to osimertinib. Sequist et al. found that the allele frequency of the EGFR T790M mutation correlated with increased response to an alternative third-generation EGFR TKI rociletinib [22]. This suggests that co-occurring events that bypass EGFR oncogene dependence could be driving incomplete response to therapy.

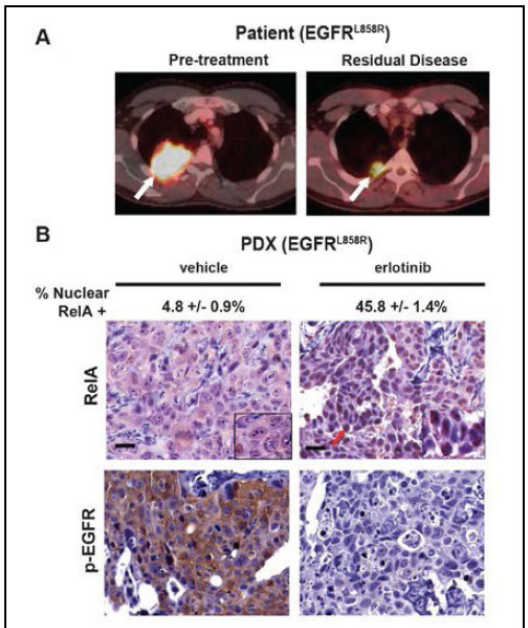


Figure 1: (A) FDG-PET CT imaging of a patient’s thorax with metastatic EGFR-mutant NSCLC prior to treatment with erlotinib, and post-erlotinib with residual disease present. **(B)** Representative IHC staining for the indicated proteins in patient-derived xenograft (PDX) demonstrating increase in RelA nuclear localization upon erlotinib treatment [1].

1.3.2 Tumor-associated macrophages (TAMs)

Tumor-associated macrophages (TAMs) promote NF-kB signaling in non-small cell lung cancer cells, the upregulation of which promotes survival of epidermal growth factor receptor-mutant non-small cell lung cancer in response to treatment with epidermal growth factor receptor tyrosine kinase inhibitors

NF-kB is a transcription factor that regulates numerous biological processes, including cell proliferation and apoptosis, as well as a critical mediator of both innate and adaptive immune cell activity [40].

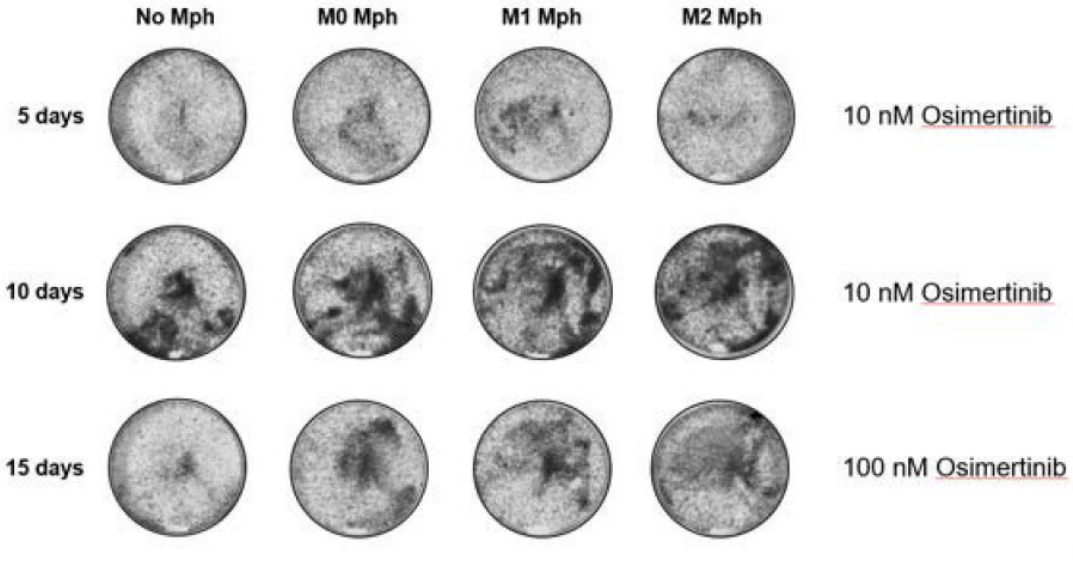
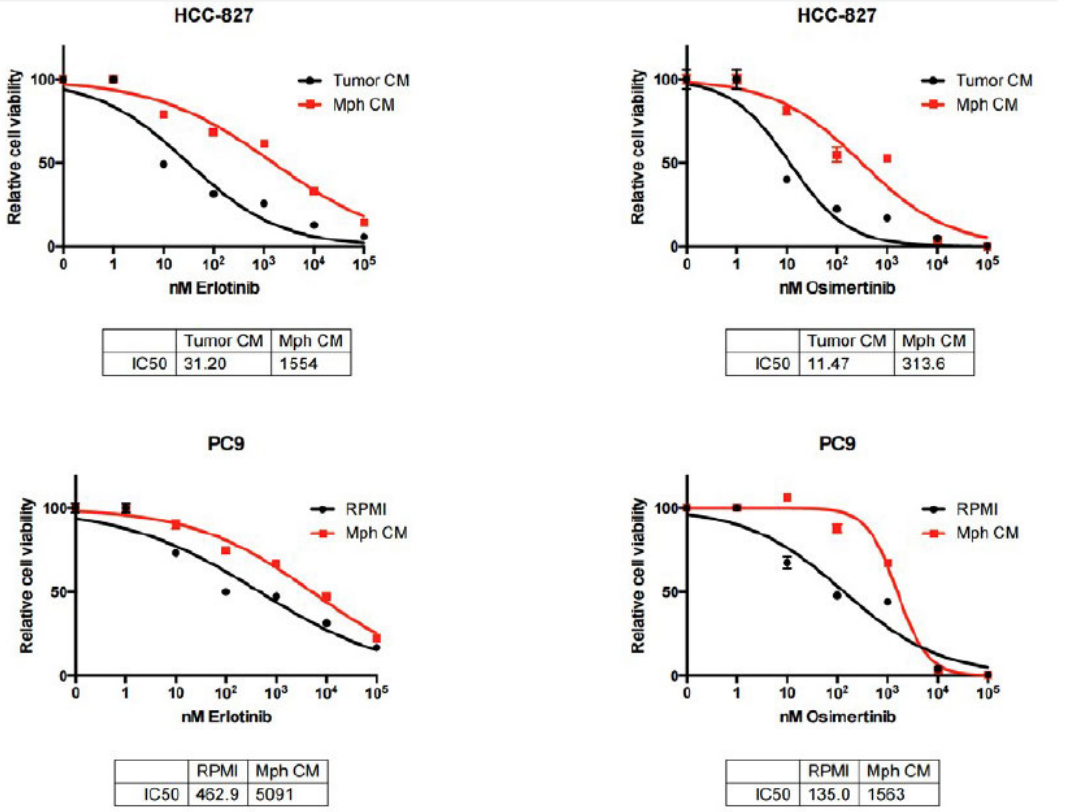


Figure 2: HCC827 NSCLC cells, which harbor the EGFR exon 19 deletion activating mutation, were either co-cultured with macrophages that were unpolarized (M0), or treated with cytokines to polarize to the M1 (IFNγ with LPS) or M2 (IL4 with IL13) phenotype. A control culture grown without exposure to macrophages is shown in the first column. Cells were then treated with osimertinib for the indicated number of days and culture plates were visualized to determine whether resistance to erlotinib treatment could be detected. HCC827 cells cultured without macrophages showed complete cell death that persisted to 15 days. In the macrophage co-culture experiments, tumor cell growth, and thus resistance to osimertinib treatment, could be detected as early as 5 days (Bivona lab, unpublished data).

Crosstalk between tumor cells and TAMs within the tumor microenvironment may contribute both to NSCLC development and to tumor cell survival in response to treatment with EGFR TKIs. These myeloid-derived cells serve diverse functions in host defense and tissue repair. TAMs subsequently influence diverse elements of tumor progression, including angiogenesis, modulation of local immune response, and promotion of metastasis. In order to carry out these roles, TAMs exist within the microenvironment in multiple functional states, broadly characterized as either M1 or M2 polarization states. M1 polarized macrophages serve a pro-inflammatory role including promotion of T cell cytotoxicity and secretion of pro-inflammatory cytokines, and ultimately serve an antitumor role. Conversely, M2 polarized macrophages have reduced antigen presenting capabilities, restrain the cytotoxic T cell response, and thereby produce a microenvironment which is more permissive of tumor progression. Co-culture of macrophages or macrophage-conditioned media with EGFR-mutant lung adenocarcinoma cell lines makes tumor cells relatively resistant to osimertinib treatment **(Figs 2 and 3)**. Shifts in programmed cell death protein 1 (PD-1) and PD-L1 expression have also been linked to NF-kB activity [41]. We hypothesize that osimertinib treatment will induce a pro-tumor immune microenvironment that allows for tumor cell persistence through inducing TAM infiltration, or through effects on adaptive immune cells, including CD4+ TREGs, or through altering PD-1 and PD-L1 expression.



	Tumor CM	Mph CM
IC50	31.20	1554

	Tumor CM	Mph CM
IC50	11.47	313.6

	RPMI	Mph CM
IC50	462.9	5091

	RPMI	Mph CM
IC50	135.0	1563

Figure 3: NSCLC cells lines HCC-827 and PC9, both harboring the EGFR exon 19 deletion, were grown in either control media (RPMI or tumor conditioned media) or in macrophage-conditioned media. These cell lines were then exposed to increasing concentrations of either erlotinib or osimertinib for determination of the IC_{50} in each condition. A substantially increased IC_{50} for each drug was seen treating cells exposed to macrophage conditioned media (Bivona lab, unpublished data).

1.3.3 Concurrent tumor genomic alterations influence osimertinib response

These data suggest a potential role for genetic epistasis in controlling tumor progression and EGFR inhibitor response in *EGFR*-mutant NSCLC patients. If this hypothesis is true, then the presence of specific co-occurring genetic alterations would be enriched in non-responder versus responder patients. We found that primary resistance of *EGFRT790M*-positive NSCLCs to initial osimertinib treatment was associated with the presence of alterations in cell cycle genes such as *CDK4/6* (5/13, 38% vs. 0/14, 0%, p = 0.02), and a trend towards alterations in *MET* (3/13, 23% vs. 0/14, 0%, p = 0.09) and *TP53* (8/13, 69% vs. 5/14, 36%, p=0.12) prior to treatment **(Fig. 2A,B)** [42]. While mechanisms of acquired osimertinib resistance have been reported [21, 43, 44], these data uncover potential clinically-relevant mechanisms that may limit the initial response to osimertinib treatment (i.e. promote primary resistance). The findings suggest that multiple co- alterations in specific signaling pathways that promote biological processes critical for cancer growth may help limit EGFR inhibitor response, even in cancers with *EGFRT790M*. This finding of polygenic driver alterations in the *EGFRT790M*-positive cases may help explain why clinical responses to EGFRT790M-directed therapies such as osimertinib occur in only 60-70% of *EGFRT790M*-positive NSCLC patients and are almost always incomplete [19, 45]. Altogether, the data argue that *EGFR*-mutant NSCLC clinical outcomes are impacted by the widespread presence of combinations of functional genetic alterations that are present and undergo selection before and during EGFR inhibitor treatment and tumor progression.

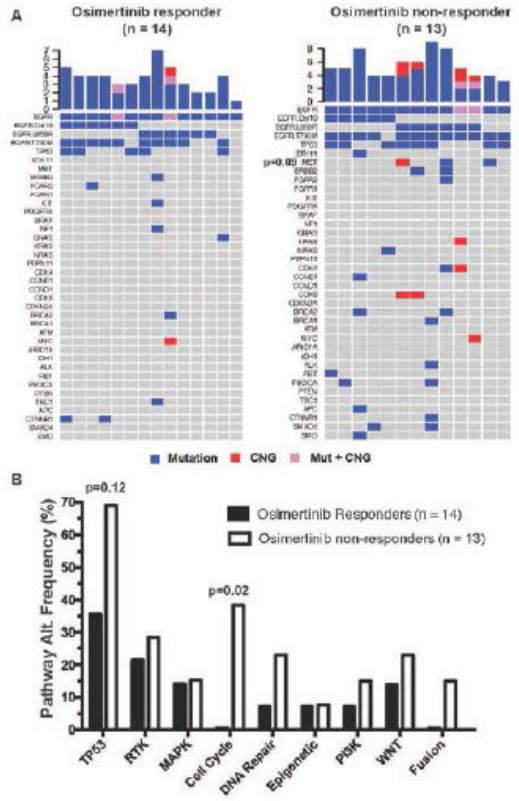


Figure 4. Correlation between pre-treatment ctDNA alterations and osimertinib response. (A) Genomic alterations detectable in ctDNA of patients who were subsequently treated with osimertinib and exhibited a radiographic response (left, demonstrated PR on imaging by clinician assessment) versus patients who did not respond (right, SD or PD on radiographic imaging by clinician assessment, or clinical progression leading to death prior to imaging being performed). **(B)** Cancer-related pathway alterations in osimertinib responders vs. non-responders demonstrated increased cell cycle gene alterations in non-responders. P-values determined by two-tailed Fisher's test.

1.3.4 Rationale for osimertinib neoadjuvant clinical trial

Access to patient tissue during the initial acute period of EGFR TKI treatment will be critical to defining the molecular and cellular mechanisms that underlie incomplete responses to EGFR TKI therapy. The availability of such tissue is incredibly limited, as EGFR TKI treatment is not standardly given prior to surgical resection of early stage NSCLCs.

Induction therapy with platinum-based chemotherapy given prior to surgical resection for patients with resectable lymph node-positive NSCLC is a safe and acceptable practice [29]. The role of EGFR TKI therapy as induction therapy for patients with EGFR-mutant NSCLC remains incompletely explored. In an unselected study of 50 patients with stage I or II NSCLC treated with gefitinib, 17 of 21 patients found to have activating EGFR mutations in their resected tumor specimens had a radiographic response to treatment [30]. In a separate study of an enriched

population of 60 non-squamous patients with early stage lung cancer treated with erlotinib for 21 days prior to surgery, patients with EGFR-activating mutations (n=7), 40% (3 of 7) had a pathological response with >50% tumor necrosis at the time of resection. In contrast, only 23% (8 of 35 patients) with WT EGFR exhibited >50% necrosis in their tumors at the time of resection [25]. While these results suggest that neoadjuvant therapy may be beneficial to patients with EGFR-activating mutations prior to surgery, a prospective trial in pre-selected EGFR-mutant lung cancer patients has not been performed.

We hypothesize that neoadjuvant treatment with osimertinib, an EGFR TKI that targets T790M in addition to common activating mutations in EGFR, will improve patient responses to induction therapy. Furthermore, the neoadjuvant design of this trial will allow us to perform comprehensive molecular analyses on tumor specimens pre-treatment and after initial response to osimertinib. We anticipate that this information will allow us to define mechanisms of incomplete initial response to osimertinib and facilitate development of rational companion therapies that when combined with osimertinib in the first line setting could result in more complete and durable responses for patients.

1.4 Correlative Studies

Biopsies for tissue sampling will be obtained as described in detail in study procedures and as summarized here. A fresh tissue biopsy will be required prior to enrollment, permitting a baseline analysis.

Peripheral blood samples will be drawn for correlative studies at enrollment, serially during therapy, and following surgical resection. This tissue and blood collection will allow for serial assessment of correlative studies, in order to better understand mechanisms of disease persistence and resistance during treatment with EGFR TKI therapy.

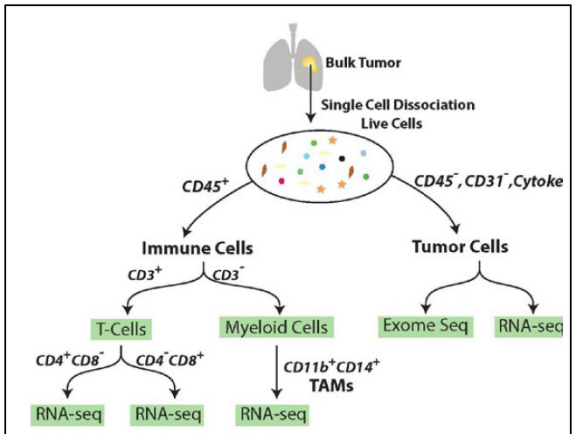


Figure 5. Schema of tumor and immune cell isolation strategy. Pre-treatment tumor biopsies and post-surgical specimens will undergo single-cell dissociation and FACS analysis to isolate tumor cells $CK^+CD45^-CD31^-$, $CD4^+$ and $CD8^+$ T-cells, and Tumor Associated Macrophages (TAMs). Exome and RNA sequencing will be performed

Tissue and peripheral blood sample analysis will be carried out in collaboration with the Bivona Lab (UCSF) and the Chan Zuckerberg Biohub. Organoid generation will be carried out through collaboration with the Kuo Lab (Stanford University). Patient-derived xenografts (PDXs) generation will be carried out at the UCSF Tissue Core. Circulating tumor DNA (ctDNA) analysis will be performed in collaboration with Guardant Health or the Chan Zuckerberg Biohub.

1.4.1 Exome and transcriptome sequencing

We will perform RNA sequencing and whole exome sequencing analysis on isolated cancer cell populations (Fig. 5) from pre- treatment tumor biopsy specimens, as well as tumor tissue acquired at the time of surgical resection (post- osimertinib). Gene Set Enrichment Analysis will be performed to identify osimertinib-induced changes in common cancer related pathways, including: RAS-RAF- MAPK, PI3K-AKT, WNT- β -catenin, JAK-STAT, HGF-MET, and IGF-1R, as well as emerging pathways of resistance (i.e. NF-kB and Hippo- YAP) [1, 46, 47]. We will determine whether there is a statistically significant increase in oncogenic/survival pathway related gene expression signatures in the post-osimertinib compared to the pre-treatment sample using established methods [48]. We will compare MPR rates in tumors that exhibit

specific oncogenic/survival pathway activation post-osimertinib treatment compared to tumors that do not. Immunohistochemistry (IHC) analysis will be performed on pre-treatment and post-surgical specimens to confirm pathway activation identified by transcriptional analysis (i.e. phosphorylated-ERK (indicative of MAPK signaling), phosphorylated-AKT (indicative of PI3K signaling) or nuclear NF-kB (RELA), or beta-catenin expression).

1.4.2 Immune profiling

We will assess for shifts in the cellular make-up of the tumor microenvironment induced by osimertinib treatment by performing single cell dissociation and fluorescence associated cell sorting (FACS) on fresh pre-treatment tumor biopsies and post-osimertinib tumor resection specimens. Using FACS gating strategies established and validated by the Krummel lab at UCSF [49], we will isolate CD45+ immune cells and determine how osimertinib treatment alters the proportions of cells that make up the lymphoid (CD4+ and CD8+ T cells, Tregs, NK cells, B cells) and myeloid (macrophages, neutrophils, mast cells, dendritic cells) compartments. We will then use RNA-Seq to assess the transcriptional profiles of populations of TAMs, CD4+ and CD8+ T Cells (Fig. 5). We hypothesize that osimertinib treatment will induce a pro-tumor immune microenvironment that allows for tumor cell persistence. Specifically, we will assess the polarization of TAMs by assessing the mRNA expression profiles of genes classically associated with TH1-skewed (i.e. TNF-α, IL-6, IL-12p40, and IL-1β, and Nos2) and TH2-skewed polarization (i.e. ARG1, TGFB, CD163, CD206), many of which are targets of NF-kB transcriptional activation[50]. We will also investigate whether osimertinib affects T-cell phenotypes. CD4+ T cells will be assessed for the expression of genes indicative of TREG, TH1, TH2, or TH17 activity (i.e. GATA3, T-bet, FOXP3, IFNgamma, IL-4, IL-13, IL-10, and IL-17a)[50], and CD8+ T cells will be assessed for expression of cytotoxic effector molecules (IFNgamma, GRZA, GRZB, and PRF1)[50]. Finally, tumor cells and infiltrating immune cells will be assessed for shifts in PD-1 and PD-L1 expression (by RNA-Seq and IHC), a phenomenon that has been linked to NF-kB activity[41], and which may indicate changes in anti-tumor immunity induced by osimertinib. When possible, we will perform single cell RNA-sequencing on tumor biopsy and resection specimens at the Chan Zuckerberg Biohub.

1.4.3 Derivation of patient-derived xenografts and organoids

When adequate tissue is available, PDXs and organoids derived directly from patients' resected tumors will be generated, as previously described (23). PDX-bearing mice will be treated with osimertinib or osimertinib in combination with therapies (acquired through commercial vendors) that target the putative resistance mechanisms identified, including tumor cell intrinsic or extrinsic targets. PDXs that are generated will be shared with AstraZeneca.

1.4.4 Peripheral Blood circulating tumor DNA Collection

Serial peripheral blood and plasma samples will be stored for ctDNA analysis, and changes in peripheral immune cells.

2 Objectives of the Study

2.1 Primary

- To evaluate the efficacy of osimertinib as neoadjuvant therapy in patients with surgically resectable EGFR-mutant NSCLC.

2.2 Secondary

- To evaluate the safety of osimertinib given as neoadjuvant therapy in early stage EGFR-mutant NSCLC patients.
- To evaluate whether neoadjuvant osimertinib treatment increases the frequency of

tumors that are unresectable due to AEs or PD.
- To evaluate secondary measures of clinical efficacy in early stage EGFR-mutant NSCLC patients treated with osimertinib induction therapy.

2.3 Exploratory
- To evaluate long-term measures of efficacy in patients treated with osimertinib neoadjuvant therapy.
- To explore tissue and cell-free biomarkers that may be predictive of response or primary resistance to osimertinib neoadjuvant therapy.

2.4 Endpoints
2.4.1 Primary Endpoint
- To determine the MPR rate, defined as ≤ 10% viable tumor present histologically in the resected tumor specimen as has been previously defined.

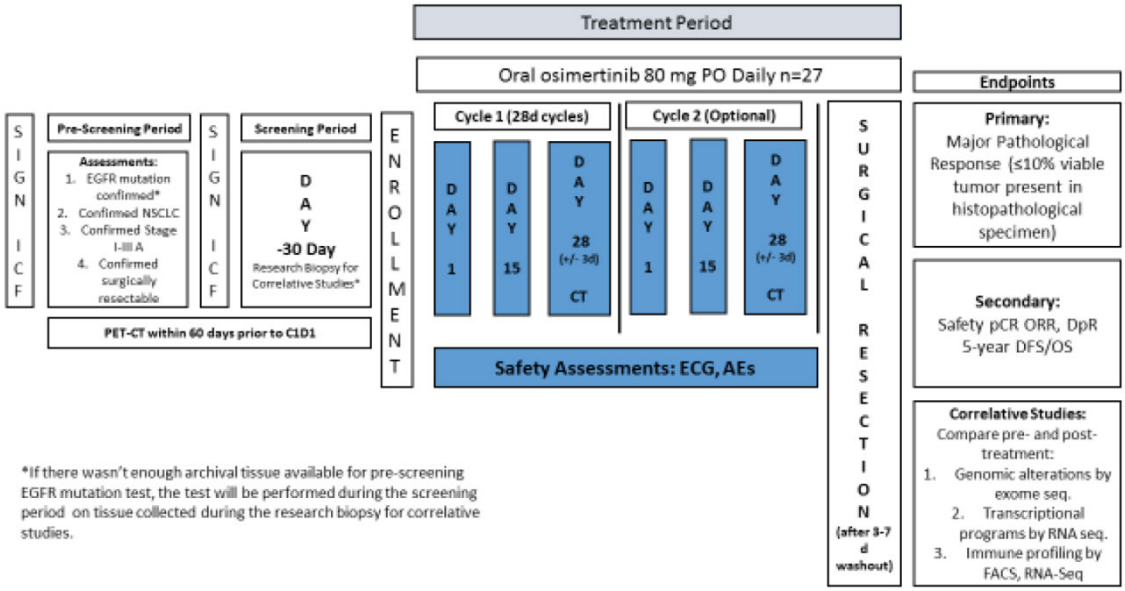
2.4.2 Secondary Endpoints
- Radiographic decrease in maximum tumor diameter
- DpR
- 5-year DFS
- 5-year OS
- Complete pCR
- Treatment-emergent AEs, laboratory abnormalities and ECG abnormalities as determined by National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.03 by investigator
- Rate of conversion to inoperable status due to treatment-related toxicity or PD
- Rate of surgical complications occurring prior to the end of treatment visit

2.4.3 Exploratory Endpoints
- Evaluate for adverse pathologic outcomes including pathologic upstaging as compared to clinical staging by pre-operative scans, rate of LVI, and rate of positive margins on resection specimens.
- Evaluate genomic and transcriptional changes on baseline and resected tumor specimens.
- Evaluate changes in immune cell infiltration on baseline and resected tumor specimens.
- Serial peripheral blood collection for exploratory biomarker assessment
- Changes in ctDNA

3 Study Design
3.1 Characteristics
This is a Phase 2, single arm, open-label, multicenter study evaluating the safety and efficacy of osimertinib administered orally daily to patients with stage I-IIIA, EGFR-mutant NSCLC who are planning to undergo surgical resection of their cancer.

Patients will undergo a research biopsy for correlative studies during screening prior to starting osimertinib treatment. Treatment will consist of osimertinib 80 mg by mouth daily in 28 day cycles given as neoadjuvant therapy. Patients may receive a second cycle of osimertinib at investigator's discretion. Patients will undergo serial assessments for anti-tumor efficacy and drug safety. The last dose of study drug will occur 3-7 days prior to planned surgical resection, which will occur within 14 days of the patient's most recent disease assessment scan.

Study Schema:



3.2 Number of Participants

27 evaluable patients will be enrolled in the study.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. Males and females ≥18 years of age.
2. Histologically or cytologically confirmed NSCLC, performed on a biopsy that occurred within the last 90 days. This biopsy can be deferred if the procedure is deemed to represent an unacceptable safety risk to the patient by the Principal Investigator and as long as the patient has a prior biopsy showing non-small cell lung cancer.
3. Documented activating EGFR mutation (Exon 19 deletion, T790M, or L858R) on tumor samples by Clinical Laboratory Clinical Laboratory Improvement Amendments (CLIA)-approved test.
4. Patients treated with osimertinib or another EGFR TKI (including erlotinib, afatinib, gefitinib, & rocelitinib) are eligible if they received no more than 28 days of treatment, and if there is no evidence of grade 2 or greater treatment adverse events possibly related to treatment with the EGFR TKI.
5. PET-CT (computerized tomography) within the last 60 days showing radiographic stage I to IIIa lung cancer (mediastinal staging biopsy is allowed but not required).
6. Brain magnetic resonance imaging (MRI) (or CT if contraindication to MRI) within the last 60 days showing no evidence of metastatic disease.
7. Documentation that the patient is a candidate for surgical resection of their lung cancer by an American Board of Thoracic Surgery certified surgeon.

8. The patient must have a tumor size ≥1 cm in its longest diameter.
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
10. Any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of starting study treatment, with the exception of alopecia and grade 2 prior platinum-therapy–related neuropathy is allowed
11. Adequate organ function:

    Hepatic Function:
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN).
    - Bilirubin ≤1.5× ULN, (Patients with documented Gilbert's syndrome and conjugated bilirubin within the normal range may be allowed into the study. In this event, it will be documented that the patient was eligible based on conjugated bilirubin levels).

    Electrolytes: Potassium, magnesium, and calcium within normal range, patients may receive supplements to meet this requirement.

    Hematologic Function:
    - Leukocytes >3,000/mcL
    - Hemoglobin (Hgb) ≥9 g/dL, with no blood transfusions in the 28 days prior to study entry
    - Absolute neutrophil count >1,500/mcL
    - Platelets >100,000/mcL

    Renal Function: CrCl > 50 mL/min for patients with SCr > 1.5 x ULN.
12. Ability to swallow oral medications
13. Women of childbearing potential must have a negative serum pregnancy test within 3 days prior to the first dose of study treatment and agree to use highly effective contraception, during the study and for 90 days following the last dose of osimertinib

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

    Women NOT of Childbearing Potential: Women who are permanently or surgically sterilized or postmenopausal (definitions below):

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

    - Women who have undergone tubal occlusion should be managed on trials as if they are 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

Acceptable contraception methods are:

- Total sexual abstinence (abstinence must be for the total duration of the trial and the follow-up period)
- Vasectomized sexual partner plus male condom (with 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, Norplant) 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)

Unacceptable Contraception Methods

The following methods are considered not to be highly effective and are therefore not acceptable contraceptive methods:

- 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

14. Men with a female partner of childbearing potential must have either had a prior vasectomy agree to use effective contraception as described in the full protocol for at least 14 days prior to administration of the first dose of study treatment, during the study, and for 120 days following the last dose of osimertinib. Men also can not donate sperm within this time period.

3.3.2 Exclusion Criteria

Any of the following criteria will exclude patients from study participation:

1. Leptomeningeal carcinomatosis or other CNS metastases.
2. Stage IIIB, or distant metastases (including malignant pleural effusion) identified on PET-CT scan or biopsy (PET abnormalities that are negative for malignancy on biopsy will be considered on a case by case basis).
3. Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.
4. Patients who are known to be serologically positive for human immunodeficiency virus (HIV)
5. Active second malignancy, i.e. patient known to have potentially fatal cancer present for which he/she may be (but not necessarily) currently receiving treatment. Patients with a

history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy for prior malignancy was completed >12 months prior and/or bone marrow transplant >2 years prior.

6. Patients who are currently receiving treatment with contraindicated QTc prolonging medications or potent CYP3A4 inducers (at least 3 weeks prior) (Appendix 6), if that treatment cannot be either discontinued or switched to a different medicationprior to first day of study treatment. Listing of contraindicated QTc prolonging and CYP3A4 inducing/inhibiting medications is provided in Tables 4.1, 4.2, and 4.3, with washout periods. All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects.
7. Any of the following cardiac abnormalities or history:
    - Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine derived QTc value.
    - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG e.g. complete left bundle branch block, third degree heart block and second degree heart block.
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, electrolyte abnormalities (including: Serum/plasma potassium < LLN; Serum/plasma magnesium < LLN; Serum/plasma calcium < LLN) , 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.
8. Treatment with prohibited medications (concurrent anticancer therapy including chemotherapy, radiation, hormonal treatment [except corticosteroids and megesterol acetate], or immunotherapy) ≤ 14 days prior to treatment with osimertinib.
9. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol, or known active infection including chronic active hepatitis B virus (HBV), hepatitis C virus, and HIV. Screening for chronic conditions is not required. Patients with chronic HBV with negative HBV viral load on appropriate antiviral therapy will be permitted, if able to continue appropriate antiviral therapy throughout treatment period.
10. Active tuberculosis.
11. Signs or symptoms of infection within 2 weeks prior to first day of study.
12. Therapeutic oral or IV antibiotics within 2 weeks prior to first day of study treatment:
    - Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible.
13. Class II to IV heart failure as defined by the New York Heart Association functional classification system.
14. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF <50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate, to be eligible.
15. Patients who have experienced untreated and/or uncontrolled cardiovascular conditions and/or have symptomatic cardiac dysfunction (unstable angina, congestive heart failure, myocardial infarction within the previous 3 months; coronary angioplasty, or stenting or bypass grafting within the past 6 months; cardiac ventricular arrhythmias requiring medication; any history of 2nd or 3rd degree atrioventricular conduction defects);

16. Females who are pregnant or breastfeeding;
17. Presence of active gastrointestinal (GI) disease (including GI bleeding or ulceration) or other condition that could affect GI absorption (e.g., malabsorption syndrome, history of biliary tract disease), including refractory nausea or vomiting, or chronic GI disease which may affect absorption or tolerance to oral medications.
18. History of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib.
19. Involvement in the planning and/or conduct of the study (applies to both Investigator staff and/or staff at the study site).
20. Participation in another clinical study with an investigational product (IP) during the last 3 months or within five half-lives of the compound, whichever is longer.
21. Uncontrolled medical, psychological, familial, sociological, or geographical conditions that interfere with the patient's safety, ability to provide informed consent, or ability to comply with the protocol.

3.4 Duration of Therapy

Patients may receive up to 2 cycles of therapy prior to surgery. Surgery must occur within 14 days of final scans. Patients will continue the study drug following final scans and then discontinue the study drug between 3 and 7 days prior to surgery, and thus may ultimately receive up to two weeks additional therapy with study drug beyond end of cycle 1 (or cycle 2) while awaiting surgery. No treatment with the study drug will be given after surgery.

Criteria for treatment with Cycle #2:

- No Grade 3 or higher AEs with Cycle #1
- No evidence of PD by RECIST 1.1 criteria at end of Cycle #1 scan.
- Additional reduction in tumor size deemed to be potentially beneficial by thoracic surgeon planning to perform resection.

Treatment may be stopped for any of the following reasons:

- The patient or legally authorized representative withdraws consent.
- Any AE that in the opinion of the investigator would pose an unacceptable safety risk to the patient.
- Closure of the study.

3.5 Duration of Follow Up

Patients will be followed for safety assessments 30 days following the Day 15 post-operative visit, or removal from study, or until death, whichever occurs first. Patients removed from study for unacceptable treatment-related AE(s) will be followed until resolution or stabilization of all treatment related AEs to Grade 2 or lower. Patients whose disease is not resectable at the time of scheduled surgery will be managed per standard of care for patients with unresectable EGFR-mutant NSCLC. All patients will be followed for disease relapse and OS for up to 5 years.

3.6 Randomization Procedures

There is no randomization in this study.

3.7 Study Timeline

3.7.1 Primary Completion

Accrual in this study is expected to require 36 months. Data collection will be complete 60 months after enrollment of the last patient.

3.7.2 Study Completion
In total, this study is expected to reach completion approximately 96 months from the time accrual opens.

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Osimertinib
Osimertinib is provided as beige, film-coated tablets, containing either 40 or 80 mg osimertinib expressed as a free base. Osimertinib tablets are packed in high-density polyethylene bottles with desiccant, sealed with a child-resistant closure and induction-sealed membranes.

Osimertinib tablets contain osimertinib mesylate, mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose and sodium stearyl fumarate. The tablet film-coat contains polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, yellow iron oxide, red iron oxide and black iron oxide.

Classification
Osimertinib is a small molecule EGFR TKI, FDA-approved for patients with metastatic EGFR-mutated NSCLC with a T790M mutation, who have progressed on prior EFR TKI therapy.

Mechanism of Action
Irreversible EGFR TKI for specific mutated forms of EGFR, including T790M, L858R, and exon 19 deletion. Biochemical studies showed osimertinib to be a potent and selective inhibitor of mutant EGFRs binding at approximately 9-fold lower concentrations as compared to wild-type EGFR (IC50 of 12 nM for mutant EGFR and 185 nM for wild-type). In a screen against 265 other protein kinase, osimertinib had significant activity, as defined by >60% inhibition at 1nM, against only 18 other kinases, including ACK1, BLK, ErbB2, ErbB4, BRK, MLK1, and MNK2. In cellular assays, osimertinib potently inhibited both EGFR-mutant cell lines and cell lines bearing an additional T790M mutation (IC50 6 nM to 54nM), with weaker inhibition of wild-type EGFR cell lines (IC50 480 nM to 1.8 μ). This correlated with reduced cell proliferation upon osimertinib exposure and to tumor regression in EGFR-mutant mice bearing xenograft tumors both with and without the T790M mutation. Tumor regression was accompanied by pharmacodynamic inhibition of pEGFR and downstream biomarkers pAKT and pERK.

Metabolism

PKs were linear over a 20 to 240 mg dose range and steady state is reached at approximately 15 days treatment. Osimertinib showed a high volume of distribution and is predicted to bind plasma proteins. The mean half-life of osimertinib was 48 hours. In animal studies, tissue distribution was widespread, with highest concentrations at the uvea and retinal pigment epithelium, renal cortex, pituitary, spleen, bile ducts, lung, and Hadarian gland.

Metabolism is primarily via the CYP3A4/5. Two pharmacologically active metabolites (AZ7550 and AZ5104) are generated with similar kinase selectivity and accounted for less than 10% of exposure compared to osimertinib. Renal clearance accounts for less than 1% of overall clearance. Excretion is primarily fecal (68%), with minor urinary excretion (14%). PKs have been studied in patients with moderate renal impairment (CrCl 30-59 mL/min) and with mild hepatic impairment (AST greater than ULN with normal bilirubin, or total bilirubin 1-1.5xULN with any AST). PKs in patients with more severe renal or hepatic impairment are unknown.

Contraindications

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).

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 website: https://www.crediblemeds.org/. The website categorizes drugs based on the risk of inducing Torsades de Pointes (TdP).

During screening the drugs that patients are currently prescribed should be checked oppsite the ArizonaCert website.

Drugs with a known risk of Torsades de Pointes

The following drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended. These drugs must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table 3 and should not be co-administered with study treatment (osimertinib) and for a period of two weeks after discontinuing study treatment. **The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such, investigators are recommended to search the website to provide the most up to date information.**

Table 4.1 Drugs prolonging the QT interval

Contraindicated drug	Withdrawal period prior to osimertinib start
Clarithromycin, droperidol, erythromycin, procainamide, aclarubicin, anagrelide, ciprofloxacin, cocaine, levofloxacin, ondansetron, papaverine hydrochloride, sulpiride, sultropride, terfenadine terlipressin	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*
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

*Estimated value as PKs of arsenic trioxide has not been studied

Metabolism of osimertinib is primarily carried out by CYP3A4/5. A drug-drug interaction study of osimertinib evaluated in patients showed that there is potential for osimertinib being a victim when co-administered with strong inducers of CYP3A4 (osimertinib concentrations are decreased when co-dosed with rifampicin)

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

Table 4.2 Drugs inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to osimertinib start
Carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine	3 weeks
St John's Wort	
Phenobarbitone	5 weeks
This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required.	

Osimertinib and its metabolites are substrates for P-gp and BCRP. Osimertinib may increase the concentration of sensitive BCRP and Pgp substrates (concentration of the sensitive BCRP substrate, rosuvastatin and sensitive Pgp substrate, fexofenadine, are increased).

Table 4.3 Exposure may be increased by osimertinib treatment

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine Doxorubicin Daunorubicin Topotecan Dabigatran Aliskiren Digoxin	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.

With the exception of contraindicated drugs listed above, therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and should be documented on the eCRF. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided.

Herbal and complementary therapies are not permitted as potential drug-drug interaction cannot be definitively excluded.

No other anti-cancer therapies (including chemotherapy, radiation, hormonal treatment [except corticosteroids and megestrol acetate], antibody or other immunotherapy or other experimental drugs) of any kind are permitted.

Availability
Osimertinib is absorbed orally, with a median time to maximum concentration (Cmax) of 6 hours (range 3-24 hours). Oral bioavailability was similar in the fasting state and following a high-fat meal. Absorption is not affected by gastric pH.

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

Osimertinib should be stored in its original packaging at 25°C (77°F); excursions to 15-30°C are permitted.

Side Effects

Table 4.4 Adverse Reactions as Reported in the AURA Studies (Phase II and Phase III) [51]

Category	Adverse Event	CIOMS Descriptor (Overall Frequency)	Frequency of CTCAE Grade 3 or Higher
Pulmonary	ILD	Common (3.2%)	1.3%
Gastrointestinal	Diarrhea	Very common (44%)	1%
	Stomatitis	Very common (15%)	0%
Ocular	Keratitis	Uncommon (0.9%)	0%
Dermatologic	Rash	Very common (41%)	0.7%
	Dry skin	Very common (29%)	0%
	Paronychia	Very common (27%)	0%
	Pruritus	Very common (15%)	0%
Cardiac	QTc interval prolongation	Uncommon (0.7%)	0.7%
Hematologic	Platelet count decreased	Very common (54%)	2.1%
	Leucocytes decreased	Very common (66%)	2.4%
	Neutrophils decreased	Very common (32%)	4.3%

Complete and updated AE information is available in the Investigational Drug Brochure and product package insert.

4.2 Drug Accountability
The Investigational Pharmacist will manage drug accountability records.

4.3 Drug Ordering
UCSF will obtain osimertinib directly from AstraZeneca as study supply.

4.4 Packaging and Labeling of Study Drugs
Drugs will be packaged and labeled per UCSF institutional standards, adhering to applicable local and federal laws.

5 Treatment Plan

5.1 Dosage and Administration
Treatment will be administered on an outpatient basis.

Table 5.1 Regimen Description

Study Drug	Premedication; precautions	Dose (mg/day)	Route	Schedule	Cycle Length
Osimertinib1	Can be taken with or without food	80 mg	Oral	Daily	4 weeks (28 days)

Osimertinib is administered as an 80 mg tablet orally once daily. Osimertinib can be taken without regard to food. Osimertinib 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. Each dose should be taken with 8 oz (240 mL) of water.

The patients will be requested to maintain a medication diary for each dose of medication. The medication will be returned to clinic staff at the end of each cycle. Any change in dosing schedule, dose interruptions, or dose reductions should be recorded.

5.1.1 Other Modalities or Procedures

Surgery/Anesthesia: Surgical resection of the patients lung cancer will be carried out in accordance with the institutions standard practice and surgical guidelines. The last dose of study drug prior to surgery will be taken by the study participant between 3 and 7 days prior to surgery. The attending anesthesiologist for the case will be notified and informed of the QTc prolonging potential of the study drug. Drugs that are known to cause or possibly cause QTc prolongation (See crediblemeds.org) should be avoided. Anesthesiologists should be made aware that this list includes Sevoflurane and Propofol, which should be avoided as anesthetics if possible.

5.2 Dose Modifications and Dosing Delays

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity including a DLT, not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

If a 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) or a lower dose (40 mg) using the rules below for dose modifications (Table 5.2) and with discussion and agreement with Principal Investigator (PI). There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption.

On resolution of toxicity within 3 weeks: If an AE subsequently requires dose interruption, osimertinib may restart at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the Investigator.

Table 5.2 Dose Modifications and Dosing Delays

Dose Level	Osimertinib (PO daily) Each Cycle 28 Days
0	80 mg
-1	40 mg

Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI CTCAE Version 4.03.

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity including a DLT, not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

If toxicities do not resolve to less than or equal to Grade 2 after 2 weeks despite supportive care, then the participant should be withdrawn from the study.

Table 5.3 Dose Modifications and Dosing Delays Tables for General Adverse Events

Grade of Event	Management/Next Dose for Osimertinib
≤ Grade 1	No change in dose
Grade 2	Hold until ≤Grade 1 if clinically significant, otherwise no change in dose
	Resume at same dose level
Grade 3	Hold* until <Grade 2
	Resume at one dose level lower, if indicated**
Grade 4	Off protocol therapy

*Patients requiring a delay of >2 weeks should go off protocol therapy
**Patients who do not tolerate 40 mg PO daily dose will be taken off protocol therapy
***Alopecia/hair color changes are excluded from requirement for dose delays or modifications

Dose Modifications and Dosing Delays Tables for Specific Adverse Events

Table 5.4 Adverse Event: Diarrhea

Grade of Event	Management/Next Dose for Osimertinib
≤ Grade 1	No change in dose
Grade 2	Hold until ≤Grade 1 if clinically significant, otherwise no change in dose
	Resume at same dose level
Grade 3	Hold* until ≤Grade 2
	Resume at one dose level lower**
Grade 4	Off protocol therapy

Recommended management: Loperamide antidiarrheal therapy, see section 5.3.1
*Patients requiring a delay of >2 weeks should go off protocol therapy
**Patients who do not tolerate 40 mg PO daily dose will be taken off protocol therapy

Table 5.5 Adverse Event: Pulmonary/Cardiac Toxicity

PULMONARY Notes: • Withhold osimertinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD. • During evaluation of potential grade 2, 3, and 4 pneumonitis, if an infectious etiology is confirmed (i.e., pneumonia) and pneumonitis is excluded, then consider resuming at current dose level after the pneumonia resolves.	
ILD/Pneumonitis	
Grade of Event	**Dose Modifications for osimertinib**
Grade 1 or greater	Permanently discontinue osimertinib
CARDIAC INVESTIGATIONS	
Abnormal LVEF	
Symptomatic congestive heart failure or asymptomatic left ventricular systolic dysfunction which persists for ≥ 4 weeks	Permanently discontinue osimertinib
Electrocardiogram QT corrected (QTc) interval prolonged* **	
Grade 1 (QTc 450-480 ms) Grade 2 (QTc 481-500 ms)	Maintain dose level
Grade 3 (QTc ≥ 501 ms)	• Perform an analysis of serum potassium, magnesium, calcium, and phosphorus, and if below lower limit of normal, correct with supplements to within normal limits. Review concomitant medication uses for an agent which may cause prolonged QTc and discontinue if clinically feasible. • Hold osimertinib until QTc is less than 481 ms or to baseline if baseline is >481 ms, then resume treatment, with osimertinib dose- if recovery within 3 weeks of onset, then restart at a reduced (40 mg) or at 80 mg (at the discretion of the investigator).* If QTc prolongation recurs patient will be permanently discontinued from the study. • Repeat ECG in 24 hours, or less, as clinically indicated; continue monitoring as clinically indicated until QTc <481 ms. • Repeat ECGs 7 days after dose resumption for all patients who had therapy interrupted due to QTc ≥501 ms.
Grade 4 (QTc ≥501 or >60ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue patient from study
*Patients requiring a delay of >2 weeks should go off protocol therapy **Patients who do not tolerate dose level -1 dosing should go off protocol therapy ***QTc prolongation as confirmed on three separate ECGs	

Table 5.6 Adverse Event: Dermatologic

Grade of Event	Management/Next Dose
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Hold* until <Grade 2 Resume at one dose level lower
Grade 4	Hold* until <Grade 2 Resume at one dose level lower

Please see Section 5.3.1 for recommendations regarding supportive care to be undertaken in patients experiencing dermatologic AEs on study
*Patients requiring a delay of >2 weeks should go off protocol therapy
**Patients who do not tolerate dose level -1 dosing should go off protocol therapy

5.3 Monitoring and Toxicity Management

Each patient receiving osimertinib will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, ECG findings, echocardiography findings, and spontaneous reports of AEs reported to the investigator by patients.

Each patient will be assessed periodically for the development of any toxicity as outlined in Section 6 Study Procedures and Observations. Toxicity will be assessed according to the NCI CTCAE v4.03. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

We will monitor for potential adverse effects including but not limited to fatigue, nausea, vomiting, dehydration, cytopenias, and signs and symptoms of infection. In addition we will monitor specifically for the following AEs of special interest (Please see the corresponding subsections in Section 6.2 for acute toxicity management and dose modifications).

- Rash/Dry Skin
- Diarrhea
- Ejection Fraction Changes
- Prolonged QTc
- Pneumonitis/ILD
- Liver Chemistry Elevations
- Hyperglycemia

Management of any grade 3 or higher toxicity should be discussed with the PI of the study.

5.3.1 Other toxicities

Toxicity will be managed according to local guidelines.

Rash and Dry Skin

Rash, acneiform rash, and dry skin are common AEs experienced on osimertinib therapy. The following guidelines are provided to facilitate supportive care in patients experiencing these findings. These skin adverse effects may occur at any time but are most likely to start within two weeks of starting treatment.

We recommend application of over-the-counter moisturizing cream to face, hands, and feet twice daily from the start of treatment with osimertinib.

For **Grade 1 or 2 rash and acne** we recommend initiation of emollient cream and/or a topical moderate strength steroid BID and/or a topical antibiotic BID. For **grade 2 rash/acne,** a six-week course of oral antibiotics can be considered. For **grade 3 or greater rash/acne,** we recommend a topical moderate strength antibiotic BID in combination with a 6-week course of oral antibiotic.

For **grade 1 or 2 dry skin** consider over the counter moisturizing cream or ointment BID to face/hands/feet with ammonium lactate 12% cream or salicylic acid 6% cream BID to the body. For **grade 3 or greater dry skin** add a topical moderate strength steroid to eczematous areas of the body.

For patients experiencing **grade 1 pruritus** consider a topical moderate strength steroid or topical antipruritic BID to localized areas. For patients with **grade 2 pruritus** consider an oral antihistamine. For **grade 3 or greater pruritus,** consider addition of a GABA agonist (such as gabapentin).

Diarrhea
Initiate dietetic measures including discontinuing lactose-containing products, frequent small meals, increased fluid intake with 8 to 10 glasses of clear liquids per day, and a low fat regimen enriched with rice, bananas, and applesauce.

For **grade 1 or 2 diarrhea,** initiate pharmacologic treatment with loperamide as per the following dosage schedule: Loperamide 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage 16 mg/24 hours). Grade 1 intermittent diarrhea may not require treatment. Adjunct anti-diarrheal therapy is permitted and should be recorded when used. Use electrolyte replacement as appropriate. In patients with **≥ grade 3 diarrhea,** consider IV fluids and more frequent electrolyte monitoring as indicated, with consideration for prophylactic antibiotics if diarrhea is persistent beyond 24 hours, there is fever, or ≥ grade 3 neutropenia.

Left Ventricle Ejection Fraction Changes
Osimertinib and its active metabolites may inhibit HER2 and a low rate of LVEF decrease from baseline has been reported in patients treated with osimertinib. Patients will be evaluated for abnormal LVEF at baseline. Subsequently, measurement of LVEF should be performed if the investigator has clinical suspicion of new onset impaired cardiac function. Patients are to be managed clinically according to standard of care, with cardiologic consultation at the investigator's discretion. Patients with asymptomatic reduction in LVEF which persists for greater than 4 weeks, or with symptomatic congestive heart failure, should permanently discontinue treatment with osimertinib.

Prolonged QTc
In light of the potential for QT changes associated with osimertinib, electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) must be correct to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment.

Electrocardiograms will be performed throughout the study as described. Readings for QTc prolongation will be based on the average of a single ECG for each time point. For patients found to have grade 3 or greater QTc prolongation, test serum potassium, calcium, phosphorus, and magnesium and correct per routine clinical practice to within normal limits. Review concomitant medications for medications that may cause prolongation of the QTc and discontinue if clinically feasible. Patients should have regular ECGs until return of QTc to

baseline. If the toxicity does not resolve to ≤ grade 1 within 21 days the patient will be permanently withdrawn from the study treatment. Further recommendations regarding dose adjustments and management are found in Table 5.5.

Pneumonitis/ILD
Pneumonitis/ILD can occur in patients treated with osimertinib. Patients with new or worsening dyspnea, cough, or new pulmonary radiological abnormality while receiving treatment, without clinically evident alternative etiology, should hold osimertinib, undergo a high resolution CT scan of the chest and the investigator should be notified. It is strongly recommended to perform a full diagnositic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema or pulmonary hemorrhage. The results of full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters) will be captured by eCRF. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of intersititial 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. Permanently discontinue osimertinib for any grade ILD/pneumonitis.

Liver Chemistry Elevations
Patients with combined increases in transaminases (AST or ALT to greater than 3x the ULN) and total bilirubin (to greater than 2x the ULN) should be reviewed for compatibility with Hy's law (Appendix 7). An appropriate diagnostic evaluation for alternative etiologies should be completed within a three-week period. Patients with both an increased in AST or ALT to greater than 3x the ULN AND subsequent or coincident elevation in total bilirubin to greater than 2x ULN, without an alternative explanation upon clinical evaluation (i.e. cholestasis, viral hepatitis, another drug exposure), are found to meet the criteria for Hy's Law and should be reported as an SAE.

Hyperglycemia
Treatment with osimertinib may result in hyperglycemia in some patients, most commonly in the first week of treatment. Regular monitoring of fasting or non-fasting blood glucose (FBG) will be completed as described in the study procedures in section 6.1. If a patient has a non-fasting glucose level of > 140 mg/dL (ULN for glucose within 2 hours of eating), then they must have a fasting glucose drawn and followed with fasting glucose for all future monitoring. Investigators should use discretion on an individual patient basis regarding need for more frequent monitoring: for example, patients with pre-existing diabetes or glucose intolerance. These patients should perform home monitoring at least once weekly during the first two cycles of treatment. Patients should be educated to contact the site if they have any positive urine glucose test or a home blood glucose reading of >160 mg/dL (>8.9 mmol/L) and any time they experience symptoms that have correlated with osimertinib-induced hyperglycemia, including increases in nausea, vomiting, anorexia, diarrhea, fatigue, polydipsia, polyuria, and polyphagia. Upon reports of positive home tests and/or symptoms suggesting hyperglycemia, local laboratory FBG tests should be performed.

The following guidelines serve as recommended management guidelines for hyperglycemia; however, management of individual patients is deferred to the treating physician's judgement.

Table 5.7 Management Guidelines for Hyperglycemia

FBG Result	Antihyperglycemic Intervention[a]	Osimertinib Dose Modification
Grade 2 (>160 to 250 mg/dL; >8.9 to 13.9 mmol/L)	• If asymptomatic,[b] repeat test within 1 week; if results in this range at least twice in 1 week, start antihyperglycemic[c] and continue home monitoring; • If symptomatic,[b] start antihyperglycemic and continue home monitoring.	• Osimertinib may continue without interruption or dose reduction.
Grade 3 (>250 to 500 mg/dL; >13.9 to 27.8 mmol/L)	• Start antihyperglycemic and continue home monitoring.	• If asymptomatic,[b] osimertinib may continue without interruption or dose reduction; • If symptomatic,[b] interrupt osimertinib until resolution/improvement in symptoms and FBG <250 mg/dL (<13.9 mmol/L).[c]
Grade 4 (>500 mg/dL; >27.8 mmol/L)	• Start antihyperglycemic and continue home monitoring. • Consider adding a second antihyperglycemic agent.[d]	• Interrupt osimertinib dosing until resolution/improvement in symptoms and FBG <250 mg/dL (<13.9 mmol/L).[c]

FBG, fasting blood glucose
[a] Oral antihyperglycemic agent (e.g., metformin), which may need to be maintained for duration of osimertinib treatment. Use of insulin or agents that increase insulin production (e.g., sulphonyl ureas) is generally not recommended because the mechanism of osimertinib-induced hyperglycemia is not due to a deficit in insulin production.
[b] Increased nausea, vomiting, anorexia, diarrhea, and fatigue have been most common symptoms of hyperglycemia.
[c] Per Investigator discretion, osimertinib may be restarted at the same dose. A reduced dose may also be considered if glucose levels prove difficult to control.
[d] Additional anti-hyperglycemia agents such as SGLT2 inhibitors (e.g., dapagliflozin) or pioglitazone, which increase glucose uptake or increase glucose excretion, may be added to metformin.

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in the schedule of study procedures and assessments. Screening assessments must be performed within 30 days prior to the first dose of IP. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed **a window of ± 3 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the participant and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.1.1 Pretreatment Period

6.1.1.1 Pre-Screening Assessments

If EGFR mutation status is unknown, archived FFPE NSCLC specimen may be tested by local laboratory (UCSF or laboratories affiliated with participating sites) or investigator's choice of CLIA- approved laboratory.

Assessment of cardiac function for changes in cardiac contractility must adhere to the **'Special warnings and special precautions for use'** in the current approved TAGRISSO core data sheet.

6.1.1.2 Screening Assessments

The Screening procedures and assessments must be completed withing 30 days prior to Day 1 Visit, except for, pregnancy testing, which must be completed within 3 days prior to Day 1.

- IR-guided core biopsy tumor specimen of a soft tissue lesion within 30 days prior to starting study drug for correlative studies. A repeat biopsy is permitted if quantity of tissue is insufficient. This biopsy can be deferred if the procedure is deemed to represent an unacceptable safety risk to the patient by the principal investigator.
- If there was not enough archival tissue for a pre-screening EGFR mutation testing, this research biopsy will be used to obtain tissue for EGFR mutation testing as well as the correlative studies. EGFR mutation tests will be done at a local laboratory (UCSF or laboratories affiliated with participating sites) or investigator's choice of CLIA-approved laboratory.
- If there is enough archival tissue left over, it will be sent to Guardant (Redwood City) for DNA analysis.
- 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, musculoskeletal (including spine and extremities) and neurological systems.
- Vital signs
- Complete medical history, including history of prior treatments and any residual toxicity relating to prior treatment.
- Baseline conditions assessment
- Performance status (ECOG)
- Baseline medications taken within 30 days of Day 1.
- Complete blood cell count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
    - Alkaline phosphatase (ALP), AST/ALT, total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting or non-fasting glucose, potassium, magnesium, sodium, chloride, bicarbonate.
- Coagulation assessment, including prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)

- Urinalysis
- For female patients, serum or urine pregnancy test within 3 days prior to the start of study drug
- Contraceptive counseling
- Confirmation of no evidence of metastatic disease by PET-CT and brain imaging (MRI or CT) within 60 days of Day 1.
- Disease assessment by CT of the chest, abdomen, pelvis (MRI acceptable if contraindications to CT) within 30 days of Day 1.
- Cardiac assessment (MUGA or TTE). Allowed within 30 days of Day 1.
- Electrocardiogram (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, single ECG recording should be taken at about 5 minute intervals. A standardized 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.
- Peripheral blood collection for exploratory biomarker analysis

For each participant, the Pre-Treatment Period ends upon receipt of the first dose of the study treatments or final determination that the participant is ineligible for the study.

6.1.2 Treatment Period

6.1.2.1 Study Procedures, Cycle 1, Day 1

- Screening laboratory tests completed within 3 days of Cycle 1 Day 1 do not need to be repeated.
- Physical examination
- Vital signs
- Performance status
- Evaluation of AEs
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including:
    - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting or non-fasting glucose, potassium, sodium, chloride, bicarbonate
- Coagulation assessment, including PT/PTT/INR
- Urinalysis
- Serum or urine pregnancy test
- Electrocardiogram (ECG)
- Patient medication diary will be provided to patients
- Osimertinib tablets will be dispensed to patient
- Peripheral blood collection for exploratory biomarker analysis.

6.1.2.2 Study Procedures Cycle 1, Day 15

- Physical examination

- Vital signs
- Performance status
- Evaluation of AEs
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including:
  - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting or non-fasting glucose, potassium, sodium, chloride, bicarbonate
- Coagulation assessment, including PT/PTT/INR
- Electrocardiogram (ECG)

6.1.2.3 Study Procedures Cycle 1, Day 28 – if not receiving optional second cycle of osimertinib

- Physical examination
- Vital signs
- Performance status
- Evaluation of AEs
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including:
  - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting or non-fasting glucose, potassium, sodium, chloride, bicarbonate
- Coagulation assessment, including PT/PTT/INR
- Optional post-treatment research biopsy within 30 days of C1D28 for patients who are determined to both be unable to undergo surgical resection of their tumor and who will not be proceeding with Cycle 2 of osimertinib therapy.
- Peripheral blood collection for exploratory biomarker analysis.
- Urinalysis is optional or as clinically indicated
- Serum or urine pregnancy test is optional or as clinically indicated
- Electrocardiogram (ECG)
- Disease assessment (includes measurable disease per RECIST) and imaging including CT of the chest, abdomen, pelvis (MRI if contraindications to CT).
- Cardiac assessment (MUGA or TTE)
- Review of patient diary for Cycle 1
- Patients will undergo surgical resection of their lung cancer within 14 days after the C1D28 restaging systemic scan.
- Osimertinib tablets will be dispensed, for up to a 14 day supply to be taken by patient until 3-7 days prior to surgery
- Patients must be assessed by a study investigator within approximately 14 days prior to surgery.

6.1.2.4 Study Procedures Cycle 2, Day 1 – if receiving optional second cycle of osimertinib

- Physical examination
- Vital signs
- Performance status
- Evaluation of AEs
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including:
  - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein,

albumin, fasting or non-fasting glucose, potassium, sodium, chloride, bicarbonate
- Coagulation assessment, including PT/PTT/INR
- Peripheral blood collection for exploratory biomarker analysis.
- Urinalysis
- Serum or urine pregnancy test
- Electrocardiogram (ECG)
- Disease assessment (includes measurable disease per RECIST)) and imaging including CT of the chest, abdomen, pelvis (MRI if contraindications to CT).
- Cardiac assessment (MUGA or TTE). For patients receiving the second of cycle of osimertinib, TTE is optional except for patients with pre-existing risk factors as clinically indicated
- Review of patient diary for prior cycle
- Osimertinib tablets will be dispensed

6.1.2.5 Study Procedures Cycle 2, Day 15 – if receiving optional second cycle of osimertinib
- Physical examination
- Vital signs
- Performance status
- Evaluation of AEs
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including:
  - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting or non-fasting glucose, potassium, sodium, chloride, bicarbonate
- Coagulation assessment, including PT/PTT/INR

6.1.2.6 Study Procedures Cycle 2, Day 28 – if receiving optional second cycle of osimertinib
- Physical examination
- Vital signs
- Performance status
- Evaluation of AEs
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including:
  - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting or non-fasting glucose, potassium, sodium, chloride, bicarbonate
- Coagulation assessment, including PT/PTT/INR
- Electrocardiogram (ECG)
- Cardiac assessment (MUGA or TTE)
- Disease assessment (includes measurable disease per RECIST) and imaging including CT of the chest, abdomen, pelvis (MRI if contraindications to CT).
- Optional post-treatment research biopsy within 30 days of C2D28 for patients who are unable to undergo surgical resection of their tumor.
- Peripheral blood collection for exploratory biomarker analysis
- Review of patient diary for Cycle 2
- Patients will undergo surgical resection of their lung cancer within 14 days of C2D28 systemic restaging scan.
- Osimertinib tablets will be dispensed, for up to 14 day supply to taken by patient until 3-7 days prior to surgery

6.1.2.7 Study Procedures on day of surgery

- CBC with differential and platelet count
- Blood chemistry assessment, including:
  - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting or non-fasting glucose, potassium, sodium, chloride, bicarbonate
- Coagulation assessment, including PT/PTT/INR
- Peripheral blood collection for exploratory biomarker analysis (ctDNA analysis and PBMCs)
- Electrocardiogram (ECG)

6.1.3 Study Procedures, D15 following surgery

Peripheral blood collection for exploratory biomarker analysis (ctDNA analysis and PBMCs)

6.1.4 End-of-Treatment Study Procedures

To be completed at 30 days of post-operative D15 study visit.

- Physical examination
- Vital signs
- Performance Status
- Evaluation of AEs
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including:
  - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting or non-fasting glucose, potassium, sodium, chloride, bicarbonate
- Coagulation assessment, including PT/PTT/INR
- Urinalysis
- Serum or urine pregnancy test
- Electrocardiogram (ECG)
- Peripheral blood collection for exploratory biomarker analysis

6.1.5 Long Term/Survival Follow-up Procedures

Patients will continue to be followed as per standard of care every three months (+/- 2 weeks) following the end-of-treatment visit for a period of up to one 5 years, or until death or closure of the study. This follow up will include assessment of survival status and subsequent therapies for NSCLC. Standard of care tumor scans (CT chest/abdomen/pelvis or PET/CT) will occur every 6 months, unless local requirements or investigator opinion warrant more frequent scans. After the first year, assessment of survival status and subsequent therapies will occur via telephone or via routine clinic visits every six months (+/- 2 weeks) for 5 years post-surgery.

6.1.6 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, PD, the occurrence of an AE or a concurrent illness, a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

6.2 Specimen Acquisition for Exploratory/Correlative Studies/Specimen Banking

6.2.1 Peripheral Blood

Peripheral blood will be collected for exploratory biomarker assessment, including cytokine and ctDNA profiling before starting treatment, as well as serially during and following treatment. Approximately 40 mL of blood will be collected for this purpose at each blood draw, divided between plasma, serum, and whole blood. Detailed instructions for sample collection and processing are included in the lab manual.

6.2.2 Specimen acquisition from screening biopsies

Lesions will be chosen based upon the strength of the evidence suggesting the presence of active malignant disease and accessibility to biopsy. If the radiologist in charge of the procedure cannot identify a lesion amenable for biopsy, the biopsy will be deferred. This biopsy can also be deferred if the procedure is deemed to represent an unacceptable safety risk to the patient by the principal investigator.

The biopsies will be performed in an interventional radiology suite with radiological guidance (typically CT or MRI or ultrasound) in accordance with the standard operating procedure per institutional standards. CT, ultrasound, or MRI will confirm designated lesions immediately prior to biopsy. A separate consent will be obtained prior to biopsy as per usual standard of care. Once the target lesion(s) is identified, up to six (6) biopsies will be performed.

Core biopsies are preferred, however if it is deemed technically infeasible, or if a core biopsy is deemed high risk by the biopsying physician, then an FNA would be acceptable. Preferably, a biopsy needle with an equivalent 18g bore will be used to biopsy the tumor lesions. Core biopsies will be extracted: up to 1 will be placed in neutral-buffered formalin, up to 1-2 will be immediately frozen on a pre-frozen bed of OCT (Optimal Cutting Temperature compound used for frozen sections), 1 will be snap frozen in liquid nitrogen or prechilled isopentane in a dry ice bath, and 1-2 will be placed in culture media as a fresh tumor specimen.

Total number of core biopsies extracted will be determined based on technical feasibility (lesion size, location) and safety as per the biopsying physician's judgement. An adequate pretreatment biopsy will be defined as at least one tissue core.

6.2.3 Specimen acquisition from surgical resection

Tissue will be sent for pathologic review as per usual standard of care. Tumor samples from the resection specimen will be obtained for research purposes including the following: 1 will be placed in neutral-buffered formalin, 1-2 will be immediately frozen on a pre-frozen bed of OCT (Optimal Cutting Temperature compound used for frozen sections), 1-2 will be snap frozen in liquid nitrogen or prechilled isopentane in a dry ice bath, and 2-4 will be placed in culture media as a fresh tumor specimen.

6.2.4 Banking of leftover specimens

Leftover specimens (peripheral blood, tumor biopsies and surgical resection) will be banked under UCSF Protocol CC# 136512 (Molecular Profiling in Thoracic Malignancies) at the following location:

UCSF Mt. Zion Tissue Core
UCSF Helen Diller Family Comprehensive Cancer Center
[redacted]
San Francisco, CA 94143[redacted]
[redacted]

6.3 Usage of Concurrent/Concomitant Medications

Osimertinib is metabolized by CYP3A4 and CYP3A5 enzymes.

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

The following potent inducers of CYP3A4 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.

Medicines Whose Exposures May be Affected by Osimertinib That are 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 Dabigatran Aliskiren Digoxin	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.

6.4 Dietary Restrictions

Osimertinib can be taken with or without food, with at least 240 mL (8 oz.) of water.

6.5 Prohibited Medications Other anticancer therapy

Systemic anticancer therapy (chemotherapy, targeted therapy, biologic therapy, or radiation therapy), other than the osimertinib treatment, must not be given to patients while they are enrolled in the treatment portion of the trial. If such agents are required then the patient must be permanently discontinued from the treatment portion of the study.

Other investigational therapies

Other investigational therapies must not be used while the patient is on the study.

Potent CYP3A inducers

Potent inducers of CYP3A4/5 are prohibited. Patients receiving concomitant medications known to potently induce CYP3A4/5 that are deemed medically necessary should be excluded from the study. Please see section 4.1.1 and 6.3 for additional details.

Herbal medications
Herbal preparations/medications are not allowed throughout the study, as a potential drug-drug interaction is always possible. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

Medications that may prolong the QT interval or have a known risk of inducing Torsades de Pointes
Medications known to produce QTc prolongation should be avoided during treatment of patients with osimertinib. See section 4.1 for lists of QTc prolonging medications. Please note potential QTc prolonging medications contain common supportive medications, such as anti-emetics (ondansetron [and other 5HT3 antagonists], metoclopramide, hydroxyzine), antibiotics (azithromycin, ciprofloxacin, metronidazole) and anti-depressants (escitalopram).

Medications to consider for nausea that are not associated with QT prolongation include:

- Steroids (dexamethasone, methylprednisolone)
- Benzodiazepines
- Aprepitant
- Select anticholinergic agents (scopolamine)
- Trimethobenzamide
- Cannabinoids

If a drug that has the potential to cause QTc prolongation is indicated to control AEs (*e.g.* 5HT3 inhibitor for nausea/vomiting), then additional ECGs should be performed to monitor for potential QTc changes.

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 website: https://www.crediblemeds.org/. The website categorizes drugs based on the risk of inducing Torsades de Pointes (TdP).

During screening, the drugs that patients are currently prescribed should be checked opposite the ArizonaCert website.

Drugs with a known risk of Torsades de Pointes
The following drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended. These drugs must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table 3 and should not be co-administered with study treatment (osimertinib) and for a period of two weeks after discontinuing study treatment. **The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such, investigators are recommended to search the website to provide the most up to date information**.

Drugs with a known risk of TdP

Drug name	Withdrawal period prior to study treatment start

Aclarubicin, anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine terlipressin	2 days
Cilostazol, Cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days
Azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide*, Ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, Probucol, vandetanib	4 months
Amiodarone, chloroquine	1 year

*** Estimated value as pharmacokinetics of arsenic trioxide has not been studied**

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

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

Guidance regardless of TdP risk category
Following study treatment initiation if it is considered essential for patient management to give drugs known to prolong QTc interval, **regardless of TdP risk category**, close monitoring with ECGs and electrolytes is recommended.

6.6 Contraceptive Counseling

1. Females of child-bearing potential should use reliable methods of contraception from the time of screening until 3 months after discontinuing osimertinib. Acceptable methods of contraception are described in Section 3.3.1.

7 Reporting and Documentation of Results

7.1 Antitumor Effect – Solid Tumors

Response and progression in this study will be evaluated 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.

7.2.1 Definitions

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

Evaluable for objective response
Only those patients 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 patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective PD prior to the end of Cycle 1 will also be considered evaluable.)

7.2.2 Disease Parameters

Measurable disease
Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm), 10mm caliper measurement by clinical exam (when superficial), and/or 20mm by chest X-ray (if clearly defined and surrounded by aerated lung).

All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Target lesions
All measurable lesions, up to a maximum of 5 lesions total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions will 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 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). Bone lesions may be measureable if ≥1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

Non-measurable disease (Tumor Markers)
Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan).

Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable (e.g. PSA, CA-125, CA19-9, CEA).

7.2.3 Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique will 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
CTs should be performed with cuts of 10 mm or less in slice thickness contiguously.

Cytology, Histology
The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease (SD) is mandatory to differentiate between response or SD and PD.

7.2.4 Response Criteria

Evaluation of Target Lesions

Complete Response

Disappearance of all target lesions, confirmed as permitted by observation on two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes). There can be no appearance of new lesions.

By nature of neoadjuvant study design, responses will be unconfirmed in many patients in this study, as resection will often occur less than 4 weeks after scans.

Partial Response

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

Progressive Disease

At least a 20% increase in the sum of the SLD of target lesions, taking as reference the smallest SLD recorded since the treatment started and minimum 5 mm increase over the nadir, or the appearance of one or more new lesions.

Stable Disease

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest SLD since the treatment started.

Evaluation of Non-Target Lesions

Complete Response

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Incomplete Response/Stable Disease

Persistence of one or more non-target lesion(s).

Progressive Disease

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response

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

Table 7.1 Response Criteria

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	>4 weeks confirmation**
CR	Non-CR/ Non-PD	No	PR	>4 weeks confirmation**
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once >4 weeks from baseline
PD	Any	Yes or No	PD	
Any	PD*	Yes or No	PD	No prior SD, PR or CR
Any	Any	Yes	PD	

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD
**Due to neoadjuvant nature of this study, radiographic responses will often be unconfirmed due to surgical resection prior to repeat scans

Disease-Free Survival

DFS is defined as the duration of time from surgical resection to time of disease recurrence.

7.2 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v4.03 for reporting of non-hematologic AEs and modified criteria for hematologic AEs.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An AE (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an AE (can be any unfavorable and unintended sign (e.g., an abnormal laboratory

finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

AEs based on signs and symptoms

All AEs spontaneously reported by the participant or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to the recording 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.

AEs based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, QTc, LVEF, and DLCO should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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., anemia versus low Hgb 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 PD, 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.

7.3.2 Adverse reaction

An adverse reaction is defined as any AE caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.2.1 Suspected

A suspected adverse reaction is defined as any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.2.2 Unexpected

An AE or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated

from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

AEs that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some AEs are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

7.3.3 Serious

An AE or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined earlier in this section. 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 above. 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 above.

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

7.3.4 Life threatening

An AE or suspected adverse reaction is considered *life threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.3.5 Overdose

A maximum tolerated dose has not been established for osimertinib. An overdose is any dose which exceeds the daily dose that is defined in the clinical study protocol.

There is no specific treatment in the event of osimertinib overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

For overdoses associated with a SAE, the standard agreed reporting timelines apply.

7.3.6 Maternal and Paternal Exposures

Maternal Exposure

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

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

If any pregnancy occurs in the course of the study and within 6 weeks of the last dose of osimertinib, then the Investigator or other site personnel informs the appropriate sponsor representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The same timelines apply when outcome information is available.

Paternal Exposure

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

To capture information about a pregnancy from the partner of a male participant, the male participant's partner's consent must be obtained to collect information related to the pregnancy and outcome; the male participant should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 6 months after dosing ends should be followed up and documented.

7.3.7 Disease progression

PD can be considered as a worsening of a participant's condition attributable to the disease for which the IP 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 PD and not an AE. Events, which are unequivocally due to PD, should not be reported as an AE during the study.

7.3.8 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 PD.

7.3.9 Lack of efficacy

When there is progression or deterioration related to NSCLC, 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.

7.3.10 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 that is clearly the result of PD 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 7.2.2.3 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 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 the study sponsors within the usual timeframes.

7.4 Recording of an Adverse Event

All grade 3 and above AEs will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v4.03.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as AEs will be graded and recorded by the Investigator according to the CTCAE. When specific AEs are not listed in the CTCAE, they will be graded by the Investigator as none, mild, moderate or severe according to the following grades and definitions:

Grade 0:	No AE (or within normal limits)
Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2:	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4;	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

7.5 Follow-up of Adverse Events

All AEs will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable AEs will be followed until resolution or stabilization of the AE. For AEs that do not require permanent discontinuation after stopping administration of the study drug, a re-challenge of the participant may be conducted if considered both safe and ethical by the investigator.

7.6 Adverse Events Monitoring

All AEs, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all AEs and determine reportability requirements to the UCSF DSMC and UCSF's IRB; and, when the study is conducted under an Investigational New Drug (IND) Application, to the FDA if it meets the FDA reporting criteria.

All AEs entered into OnCore® will be reviewed by the HDFCCC Site Committee on a monthly basis. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the AE to the administration of the study drug(s).

In addition, all AEs and suspected adverse reactions considered "serious" that are entered into OnCore® will be reviewed and monitored by the DSMC on an ongoing basis. They will be discussed at DSMC meetings, which take place every six (6) weeks.

For a detailed description of the Data and Safety Monitoring Plan (DSMP) for a Multicenter Phase 2 or 3 Institutional Study at the HDFCCC, please refer to Appendix 3 DSMP* for Phase II/III Multicenter Institutional Studies.

7.7 Expedited Reporting

Reporting to the DSMC

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF IRB

The PI must report events meeting the UCSF IRB definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Expedited Reporting to the FDA

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report via an IND safety report any suspected adverse reaction that is SUSAR (Suspected unexpected serious adverse reaction). The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 7.2.2.1)
- Unexpected (as defined in 7.2.2.2)
- Serious (as defined in 7.3.3.3)

If the AE does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Reporting to Pharmaceutical Companies providing Study Drug

AstraZeneca/MedImmune retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

All SAEs will be reported, whether or not considered causally related to the IP or to the study procedure(s). The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The following variables will be collected for AEs, for reporting to AstraZeneca

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE Grade
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no), comparator/combination drug (yes/no)
- Action taken with regard to IP/comparator/combination agent
- AE caused participant's withdrawal from study *(*yes or no*)*
- Outcome

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- 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 Drugs
- Description of AE

The investigator and/or sponsor must inform the FDA, via a MedWatch form, of any serious or unexpected AEs that occur and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch report must be emailed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor 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.

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

SAEs that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the Medical Dictionary for Regulatory Activities (MedDRA) coding language for SAEs. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

*A ***cover page*** should accompany the ***MedWatch*** 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 PD***, as determined by the PI.

Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox: [redacted]. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the IP. 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 AEs 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, participants 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.

8 Statistical Considerations and Evaluation of Results

Table 8.1 Study Endpoints

	Objective	Endpoint
Primary	To evaluate the efficacy of osimertinib as neoadjuvant therapy in patients with surgically resectable EGFR-mutant NSCLC.	To determine the MPR rate, defined as ≤ 10% viable tumor present histologically in the resected tumor specimen.
Secondary	To evaluate the safety and tolerability of osimertinib given as neoadjuvant therapy in early stage EGFR-mutant NSCLC patients. To evaluate secondary measures of clinical efficacy in early stage EGFR-mutant NSCLC patients treated with osimertinib induction therapy.	• Radiographic decrease in maximum tumor diameter • 5-year DFS • 5-year OS • DpR • Complete pathological response rate • Treatment-emergent AEs, laboratory abnormalities and ECG abnormalities as determined by NCI-CTC version 4.0 by investigator. • Rate of inability to undergo surgical resection due to treatment-related AE. • Rate of surgical complications occurring prior to end of treatment visit.
Exploratory	To evaluate long-term measures of efficacy in patients treated with osimertinib neoadjuvant therapy. To explore tissue and cell-free biomarkers that may be predictive of response or primary resistance to osimertinib neoadjuvant therapy.	• Evaluate rates of adverse pathologic features on resection specimens. • Evaluate genomic and transcriptional changes on baseline and resected tumor specimens. • Evaluate changes in immune cell infiltration on baseline and resected tumor specimens. Changes in ctDNA.

8.1 Sample Size and Accrual Rate Considerations

8.1.1 Sample Size and Power Estimate

27 evaluable patients will provide 87% power to detect a MPR rate of 50% as compared to a null rate of 22%, at the 5% significance level.

8.1.2 Replacement Policy

All patients who receive a dose of osimertinib will be analyzed for safety and efficacy. Participants who discontinue from study participation prior to surgical resection may be replaced after discussion with the PI. Patients removed from study for unacceptable treatment related AE(s) will be followed until resolution or stabilization of all treatment related AEs to grade 2 or lower; however, they will not be replaced.

8.1.3 Accrual estimates

This is a multi-institution study (UCSF and participating sites). Thoracic oncology sees approximately 300 new early stage lung adenocarcinoma patients per year with ~ 25% of these patients harboring EGFR-activating mutations We predict that ~ 25 patients per year will be eligible for this study. UCSF and participating sites currently have no competing trials for this

patient population. We expect to fully accrue this study within 36 months of opening for patient enrollment.

8.2 Interim Analyses and Stopping Rules

An interim safety analysis will be performed following enrollment of 9 patients (33% of planned study population). A 97% disease control rate has been previously reported to osimertinib in the first-line setting in advanced EGFR-mutated NSCLC.[35] Even in the setting of standard of care resection, there is a high rate of pathologic upstaging relative to initial clinical staging. For example, among patients enrolled in CALGB9761 with clinical stage I NSCLC and PET scans negative for additional disease, 38.3% were subsequently upstaged on pathology.[52]

We would therefore consider conversion to unresectable status in two or more patients to reach threshold for early study discontinuation. In patients with evidence of clinical benefit (SD or PR) to osimertinib therapy on preoperative imaging, pathologic upstaging will not be considered an indication for study discontinuation unless it occurs at a rate greater than previously reported to standard of care (i.e., in 4 or more patients), as overall presence of disease response on imaging renders isolated occult lymph node progression unlikely.

Safety of the study will be continuously assessed by the PI and the DSMC. The study may be stopped early if there is deemed to be an unacceptable safety risk by either the PI or the DSMC.

8.3 Analyses Plans

8.3.1 Analysis Population

All patients who receive a dose of osimertinib will be analyzed for safety and efficacy. Participants who discontinue from study participation prior to surgical resection may be replaced after discussion with the Study PI.

Demographic and baseline characteristics will be summarized. In general, frequency distribution and percentage will be used to summarize categorical measurements, while mean with standard deviation and median with interquartile range will be used to describe symmetric and skewed continuous measurements, respectively. Univariate analysis among variables will be assessed using the two-sample t-test, Wilcoxon-rank-sum test, or Chi-square test, as appropriate.

8.3.2 Primary Analysis (or Analysis of Primary Endpoints)

MPR rate (primary endpoint) will be determined in patients who receive at least one dose of study drug.

Patients who receive one dose of study drug and become ineligible for surgery either because of disease progression or adverse event will be deemed not to have achieved MPR.

In patients who undergo surgical resection or their lung tumor resection specimens will be processed at the local institution following CAP and CLIA guidelines. Immediate sampling of the tumor and overnight fixation in 10% buffered formalin for paraffin embedding, usually within 20-24 hours after fixation. For histopathological evaluation, at least one sample per every 1-cm of diameter will be submitted for FFPE processing and pathology analysis. The local institutional study pathologist will assess each case for MPR, using percentage of viable tumor cells (cutoff as + MPR is ≤ 10% of viable tumor cells) as has been reported [24]. The pathological response should be reported as average percentage of viable tumor cells by slide examined.

Pathology slides (H&E and IHC and special stains) will be forwarded to the designated central pathologists for the study and MPR will be determined as described above.

In order to more fully evaluate the specimens associated with this trial, the central review pathologists will score the material using criteria as follows:

Pathological CR: Residual viable tumor: 0% MPR: Residual viable tumor: ≤ 10%

Pathological response (not meeting major response criteria) 11-49% residual viable tumor. No pathological response: 50% or greater residual viable tumor.

Predominant reaction type: Necrosis, Fibrosis

Tumors that exhibit ≤ 10% **viable tumor will meet the criteria for an MPR as has been previously described [24].** The MPR rate will be reported with 95% confidence intervals.

As needed, a sub-set of tissues will be independently evaluated by both pathologists for assessment of inter-pathologist reproducibility for this scoring.

Whenever possible, the following will be included:

- Concurrent submission of pre-treatment biopsy or FNA sample. This can help inform pathologic evaluation in that pre-treatment necrosis can be assessed, within the context of potential sampling bias.
- Whenever feasible, all post-treatment surgical tumor samples will be submitted for pathologic examination (full lesion block-in), after tissue procurements have been completed.
- Samples will be identified, accrued and sent for central review in groups of no less than 10 cases to minimize criteria drift. If fewer than 10 cases are sent in any individual batch, the cases will be held until a minimum of 10 cases are available for review.

8.3.3 Secondary Analysis (or Analysis of Secondary Endpoints)

5-Year DFS: DFS will be calculated as 1+ the number of days from date of surgical resection to documented radiographic relapse/progression or death due to any cause over a period of 60 months. The Kaplan-Meier analysis will be used to calculate the median DFS with 95% confidence interval. 5-year DFS rate will be calculated as the percentage of patients who are disease free at 5 years. This will be calculated using the Kaplan-Meier method.

Assuming alpha of 0.05 and a set sample size of 27, as well as a null hypothesis of 50% 5-year DFS [53], we will have a power of 80% to detect a 25% increase in 5-year DFS.

Objective Response Rate: The objective response rate is defined as the best overall response recorded from the start of the treatment until time of surgery. The frequency and percentages of patients with a best ORR of CR, PR, SD, or PD will be determined. The objective response rate will be reported with 95% confidence intervals.

Pathologic Complete Response Rate (pCR): The pCR is defined as absence of (0%) viable tumor present histologically in the resected tumor specimen. Scoring for pathologic response is described above.

5-Year Overall survival (OS) rate: 5-year OS rate will be calculated using the Kaplan-Meier method . OS will be defined as the 1+ the number of days from surgical resection to death due to any cause over a period of 60 months. The Kaplan-Meier analysis will be used to calculate the median OS with 95% confidence interval.

Depth of Response (DpR): DpR will be defined as the percentage change in tumor burden by RECIST criteria at best response versus baseline imaging. DpR will be summarized using descriptive statistics and correlated with patient outcomes using hazard ratios via the Cox proportional hazards model.

Safety and Tolerability: AE terms recorded on the CRFs will be mapped to preferred terms using the MedDRA. Seriousness, severity grade and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the NCI CTCAE v4.03. Listings of AEs will be provided. Rate of conversion from operable to non-operative will be recorded as rate of patients initially assessed as surgically resectable, who are subsequently unable to undergo surgical resection due to either treatment-related AEs or PD. Rate of surgical complications occurring prior to the end of treatment visit will be recorded.

8.3.4 Other Analyses/Assessments

Exploratory Analysis:

- We will record rates of adverse pathologic features including rates of positive margins, LVI, and pathologic upstaging (e.g., by T or N status) as compared to clinical staging based on pre-operative scans, for comparison to historical controls.
- We will perform RNA sequencing and whole exome sequencing analysis on isolated cancer cell populations from pre-treatment tumor biopsy specimens, as well as tumor tissue acquired at the time of surgical resection (post-osimertinib). Gene Set Enrichment Analysis will be performed to identify osimertinib-induced changes in common cancer related pathways, including: RAS-RAF-MAPK, PI3K-AKT, WNT- β catenin, JAK-STAT, HGF-MET, and IGF-1R, as well as emerging pathways of resistance (i.e. NF-kB and Hippo-YAP) [1, 46, 47]. We will determine whether there is a statistically significant increase in oncogenic/survival pathway related gene expression signatures in the post-osimertinib compared to the pre-treatment sample using established methods [48]. We will compare MPR rates in tumors that exhibit specific oncogenic/survival pathway activation post-osimertinib treatment compared to tumors that do not. IHC analysis will be performed on pre-treatment and post-surgical specimens to confirm pathway activation identified by transcriptional analysis (i.e. phosphorylated-ERK (indicative of MAPK signaling), phosphorylated-AKT (indicative of PI3K signaling) or nuclear NF-kB (RELA), or - β -catenin expression). Samples will be scored in a continuous manner and difference among time points will be determined by a two-tailed T-test.
- We will assess for shifts in the cellular make-up of the tumor microenvironment induced by osimertinib treatment by performing single cell dissociation and fluorescence associated cell sorting (FACS) on fresh pre-treatment tumor biopsies and post-osimertinib tumor resection specimens. Using FACS gating strategies established and validated by the Krummel lab at UCSF [49], we will isolate CD45+ immune cells and determine how osimertinib treatment alters the proportions of cells that make up the lymphoid (CD4+ and CD8+ T cells, Tregs, NK cells, B cells) and myeloid (macrophages, neutrophils, mast cells, dendritic cells) compartments. We will then use RNA-Seq to assess the transcriptional profiles of populations of TAMs, CD4+ and CD8+ T Cells **(Fig. 5)**. We hypothesize that osimertinib treatment will induce a pro-tumor immune microenvironment that allows for tumor cell persistence. Specifically, we will assess the polarization of TAMs by assessing the mRNA expression profiles of genes classically associated with TH1-skewed (i.e. *TNF-α, IL-6, IL-12p40, and IL-1β, and Nos2*) and TH2-skewed polarization (i.e. *ARG1*, *TGFB*, *CD163*, *CD206*), many of which are targets of NF-kB transcriptional activation[50]. We will also investigate whether osimertinib affects

T-cell phenotypes. CD4+ T cells will be assessed for the expression of genes indicative of TREG, TH1, TH2, or TH17 activity (i.e. *GATA3, T-bet, FOXP3, IFNγ, IL-4, IL-13, IL-10*, and *IL-17a*)[50], and CD8+ T cells will be assessed for expression of cytotoxic effector molecules (*IFN*□, *GRZA, GRZB, and PRF1)[50]*. Finally, tumor cells and infiltrating immune cells will be assessed for shifts in PD-1 and PD-L1 expression (by RNA-Seq and IHC), a phenomenon that has been linked to NF-kB activity[41], and which may indicate changes in anti-tumor immunity induced by osimertinib. Comparisons will be made to PBMCs when possible. Assessment of TIL and TAM infiltration into the tumor microenvironment, and of TAM polarization will be confirmed by IHC analysis for relevant macrophage attributes including CD68, CD163, CD206, iNOS, HLA-DR, as well as for CD4, CD8, and PD-L1, as well as for cancer-associated fibroblasts. Comparisons will be made to PBMCs when possible. Samples will be scored in a continuous manner and difference among time points will be determined by a two-tailed T-test.

- We will assess peripheral blood samples for ctDNA analysis. Descriptive statistics and graphical methods will be used to analyze the data.

8.4 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.03.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the IRB for the protocol, written informed consent form, participant recruitment materials, and any other written information to be provided to participants before any protocol related procedures are performed on any participants.

The clinical investigation will not begin until either FDA has determined that the study under the IND Application is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP- International Conference on Harmonization (ICH) guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 IRB Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB. Prior to obtaining IRB approval, the protocol must be approved by the HDFCCC Site Committee and by the PRC. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation.

The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5 Handling and Documentation of Clinical Supplies

The UCSF PI and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor- investigator will maintain written records of any disposition of the study drug.

The PI shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the PI will not allow the investigational drug to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms

The PI and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific CRFs will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The PI will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

Each participating site will complete study specific CRFs for safety monitoring and data analysis. Each site will enter the study data into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The participating site's CRC will complete the CRFs; the Investigator will review and approve the completed CRFs – this process must be completed within 3 business days of the visit. Study data from the participating site will be reported and reviewed in aggregate with data from patients enrolled at the coordinating center, UCSF. All source documentation and CTMS data will be available for review/monitoring as needed.

9.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Semiannual auditing (depending on trial accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

For more information regarding the Data Safety and Monitoring Plan, see Appendix 3.

9.8 Multicenter Communication

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

- Enrollment information.
- Adverse events (i.e., new adverse events and updates on unresolved adverse events and new safety information).
- Protocol Violations.
- Other issues affecting the conduct of the study.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The data (i.e., copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the remote monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and applicable FDA regulations.

9.9 Record Keeping and Record Retention

The PI is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by participants, as well as written records of the disposition of the drug when the study ends.

The PI is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the CRFs and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, 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.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed, or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

9.10 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

9.11 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF IRB. Prior to implementing this protocol at the participating sites, approval for the UCSF IRB approved protocol must be obtained from the participating site’s IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form, and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB’s Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional

- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals.

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment. For more information on participating site required documents, see Appendix 5.

10 Protection of Human Subjects

10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all participants involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the participant's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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Appendix 1 Schedule of Study Procedures and Assessments

Period/Procedure	**Pre-screening[1]**	**Screening**	**Cycle 1**			**Cycle 2[4]**			**Day of Surgery**	**D15 Post-op Lab Draw**	**End of Treatment**	**Long Term Follow Up**
Study Day/Visit Day[1]	**Within 60 days of D1**	**-30 to 0**	**1**	**15**	**28[3]**	**1**	**15**	**28**		**15D post-op**	**30D after D15 post-op**	**Every 3/6 mo after EOT**
Informed consent		X										
EGFR mutation testing (if status unknown)	X	X[5]										
Baseline conditions [2]		X										
Contraceptive counseling		X										
AE assessment			X	X	X	X	X	X			X[12]	
Concomitant medications		X	X	X	X	X	X	X			X	
Tumor tissue for correlative studies[5]		X			X[13]			X[13]	X			
Survival status and other therapies												X[17]
Treatment/Drug Administration												
Osimertinib Dispensing			X		X[14]	X		X				
Clinical procedures												
Physical exam		X	X	X	X	X	X	X			X	
Vital signs		X	X	X	X	X	X	X			X	
Medical history		X	X	X	X	X	X	X			X	
Disease assessment		X			X	X		X				
Performance status		X	X	X	X	X	X	X			X	
Biopsy or archived tissue procurement		X[5]			X[13]			X[13]				
Laboratory procedures												
CBC w/ Diff[6]		X	X	X	X	X	X	X	X		X	
Blood Chemistry[7]		X	X	X	X	X	X	X	X		X	
Coagulation[8]		X	X	X	X	X	X	X	X		X	
Urinalysis		X	X		X[19]	X					X	
Pregnancy test (HCG)[9]		X	X		X[19]	X					X	
Blood for ctDNA and PBMCs		X	X	X	X	X		X	X	X	X	
Imaging procedures												
Imaging (CT) C/A/P		X[10]			X	X		X				X[18]

Period/Procedure	**Pre-screening[1]**	**Screening**	**Cycle 1**			**Cycle 2[4]**			**Day of Surgery**	**D15 Post-op Lab Draw**	**End of Treatment**	**Long Term Follow Up**
Study Day/Visit Day[1]	**Within 60 days of D1**	**-30 to 0**	**1**	**15**	**28[3]**	**1**	**15**	**28**		**15D post-op**	**30D after D15 post-op**	**Every 3/6 mo after EOT**
PET-CT	X[16]											
MRI Brain	X[16]											
ECG/EKG		X	X	X		X		X	X		X	
MUGA or TTE		X			X[15]	X[15]		X				

[1] Window for each study visit is +/- 3 days. Screening procedures allowed within 30 days prior to day 1.
[2] Baseline conditions assessment per DSMC policy (Baseline Conditions VI Form)
[3] C1D28 visit only for patients not receiving second cycle of osimertinib
[4] Optional second cycle as per investigator discretion. Those receiving second cycle osimertinib do not attend the C1D28 visit
[5] Screening biopsy within 30 days prior to C1D1. Tissue from screening biopsy and surgical resection will be used for correlative studies (see Section 1.4). If there is not enough tissue for pre-screening EGFR mutation testing, tissue from this biopsy will also be collected for EGFR mutation testing. This biopsy can be deferred if the procedure is deemed to represent an unacceptable safety risk to the patient by the principal investigator.
[6] Including CBC with differential and platelet count
[7] Including ALP, ALT/AST total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting or non-fasting glucose, potassium, sodium, chloride, bicarbonate. Magnesium required at screening only.
[8] Including PT/PTT/INR
[9] In women of child-bearing potential. At screening to be done within 3 days of C1D1.
[10] Imaging within 28 days prior to C1D1. If CT contraindicated, MRI acceptable
[11] If not be receiving second cycle of osimertinib
[12] Including documentation of AEs leading to inability to proceed with surgical resection and of surgical complications
[13]Optional research biopsy for patients who will be unable to undergo surgical resection, within 30 days of C1D28 or C2D28
[14]Dispensing of up to 14 days' supply osimertinib for treatment until pre-surgical washout period if will be proceeding to resection after first cycle of osimertinib.
[15] TTE is only required if the patient is proceeding to surgical resection following first cycle of osimertinib therapy. For patients receiving the second of cycle of osimertinib, TTE is optional except for patients with pre-existing risk factors as clinically indicated. .
[16]PET-CT and brain MRI (standard of care procedures) must be done within 60 days of C1D1 as part of inclusion criteria (see Section 3.3.1)
[17] During the first year after the EOT visit, assessment of survival status and subsequent care for NSCLC will occur every 3 months. From the first year following EOT visit up to the 5 years post-surgery, assessment of survival status and subsequent therapies will occur every 6 months via telephone or routine clinic visits.
[18] LTFU imaging will be performed every 6 months as standard of care. LTFU may be performed with greater frequency per the investigator's discretion or local institutional requirements
[19] Urinalysis and pregnancy test are optional at C1D28 or as clinically indicated.

Appendix 2 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory 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)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed <50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed >50% of the time Capable of only limited self- care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 3 Data and Safety Monitoring Plan for a Multicenter Study Phase II or III Trial

Data and Safety Monitoring Plan for a Multicenter Study Phase II or III Trial

Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Semiannual auditing (depending on accrual).
- Review of serious adverse events.
- Minimum of a biennial regulatory auditing visit.

Monitoring and Reporting Guidelines

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the trial and for auditing its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and participant safety at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

All institutional Phase II or III therapeutic trials are designated with a moderate risk assessment. The data is audited by a DSMC Monitor/Auditor on a semiannual basis with a random selection of twenty percent of the participants (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in the participants selected for review or until the selected participants discontinue study participation or the trial is closed with the IRB. Additionally, the assigned DSMC Monitor/Auditor will review no more than 10 total participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

The participating site's source documents are audited remotely via either review of redacted source documents downloaded by the site into the CRA console of OnCore and/or via access to the site's electronic medical records. The DSMC Monitor/Auditor will audit no more than three participant charts at each participating site during the course of auditing this trial.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

Multicenter communication

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

- Enrollment information.
- Adverse events (i.e., new adverse events and updates on unresolved adverse events and new safety information).
- Protocol Violations.
- Other issues affecting the conduct of the study.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The data (i.e., copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the remote monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and applicable FDA regulations.

Review and Oversight Requirements

Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), regardless of being unexpected or considered to be associated with the use of the study drug will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to the investigational agent(s) or study procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center Site Committee meetings. All grade 3-5 adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event

or during the next scheduled monthly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment from the UCSF Coordinating Center and the participating sites.

Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All Serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within one business days of becoming aware of the event. The SAEs are reviewed and audited by the UCSF Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or Vice Chair and the DSMC Director within 1 business day of this notification.

Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC Chair (or Vice Chair) and the DSMC Director at the time the increased rate is identified via a report. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified within their reporting guidelines.

Data and Safety Monitoring Committee Contacts:

Katie Kelley, MD (DSMC Chair)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158

John McAdams (DSMC Director)
[redacted]
UCSF HDFCCC
San Francisco, CA 94143

Appendix 4 UCSF Policy/Procedure for Required Regulatory Documents for UCSF Multicenter Investigator-Initiated Oncology Clinical Trials with an Investigator held IND

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the HDFCCC where the PI holds the IND.

Background

The ICH-GCP Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iRIS:

- IRB approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- IRB approval letters and ICF(s)
- Current and prior versions of the Investigator Brochure (IB).
- SAE Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to IRB with supporting fax documentation

Documents Filed in OnCore®:

- Package Insert (if the study drug is commercial) or Investigator Brochure
- PRC-approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- DSMC monitoring reports
- OnCore® CRF completion manual

Documents Filed in Regulatory Binder:

- Completed FDA 1572 document with PI's signature
- For all PIs and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency Licenses, and Staff Training Documents (i.e., Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- SAE reports to IRB and sponsor.
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form

- Drug Destruction SOP
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

2. Additional Essential Documents for Multicenter Trials for the Coordinating Center (filed in Regulatory Binder or OnCore)

- IRB approval letters, IRB roster, ICF, and HIPAA Consent Form for the Participating Site(s)
- For all PIs and Sub-Investigators listed on the 1572 at the Participating Site(s) – Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. CITI, etc.) (for IND Application)
- SIV minutes and correspondence with Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s)
- Protocol Violations and SPE reports to IRB with supporting fax documentation for Participating Site(s)
- Drug Destruction SOP for the Participating Site(s)
- DSMC monitoring reports for the Participating Site(s)
- For all laboratories listed on FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges for the Participating Site(s)
- Copy of the DSMP Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study)
- SAE forms submitted to both the IRB and the sponsor for the Participating Site(s)

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Appendix 5 Required Regulatory Documents for Sub-sites Participating in a UCSF Investigator Initiated Multicenter Trial (Checklist)

Directions:

1) Fax the documents listed below to the UCSF Coordinating center at 415-514-6995 *or*

2) Scan the documents and upload to OnCore® and create a Note to File for the on-site Regulatory binder to indicate where these documents may be found

1572

PI and Sub investigators:

CV and Medical license
Financial disclosure form
NIH or CITI human subject protection training certification

Laboratories

CLIA and CAP
CV of Lab Director and Lab Licenses
Laboratory reference ranges

Local IRB

IRB Approval letter

Reviewed/Approved documents

- Protocol version date: _____
- Informed consent version date: _____
- Investigator Brochure version date: _____
- HIPAA

Current IRB Roster

Other

Delegation of Authority Log

- Include NIH or CITI human subject protection training certificates or GCP training certification

Pharmacy

- Drug destruction SOP and Policy

Protocol signature page

Executed sub contract

Appendix 6 Prohibited Medications

Drug	Trade name (if applicable)
Aclarubicin	
Aliskiren	
Amiodarone	
Anagrelide	
Arsenic trioxide	
Astemizole	
Azithromycin bepridil	
Carbamazepine	
Chloroquine	
Chlorpromazine	
Cilostazol	
Ciprofloxacin	
Cisapride	
Citalopram	
Clarithromycin	
Cocaine	
Dabigatran	
Daunorubicin	
Digoxin	
Disopyramide	Norpace
Dofetilide	Tikosyn
Domperidone	
Dronedarone	
Donepezil	
Droperidol	
Doxorubicin	
Erythromycin	
Escitalopram	
Flecainide	
Fluconazole	
Flecainide	
Gatifloxacin	

Grepafloxacin	
Halofantrine	
Haloperidol	
Ibogaine	
Ibutilide	Corvert
Levofloxacin	
Levomepromazine	
Levomethadyl	Orlaam
Levosulpiride	
Mesoridazine	
Methadone	
Moxifloxacin	
Ondansetron	
Oxaliplatin	
Papaverine hydrochloride	
Pentamidine	
Phenobarbital	
Phenobarbitone	
Phenytoin	Dilantin
Pimozide	
Probucol	
Procainamide	
Propofol	
Quinidine	
Rifabutin	
Rifampicin	
Rifapentin	
Rosuvastatin	
Roxithromycin	
Sevoflurane	
Sotalol	
Sparfloxacin	
St John’s Wort	
Sulfasalazine	
Sulpiride	
Sultopride	
Terfenadine	

Terlipressin	
Terodiline	
Thioridazine	Mellaril
Topotecan	
Vandetanib	

Appendix 7 Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

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. Specific guidance on the managing of liver abnormalities can be found in Section 5.3.1 of the protocol.

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets 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.

Definitions

Potential Hy's Law (PHL)
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** total bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, 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.

Identification of Potential Hy's Law Cases
In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

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

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

Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met
If the patient does not meet PHL criteria, the Investigator will:

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

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

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.

Complete the three Liver CRF Modules as information becomes available

If at any time the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

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, Investigator reviews available data and agrees on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP.

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

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.

If No: follow the process described in 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 above in 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.