SUMMARY OF CHANGES – Protocol

For Protocol Amendment #10 to: A Phase II trial of Osimertinib (AZD9291) (osimertinib) with or without bevacizumab in patients with EGFR mutation positive NSCLC and brain metastases

Protocol Version Date: 03/27/2023

NCI Protocol #: 10042

Local Protocol #: 2000021123

I. Comments Requiring a Response – Major Issues (CTEP Amendment Review Letter dated March 22, 2023):

#	Section	Comments
1.	Overall 8.1.1 Appendix C	Pharmaceutical comments from the last amendment review have not been addressed in this amendment. The PMB-supplied investigational label AZD9291 (osimertinib) has transitioned to PMB-supplied commercial label osimertinib (AZD9291). The following comments must be addressed: • Update the primary agent name to the generic name osimertinib. The code name AZD9291 can be retained as a secondary name, such as "osimertinib (AZD9291)". • Replace the entire pharmaceutical section with the updated CTEP/PMB drug monograph (attached file: Osimertinib (AZD9291) - 781254 – 1120) for consistency with the FDA approved package insert. Remove the current version of Patient Drug Information Appendix and replace with the updated CTEP template for marketed agents ***TEMPLATE B:*** **PATIENT CLINICAL TRIAL WALLET CARD** (attached file: APPENDIX DDI HANDOUT AND WALLET CARD). **PI Response: The changes have been made as requested.**

II. CTEP Request for Rapid Amendment (RRA) dated February 28, 2023:

#	Section	Change

1.	7.1.1	Updated AZD9291 CAEPR to Version 2.8, February 9, 2023 as per RRA instructions
		• Added New Risk:
		  • Rare: Blood and lymphatic system disorders - Other (aplastic anemia)
		  • Also Reported on Osimertinib Trials But With Insufficient Evidence for Attribution: Eye disorders - Other (corneal epithelium defect); Eye disorders - Other (corneal erosion);

		Eye disorders - Other (eyelids pruritus); Infections and infestations - Other (pustule); Skin and subcutaneous tissue disorders - Other (onychalgia); Skin and subcutaneous tissue disorders - Other (onychomalacia); Urticaria
		
		• Increase in Risk Attribution:
		  • Changed to Less Likely from Also Reported on Osimertinib Trials But With Insufficient Evidence for Attribution: Constipation; Cough; Fatigue
		
		• Decrease in Risk Attribution:
		  • Changed to Less Likely from Likely: Diarrhea; Dry skin; Mucositis oral; Rash maculo-papular
		  • Changed to Also Reported on Osimertinib Trials But With Insufficient Evidence from Less Likely: Creatinine increased; Epistaxis; Skin and subcutaneous tissue disorders - Other (skin fissures)
		  • Changed to Also Reported on Osimertinib Trials But With Insufficient Evidence from Rare: Ejection fraction decreased

II. Additional Changes by Principal Investigator:

#	Section	Change
1.	All	Updated Version Date in Header
2.	Title Page	Updated Protocol Type / Version # / Version Date

NCI Protocol #: 10042

Local Protocol #: 2000021123

ClinicalTrials.gov Identifier: NCT02971501

TITLE: A Phase II trial of Osimertinib (AZD9291) with or without bevacizumab in patients with EGFR mutation positive NSCLC and brain metastases

Corresponding Organization: LAO-CT018 / Yale University Cancer Center LAO

Principal Investigator: Sarah Goldberg, MD, MPH
Yale Cancer Center
333 Cedar Street, FMP-130
New Haven, CT 06520
Phone: [redacted]
E-mail: [redacted]

Participating Organizations

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
EDDOP / Early Drug Development Opportunity Program

Statistician:
[redacted]
Center for Quantitative Sciences
571 Preston Building
Nashville, TN, 37232-6848
Telephone: [redacted]
Fax: [redacted]
Email: [redacted]

Study Coordinator:
[redacted]
Thoracic Oncology
Yale Cancer Center
300 George Street, Suite 120
New Haven, CT 06511
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

NCI-Supplied Agents: Osimertinib (AZD-9291) NSC# 781254; Bevacizumab NSC# 704865

Other Agent(s): None

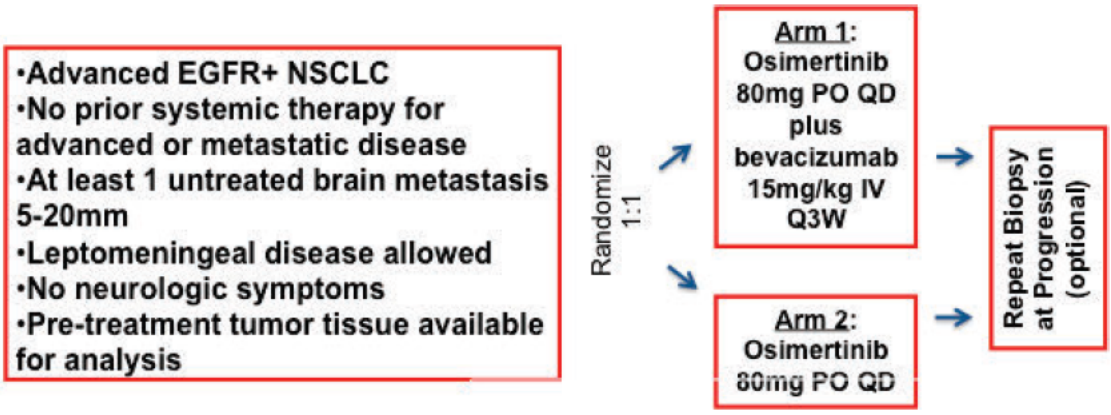
IND #: [redacted]

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

Revision / Version #2 / January 17, 2017
Revision /Version #3 /April 10, 2017
Revision / Version #4 / April 27, 2017
Revision / Version #5 / May 24, 2017
Amendment (1) / Version #6 / August 4, 2017
Amendment (2) / Version #7 / December 6, 2017
Amendment (3) / Version #8 / March 8, 2018
Amendment (4) /Version #9 / June 13, 2018
Amendment (5) / Version #10 / September 24, 2018
Amendment (6) / Version #11 / February 13, 2019
Amendment (7)/ Version #12/ October 10, 2019
Amendment (8)/ Version #13/ June 11, 2020
Amendment (9)/ Version #14/ December 11, 2020
Amendment (10)/ Version #15/ March 27, 2023

SCHEMA



Primary Endpoint:
•Progression-free survival

Secondary Endpoints:
•Safety/Tolerability
•Overall response rate
•Brain metastasis response rate
•Time to CNS progression
•Overall survival
•Toxicity

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the progression-free survival with Osimertinib (AZD9291) plus bevacizumab compared to Osimertinib (AZD9291) alone

1.2 Secondary Objectives

1.2.1 To assess the safety and tolerability of the combination of Osimertinib (AZD9291) and bevacizumab
1.2.2 To evaluate the time to progression in the CNS with Osimertinib AZD9291 plus bevacizumab versus single-agent osimertinib (AZD9291)
1.2.3 To determine the overall response rate and the intracranial response rate to the combination versus single agent
1.2.4 To assess the overall survival in patients receiving Osimertinib (AZD9291) plus bevacizumab compared to Osimertinib (AZD9291) alone

1.3 Translational Objectives

1.3.1 To investigate mechanisms of sensitivity and resistance to combination Osimertinib (AZD9291) plus bevacizumab versus Osimertinib (AZD9291) by molecularly characterizing tumor samples including T790M status
1.3.2 To assess whether circulating tumor DNA in plasma can be used as an indicator of sensitivity and resistance to treatment
1.3.3 To determine whether an angiogenic signature using a multiplex panel array is associated with benefit from the combination of Osimertinib (AZD9291) plus bevacizumab
1.3.4 To investigate angiogenesis, immune and signaling pathway markers in tumor samples to determine biomarkers predictive of benefit from combination therapy

2 BACKGROUND

2.1 Study Disease: EGFR mutation-positive NSCLC

NSCLC is the leading cause of cancer-related death worldwide, and results in over 160,000 deaths in the United States per year.(2) In patients with advanced or metastatic disease, platinum-based chemotherapy has been the mainstay of management for the past several decades, however responses are usually transient and survival is limited for the majority of patients. More recently, identification of oncogenic drivers of NSCLC and targeted therapies that inhibit these drivers have revolutionized the way in which lung cancer is treated. Approximately 15% of all patients with NSCLC harbor a somatic mutation in the Epidermal Growth Factor Receptor (EGFR) gene.(3-5) Most of these mutations affect discrete regions of the gene within exons 18 to 21 that code for the EGFR tyrosine kinase domain. The most common mutations result in an in-frame 15-bp deletion in exon 19 and a point mutation resulting in an amino acid substitution at codon 858 (L858R) in exon 21. Several small molecule tyrosine kinase inhibitors (TKIs) have been approved by the US FDA for treatment of EGFR-mutation positive NSCLC, including the first-generation TKIs

erlotinib and gefitinib and the second-generation TKI afatinib. These drugs act as ATP analogues and compete for the tyrosine kinase catalytic site thus interfering with inhibition of receptor activation. EGFR TKIs are extremely effective in treating patients with EGFR-mutated cancers, especially compared to chemotherapy(6-8). However, resistance to these agents inevitably develops, resulting in disease progression. Osimertinib (AZD9291) has been developed as an agent to treat EGFR-mutant NSCLC after the development of resistance to first- and second-generation EGFR TKIs.

2.2 CTEP IND Agents:

2.2.1 **Osimertinib (AZD9291)**

Osimertinib (AZD9291) is a potent irreversible tyrosine kinase inhibitor of both sensitizing EGFR mutations and the resistance T790M EGFR mutation, with a significant selectivity margin over wild-type EGFR. Osimertinib (AZD9291) effectively blocks EGFR signaling in both EGFR single mutant cells with activating EGFR mutations and double mutant cells bearing both primary EGFR activating and secondary resistance T790M mutation. Osimertinib (AZD9291) is currently FDA approved for patients with advanced EGFRm+ NSCLC who have previously failed an EGFR TKI when the T790M mutation is present, and for the first-line treatment of patients with metastatic EGFRm+ NSCLC.

2.2.1.1 Clinical Studies

A phase 1, open-label, multicenter study of Osimertinib (AZD9291) administered once daily was conducted to evaluate the safety and tolerability in EGFR-TKI refractory patients (AURA, NCT01802632). Osimertinib (AZD9291) was given across 5 cohorts from 20mg daily to 240mg daily. The overall confirmed ORR was 51% (123/239; 95% Cl 45, 58) with disease control rate (DCR) [complete response (CR) + partial response (PR) + stable disease (SD)] of 84% (201/239; 95% Cl 79,88). In patients with T790M mutation identified at time of acquired resistance to EGFR TKI, ORR was 61% (78/127; 95% Cl 52, 70) and DCR was 95% (121/127; 95% Cl 90, 98). Median progression free survival (PFS) for patients with T790M+ was 9.6 months. In patients without the T790M mutation identified at time of acquired resistance, ORR was 21% (13/61; 95% Cl 12, 34) and DCR was 61% (37/61; 95% Cl 47, 73), with median PFS of 2.8 months (9).

An expansion cohort of the AURA trial enrolled 60 additional patients with EGFR TKI naïve EGFR mutant NSCLC. Thirty patients received 80mg/day and 30 patients received 160mg/day of Osimertinib (AZD9291) . Across both doses, ORR was 73% with DCR of 97% and PFS rate at one year of 75%. ORR was 63% with DCR of 93% and PFS rate at 9 months and 1 year of 83% and 73% respectively in the 80mg/day arm. ORR was 83% with DCR 100% and PFS rate at 9 months and 1 year of 78% and 'not calculated' respectively in the 160mg/day arm(10).

The FLAURA trial (11) enrolled patients with previously-untreated advanced EGFR mutant NSCLC and randomized them to Osimertinib (AZD9291) or standard EGFR TKI (gefitinib or erlotinib). This trial demonstrated a PFS of 18.9 months with Osimertinib (AZD9291) compared to 10.2 months in the standard arm ($p<0.001$), leading to FDA-approval of this agent for patients

without prior therapy for metastatic disease.

2.2.1.2 Safety Profile

Safety data from the AURA trial described above are available for 253 patients with advanced EGFR-TKI refractory NSCLC. Overall, 13% of patients had Grade 3 or higher treatment related adverse events. There was one treatment related death due to pneumonia. Grade 3 or higher rash was observed in 1% of patients and grade 3 diarrhea in 2% of patients. Grade 3 or higher drug-related adverse events were seen in 10% (2/21) of patients who were dosed at 20mg daily, 3% (2/58) at 40mg daily, 11% (10/90) at 80mg daily, 25% (16/63) at 160mg daily, and 14% (3/21) at 240mg daily. The most common adverse events that occurred in >10% of patients across all doses included diarrhea (47%), rash (40%), nausea (22%), decreased appetite (21%), dry skin (20%), pruritus (19%), fatigue (17%), paronychia (17%), constipation (15%), cough (15%), stomatitis (12%), vomiting (11), anemia (11%), dyspnea (11%), upper respiratory infections (10%), and headache (10%). Less common side effects (<10% of patients), included hyperglycemia (2%), QTC prolongation (4%) and pneumonitis-like events (2%).

Safety data is also available from the FLAURA trial (11) for patients with previously-untreated EGFR-mutant NSCLC. 34% of patients had grade 3 or greater adverse events and 22% had serious adverse events. The most common adverse events due to any cause were rash or acne (58%), diarrhea (58%), and dry skin (36%). Cardiac events of note included QTc prolongation in 10% of patients, of which only 2% were grade 3 or greater. Interstitial lung disease was observed in 4% of patients and none were fatal.

2.2.1.3 Pre-Clinical Studies

Pre-clinical data provides good evidence to support Osimertinib (AZD9291) as a potentially better treatment option for first-line advanced and early stage EGFRm+ NSCLC compared to currently approved EGFR TKIs. Unlike gefitinib, erlotinib, and afatinib, emergence of T790M does not appear to be a mechanism of preclinical resistance to Osimertinib (AZD9291) (12) and in vitro data supports a slower time to resistance in response to AZD9291 treatment than that of first and second generation EGFR TKIs. In a pre-clinical mouse model of EGFRm+ NSCLC, Osimertinib (AZD9291) achieved superior durable complete responses compared to those achieved with gefitinib.(12)

2.2.1.4 Brain Metastases

Emerging preclinical data indicate that Osimertinib (AZD9291) may have the potential to target brain metastases (a common site of relapse in NSCLC) more effectively than current EGFR TKIs(13). Brain metastases are detected in 20 to 30% of patients with advanced NSCLC upon initial diagnosis, and are associated with a poor prognosis.(14) Up to 50% of lung cancer patients will develop brain metastases at some point during the course of their disease. The first generation EGFR-TKI agents have demonstrated only limited efficacy in treating brain metastases(15, 16). Preclinical data suggest that Osimertinib (AZD9291) may be capable of crossing the blood brain barrier and may potentially offer better exposure in this anatomically protected location. The

central nervous system (CNS) is a common site of first progression for patients receiving treatment with a standard TKI, despite concomitant systemic disease control. Use of a drug which may more effectively penetrate the CNS has the potential to control prevent or delay the growth of subclinical brain metastases that were below the limits of detection at the time of diagnosis. Results from the FLAURA trial (11) suggested better CNS activity with Osimertinib (AZD9291) compared with first-generation agents, with a median PFS amongst patients with CNS metastases of 15.2 months versus 9.6 months in the standard TKI arm ($p<0.001$). Leptomeningeal disease has also been demonstrated to be controlled with Osimertinib (AZD9291) (17).

2.2.2 Bevacizumab (rhuMAb VEGF)

Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human vascular endothelial growth factor (VEGF, or VEGF-A) with high affinity (Kd=1.1 nM)(18). The antibody consists of a human IgG1 framework and the antigen-binding complementarity-determining regions from the murine anti-VEGF MAb A.4.6.1.(18-20)

2.2.2.1 Mechanism of Action

Of known proangiogenic factors, VEGF is one of the most potent and specific, and has been identified as a crucial regulator of both normal and pathological angiogenesis. VEGF is a secreted, heparin-binding protein that exists in multiple isoforms. Action of VEGF is primarily mediated through binding to the receptor tyrosine kinases, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). The biological effects of VEGF include endothelial cell mitogenesis and migration, increased vascular permeability, induction of proteinases leading to remodeling of the extracellular matrix, and suppression of dendritic cell maturation. Neutralization of VEGF by A.4.6.1 or bevacizumab has been shown to inhibit the VEGF-induced proliferation of human endothelial cells in vitro, and decrease microvessel density and interstitial pressure in tumor xenografts in vivo. In patients, preliminary results from a neoadjuvant trial in rectal cancer demonstrated a decrease in blood perfusion/permeability and interstitial fluid pressure in tumors after one dose of bevacizumab.(21)

2.2.2.2 Nonclinical Studies

The murine parent MAb of bevacizumab, A4.6.1, has demonstrated potent growth inhibition in vivo in a variety of human cancer xenograft and metastasis models, including those for SK-LMS-1 leiomyosarcoma, G55 glioblastoma multiforme, A673 rhabdomyosarcoma, Calu-6, and MCF-7 cell lines.(18, 20, 22, 23) The antitumor activity was enhanced with the combination of A4.6.1 and chemotherapeutic agents compared to either agent alone. Combined blockage of the VEGF and other growth factor pathways (e.g., epidermal growth factor receptor [EGFR] or Platelet Derived Growth Factor Receptor [PDGFR]) has also demonstrated additive effects in vivo.(24, 25) Associated with the anti-tumor activity of anti-VEGF MAbs were findings of reduced intratumoral endothelial cells and microcapillary counts as well as reduced vascular permeability and interstitial pressure

Nonclinical toxicology studies have examined the effects of bevacizumab on female reproductive function, fetal development, and wound healing. Fertility may be impaired in cynomolgus

monkeys administered bevacizumab, which led to reduced endometrial proliferation and uterine weight as well as a decrease in ovarian weight and number of corpora lutea. Bevacizumab is teratogenic in rabbits, with increased frequency of fetal resorption, and specific gross and skeletal alterations. In juvenile cynomolgus monkeys with open growth plates, bevacizumab induced physeal dysplasia which was partially reversible upon cessation of therapy. Bevacizumab also delays the rate of wound healing in rabbits, and this effect appeared to be dose-dependent and characterized by a reduction of wound tensile strength.

2.2.2.3 Clinical Studies

Pharmacokinetics and MTD: The pharmacokinetics (PK) of bevacizumab have been characterized in several phase 1 and phase 2 clinical trials, with doses ranging from 1 to 20 mg/kg administered weekly, every 2 weeks, or every 3 weeks. The estimated half-life of bevacizumab is approximately 21 days (range 11-50 days). The predicted time to reach steady state was 100 days. The volume of distribution is consistent with limited extravascular distribution.

The maximum tolerated dose (MTD) of bevacizumab has not been determined; however, the dose level of 20 mg/kg was associated with severe headaches.(26) The dose schedule of either 10 mg/kg every 2 weeks, or 15 mg/kg every 3 weeks is used in most phase 2 or 3 trials with only a few exceptions (e.g., the pivotal phase 3 trial in colorectal cancer, in which bevacizumab was given at 5 mg/kg every 2 weeks).

Clinical efficacy of bevacizumab: Clinical proof of principle for anti-VEGF therapy with bevacizumab has been observed in several solid tumors. In first- and second-line metastatic colorectal cancer (mCRC), the combination of bevacizumab with 5-FU-based chemotherapy improved the overall survival (OS), progression-free survival (PFS), and response rate (RR) as compared to chemotherapy alone.(27, 28) There was also improved overall survival in first-line NSCLC patients (E4599) treated with carboplatin/paclitaxel with bevacizumab compared with chemotherapy alone. Bevacizumab in combination with chemotherapy has been approved by the Food and Drug Administration (FDA) for treatment in mCRC (first and second lines) and in NSCLC.

In untreated advanced and metastatic breast cancer, addition of bevacizumab to paclitaxel also significantly improved the RR and PFS (E2100)(29). However, in the phase 3 trial in doxorubicin- and paclitaxel-refractory metastatic breast cancer, the addition of bevacizumab to capecitabine did not show an improvement in PFS despite an increase in the RR.(30) In locally advanced and metastatic pancreatic cancer, a Phase 3 also failed to demonstrate an overall survival (OS) or PFS advantage by adding bevacizumab to gemcitabine (CALGB-80303).(31)

Bevacizumab has been studied as monotherapy in renal cell cancer (RCC). In a three-arm, double-blind, placebo-controlled phase 2 trial,(32) patients with previously treated stage IV RCC were randomized to high-dose (HD) bevacizumab (10 mg/kg every 2 weeks), low-dose (LD) bevacizumab (3 mg/kg every 2 weeks), or placebo. The study demonstrated a highly significant prolongation of time to progression (TTP) in the HD arm (4.8 months) as compared with the placebo (2.6 months) (hazard ratio [HR]=2.55, P=0.0002); the LD arm was associated with a smaller difference in TTP (3.0 months) of borderline significance. The tumor response rate was

10% in the HD arm but 0% in the LD and placebo groups.

A Phase 3 study (BO17705) with bevacizumab (10 mg/kg every 2 weeks) plus interferon-α2a versus interferon-α2a plus placebo as first-line therapy in patients with advanced and/or metastatic RCC demonstrated statistically significant and clinically relevant improvements in PFS (10.2 vs. 5.4 months), and objective response rate (ORR) (31.4 vs. 12.8%).

The Phase 3 study BO17706 indicated no statistically significant improvement in OS when bevacizumab (5 mg/kg every 2 weeks) was added to the gemcitabine/erlotinib combination in the first-line treatment of advanced pancreatic cancer. The Phase 3 NCI-sponsored CALGB-80303 study investigating the use of bevacizumab (10 mg/kg every 2 weeks) combined with gemcitabine was prematurely terminated after the CALGB Data Safety Monitoring Board (DSMB) concluded that the futility boundary defined for the primary efficacy parameter (OS) had been crossed in a protocol-specified interim analysis (dated June 16th, 2006).

Bevacizumab has been extensively studied in patients with NSCLC. In a large Phase III randomized trial of carboplatin/paclitaxel with or without bevacizumab, the addition of bevacizumab resulted in an approximately 2 month improvement in overall survival,(33) leading to the FDA approval of this agent for use in first-line therapy for patients with non-squamous NSCLC. Bevacizumab has also been combined with EGFR inhibitors with varying degrees of success; details of these trials are in Section 2.4.

2.2.2.4 Safety Profile

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events (AEs) of any severity included asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea, dermatitis, and proteinuria. The most common grade 3-4 AEs were asthenia, pain, hypertension, diarrhea, and leukopenia.

The major bevacizumab-associated AEs identified in phase 1 to phase 3 trials include hypertension, proteinuria, arterial thromboembolic events (ATEs), hemorrhage, congestive heart failure (CHF), gastrointestinal (GI) perforations, and wound healing complications. Other serious AEs (SAEs) observed with bevacizumab therapy include reversible posterior leukoencephalopathy syndrome (RPLS) and fistula formation.

The following details a description of major AEs associated with bevacizumab therapy. In addition, a list of Comprehensive Adverse Events and Potential Risks (CAEPR) in NCI-Common Terminology Criteria for Adverse Events (CTCAE) terms is included in Section 7.1 of the protocol. Reference may also be made to the Investigators' Brochure and the FDA package insert (www.fda.gov/cder/foi/label/2004/125085lbl.pdf).

Infusion-Related Reactions: Infusion reactions with bevacizumab were uncommon (<3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

Hypertension: Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% (all grades) across trials, with a mean increase of +5.5mmHg to +8.4mmHg for systolic pressure, or +4.1mmHg to +5.4mmHg for diastolic pressure. Incidence of grade 3 (hypertension requiring initiation of or increase in hypertensive medications) ranges from 7.8 to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 0.5% of bevacizumab-treated patients.

Hypertension associated with bevacizumab can generally be controlled with routine oral drugs while bevacizumab is continued. However, incidents of hypertensive crisis with encephalopathy (including RPLS) or cardiovascular sequelae have been rarely reported. Blood pressure (BP) should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with standard medical practice.(34) Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

Proteinuria: Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from mild asymptomatic increase in urine protein (incidence of about 38%) to rare instances of grade 3 proteinuria (>3.5gm/24 hour urine) (3%) or nephrotic syndrome (1.4%). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. The risk of protenuria may be higher in patients with advanced RCC or history of hypertension. There is also evidence from dose-finding trials that the rate of proteinuria may be dose related.

Renal thrombotic microangiopathy: Thrombotic microangiopathy (TMA) has been described in biopsy samples from case reports of patients treated with bevacizumab and other anti-VEGF agents. The presentation was mostly localized to the kidney, and systemic manifestations (e.g., thrombocytopenia or schistocytosis) were present only in some of these patients. As renal biopsies were rarely performed in patients with proteinuria or renal insufficiency, the true rate of renal-localized or subclinical TMA is not assessable. Available data indicate that systemically evident TMA (i.e., with evidence of hemolysis or thrombocytopenia) is very rare. However, the use of more than one anti-VEGF agent in combination might enhance the risk. In a phase 1 dose escalation trial of concurrent bevacizumab (10 mg/kg every 2 weeks) and escalating doses of sunitinib (25 mg, 37.5 mg or 50 mg daily for 4 out of 6 weeks) in patients with RCC, 5 of the 12 patients at the highest dose level developed systemic TMA, or microangiopathic hemolytic anemia; clinical presentations in these cases included thrombocytopenia, schistocytes, hypertension, and varying degrees of proteinuria.

Hemorrhage: Overall, grade 3 and 4 events associated with bleeding or hemorrhage were observed in 4.0% of 1,132 patients treated with bevacizumab in a pooled database from eight phase 1, 2, and 3 clinical trials in multiple tumor types. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage.

Tumor-associated hemorrhage - Major or massive pulmonary hemorrhage/hemoptysis has been observed primarily in patients with NSCLC. In a phase 2 study in NSCLC, 6 cases of life-threatening (4 fatal) hemoptysis were reported among 66 patients treated with bevacizumab and chemotherapy(35); squamous cell histology was identified as the risk factor. In the phase 3 trial in non-squamous NSCLC (E4599), the rate of Grade ≥3 broncho-pulmonary hemorrhage was <1% in the control arm (carboplatin/paclitaxel) versus 2.3% in the chemotherapy plus bevacizumab arm

(10/427 patients, including 7 deaths). Of patients experiencing pulmonary hemorrhages requiring medical intervention, many had cavitation and/or necrosis of the tumor, either pre-existing or developing during bevacizumab therapy. Patients developing lung cavitation on treatment should be assessed by the treating physician for risk-benefit.

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages. In the pivotal phase 3 trial in advanced CRC, the rate of GI (duodenal, ileal, cecal and colonic) hemorrhage (all grades) was 24% in the irinotecan, fluorouracil, and leucovorin (IFL)/bevacizumab arm compared to 6% in the IFL alone arm; grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL.

Serious tumor associated bleedings have also been observed in patients with pancreatic cancer, gastric cancer, central nervous system (CNS) metastases, hepatoma, or varices treated with bevacizumab.

Mucocutaneous hemorrhage - Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated.

These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention, and did not require any changes in bevacizumab treatment regimen.

There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Thromboembolic Events, Arterial (ATE): The risk of ATEs is increased with bevacizumab therapy; such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction (MI), and other peripheral or visceral arterial thrombosis. A pooled analysis of five randomized studies showed a two-fold increase in these events (3.8% vs. 1.7%). ATE led to a fatal outcome in 0.8% patients with bevacizumab (vs. 0.5% without bevacizumab). The rate of cerebrovascular accidents (including TIA) was 2.3% vs. 0.5%, and the rates of MI 1.7% vs. 0.7%. Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk.(36) In patients >65 years treated with bevacizumab and chemotherapy, the rate of ATE was approximately 8.5%.

Aspirin is a standard therapy for primary and secondary prophylaxis of ATE in patients at high risk of such events, and the use of aspirin ≤325 mg daily was allowed in the five randomized studies discussed above though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and ATE events, retrospective analyses of the ability of aspirin to affect the risk of ATE were inconclusive. Further analyses of the effects of concomitant use of bevacizumab and aspirin are ongoing.

Thromboembolic Events, Venous (VTE) (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis): In the phase 3 pivotal trial in mCRC, there was a slightly higher rate of VTE in patients treated with chemotherapy plus bevacizumab compared with chemotherapy alone (19% vs. 16%). The incidence of NCI-CTC Grade>3 VTEs in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6%

vs. 3.2%).

In clinical trials across all indications, the overall incidence of VTEs ranged from 2.8% to 17.3% in the bevacizumab-containing arms compared to 3.2% to 15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE compared with chemotherapy alone. However, patients with mCRC who receive bevacizumab and experienced VTE may be at higher risk for recurrence of VTE.

Perforations of GI tract: GI perforations/fistula are rare but have occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention, and some were associated with a fatal outcome. In the pivotal phase 3 trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving fluorouracil (5-FU)/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in non-CRC tumors (e.g., gastric/esophageal, pancreatic, and ovarian cancers) or nonmalignant conditions such as diverticulitis and gastric ulcer. GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain or rectal/abdominal abscess.

GI Fistula: Fistula formations, including events resulting in death, have been observed in patients receiving bevacizumab in clinical studies and post-marketing reports. Fistulae in the GI tract are common (1-10% incidence) in patients with certain metastatic tumors such as CRC or cervical, but uncommon (0.1-1%) or rare (0.01-0.1%) in other indications.

In addition, fistulae that involve areas other than the GI tract have also been observed (e.g. tracheoesophageal, bronchopleural, urogenital, and biliary). Events were reported at various timepoints during treatment, ranging from 1 week to 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Tracheoesophageal (TE) fistula: Life-threatening or fatal TE fistula has been reported in patients with small cell lung cancer (SCLC) treated with concurrent chemoradiation and bevacizumab. In a phase 2 trial of bevacizumab plus irinotecan, carboplatin, and radiation therapy (RT) followed by maintenance bevacizumab that accrued 25 patients, there have been two confirmed cases of TE fistula (one fatal) and a third case of fatal upper aerodigestive tract hemorrhage, with TE fistula suspected but not confirmed. All three events occurred during the bevacizumab maintenance phase (1.5 to 4 months after completion of chemoradiation). While pulmonary fistula (including TE fistula) has also been observed in advanced NSCLC or SCLC patients receiving bevacizumab and chemotherapy (without RT), the incidence was extremely low.

Wound Healing Complications: Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab.

The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. Across mCRC trials, at least 28 days must have elapsed following major surgery before bevacizumab could be initiated; data suggested initiation of bevacizumab 29-60 days following surgery did not appear to increase the risk of

wound healing complications compared to those treated with chemotherapy alone.

The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined. In the pivotal study in CRC, among patients who underwent major surgery while on study therapy, there was an increased rate of significant post-operative bleeding or wound healing complications in the IFL plus bevacizumab arms vs. IFL alone [10% (4/40) vs. 0% (0/25)].(37) Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, range 11-50 days).

If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure In the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery.

Heart failure (HF): The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In phase 3 trials in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 3% in the bevacizumab plus capecitabine arm compared to 1% in the capecitabine-only arm.(29) In a Phase 3 trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of left ventricular ejection fraction (LVEF) decrease (defined as NCI CTC Grade 3 or 4) in the paclitaxel plus bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm

In phase 2 study of 48 patients with refractory acute myelogenous leukemia treated with cytarabine, mitoxantrone, and bevacizumab, five cases of cardiac dysfunction (CHF) or LVEF decreases to <40% were reported. All but one of these subjects had significant prior exposure to anthracyclines as well. Two additional studies investigated concurrent administration of anthracyclines and bevacizumab. In 21 patients with inflammatory breast cancer treated with neoadjuvant docetaxel, doxorubicin (cumulative doses at 240 mg/m2), and bevacizumab, no patients developed clinically apparent CHF; however, patients had asymptomatic decreases in LVEF to <40%.(38) In a small phase 2 study in patients with soft tissue sarcoma, 2 of the 17 patients treated with bevacizumab and high-dose doxorubicin (75 mg/m2) developed CHF (one Grade 3 event after a cumulative doxorubicin dose of 591 mg/m2 and one Grade 4 event after a cumulative doxorubicin dose of 420 mg/m2); an additional 4 patients had asymptomatic decreases in LVEF.(39) Patients receiving anthracyclines or with prior exposure to anthracyclines should have a baseline Multi Gated Acquisition Scan (MUGA) or echocardiogram (ECHO) with a normal ejection fraction.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), Posterior Reversible Encephalopathy Syndrome (PRES), or similar leukoencephalopathy syndrome: RPLS/PRES are clinical syndromes related to vasogenic edema of the white matter and have rarely reported in association with bevacizumab therapy (<1%). Clinical presentations may include altered mental status, seizure, visual disturbance or cortical blindness, with or without associated hypertension. MRI scans are required for diagnosis. Typical findings are vasogenic edema (enhanced intensity

in T2 and FLAIR sequences on non-contrast magnetic resonance imaging [MRI]) predominantly in the white matter of the posterior parietal and occipital lobes, and less frequently, in the anterior distributions and the gray matter.

RPLS/PRES is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent irreversible tissue damage. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known.(40, 41)

Neutropenia: In the phase 3 trial with IFL plus or minus bevacizumab in CRC, Grade 3-4 neutropenia was 21% with bevacizumab plus IFL vs. 14% with IFL alone (Grade 4 neutropenia was 3% vs. 2%). Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab. In a phase 3 trial in NSCLC, the carboplatin and paclitaxel plus bevacizumab arm was associated with increased rate of Grade 4 neutropenia (27% vs. 17%), febrile neutropenia (5.4% vs. 1.8%), and infection with neutropenia (4.4% vs. 2.0%) with three fatal cases.(33)

Bone metaphyseal dysplasia in children with active (open) growth plates: Inhibitors of VEGF/VEGFR pathways have been shown to induce physeal dysplasia in juvenile cynomolgus monkeys with open growth plates. Asymptomatic metaphyseal bone lesions were also observed in a 4.5-month old infant after 4 doses (8 weeks) of bevacizumab for treatment of cutaneovisceral angiomatosis with thrombocytopenia (CAT). The radiographic findings included lytic lesions in the metaphyses of upper and lower extremity long bones, which reversed following cessation of bevacizumab.(42) In a phase 1 pediatric study with bevacizumab, metaphyseal expansion was not observed in the three patients with open growth plates at baseline; however, the duration of treatment was limited.(43) At this time, experience is limited for prolonged treatment with bevacizumab in children, and no data are available for the long term impact of bevacizumab on growth.

Additional Adverse Events: See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, ranging from 11 to 50 days).

Immunogenicity: As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

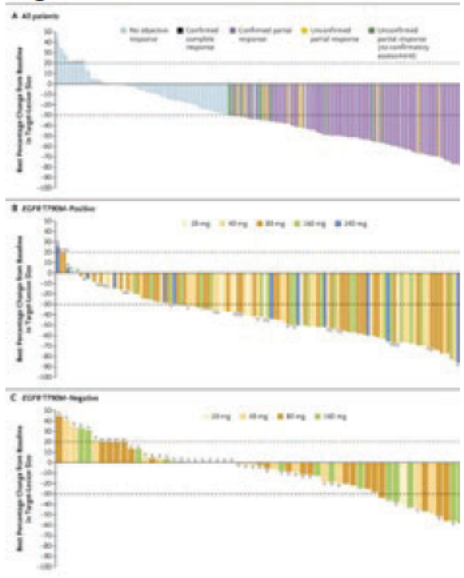
2.3 Other Agents
Not Applicable

2.4 Rationale

EGFR TKIs and the use of Osimertinib **(AZD9291)**
Osimertinib (AZD9291) was initially developed to overcome resistance to first-line first- or second-generation EGFR TKIs mediated by the acquisition of the T790M mutation.(44) Except for the use of Osimertinib (AZD9291) at the time of resistance, no other therapeutic strategies to overcome resistance have been approved to date.(45)

The activity of Osimertinib (AZD9291) was first demonstrated in in Phase 1-2 trials (Figure 1).(46) Osimertinib (AZD9291) is a novel, potent, small molecule irreversible TKI that selectively targets mutant forms of EGFR. It inhibits the EGFR sensitizing mutations as well as the T790M resistance mutation, with minimal inhibitory activity towards the wild-type EGFR at clinically relevant doses, resulting in less toxicity. Common treatment-related adverse events in the Phase II trial included diarrhea, rash, nausea, and decreased appetite. Other notable toxicities included pneumonitis, and QT interval prolongation.

Figure 1.



First-line treatment with Osimertinib (AZD9291)
Once the benefit of Osimertinib (AZD9291) was established after progression on a prior EGFR TKI, its use was investigated in the first-line setting. The FLAURA trial (11) randomized patients with previously-untreated, advanced, EGFR-mutant NSCLC to Osimertinib (AZD9291) or standard TKI (gefitinib or erlotinib) with a primary endpoint of PFS. Osimertinib (AZD9291) was determined to be superior to standard EGFR TKI with a median PFS of 18.9 months compared to 10.2 months. Overall survival also favored Osimertinib (AZD9291) although the difference has not reached statistical significance and the data is immature.

Brain metastases in EGFR-mutant NSCLC
A major unmet need in the patient population with EGFR-mutant NSCLC is treatment of brain metastases, as the CNS is a common site of disease progression after initial TKI treatment.(47) The standard treatments for brain metastases include surgery or radiotherapy which can lead to significant toxicity and delay systemic therapy. However, as systemic therapies have become more effective for the treatment of advanced lung cancer, there has been investigation into their use in patients with brain metastases. Treating patients with a systemic therapy carries the advantage of managing disease in the brain and body simultaneously, but also importantly avoids the potential toxicity and delay in treatment that can occur with radiation therapy or surgery.

For patients who are EGFR TKI-naïve, only a few trials have included (or focused on) patients with untreated brain metastases to determine efficacy of EGFR TKIs in the CNS. One trial studied the use of erlotinib in patients with lung adenocarcinoma with disease progression in the brain, and demonstrated an overall response rate of 58% and PFS of about 10 months.(48) Although about 30% of patients in this trial were wild-type for EGFR, the ORR and PFS was similar to that seen with erlotinib in trials of EGFR-mutant patients that required local therapy of brain metastases prior to enrollment.[6] In a retrospective study of 110 patients with EGFR mutation positive NSCLC, upfront erlotinib was compared to WBRT or SRS in patients with brain metastases.(49) There was a longer time to intracranial progression for patients treated with radiation compared to erlotinib alone, however overall survival was similar.

Although the use of an EGFR inhibitor has not been formally compared to radiation therapy in a prospective randomized trial, there is clearly CNS activity with first-generation EGFR inhibitors and they are often used in lieu of local therapy in patients with newly-diagnosed EGFR-mutant NSCLC with small, asymptomatic brain metastases. However, patients with EGFR TKI resistance with disease progression in the brain often present a clinical challenge as there are no studies (to our knowledge) that specifically assess activity of third-generation EGFR inhibitors in the CNS. Interestingly, the prevalence of T790M in brain metastases after treatment with a first-generation EGFR TKIs is 16% whereas in systemic metastases the prevalence is 50-60%, indicating a different etiology of drug resistance in the CNS.(50)

Activity of Osimertinib (AZD9291) for brain metastases

Preclinical data suggests that Osimertinib (AZD9291) has better activity in brain metastases in animal models of EGFR-mutant NSCLC compared to several other EGFR TKIs (51). Osimertinib (AZD9291) has been studied in patients with brain metastases from lung cancer, and early data suggests that there is activity in the CNS. Among 3 EGFR-mutant patients who developed new brain metastases during treatment with rociletinib (another EGFR inhibitor), all of them had a CNS response to Osimertinib (AZD9291).(52) Additionally, a Phase I trial of patients with EGFR-mutant lung cancer and leptomeningeal disease found that Osimertinib (AZD9291) resulted in a radiographic improvement in 8 of 11 patients.(53) Although this suggests that there is penetration of the drug into the CNS, most of these patients had prior brain radiation, so the independent effect of the drug in the CNS remains unknown. The largest study to date of Osimertinib (AZD9291) in patients with CNS disease from EGFR mutant NSCLC is the BLOOM trial(54) which included 20 patients with leptomeningeal disease who had progressed on a prior EGFR TKI. Patients were treated with Osimertinib (AZD9291) 160mg daily. Of the 12 patients who reached imaging assessment, 7 had radiographic improvement, 2 had stable disease, and 3 were not evaluable. Of the 7 symptomatic patients, 3 had improvement in symptoms, 1 had no change and 2 were not evaluable; of the 5 asymptomatic patients, 2 had worsening symptoms and 3 remained asymptomatic. Toxicity was consistent with that of other studies of Osimertinib (AZD9291) with no unexpected AEs. This study demonstrated that Osimertinib (AZD9291) can have activity in the CNS in patients with previously treated EGFR-mutant NSCLC in a subset of patients. The FLAURA trial (11) also demonstrated a superior PFS with Osimertinib (AZD9291) compared to standard EGFR TKIs among patients with brain metastases, indicating that there is superior CNS activity with this agent.

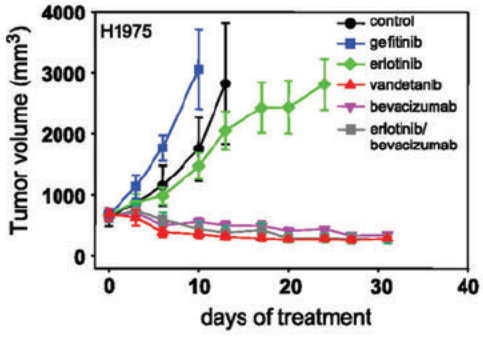
Combining EGFR plus VEGF inhibition in NSCLC

A strategy to improve both the overall clinical benefit with EGFR inhibitors and enhance CNS control is to combine an EGFR inhibitor with a VEGF inhibitor.

Bevacizumab is a monoclonal antibody against VEGF approved for use in metastatic NSCLC in combination with chemotherapy based on an improvement in survival.(33) Bevacizumab has been demonstrated to be safe in patients with untreated brain metastases from NSCLC(55). It has also been shown to have clinical benefit in patients with NSCLC and brain metastases, with evidence of improved symptoms related to CNS disease as well as reduction in corticosteroid requirement.(56) Additionally, in patients with glioblastoma, adding bevacizumab to temozolomide plus radiotherapy improves progression-free survival and quality of life.(57) Bevacizumab mechanisms of action includes blockade of mitogenic and pro-survival activity signals for the vascular endothelial cells and enhanced drug delivery by decreasing microvascular permeability.(58, 59) An immunomodulatory anti-tumor effect of bevacizumab has also been proposed.(60)

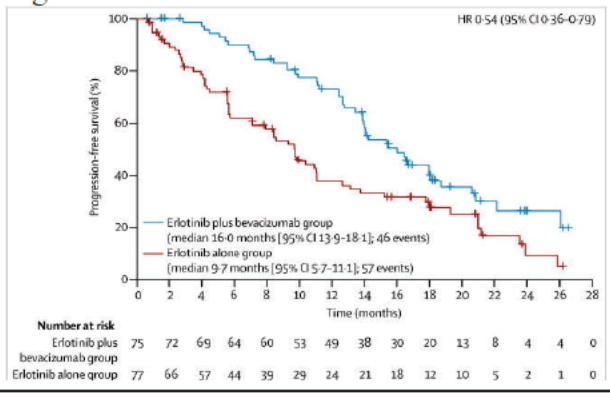
Preclinical studies have demonstrated the potential benefit of combining an EGFR and a VEGF inhibitor in EGFR mutant tumors. One study looked at EGFR/VEGFR pathway inhibition with the drug vandetanib or the combination of erlotinib plus bevecizumab in xenograft models of EGFR TKI resistance (Figure 2).(61) They found an increase in VEGF expression in erlotinib-resistant tumors, as well as a high response rate to both vandetanib and erlotinib plus bevacizumab in the erlotinib-resistant tumors. Additionally, they demonstrated that the benefit of VEGF inhibition may be due in part to antiendothelial effects.

Figure 2.



Clinical trials have shown that erlotinib and bevacizumab can be safely combined at full doses, and that the combination improves PFS (but not OS) in an unselected patient population.(62) The trial JO25567 has shown that erlotinib plus bevacizumab in the first-line treatment of EGFR-mutant NSCLC significantly improves PFS compared to erlotinib alone (median 16.0 vs 9.7 months, p 0.0015, Figure 3).(63)

Figure 3.



Osimertinib (AZD9291) and bevacizumab have been studied in a phase I trial of patients with previously-untreated EGFR-mutant lung cancer (64). There were no dose-limiting toxicities observed among the first 22

patients enrolled on the trial, and the maximally tolerated doses were the standard doses of both drugs (Osimertinib (AZD9291) 80mg po daily and bevacizumab 15mg/kg IV every 21 days). There were no dose reductions or treatment discontinuations due to toxicity required. There was only one SAE of hypertension that resolved with therapy. In this trial, there were 12 patients with brain metastases, 8 of whom had untreated brain metastases at study initiation. Among the 8 patients with untreated brain metastases, there were 3 SAEs: one of grade 3 dyspnea that was considered possibly related to therapy, and 2 SAEs that were considered unrelated to study therapy. There were no neurologic SAEs (personal communication, unpublished data).

There is no data available specifically for the activity of combination EGFR and VEGF therapy in the CNS. Additionally, there is currently no data available for the combination of a third-generation EGFR inhibitor with activity against T790M such as Osimertinib (AZD9291) plus a VEGF inhibitor. Therefore, this trial aims to test the combination of Osimertinib (AZD9291) plus bevacizumab in patients with EGFR-mutant NSCLC with brain metastases as initial treatment of advanced disease.

We hypothesize that the addition of bevacizumab to Osimertinib (AZD9291) will improve the progression-free survival in patients with EGFR-mutant NSCLC and brain metastases.

Additionally, we hypothesize that the combination of Osimertinib (AZD9291) plus bevacizumab will be safe and tolerable, and will improve other markers of clinical benefit including time to CNS progression, overall response rate, intracranial response rate, and overall survival.

2.5 Correlative Studies Background

The goal of the correlative studies that accompany this trial is to identify factors associated with benefit from Osimertinib (AZD9291) +/- bevacizumab in patients with EGFR mutant lung cancer and brain metastases. To achieve this goal we will perform a comprehensive set experiments that will evaluate the genomic landscape, angiogenesis markers, expression signatures and immune infiltrates of tumors on each arm of the study. Detailed information on the correlative studies is provided in Section 9.

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 NSCLC with an activating EGFR mutation (exon 19 deletion, L858R point mutation, or any other mutation known to be associated with EGFR TKI sensitivity). Presence of an activating EGFR mutation may be documented in tumor tissue or by plasma testing if performed in a CLIA-certified laboratory.

3.1.2 No prior treatment with an EGFR TKI. Patient may have received prior chemotherapy for early-stage or advanced disease but this is not required. Prior immunotherapy is not allowed.

3.1.3 Patients must have at least one measurable CNS lesion that is asymptomatic, untreated, and does not require local therapy at the time of enrollment. Measurable CNS disease is defined as a brain metastasis that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥5 mm (≥0.5 cm) with brain MRI. If the lesion is 5-10mm in size and is the only measurable disease, MRI imaging must be performed with 1.5 mm slice thickness or less.

A history of previously treated brain metastases is allowed, however any lesion present at the time of whole brain radiotherapy or included in the stereotactic radiotherapy field (or within 2mm of the treated lesion) will NOT be considered "untreated" unless it is new or documented to have progressed unequivocally since treatment.

See Section 11 for the evaluation of measurable disease.

3.1.4 Patients are not required to have measurable systemic (i.e. non-CNS) disease. If present, measurable systemic disease must be able to be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) with conventional techniques or as ≥10 mm (≥1 cm) with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.5 Age ≥18 years.

3.1.6 ECOG performance status ≤2.

3.1.7 Life expectancy of greater than 3 months.

3.1.8 The use of anti-convulsants is allowed, as long as the patient is on a stable dose with no seizure activity for at least 2 weeks prior to initiating trial therapy.

3.1.9 Female subjects should be using highly effective contraceptive measures, and must have a negative pregnancy test and not be breast-feeding prior to start of dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

- Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments
- Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution
- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral

oophorectomy or bilateral salpingectomy but not tubal ligation

Fertile men should be willing to use barrier contraception. during and for 4 months after Osimertinib (AZD9291) , and fertile women must agree to use adequate contraceptive measures during and for 6 weeks after Osimertinib (AZD9291) . Fertile men and women must agree to use adequate contraceptive measures during study therapy and for at least 6 months after the completion of bevacizumab therapy. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, the patient should inform the treating physician immediately.

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Symptomatic brain metastases or symptomatic leptomeningeal disease. Asymptomatic leptomeningeal disease is allowed.

3.2.2 Patients with brain metastases for whom complete surgical resection is clinically appropriate.

3.2.3 Prior treatment with any EGFR TKI.

3.2.4 Prior treatment with agents targeting the VEGF pathway, including bevacizumab.

3.2.5 The use of corticosteroids to control cerebral edema or treat neurologic symptoms will not be allowed, and patients who previously required corticosteroids for symptom control must be off steroids for at least 3 days without recurrence of symptoms prior to starting trial therapy. Corticosteroids for other indications is allowed.

3.2.6 Patients may not be receiving any other investigational agents and may not have participated in a study of an investigational agent or using an investigational device within five half-lives of the compound or 3 months, whichever is greater.

3.2.7 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 platinum-therapy related neuropathy.

3.2.8 Concurrent, active malignancies in addition to that being studied (other than cutaneous squamous cell carcinoma or basal cell carcinoma).

3.2.9 Any contraindication to MRI (i.e. patients with pacemakers or other metal implanted medical devices).

3.2.10 Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease

3.2.11 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Osimertinib (AZD9291) or bevacizumab.

3.2.12 Urine protein should be screened by urine analysis. If protein is 2+ or higher, 24-hour urine protein should be obtained. Patients with 24-hour urine protein $\geq$ 1000 mg are excluded.

3.2.13 Serious or non-healing wound, ulcer or bone fracture.

3.2.14 History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to day 1.

3.2.15 Invasive procedures defined as follows:

a. Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to Day 1 therapy

b. Anticipation of need for major surgical procedures during the course of the study

c. Core biopsy within 7 days prior to D1 therapy

3.2.16 Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1.

3.2.17 Patients with clinically significant cardiovascular disease are excluded.

a. Inadequately controlled HTN (SBP >160mmHg and/or DBP >90 mmHg despite antihypertensive medication)

b. History of CVA within 6 months (see additional requirement for adjuvant protocols)
c. Myocardial infarction or unstable angina within 6 months (see additional requirement for adjuvant protocols)
d. New York heart association grade II or greater congestive heart failure
e. Serious and inadequately controlled cardiac arrhythmia
f. Significant vascular disease (e.g. aortic aneurysm, history of aortic dissection)
g. Clinically significant peripheral vascular disease

3.2.18 Any of the following cardiac criteria:
a. Mean resting corrected QT interval (QTcF) > 470 ms obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine derived QTc value

b. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block)
c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, 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.

3.2.19 Evidence of bleeding diathesis or coagulopathy (including clinically significant hemoptysis).

3.2.20 Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of Osimertinib (AZD9291) .

3.2.21 Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

3.2.22 Patients currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inducers of CYP3A4 (at least 3 week prior). All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4.

3.2.23 Any evidence of severe or uncontrolled systemic diseases, including, but not limited to, uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.

3.2.24 History of hypersensitivity active or inactive excipients of Osimertinib (AZD9291) or drugs with a similar chemical structure or class to Osimertinib (AZD9291).

3.2.25 Inadequate bone marrow reserve or organ function (as demonstrated by any of the following laboratory values: absolute neutrophil count <1.5 x 109/L; platelet count <100 x 109/L; haemoglobin <90 g/L; alanine aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases; aspartate aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases; total bilirubin >1.5 times ULN if no liver metastases or >3 times ULN in the presence of documented Gilbert's Syndrome [unconjugated hyperbilirubinaemia] or liver metastases; serum creatinine >1.5 times ULN concurrent with creatinine clearance <50 mL/min [measured or calculated by Cockcroft and Gault equation]—confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN.

3.2.26 Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4 REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	

Documentation Required	IVR	NPIVR	AP	A
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU

which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the NCI protocol #10042 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-CT018, and protocol #10042.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

4.2.3 Requirements For 10042 Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.4 Checking Site Registration Status

You can verify your site registration status on the members' section of the CTSU

website.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Regulatory tab at the top of your screen.
- Click on the Site Registration subtab.
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk: 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 10-14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5 TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Arm 1: Osimertinib (AZD9291) 80mg PO QD plus bevacizumab 15mg/kg IV q3w

Arm 2: Osimertinib (AZD9291) 80mg PO QD

Patients will be randomized in a 1:1 fashion to Arm 1 (osimertinib plus bevacizumab) or Arm 2 (osimertinib alone).

Treatment in all arms will continue unless one of the follow criteria applies:

- Disease progression as per RECIST 1.1 or RANO-BM and absence of clinical benefit
- Symptomatic deterioration
- Unmanageable toxicity

Patients who experience either CNS or systemic progression but have documented response in the other site (systemic or CNS), and who are otherwise benefiting from treatment, are allowed to undergo local

therapy to the progressive disease followed by continuation on study treatment; if the best response in the other site is only stable disease, the evidence of clinical benefit and decision to continue study therapy should be discussed with the Study Chair and the sponsor (CTEP). Patients who experience tumor progression in both the CNS and in an extracranial site will come off therapy due to disease progression

Patients who discontinue trial therapy will be followed off trial for survival endpoints.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Osimertinib (AZD9291)	None	80mg	PO	Daily Days 1-21	21 days (3 weeks)
Bevacizumab (arm 1 only)	None*	15mg/kg IV	IV	Day 1 Q21 days	

* If infusional reactions occur, acetaminophen, diphenhydramine, steroids, or other medications may be given for symptom control and for premedication as needed. Anaphylactic precautions should be observed during bevacizumab administration.

The patient will be requested to maintain a medication diary (Appendix F) of each dose of Osimertinib (AZD9291). The medication diary will be returned to clinic staff at the end of each cycle.

5.1.1 CTEP IND Agents

5.1.1.1 **Osimertinib (AZD9291)**
Osimertinib (AZD9291) will be provided as tablets for oral administration as a single daily dose of 80 mg. A desiccant is included with the tablets.
Patients should swallow 1 tablet once daily, commencing on Day 1 but no later than within 2 days from randomization day. Tablets should be taken whole with water.

The initial dose of Osimertinib (AZD9291) 80 mg once daily can be reduced to 40 mg once daily.

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 scheduled 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 study drug, they should not make up for this dose, but should take the next scheduled dose.

Any change from the dosing schedule, dose interruptions, or dose reductions should be recorded in the eCRF.

Additional information about Osimertinib (AZD9291) may be found in the Investigator's Brochure

5.1.1.2 Bevacizumab

Bevacizumab is administered by intravenous (IV) infusion. The dose should be based on the patient's actual body weight; the dose will be recalculated if there is a weight change of >10% from baseline.

The first dose of bevacizumab should be given over a minimum of 90 minutes. If well tolerated, the second dose can be given over a minimum of 60 minutes. If this dose is well-tolerated, then all subsequent infusions can be administered over a minimum of 30 minutes. If an infusion reaction occurs, subsequent doses of bevacizumab should be administered over the shortest period that was well tolerated.

Special Precautions/Safety Issues:

Prior to each treatment, the patient should be carefully assessed with special attention to blood pressure, proteinuria, bleeding and cardiovascular events, as well as symptoms or signs of bowel perforation and RPLS. Decisions for retreatment or dose modification/interruption should follow the dose modification guidelines in Section 6.1.

Patients who have an ongoing study agent-related SAE upon study completion or at discontinuation from the study will be contacted by the investigator or his/her designee periodically until the event is resolved or determined to be irreversible.

Infusional reactions: Routine premedication is not required for the first dose of bevacizumab. If infusional reactions occur, acetaminophen, diphenhydramine, steroids, or other medications may be given for symptom control and for premedication as needed. Anaphylactic precautions should be observed during bevacizumab administration.

Hypertension: Patients should have BP monitored prior to each infusion of bevacizumab. Hypertensive medication should be initiated or increased for optimal BP control according to standard public heath guidelines.

Proteinuria: Proteinuria should be monitored by dipstick at least every 6 weeks.

Surgery and wound complication issues and surgery: The appropriate interval from discontinuation of bevacizumab to subsequent elective surgery required to reduce the risk of impaired wound healing has not been determined. Decision on such an interval should take into consideration the half-life of bevacizumab. It is generally recommended that bevacizumab should be discontinued at least 4-8 weeks prior to major elective surgery. In addition, bevacizumab should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed; in cases of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that bevacizumab be resumed no earlier than 8 weeks after surgery.

5.2 General Concomitant Medication, Restrictions and Supportive Care Guidelines

Once enrolled, guidelines regarding concomitant medications listed in Appendix B must be followed. Patients may receive any medication that is clinically indicated for treatment of AEs.

Drugs that are not allowed must have been discontinued for an appropriate period before they enter screening (as indicated in Appendix B). All concomitant medications should be captured on the electronic case report form (eCRF).

1. Female patients of child-bearing potential should use reliable methods of contraception from the time of screening until 6 weeks after discontinuing Osimertinib (AZD9291) and 6 months after discontinuing bevacizumab.
2. Male patients should be asked to use barrier contraceptives (i.e., by use of condoms) during sex with all partners during the trial and for a washout period of 4 months after Osimertinib (AZD9291) or 6 months after bevacizumab. Male patients should avoid procreation for 4 months after Osimertinib (AZD9291) or 6 months after bevacizumab. Patients should refrain from donating sperm from the start of dosing until 4 months after discontinuing Osimertinib (AZD9291) and 6 months after discontinuing bevacizumab.
3. Once enrolled all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known to be potent inducers of CYP3A4 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of adverse events. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of Osimertinib (AZD9291). All concomitant medications should be captured on the eCRF. Guidance on medicines to avoid, medications that require close monitoring and on washout periods is provided (see Appendix B).
4. If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see above), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon BCRP and/or P-glycoprotein (P-gp) and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving Osimertinib (AZD9291). Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Appendix B).

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

Appendix C presents guidelines for patients, their caregivers and non-study healthcare team members on identifying medications/substances that could potentially interact with the study agent(s).

Patients taking warfarin should be monitored regularly for changes in prothrombin time or International Normalized Ratio (INR).

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

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression in the absence of clinical benefit,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Subjects may be discontinued from investigational product (IP) in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without predjudice to further treatment
- Adverse Event
- Severe non-compliance with the study protocol

Patients experiencing any of the following adverse events will not be permitted to restart study treatment:

- Interstitial Lung Disease (ILD)
- QTc interval prolongation with signs/symptoms of serious arrhythmia

5.4 Duration of Follow Up

Patients will be followed for a minimum of 4 weeks after removal from study treatment or until death, whichever occurs first. As a minimum, telephone contact should be made with the patient 28 days following the discontinuation of Osimertinib (AZD9291) to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy). Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event (≤ grade 1). Survival data will be followed until death from any cause.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6 DOSING DELAYS/DOSE MODIFICATIONS

6.1 Osimertinib (AZD9291)

6.1.1 Dose reduction levels for Osimertinib (AZD9291) are provided in Table 6.1.

Table 6.1 Dose reduction levels

	Osimertinib
Starting dose	Osimertinib (AZD9291) 80 mg
Reduced dose	Osimertinib (AZD9291) 40 mg

6.1.2 General dose adjustments on adverse events

All patients to commence treatment of Osimertinib (AZD9291) at the starting dose level of 80mg daily as shown in Table 6.1.

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade), where the clinician considers the event of concern to be specifically associated with Osimertinib (AZD9291) (and not attributable to the disease or disease-related processes for which patient is being treated), dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. If a toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset, treatment with Osimertinib (AZD9291) may be restarted at the same dose (80 mg) or a lower dose (40 mg) using the rules above for dose modifications (Table 6.1) and with discussion and agreement with the Sponsor Study Team Physician as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption.

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

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

Table 6.2. Dose adjustment information for adverse reactions		
Target Organ	Adverse Reaction	Dose Modification
Pulmonary	ILD/Pneumonitis	Permanently discontinue osimertinib
Cardiac	QTc interval greater than 500	Withold osimertinib until

	msec on at least 2 separate ECGs	QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Other	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of osimertinib for up to 3 weeks	Osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue osimertinib

On resolution of toxicity within 3 weeks:

- If an AE subsequently requires dose interruption, Osimertinib (AZD9291) may restart at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the Investigator.

Patients experiencing any of the following adverse events will not be permitted to restart study treatment:

- Interstitial Lung Disease (ILD)
- QTc interval prolongation with signs/symptoms of serious arrhythmia

There is no dose reduction allowed below 40mg. If a patient experiences toxicity such that 40mg is no longer considered tolerable, the patient should discontinue study treatment.

Skin reactions

It is recommended that all patients follow a program of sun protective measures while receiving study drug and for 3 to 4 weeks after discontinuing study drug.

The aim is to reduce the risk of development of skin reactions or minimize the severity of skin reactions and minimize the requirement for dose reduction of study drug. Toxicity will be managed according to local guidelines.

Skin reactions are to be reported as AEs in the eCRF, with additional details captured in the "SKNREAC" eCRF such as:

- Changes in the characteristics of skin reactions will be collected in the "SKNREAC" eCRF.

- Changes in the CTCAE grade of skin reactions will be collected in the AE eCRF.

Skin biopsies of skin reactions may be taken.

Photographs of skin reactions may be collected and these photographs should be available for central review by the Sponsor and the Company and for external expert dermatological review if required, if patient consent is obtained.

Gastrointestinal toxicities

Nausea, vomiting, or both may be controlled with anti-emetic therapy according to local guidelines.

Dose Modification and Supportive Care for Diarrhea

Severity (CTCAE Grading)	**Description**	**Intervention concerning Osimertinib (AZD9291) treatment**	**Specific intervention**
Mild (Grade 1)	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue same dose	Toxicity will be managed as per local guidelines. .
Moderate (Grade 2)	Increase of 4-6 stools per day over baseline; i.v. fluids indicated < 24 hours; moderate increase in ostomy output compared with baseline; not interfering with ADL	Continue same dose with medical management unless investigator determines clinically significant and persists > 72 hours. Then interrupt Osimertinib (AZD9291) until grade ≤ 1 and consider a dose reduction.	Toxicity will be managed as per local guidelines.
Severe (Grade 3)	Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids > 24 hours; hospitalization; severe increase in ostomy output compared with baseline; interfering with ADL	Dose interruption until recovered to ≤Grade 1 followed by dose reduction.	Toxicity will be managed as per local guidelines.

Life threatening (Grade 4)	Life-threatening consequences (e.g. haemodynamic collapse)	Dose interruption until recovered to ≤Grade 1 followed by dose reduction	Toxicity will be managed as per local guidelines.

Appropriate management of diarrhea, including dose adjustments for AEs of diarrhea that are of CTCAE Grade ≥3 or that are clinically significant and/or intolerable and considered by the Investigator to be causally related to Osimertinib (AZD9291) , should be undertaken as per standard practice and guidelines for dose adjustments above. Changes in CTCAE grade of diarrhea will be captured in the AE eCRF.

QTc prolongation

Patients with QTcF prolongation to >500 msec should have study treatment interrupted and regular ECGs performed until resolution to <481 msec or recovery to baseline if baseline QTcF is >481 msec and then restarted at a reduced dose of 40mg. If the toxicity does not resolve to ≤ grade 1 within 21 days the patient will be permanently withdrawn from study treatment.

Interstitial lung disease (ILD)/Pneumonitis-like toxicity

If a new or worsening of pulmonary symptoms (e.g., dyspnea) or occurrence of a radiological abnormality suggestive of ILD is observed, an interruption in study drug dosing is recommended, and the Study Physician should be informed. It is strongly recommended to perform a full diagnostic workup to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and study drug permanently discontinued. In the absence of a diagnosis of ILD, study drug may be restarted following consultation with the Study Physician.

Note: Patients experiencing ILD will not be permitted to restart study drug.

Keratitis

Keratitis was reported in 0.7% (n=6) of the 833 patients treated with Osimertinib (AZD9291) in the AURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

Changes in cardiac contractility

Across clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases greater than or equal to 10% and a drop to less than 50% occurred in 4.0% (26/655) of patients treated with Osimertinib (AZD9291) who had baseline and at least one follow-up LVEF assessment. Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and Osimertinib (AZD9291) has not been established. Whilst Osimertinib

(AZD9291) is not known to be associated with changes in left ventricular function, bevacizumab is known to be associated with changes in left ventricular function and cardiac failure, therefore patients should have assessment of left ventricular function at baseline and on treatment. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered. For symptomatic congestive heart failure, permanently discontinue Osimertinib (AZD9291) .

Permanent discontinuation due to toxicity

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

6.2 Bevacizumab

Treatment should be modified for toxicity as per the table below. There will be no dose reduction for bevacizumab. If bevacizumab is held or discontinued for toxicity, patient may continue treatment with Osimertinib (AZD9291). If Osimertinib (AZD9291) is discontinued for toxicity, patient must also discontinue bevacizumab and therefore must be removed from study. If Osimertinib (AZD9291) is held for toxicity, bevacizumab may be continued at the discretion of the treating investigator.

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V5 Grade**	**Action to be Taken**
Allergic reactions Or **Infusion-related reactions** Or **Anaphylaxis**	Grade 1-2	• Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. • For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle. • Subjects who experience bronchospasm (regardless of grade) should discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V5 Grade**	**Action to be Taken**
Thromboembolic Event (Arterial), arterial ischemia - Cardiac ischemia - Myocardial infraction - CNS ischemia (TIA, CVA) - Any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (new or worsening since bevacizumab	Discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event (Venous)	[Note: Patients with primary lung cancer requiring therapeutic anticoagulation should discontinue bevacizumab]	
	Grade 3 OR asymptomatic Grade 4	▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. ▪ If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during full-dose anticoagulation **IF** <u>all</u> of the criteria below are met: - The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) - The subject must not have had hemorrhagic events while on study - The subject must be on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. ▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 (symptomatic)	Discontinue bevacizumab
Hypertension	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V5 Grade**	**Action to be Taken**
	Grade 1 (SBP 120-139 mmHg or DBP 80-89 mmHg)	Consider increased BP monitoring; start anti-hypertensive medication if appropriate
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mmHg)	Begin anti-hypertensive therapy and continue bevacizumab
	• Grade 2 symptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg) • Grade 3 (SBP ≥160 mmHg or DBP ≥100 mmHg)	• Start or adjust anti-hypertensive medication • Hold bevacizumab until symptoms resolve **AND** BP < 160/90mmHg* • For hypertension that is refractory requiring delay of bevacizumab for > 4 weeks, discontinue bevacizumab
	Grade 4 (Hypertensive crisis or malignant hypertension)	Discontinue bevacizumab
Heart Failure OR **Left Ventricular (LV) dysfunction**	• Heart failure ≥Grade 2 • LV dysfunction ≥Grade 3	Discontinue bevacizumab
Proteinuria Proteinuria will be monitored by urine analysis dipstick. If Dipstick ≥2+ proteinuria, 24-hour urine protein should be obtained	Dipstick ≥ 2+	Hold bevacizumab and obtain 24 hour urine protein
	If 24-h urine protein <2g	Continue bevacizumab
	If 24-h urine protein ≥2 g	• Hold bevacizumab until 24-hour urine protein <2.0 g • Discontinue bevacizumab if urine protein does not recover to < 2.0 g after 8 weeks of bevacizumab interruption
	Nephrotic syndrome	Discontinue bevacizumab.
Hemorrhage (intracranial or pulmonary)	Grade 2-4	• Discontinue bevacizumab
	Grade 1	• Patients receiving full-dose

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V5 Grade**	**Action to be Taken**
		anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and hemoglobin is stable - there is no bleeding diathesis that would increase the risk of therapy • there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence
Hemorrhage (not CNS or pulmonary)	Grade 3	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and hemoglobin is stable - there is no bleeding diathesis that would increase the risk of therapy - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy.
	Grade 4	Discontinue bevacizumab
RPLS (Reversible Posterior Leukoencephalopathy syndrome OR **PRES** (Posterior Reversible Encephalopathy Syndrome)	Any Grade	Discontinue bevacizumab upon diagnosis of RPLS.
Wound dehiscence OR **Wound complications**	Grade 2	Hold bevacizumab until healing
	Grade 3-4	Discontinue bevacizumab
Perforation (GI, or any other organ)	Any Grade	Discontinue bevacizumab
Fistula (GI, pulmonary or any	Any Grade	Discontinue bevacizumab

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V5 Grade**	**Action to be Taken**
other organ)		
Obstruction of GI tract	Grade 2 requiring medical intervention	Hold bevacizumab until complete resolution
	Grade 3-4	• Hold bevacizumab until complete resolution • If surgery is required, patient may restart bevacizumab after 28 days and full recovery from surgery, and at investigator's discretion
Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	• Hold bevacizumab until symptoms resolve to≤Grade 1
	Grade 4	• Discontinue bevacizumab • **Upon consultation with the study chair,** resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the Grade 4 toxicity is transient, has recovered to ≤Grade 1 and unlikely to recur with retreatment.

Note 1: There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described above.

Note 2: If bevacizumab is interrupted for ANY reasons for >4 weeks (unless otherwise specified), the patient should discontinue bevacizumab therapy on protocol.

Note 3: Continue Osimertinib (AZD9291) if toxicity leading to holding or discontinuing bevacizumab is attributed to bevacizumab only.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Sections 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform

presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for AZD9291 (osimertinib, NSC 781254)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4734 patients.* Below is the CAEPR for Osimertinib (AZD9291).

> **NOTE:** Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.8, February 9, 2023[1]

Adverse Events with Possible Relationship to Osimertinib (AZD9291) (CTCAE 5.0 Term) [n= 4734]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
		Blood and lymphatic system disorders - Other (aplastic anemia)	
CARDIAC DISORDERS			
		Heart failure	
EYE DISORDERS			
		Dry eye	
		Eye disorders - Other (thinning of the front layer of the eye)	
		Keratitis	
GASTROINTESTINAL DISORDERS			

	Constipation		
	Diarrhea		***Diarrhea (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
	Nausea		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		
INFECTIONS AND INFESTATIONS			
Paronychia			***Paronychia (Gr 2)***
INVESTIGATIONS			
	Electrocardiogram QT corrected interval prolonged		***Electrocardiogram QT corrected interval prolonged (Gr 3)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
Adverse Events with Possible Relationship to Osimertinib (AZD9291) (CTCAE 5.0 Term) [n= 4734]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough[2]		
	Respiratory, thoracic, and mediastinal disorders - Other (interstitial lung disease)[2]		***Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[2] (Gr 2)***
		Pulmonary edema	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
	Nail changes[3]		***Nail changes[3] (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
		Stevens-Johnson syndrome	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Interstitial lung disease includes the terms pneumonitis and interstitial lung disease. Dyspnea, cough and fever may be indicative of interstitial lung disease/pneumonitis.

[3]Nail changes may include the terms nail bed disorders, nail discoloration, nail disorder, nail loss, nail pigmentation, nail toxicity, nail dystrophy, nail ridging, onychoclasis, onycholysis, and onychomadesis.

Adverse events reported on Osimertinib (AZD9291) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Osimertinib (AZD9291) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Myocardial infarction; Supraventricular tachycardia
EYE DISORDERS - Eye disorders - Other (corneal erosion); Eye disorders - Other (eyelids pruritus); Eye disorders - Other (corneal epithelium defect); Vision decreased
GASTROINTESTINAL DISORDERS - Dry mouth; Dyspepsia; Dysphagia; Gastritis; Gastrointestinal disorders - Other (intestinal ischemia); Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Fever[2]; Flu like symptoms; Generalized edema; Malaise; Non-cardiac chest pain
INFECTIONS AND INFESTATIONS - Folliculitis; Infections and infestations - Other (pustule); Lung infection; Nail infection; Papulopustular rash; Rash pustular; Shingles; Upper respiratory infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (drug eruption)
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; CPK increased; Creatinine increased; Ejection fraction decreased; GGT increased; Investigations - Other (electrocardiogram QT interval abnormal); Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypermagnesemia; Hypokalemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS -; Back pain; Generalized muscle weakness; Neck pain
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Ischemia cerebrovascular; Stroke
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS -; Dyspnea[2]; Epistaxis; Hypoxia; Pleural effusion; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Eczema; Palmar-plantar erythrodysesthesia syndrome; Skin and subcutaneous tissue disorders - Other (skin fissures); Skin and subcutaneous tissue disorders - Other (onychomalacia); Skin and subcutaneous tissue disorders - Other (onychalgia); Skin and subcutaneous tissue disorders - Other (skin erosion); Urticaria
VASCULAR DISORDERS - Hematoma; Thromboembolic event

Note: Osimertinib (AZD9291) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 CAEPR for Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3540 patients.* Below is the CAEPR for bevacizumab (rhuMAb VEGF).
NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, May 2, 2018[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
		Hemolytic uremic syndrome	
CARDIAC DISORDERS			
	Cardiac disorders - Other (supraventricular arrhythmias)[2]		***Cardiac disorders - Other (supraventricular arrhythmias)[2] (Gr 3)***
		Chest pain - cardiac[3]	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction[3]	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Colitis		***Colitis (Gr 3)***
	Constipation		***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[4]	
	Gastrointestinal hemorrhage[5]		***Gastrointestinal hemorrhage[5] (Gr 2)***
	Gastrointestinal obstruction[6]		
		Gastrointestinal perforation[7]	
		Gastrointestinal ulcer[8]	
	Ileus Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 3)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 3)***
	Pain		***Pain (Gr 3)***
HEPATOBILIARY DISORDERS			
		Gallbladder perforation	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[9]		***Infection[9] (Gr 3)***
		Infections and infestations - Other (necrotizing fascitis)	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		***Infusion related reaction (Gr 2)***
		Injury, poisoning and procedural complications - Other (anastomotic leak)[10]	
	Wound complication		***Wound complication (Gr 2)***
	Wound dehiscence		***Wound dehiscence (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperglycemia		
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
		Avascular necrosis[11]	
	Generalized muscle weakness		
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[12]		
	Myalgia		***Myalgia (Gr 3)***
	Osteonecrosis of jaw[13]		

NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy[14]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr 3)***
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[15]		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 3)***
	Hoarseness		***Hoarseness (Gr 3)***
		Pulmonary hypertension	
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism[3,16]	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation, and atrial flutter.

[3]The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[4]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation.

[8]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[9]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[10]Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak.

[11]There have been reports of non-mandibular osteonecrosis (avascular necrosis) in patients under the age of 18 treated with bevacizumab.

[12]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[13]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[14]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

[15]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[16]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Adverse events reported on bevacizumab (rhuMAb VEGF) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that bevacizumab (rhuMAb VEGF) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye pain; Floaters; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Vitreous hemorrhage; Watering eyes
GASTROINTESTINAL DISORDERS - Ascites; Cheilitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Osteonecrosis; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Myasthenia gravis; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Dysuria; Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Nail loss; Pain of skin;

Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

Note: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 7.3.4.

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

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days

Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

Not applicable

7.3.5 Adverse Events of Special Interest in Bevacizumab Studies

The following AEs are considered of special interest in patients receiving bevacizumab and must be reported expeditiously through CTEP-AERS:

- Hypertension ≥ Grade 3
- Proteinuria ≥ Grade 3
- GI perforation, abscesses and fistulae, any grade
- Wound healing complications ≥ Grade 3
- Haemorrhage ≥ Grade 3
- CNS bleeding, any grade
- Hemoptysis ≥ Grade 2
- Arterial Thromboembolic event, any grade
- Venous thromboembolic events ≥ Grade 3
- Posterior Reversible Encephalopathy Syndrome (PRES), any grade
- CHF ≥ Grade 3
- Non-GI fistula or abscess ≥ Grade 2

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

7.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Sponsor and the Company during the course of the study and within 6 weeks of the last dose of Osimertinib (AZD9291).

Maternal exposure

If a subject becomes pregnant during the course of the study Osimertinib (AZD9291) and bevacizumab should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the

investigational product 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 subject was discontinued from the study.

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

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor data entry site within 1 or 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Paternal exposure

Pregnancy of the subject's partners is not considered to be an adverse event. 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 subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome; the male subject should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 4 months after dosing ends should be followed up and documented.

7.8 Overdose

In the context of a clinical study, an overdose is any dose which exceeds the daily dose that is defined in the clinical study protocol.

A maximum tolerated dose has not been established for Osimertinib (AZD9291).

Such overdoses should be recorded as follows:
Standard mandatory text in CSP template

There is no specific treatment in the event of Osimertinib (AZD9291) overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically

If an overdose on a Company study drug occurs in the course of the study, then the Investigator or other site personnel inform the appropriate Sponsor representatives immediately, or no later than

24 hours of when he or she becomes aware of it.
For overdoses associated with a SAE, the standard reporting timelines apply, see Section 7.3.
For other overdoses, reporting must occur within 30 days.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agents

8.1.1 Osimertinib (AZD9291)

Chemical Name: N-(2-{[2-(Dimethylamino)ethyl](methyl)amino}-4-methoxy-5-{[4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide methanesulfonate

Other Names: Tagrisso™, AZD9291 mesylate

Classification: Epidermal growth factor receptor (EGFR) inhibitor

Molecular Formula: $C_{28}H_{33}N_7O_2.CH_4O_3S$ **M.W.:** 595.71 (mesylate salt)
499.61
(free base)

Approximate Solubility: The solubility of osimertinib free base has been measured as 7.2 mg/mL in Simulated Gastric Fluid (pH 1.4) and 0.2 mg/mL in Fasted State Simulated Intestinal Fluid (pH 6.5).

Mode of Action: Osimertinib (AZD9291) is a potent, oral, irreversible, tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR) mutation-positive (EGFRm) and T790M mutation-positive forms of EGFR.

Description: Osimertinib mesylate is a crystalline powder.

How Supplied: Osimertinib (AZD9291) tablets are supplied by AstraZeneca and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Tablets are packaged in 30-count bottles with mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose and sodium stearyl fumarate as inactive ingredients in the following strengths:

- 80 mg tablets: beige, oval and biconvex tablet marked with “AZ 80” on one side and plain on the reverse.
- 40 mg tablets: beige, round and biconvex tablet marked with “AZ 40” on one side and plain on the reverse.

The tablet coating contains polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, ferric oxide yellow, ferric oxide red and ferric oxide black.

Storage: Store at room temperature 20° to 25°C (68° to 77°F), excursions permitted between 15 to 30°C (59 to 85°F).

If a storage temperature excursion is identified, promptly return osimertinib (AZD9291) to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Refer to the package label for expiration.

Route of Administration: Take by mouth with or without food. If a dose of osimertinib (AZD9291) is missed or vomited, do not make up the missed dose and take the next dose as scheduled.

Potential Drug Interactions: The main metabolic pathways of osimertinib (AZD9291) are oxidation (predominantly CYP3A4) and dealkylation in vitro. Avoid concomitant use of strong CYP3A4 inducers. CYP3A4 inhibitors are not likely to affect the exposure of osimertinib (AZD9291). Based on in vitro studies, osimertinib (AZD9291) is a competitive inhibitor of CYP 3A4/5 but not CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at clinically relevant concentrations. Osimertinib (AZD9291) is an inducer of CYP1A2. Use caution with coadministration of CYP 3A4/5 and 1A2 substrates.

Osimertinib (AZD9291) is a substrate of BCRP and P-gp but is unlikely to result in clinically relevant drug interactions. Osimertinib (AZD9291) is not a substrate of OATP1B1 and OATP1B3 and does not inhibit OAT1, OAT3, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2K at clinically relevant concentrations. Based on in vitro data, osimertinib (AZD9291) is an inhibitor of BCRP and may increase the exposure of BCRP substrates. Osimertinib (AZD9291) does not inhibit P-gp at clinically relevant concentrations but has the potential to increase exposure of sensitive substrates.

Avoid use of osimertinib (AZD9291) in patients with congenital long QT syndrome. For patients with normal QT interval at the trial enrollment, avoid use of concomitant drugs that are known to prolong QT interval and use caution with drugs that may prolong QT interval. Refer to a frequently updated drug information reference and to the protocol for appropriate cardiac monitoring.

Patient Care Implications: Advise women of reproductive potential to use effective contraception while receiving study treatment and for 6 weeks after the last dose of Osimertinib (AZD9291). Men should use effective contraception while receiving study treatment and for 4 months after the last dose of Osimertinib (AZD9291). Refer to the protocol document for specific guidance.

8.1.2 Bevacizumab (NSC 704865)

Other Names: rhuMAb VEGF, Avastin®

Classification:	Recombinant humanized monoclonal antibody
Molecular Weight:	Approximate molecular weight is 149,000 daltons
Mode of Action:	Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.
Description:	Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions
How Supplied:	Genentech supplies and the PMB/CTEP/DCTD/NCI distributes bevacizumab as a clear to slightly opalescent, sterile liquid for parenteral administration. Each 400 mg (25mg/ml – 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.
Preparation:	Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection. The concentration of the final bevacizumab solution should be kept within the range of 1.4 – 16.5 mg/ml.
Storage:	Upon receipt, refrigerate bevacizumab (2˚ to 8˚ C). Do not freeze. Do not shake. If a storage excursion is identified, promptly return bevacizumab to 2°C-8°C (36°F-46°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.
Stability:	Shelf-life studies of rhuMAb VEGF are ongoing. The sterile single use vials contain no antibacterial preservatives. Discard vials 8 hours after initial entry. Once diluted in 0.9% sodium chloride, administer solutions of bevacizumab within 8 hours.
Route of Administration:	Intravenous

Method of Administration: Administer the initial dose over a minimum of 90 minutes. If no adverse reactions occur, administer the second dose over a minimum of 60 minutes. If no adverse reactions occur after the second dose, administer subsequent doses over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

Availability: Bevacizumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.3 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Study agent must be ordered after patient is registered to the treatment arm as no starter supplies are available for this study.
Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.4 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability–

8.1.5 The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

8.1.6 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

We will perform correlative studies including the use of 1 integrated biomarker to be measured in the tumor and 3 exploratory biomarkers to be measured in the tumor or plasma.

Integrated biomarker:

1. Molecular profiling using the Oncomine Comprehensive Research Panel;

Exploratory biomarkers

1. Angiogenesis, Immune and Signaling Pathway Markers;
2. Circulating Tumor DNA;
3. Markers of Angiogenesis and Inflammation.

Tumor tissue will be obtained by a surgical or biopsy procedure. Tissue will be required from all patients at baseline unless not considered feasible (i.e. in the case of disease progression in the CNS only). Tissue will also be collected at the time of disease progression when the patient is undergoing biopsy for clinical purposes. Blood will be collected from patients at the following timepoints: baseline, every 6 weeks on trial therapy, and at progression.

The subject's consent to the use of donated biological samples is mandatory.

9.1 Integrated Correlative Studies

9.1.1 Molecular Profiling using the Oncomine Comprehensive Research Panel

The genomic landscape of EGFR mutant lung cancers

Using the Oncomine next generation sequencing assay, we will centrally confirm the presence of the specific sensitizing mutation in EGFR. This will be done after the patient is enrolled and treated on trial for the purposes of analyzing the data. Additionally, co-occurring mutations are often detected with EGFR mutations and little is known about how these affect response to therapies. For example, mutations in tumor suppressors like TP53 occur in >50% of EGFR mutant tumors. Tumors that do not have TP53 mutations however, have mutations in other tumor suppressor genes such as ATM, CDKN2B and RB1. The data that we collect from the Oncomine panel provide us with the unique opportunity to analyze the relationship between co-occurring mutations, response to therapy and drug resistance. We hypothesize that co-occurring mutations may impact the PFS and response to Osimertinib (AZD9291) with or without bevacizumab. The objective of this analysis is to identify genes that when altered modulate the response to Osimertinib (AZD9291) +/- bevacizumab either by affecting extracranial and CNS response rates, PFS or OS. We hypothesize that: 1) tumors with mutations in TP53 at baseline will have a worse outcome as compared to those with intact TP53, 2) mutations in genes that potentiate angiogenic signaling will be associated with reduced response to bevacizumab. In addition, to testing these specific hypotheses, this assay data will allow us to identify novel genes and pathways that may play a role in response and resistance to these drugs. To perform these experiments, we will comprehensively assess mutations and/or copy number alterations in 143 genes cancer genes using the Oncomine panel.

The Oncomine™ Comprehensive Assay is composed of primer pools for highly multiplex PCR amplification of DNA to provide substrate for next generation sequencing to detect single nucleotide variants (SNVs), small insertions and deletions (indels), copy number variants (CNVs), and gene fusions within tissue samples. The assay was developed and is manufactured by ThermoFisher Scientific for use with Ion Torrent sequencing instruments and data analysis software. The assay simultaneously interrogates DNA sequence in 143 cancer-related genes. Full coding sequences or selected regions of the genes (hotspots) are analyzed, based on the most frequent sites of alterations in cancer. Gene fusions are assayed by analysis of cDNA generated from RNA by reverse transcription prior to amplification with the Oncomine primers (RNAseq). The assay calls for 20ng of DNA and 10ng of RNA per tumor, extracted from formalin-fixed, paraffin-embedded or fresh tissue samples.

The Oncomine workflow has been extensively validated by the NCI-MATCH Trial, and the Yale Clinical Molecular Pathology Laboratory (YCMPL), which participated in this validation and is a MATCH sequencing center, has been performing sequencing of tumor DNA and RNA with the Oncomine assay for several years. The system has been optimized and updated several times during that period.

Paraffin blocks containing tissue biopsy specimens will be sent to the YCMPL for pre-analytic work up and processing. The blocks will be sectioned and one section stained with hemotoxylin and eosin for examination under the light microscope of tumor content and quality (e.g., amount of necrosis). Regions of the tissue section containing tumor will be circled on the stained slide

and corresponding regions on unstained slides bearing sections from tissue adjacent to the stained section will be manually microdissected from the sections. If the tumor cells on the slide are scattered or clustered in small clumps within normal tissue, laser capture microdissection will be used to collect the tissue for analysis.

DNA and RNA will be extracted from the deparaffinized tissue and subjected to analysis using the Oncomine primer pools and sequencing on an Ion Torrent personal genome machine (PGM), followed by a data analysis using Torrent Suite, Ion Reporter, and custom software developed at Yale. The data will be assessed by automated and manual quality control procedures, and any variants that pass filters will be evaluated manually to eliminate known artifacts and confirm accuracy.

9.1.1.1 Collection of specimen(s)

Tumor tissue will be obtained by a surgical or biopsy procedure. Tissue will be required from all patients at baseline unless not considered feasible (i.e. in the case of disease progression in the CNS only). Tissue will also be collected at the time of disease progression when the patient is undergoing biopsy for clinical purposes.

9.1.1.2 Handling of specimen(s)

See **Appendix D** for details.

9.1.1.3 Shipping of specimen(s)

See **Appendix D** for details.

9.1.1.4 Site(s) Performing Correlative Study

This assay will be performed under the direction of Dr. [redacted] at the Yale School of Medicine.

9.2 Exploratory Correlative Studies

9.2.1 Angiogenesis, Immune and Signaling Pathway Markers

The major target of bevacizumab is VEGF, which can bind to receptors expressed by endothelial cells. In addition to its known ability to modulate of endothelial cell function, angiogenesis and vascular permeability, VEGF can also regulate the mobilization of leukocytes, in particular immune cells of the myeloid lineage such as macrophages, which also express VEGF receptors. While biomarkers for bevacizumab in NSCLC are lacking, it is notable that in pre-clinical models of *EGFR* mutant lung adenocarcinoma, tumor derived VEGF production is induced by TKI resistant xenografts.(74) Moreover, combining bevacizumab with erlotinib improves progression free survival in patients with *EGFR* mutant tumors, including those with acquired drug resistance.(63)

In pre-clinical models of brain tumors, peri-vascular tumor associated macrophages can also confer acquired resistance to bevacizumab treatment. Biomarkers for bevacizumab and osimeritinb may therefore be expressed by lung cancer cells, vascular cells, or myeloid cells in the tumor

microenvironment (TME). To address these possibilities, the level of VEGF and activation state of the angiogenesis marker CD31/PECAM will be evaluated to explore whether it is correlated with sensitivity and primary or acquired resistance to Osimertinib (AZD9291) +/- bevacizumab. Using multiplexed quantitative immunofluorescence (QIF), we will establish a panel of markers to simultaneously measure the level of VEGF protein, CD31+ or CD34+ endothelial cells, cytokeratin+ tumor epithelial cells and CD68+ tumor associated macrophages (e.g. DAPI/CK/VEGF/CD31/CD68). We will study the association between the level of VEGF in vascular cells, tumor cells, stromal cells and macrophages; and response to therapy. We will also determine the level of CD31+ endothelial cells as marker of blood vessel content; and the amount of CD68+ macrophages in the samples. In addition, to address the possible immunomodulatory effect of the bevacizumab/ Osimertinib (AZD9291) therapy, we will also measure the levels of PD-L1 protein in tumor and stromal cells using QIF and a validated assay combining DAPI, cytokeratin and PD-L1.(69, 70)

The Specialized Translational Services (STS) and/or [redacted] lab will perform QIF analysis of the proposed markers/panels. Variables that might influence biomarker expression levels – specifically the ones of phosphorylated epitopes – in situ quantification of FFPE tissue will only be performed on biopsy specimens. Biopsies are routinely transferred into 10 % neutral buffered formalin (10% NBF) right after tissue accruement, without any warm ischemic time and reducing cold ischemic time to a minimum (0 to a maximum of 15 minutes). The time of infusion of formalin into the tissue is short considering few millimeter thickness of core needle biopsies. This approach allows accruement and analysis of tissue representative to the in vivo status. Although some of the phosphorylated proteins degrade rapidly during tissue processing, they can be reliably quantified in biopsy samples.

Drs. [redacted], [redacted], and [redacted] will oversee the work performed in the STS lab. The STS lab is led by Dr. [redacted] and is part of the Yale Pathology Tissue Services (YPTS) under the leadership of Dr. [redacted]. The STS lab is a CLIA certified institution focusing on in situ quantification of proteins and non-coding RNAs in formalin-fixed, paraffin-embedded (FFPE) tissue samples. The lab is well equipped for biochemical and molecular biological techniques with all necessary facilities. In addition, tissue culture work is performed in an adjacent lab space. The STS lab is equipped with a PT Module, a DAKO autostainer and a Bond RX automated staining platform, all of which are important to optimize, standardize and automate staining conditions and assays and to reduce pre-analytical variables during staining processes. The lab includes a microscopy room with three custom designed fluorescence imaging workstations (HistoRx PM-2000) necessary for quantitative immunofluorescence (QIF) using the AQUA technology. The pathology department at Yale University also has an Aperio CS workstation for bright-field slides and TMA analysis, which can be used if necessary.

Quantification of proteins in FFPE tissue is performed with quantitative immunofluorescence (QIF) using the method of automated quantitative analysis (AQUA) as described previously (75). AQUA® is a method to objectively and accurately measure biomarker expression within defined tumor areas and subcellular compartments based on co-localization with cytokeratin and DAPI. Multiplexed staining of a target of interest and cytokeratin allows to define the tumor area (in case of epithelial tumors) and to measure the pixel intensity of the target within the cytokeratin positive cells. After immunofluorescent staining of the tissue, a series of monochromatic, high resolution

images is captured using the PM2000 image workstation. For each field of view (FOV) on a whole tissue section images for three different channels are obtained. Signal from DAPI stain visualizes the nuclei, cytokeratin is visualized with Alexa 546 and the protein of interest with Cy5. Binarizing the cytokeratin signal creates a tumor mask which allows the measurement of pixels of the target of interest within this defined tumor area and/or within subcellular compartments. This method of biomarker quantification can be applied to tissue micro arrays (TMAs) and to whole tissue sections (WTSs).

For quality control purposes and standardization, each antibody is validated using a previously described antibody validation protocol (76). Antibodies are titrated on test TMAs consisting of 40 cancer specimens and the optimal titer is chosen according to an expression range graph, which allows objective assessment of the optimal dynamic range and the signal to noise ratio of a given protein of interest. Specificity is evaluated by Western Blots for every protein-specific antibody to confirm the recognition of a single band at the correct molecular weight. These assays are followed by staining and AQUA analysis of a cell line TMA and protein expression of a given antibody on cell lines on the TMA are correlated with the Western Blot result. Reproducibility of the antibody is assessed with AQUA analysis of serial sections of test arrays stained under the same conditions on different days. An r2 of 0.75 and above is defined as sufficient antibody reproducibility. Only antibodies that validate by this protocol are used for assessment of clinical specimens.

Antibodies to be used in panel are: CD34, Cytokeratin, CD68 and VEGF. A second panel will include PD-L1 clone E1L3N from CST.

All assays are standardized and automated after validation. This approach will allow us to standardize the assays and offer them as CLIA certified tests for clinical evaluation.

In addition to performing IHC on tumor samples, we will also perform RNA sequencing. The Yale Center for Genome Analysis has expertise in performing RNA sequencing on FFPE specimens. These studies will allow us to establish whether we can identify signatures of angiogenesis, hypoxia and inflammation and to determine whether these correlate with sensitivity to Osimertinib (AZD9291) +/- bevacizumab.

9.2.1.1 Collection of specimen(s)

Tumor tissue will be obtained by a surgical or biopsy procedure. Tissue will be required from all patients at baseline unless not considered feasible (i.e. in the case of disease progression in the CNS only). Tissue will also be collected at the time of disease progression when the patient is undergoing biopsy for clinical purposes.

9.2.1.2 Handling of specimen(s)

See **Appendix D** for details.

9.2.1.3 Shipping of specimen(s)

See **Appendix D** for details.

9.2.1.4 Site(s) Performing Correlative Study

These assays will be performed at the Yale School of Medicine in the following laboratories: Dr.

[redacted], PhD, [redacted], PhD, Dr. [redacted], and Dr. [redacted].

9.2.2 Circulating Tumor DNA

The release of small amounts of cell-free DNA into the bloodstream from dying tumor cells has been well documented in patients with various malignancies. Driven by improvements in assay technologies, such circulating tumor DNA (ctDNA) is showing excellent promise as a biomarker for diagnosing cancer, assessing treatment efficacy, and monitoring disease progression. A particularly compelling application of ctDNA is the non-invasive determination of a tumor's mutation profile in order to guide targeted therapy. In cases where mutations are heterogeneously present in different metastatic lesions, this "liquid biopsy" approach could provide a more comprehensive assessment of mutation status than a traditional tissue biopsy. Rather than sampling just a small portion of a tumor at a single site, circulating DNA provides an opportunity to simultaneously sample mutations in DNA derived from all metastatic tumor sites in the body. Furthermore, because it involves only a simple blood draw, ctDNA can be sampled longitudinally during treatment to monitor for the emergence of resistance mutations over time without requiring repeated tumor biopsies.

Dr. [redacted] laboratory at the Yale School of Medicine has developed an ultrasensitive assay that applies error suppression techniques to next-generation DNA sequencing technologies to measure low-abundance ctDNA with excellent sensitivity and reproducibility.(77) With further modifications of the published method, a single variant among ~5,000 DNA molecules can be detected, and thousands of possible mutations in ~50 mutation prone-regions in 24 genes can be evaluated simultaneously. A novel multiplexing strategy(78) allows batch testing of as many as 96 patient samples in a highly parallel manner. It covers most somatic mutations commonly found in non-small cell lung cancers, including true hotspot mutations occurring within oncogenes as well as mutations within warm-spot regions of tumor suppressor genes such as TP53 (see Table).

Table. Common somatic mutations in NSCLC that are covered in our assay (from TCGA data)(79) (Listed are genes that have >2% mutation frequency)

	Adenocarcinoma	Squamous cell carcinoma
Somatically mutated genes (frequency)	TP53 (51.8%) KRAS (26.3%) EGFR (11.4%) STK11 (8.8%) CDKN21 (6.6%) BRAF (6.6%) PIK3CA (4.4%) FLT3 (4.0%) CTNNB1 (3.5%) PTEN (2.2%)	TP53 (79.3%) CDKN2A (14.9%) PIK3CA (14.9%) PTEN (8.1%) BRAF (6.6%) PPP2R1A (4.6%) FLT3 (4.0%) KIT (3.5%) EGFR (2.9%) EZH2 (2.3%)

The assay is able to track quantitative changes in ctDNA levels with successful treatment or disease progression. It can identify drug-sensitizing mutations as well as the emergence of resistance mutations (including the EGFR T790M mutation) non-invasively. ctDNA levels typically drop

when a patient exhibits a good treatment response (based on imaging), and rise when disease progression occurs.

We will utilize this assay for non-invasive mutation profiling at baseline, longitudinally during therapy with Osimertinib (AZD9291) with or without bevacizumab, and at progression on study therapy to determine whether plasma-based biomarkers can predict for treatment benefit. We aim to test the hypothesis that circulating tumor DNA can be used as a quantitative biomarker of treatment response and resistance. We expect levels of mutant ctDNA to decline within a few weeks after initiation of treatment if the patient has a good therapeutic response. Such declines have been observed anecdotally in previous studies, but the timing and magnitude of decline would be important to characterize in the setting of a clinical trial where all patients are receiving a uniform therapy. Also, the development of the resistance mutation C797S has been documented in patients treated with third-generation EGFR inhibitors, and this mutation has been reported to be detectable in ctDNA. In this study, we aim to collect serial blood samples during therapy to assess whether the C797S mutation (and possibly other mutations) can be detected in the plasma of patients who progress, and whether such mutations are detectable prior to clinical evidence of progression.

9.2.2.1 Collection of specimen(s)

10 ML of blood will be collected from patients in purple top EDTA tubes at the following timepoints: baseline, every 6 weeks on trial, and at progression.

9.2.2.2Handling of specimen(s)

See **Appendix E** for details.

9.2.2.3 Shipping of specimen(s)

See **Appendix E** for details.

9.2.2.4 Site(s) Performing Correlative Study

This assay will be performed by Dr. [redacted], MD, PhD at Yale School of Medicine.

9.2.3 Blood-based Markers of Angiogenesis and Inflammation

Blood-based biomarkers

To date, the effort to identify candidate predictive blood-based markers for anti-angiogenic inhibitors has been challenging for many reasons. These include biological complexity, limitations of available reagents, limited sample collection in most trials, and a lack of randomization, which is needed to deal with the potential confounding of prognostic and predictive markers. Many of these barriers have now been overcome. Compared to tissue-based biomarkers, blood-based biomarkers have the significant advantages of low cost, universal applicability, and the ability to be followed over the course of a patient's treatment. By focusing on soluble factors of known biological relevance, further scientific, diagnostic, and therapeutic efforts are greatly facilitated.

Anti-VEGF therapies

Recently, our multiplex ELISA approach has identified several strong candidate predictors of benefit from bevacizumab. In CALGB80303, a phase III study of gemcitabine ± bevacizumab, our

group identified VEGF-D as a candidate predictor for benefit from bevacizumab(80). VEGF-D, as measured by IHC in FFPE tumor samples, was also a predictive marker for bevacizumab in the randomized phase II MAX study(81). The related factor, VEGF-C, has also been implicated as a predictive marker for bevacizumab in a non-randomized cohort comparison study(82). Processed forms of VEGF-D and VEGF-C, which are abundant in tumor tissues, can bind and activate VEGFR-2, potentially bypassing VEGF-A blockade. In addition, recent work has implicated processed forms of VEGF-A as predictive markers for bevacizumab(83, 84). While there is considerable biological overlap, processed or short isoforms of VEGF-A are generally associated with pathological angiogenesis while longer isoforms tend to be associated with physiological angiogenesis. Taken together, these findings suggest that VEGF family ligands may mediate sensitivity and resistance to the VEGF-A binder bevacizumab. Importantly, many limitations in the quality of reagents, particularly around VEGF-A and VEGF-C, have now been overcome.

Another recent and instructive success is the identification of IL-6 as a strong candidate predictive biomarker for anti-VEGF therapy in renal cell carcinoma. This marker was found to be a predictive marker in two independent phase III studies, each of which used a different VEGF inhibitor. VEG105192 was a phase III study of BSC +/- pazopanib in refractory mRCC(85) and CALGB90206 was a phase III study of IFN +/- bevacizumab in 1st line mRCC (86). Both of these studies found that high levels of IL6 predicted for greater benefit from these VEGF inhibitors(65, 87). The CALGB study with bevacizumab also found a predictive role for HGF that was IL-6 dependent (i.e., a 3-way treatment interaction)(87). The role of the IL6-Jak-Stat axis is particularly intriguing given its role in tumor associated inflammation and anti-tumor immunity. Numerous other inflammatory mediators have been shown to regulate tumor angiogenesis and sensitivity to anti-VEGF therapy(88, 89). Tumor angiogenesis, inflammation, and anti-tumor immunity have highly interconnected biologies, a topic that has been extensively reviewed(90-92). However, to date, these factors have not been systematically interrogated in most anti-VEGF therapy trials. Analysis of the role of inflammation in mediating resistance to anti-VEGF therapy is now highly clinically relevant, particularly since most of these factors are now targetable in the clinic with agents either FDA approved or in clinical trials.

Anti-EGFR therapies

Blood-based biomarkers for predicting benefit from anti-EGFR therapy have also been recently identified. Currently, in colorectal cancer treatment, RAS mutation status in the patient's tumor sample is the widely accepted gold standard predictive marker for cetuximab, as well as panitumumab. However, for a variety reasons, blood-based markers have not been extensively evaluated in large, randomized anti-EGFR trials. In the phase III trial of best supportive care ± erlotinib in non-small cell lung cancer, serum TGFα was identified as a candidate predictor(93). In colorectal cancer, several EGFR ligands have been identified as candidate predictors for cetuximab in non-randomized studies(94). Using FFPE tumor samples from the randomized phase II study CALGB80203 evaluating FOLFOX or FOLFIRI +/- cetuximab, our group recently identified gene expression of HER3 and CD73 as candidate predictors of benefit from cetuximab (95). These results are particularly intriguing since CD73 is a well-recognized modulator of inflammation and immunity and anti-EGFR therapies are well known to be associated with inflammatory responses to treatment (i.e, acneiform rash). Moreover, CD73 expression also identified a group of patients whose tumors were KRAS mutated that benefited from cetuximab; if confirmed, this finding has major implications for our understanding of RAS mutations and anti-

EGFR therapies. Other mRNA markers that showed modest trends in either PFS or OS included HER2, HER4, BTC, DUSP4, and HB-EGF.

We have recently optimized methods for the use of multiplex ELISA methods for the majority of HER axis ligands and soluble receptors in the plasma of cancer patients. We have also recently developed completely novel ELISAs that are not commercially available for both soluble HER3 and soluble CD73. Initial analyses of the plasma samples from CALGB80203 were presented at ASCO in 2014(96). In this analysis, plasma levels of EGF and sHER3 were potential predictive biomarkers for benefit from cetuximab. Low levels of EGF predicted for OS benefit from cetuximab in KRAS WT tumors and lack of benefit in KRAS mutant patients (codons 12 and 13 only), but were not predictive across all patients combined. Patients with higher sHER3 levels had significant OS benefit from cetuximab treatment. The consistent finding that HER3 is predictive in both tissue and plasma justifies further investigation.

We have also recently completed our analysis of CD73 levels in plasma samples from patients treated in CALGB80203. This analysis found plasma CD73 was strongly predictive of overall survival for cetuximab (unpublished data). The finding in CALGB80203 that both tissue and plasma CD73 are also predictive of benefit from cetuximab suggests the importance of CD73, and by extension ADCC and inflammation, as mediators of cetuximab sensitivity and resistance; these results also merit further investigation.

The application of multiplex ELISA approaches in clinical samples is rapidly evolving, having only recently shown positive results. The design of our multiplex panel array to interrogate diverse biologies related to angiogenesis is novel. Many of the analytes in our multiplex array were developed specifically for our use and have been carefully optimized for performance in plasma and serum samples from cancer patients. Our approach utilizes the Searchlight™ platform from Aushon BioSystems Inc. We have worked in tandem with the team at Aushon for over 7 years to develop multiple new assays and optimize the performance of our specific panel design (see Table 9.3.4). All antibody pairs have been validated to limit cross-reactivity and optimal dilutions were identified for every panel. Specific blocking buffers were identified, cross-reactivity of antibodies was tested and non-specific binding was minimized. Preliminary testing and plate validation were performed by both groups independently. Freeze/thaw stability tests were done for all individual analytes. Lastly, assay performance across the different tissue types (citrated plasma, EDTA plasma and serum) was evaluated.

Table 9.3.4. Plasma-based marker identification

Soluble Angiogenic Factors		**Matrix-Derived Factors**	**Markers of Vascular Activation and Inflammation**	**Anti-EGFR therapies**
ANG-2	PDGF-BB	sEndoglin	CRP	EGF
bFGF	PlGF	Osteopontin	ICAM-1	HB-EGF
HGF	VEGF-A	TGFβ1	IL-6	TGFα
IGFBP1	VEGF-D	TGFβ2	PAI-1 Active	s-EGFR
IGFBP2	sVEGFR1	TGFβRIII	PAI-1 Total	s-HER2
IGFBP3	sVEGFR2	TIMP1	SDF-1	s-HER3

PDGF-AA	sVEGFR3	TSP2	VCAM-1	s-CD73

We plan to use this approach to analyze plasma samples obtained longitudinally from patients treated with AZD9291 (osimertinib) plus bevacizumab versus Osimertinib (AZD9291) alone. Our hypothesis is that VEGF- and EGFR-related candidate markers will predict for benefit or lack of benefit from bevacizumab and Osimertinib (AZD9291), respectively. Additionally, we hypothesize that early changes in VEGF- and EGFR-related candidate markers will predict for greater or lesser benefit from bevacizumab and Osimertinib (AZD9291), respectively. Our approach is technically robust and readily adaptable to clinical practice. Because this data will be derived from patients, even preliminary data may significantly improve our understanding of how angiogenesis and tumor growth factors are regulated in cancer patients. Promising findings can be followed up in future clinical studies and in preclinical models. Because our lab serves as the core lab for multiplex ELISA analyses within the Alliance, the current profiling can be compared to the profiles seen in other studies, helping to optimize future profiling approaches and provide the disease specific context needed for clinically meaningful companion diagnostics. Given the results of our prior work and the work of others, we anticipate being able to identify and validate or refute candidate markers of benefit that are specific for anti-angiogenic agents. We also anticipate that we will identify multiple prognostic factors.

The characteristics of blood analytes will be investigated using a variety of statistical approaches. Baseline and on-treatment levels will be quantified and change from baseline will be determined for all analytes at the desired time points (waterfall plots). Linear mixed-effects model will be performed to understand the longitudinal trends of the analytes over the different time points. Coefficients of variation will be used to assess the dispersion of each analyte. Pair-wise correlations among the analytes will be estimated using Spearman's rank correlation. Descriptive statistics will also be presented.

Blood analytes will be correlated with progression-free survival (PFS) and/or overall survival, and correlations with response rate can also be explored for consistency with those seen with PFS using Cox regression analysis. Continuous analytes intensities for baseline measures and log ratios of on-treatment over baseline intensities [log(on-treatment/baseline)] will be used. For each analyte, linear regression and Pearson coefficient correlations will be used for assessing the associations with continuous response measure. Summary statistics will include, but are not limited to, the hazard ratios and associated confidence intervals. Kaplan-Meier plots and log-rank tests will be presented and performed to compare candidate biomarker groups.

9.2.3.1 Collection of specimen(s)

10 ML of blood will be collected from patients in purple top EDTA tubes at the following time points: baseline, every 6 weeks on trial therapy, and at progression.

9.2.3.2 Handling of specimen(s)

See **Appendix E** for details.

9.2.3.3 Shipping of specimen(s)
See **Appendix E** for details.

9.2.3.4 Site(s) Performing Correlative Study
These assays will be performed by Dr. [redacted], MBA, PhD, at Duke University.

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy except where indicated. Scans and x-rays (including echocardiogram) must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. All evaluations and visits can be +/- 3 days except where indicated.

	Pre-Study	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6 [n]	Disease Progression	Off Study
		Day 1	Day 8	Day 15	Day 1	Day 1	Day 1	Day 1	Day 1		
Osimertinib (AZD9291) [a]		X			X	X	X	X	X		
Bevacizumab[b]		X			X	X	X	X	X		
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X	X	X	X	X	X	X	X		X
Physical exam[c]	X	X	X	X	X	X	X	X	X		X
Vital signs	X	X	X	X	X	X	X	X	X		X
Height	X										
Weight	X	X	X	X	X	X	X	X	X		X
Performance status	X	X	X	X	X	X	X	X	X		X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X		X
Serum chemistry[d]	X	X	X	X	X	X	X	X	X		X
Urine protein[e]	X					X		X			
ECG[f]	X				X	X		X			
Echocardiogram[g]	X							X			
Adverse event evaluation		X	X	X	X	X	X	X	X		X
B-HCG[h]	X										
CT chest/abdomen/pelvis and MRI brain with associated tumor measurements[i]	X					X		X			X
Tumor biopsy	X[j]									X[k]	

Blood for correlative studies[l]	X					X		X		X	
Ophthalmic Exam[m]		At any time if patient experiences visual symptoms									

a. Osimertinib (AZD9291) : 80mg PO daily continuously in 21-day cycles for patients randomized to the combination or monotherapy arm. Drug is dispensed on Day 1 of each cycle.
b. Bevacizumab: 15mg/kg IV every 21 days (Day 1 of each cycle) for those patients randomized to the combination arm.
c. Physical exam will include assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose, and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurologic systems.
d. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
e. Urine protein should be screened by urine analysis every 6 weeks while the patient is on study treatment. At the pre-study visit, if protein is 2+ or higher, 24-hour urine protein should be obtained and the level should be <1000 mg for patient enrollment.
f. ECG to evaluate the QTc must be obtained pre-study and prior to treatment and on day 1 of cycles 2, 3 and 5. After cycle 5, ECG should be obtained every other cycle (i.e. every 6 weeks) while patient is on study therapy, or more frequently if QTc prolongation is observed. See below for details.
g. Left ventricular ejection fraction must be assessed by echocardiogram prior to treatment and every 3 months while on treatment. Evaluation can be +/- 7 days. See below for details.
h. Serum or urine pregnancy test (for women of childbearing potential).
i. CT chest/abdomen/pelvis and MRI brain must be repeated every 6 weeks while on study. Evaluation can be - 7 days. Tumor measurements include RECIST 1.1 and RANO-BM.
j. Tumor tissue must be obtained prior to treatment by a surgical or biopsy procedure. Tissue will be required from all patients unless not considered feasible (i.e. in the case of disease progression in the CNS only). Core biopsies must be performed at least 7 days prior to treatment start. Archival tissue is acceptable if no systemic therapy has been administered in the interim and sufficient material is present to meet the requirements listed in Appendix D.
k. Tumor tissue should be collected when a biopsy is occurring for clinical purposes at the time of disease progression.
l. Blood will be collected for correlative studies from patients at the following timepoints: pre-treatment (can be on C1D1 prior to administration of study treatment), every 6 weeks while on trial therapy, and at disease progression.
m. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.
n. Procedures beyond Cycle 6 should follow the procedures specified for Cycles 5 and 6 on an alternating basis (i.e. Cycle 7 should be consistent with Cycle 5, Cycle 8 should be consistent with Cycle 6, Cycle 9 should be consistent with Cycle 5, etc.).

Resting 12-lead ECG

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to assessment. All ECGs should be recorded with the patient in the same physical position. A standardized ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

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

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

Echocardiogram

An Echocardiogram to assess LVEF will be performed at screening (prior to first dose of osimertinib) and at least every 3 months throughout the treatment period. The patients should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken. A 28-day follow- up assessment will be required if an on treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect

For the purposes of this study, patients should be re-evaluated for response every 6 weeks with CT scans of the chest/abdomen/pelvis and MRI of the brain. In addition to a baseline scan, confirmatory scans should also be obtained 6 (not less than 4) weeks following initial documentation of objective response.

Response and progression of systemic disease will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).(71) Response and progression of intracranial disease will be evaluated in this study using the RANO-Brain Metastases Criteria.(72) Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Osimertinib (AZD9291) +/- bevacizumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline and received at least one cycle of therapy will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

11.1.2 Disease Parameters

Measurable disease - Non-CNS. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area may be considered measurable if they show unequivocal progression on two consecutive scans.

Measurable disease - CNS. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥5 mm (≥0.5 cm) by brain MRI with 1.5 mm slice thickness or less. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area may be considered measurable if they show unequivocal progression on two consecutive scans.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions – non-CNS. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal

lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the non-CNS disease.

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

Target lesions – CNS. All measurable brain lesions up to a maximum of 5 lesions, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the longest diameters for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of CNS disease.

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

11.1.3 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

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

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes

reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.1.4 Response Criteria for Non-CNS Disease Using RECIST 1.1

11.1.4.1 Evaluation of Non-CNS Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2 Evaluation of Non-CNS Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

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

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

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

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

11.1.4.3 Evaluation of Best Overall Non-CNS Response

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

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may

beaccepted as disease progression.

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Response Criteria for CNS Disease Using RANO-BM

11.1.5.1 Evaluation of CNS Target Lesions

Complete Response (CR): Disappearance of all CNS target lesions for at least 4 weeks with no new lesions, no use of corticosteroids, and patient is stable or improved clinically.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameters of CNS target lesions, taking as reference the baseline sum longest diameters sustained for at least 4 weeks, no new lesions, stable to decreased corticosteroid dose, stable or improved clinically.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.5.2 Evaluation of CNS Non-Target Lesions

Complete Response (CR): Disappearance of all enchancing CNS non-target lesions and no new CNS lesions.

Non-CR/Non-PD: Persistence of one or more non-target CNS lesion(s).

Progressive Disease (PD): Appearance of one or more new CNS lesions, unequivocal progression of existing non-target CNS lesions, and/or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

11.1.5.3 Evaluation of Best Overall CNS Response

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

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

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Cortico-steroids*** **	**Neurologic Status**	**Overall CNS Response**	**Best Overall CNS Response when Confirmation is Required***
CR	CR	No	None	Stable or improved	CR	≥4 wks. Confirmation*
CR	Non-CR/Non-PD	No	Stable or decreased	Stable or improved	PR	≥4 wks. Confirmation*
CR	Not evaluated	No	Stable or decreased	Stable or improved	PR	
PR	Non-CR/Non-PD/not evaluated	No	Stable or decreased	Stable or improved	PR	
SD	Non-CR/Non-PD/not evaluated	No	Stable or decreased	Stable or improved	SD	Documented at least once ≥4 wks. from baseline*
PD	Any	Yes or No	Any	Any	PD	no prior SD, PR or CR
Any	PD**	Yes or No	Any	Any	PD	
Any	Any	Yes	Any	Worse****	PD	
Any	Any	Yes or No	Any	Any	PD	

* See RANO-BM manuscript for further details on what is evidence of a new lesion. ** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. *** Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration. **** Patients with worsening clinical status without objective evidence of disease progression can qualify for PD. Patients with a global deterioration of neurologic status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic CNS deterioration.*" Every effort should be made to document the objective CNS progression even after discontinuation of treatment.

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

Non-Target Lesions	New Lesions	Overall CNS Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5.4 Evaluation of Best Overall Response (non-CNS and CNS disease)

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

Best Overall Response Assessment

Non-CNS (RECIST 1.1)	CNS (RANO-BM)	Best Overall Response
CR, PR, or SD	CR, PR, or SD	Log as CNS and non-CNS CR, PR, or SD
PD	CR, PR, or SD	Log as CNS CR, PR, or SD; log as non-CNS PD
CR, PR, or SD	PD	Log as CNS PD; log as non-CNS CR, PR, or SD
PD	PD	Log as both CNS and non-CNS PD

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression (in CNS or non-CNS disease) or death, whichever occurs first.

Bi-compartmental PFS

Non-CNS (RECIST 1.1)	CNS (RANO-BM)	Bi-compartmental PFS	Note
PD	CR, PR, or SD	Log as a PFS event	Log as non-CNS PD
CR, PR, or SD	PD	Log as a PFS event	Log as CNS PD
PD	PD	Log as a PFS event	Log as both CNS and non-CNS PD

11.1.7 Time to CNS Progression

Time to CNS Progression is defined as the duration of time from start of treatment to time of progression in the CNS.

11.1.8 Overall Survival

OS is defined as the duration of time from start of treatment to death.

12 STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.1.1 Method

CTMS Routine Monitoring:
This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.1.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials), the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

See Section 12.1.1 for details on CDUS reporting. As the data management center for this trial, Theradex is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 CTEP Multicenter Guidelines

N/A

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).

Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Patients will be randomized 1:1 to receive the combination of Osimertinib (AZD9291) plus bevacizumab or Osimertinib (AZD9291) alone. Treatment will continue until disease progression or the occurrence of one of the criteria listed in Section 5.3. However, if a patient has disease progression but is considered to be deriving clinical benefit (i.e. progression at one site of disease with other sites well-controlled) they may receive local therapy (such as radiation therapy) to the progressing lesion and continue on trial therapy.

Power analysis and sample size estimation:
The primary objective of this multi-center, randomized Phase II trial is to compare the progression

free survival (PFS) between two study arms, i.e. Osimertinib (AZD9291) alone versus Osimertinib (AZD9291) plus bevacizumab. The secondary objectives of this study are to estimate and compare the response rate (RR), intracranial response rate (IRR), time to intracranial progression, overall survival (OS), and safety profile.

The sample size estimation is completed using the log rank test. With the proposed sample size of 110 evaluable patients (55 patients for combination arm and 55 patients for Osimertinib (AZD9291) arm; 83 events are required at the final analysis), it provides at least 80% power to detect a 9 month improvement in the median PFS for the combination arm, i.e., estimated median PFS ≈ 24.2 months for the combination arm and median PFS = 15.2 months for Osimertinib (AZD9291) arm (HR = 0.63), with one-sided type I error = 10%. This calculation is based on the assumption of accrual time = 36 months, additional follow-up time = 24 months, the number of total estimated PFS events in the two arms is 84 (46 events in the single-agent arm and 38 events in the combination arm), and the accrual rate is about 3 patients / months. In addition, it is estimated that about 2% of patients of enrolled patients will not begin protocol therapy. Therefore, 112 patients will be enrolled to provide at least 110 evaluable patients which will provide sufficient statistical power to detect clinically significant difference between the combination arm and single arm.

Randomization:
The eligible patients will be randomized according to a stratified permuted block randomization scheme. Stratification will be based on EGFR mutation type (exon 19 deletion or L858R/other), number of untreated new or progressing brain metastases (≥4 or <4), and performance status (0-1 vs 2). Randomization will be proceeded within strata according to a permuted block scheme with a block size, or balancing interval, varying randomly between 3 or 6 according to the outcome of a computer generated random number. This will ensure that the cumulative number of assignments to each treatment will be in balance in 1:1 ratio after each block of assignments has been made.

Interim analysis:
The futility analysis will be based on the method proposed by Wieand et al.(99) If after 42 events (50% of the targeted information) are observed and the observed hazard ratios for combination vs. single-agent arm comparisons favor the single-agent arm (i.e. HR>1), then the combination arm will be terminated for futility and the study will be closed to accrual. We do not plan to perform a superiority test during the interim analysis as part of this study design. Accrual will not be suspended during safety and interim analyses.

Statistical analysis plan:
Demographic information, such as age and race, will be tabulated. Descriptive statistics, including means, standard deviations, and ranges for continuous parameters, as well as percents and frequencies for categorical parameters, will be presented. Adverse medical events will be tabulated. NCI toxicity Grade 1 to Grade 4 laboratory abnormalities will be listed.

For lifetime data analyses, e.g., PFS and OS, the two study arms will be compared for progression free survival with Kaplan-Meier estimates and stratified log-rank tests. The Rothman confidence interval (CI) will be reported. In addition, the possible risk factors will be compared for survival with log-rank test. For multivariate analysis, the proportional hazards Cox model will be applied

to investigate potential prognostic factors, such as age and stage of disease, as well as stratification factors of the PFS and OS data. The adjusted p-values of the hazard ratios and the adjusted 95% and 80% confidence intervals will be reported.

The objective response is defined as a complete or partial response, as determined by investigator assessment using RECIST v1.1 and confirmed by repeated assessments > 4 weeks after initial documentation. Patients with missing or no response assessments will be classified as non-responders. Similarly, RANO-BM will be used for intracranial response. The ORR and intracranial RR will be estimated using the 95% confidence interval (CI) based on Wilson's method. The Wilcoxon rank sum test and Fisher's exact test will be applied to study the association between the response status and the continuous and categorical variables respectively. The generalized non-linear model and logistic regression will be applied for multivariable data analysis. The adjusted p-value and 95% CI of the odds ratios (OR) will be reported.

We will apply the Kappa Statistic with 95% confidence interval (CI) to measure the agreement between local tests and the Oncomine Panel at a central lab.

The biomarker data, e.g., Oncomine Comprehensive Research Panel, analysis will be completed using Lasso-based elastic net method. The elastic net method is a variable selection procedure by L1 and L2 penalized estimation that enforces variable selection and shrinkage simultaneously. The penalty parameter that controls the shrinkage of fixed terms and the variable selection will be determined by k-fold cross validation. Because of the limited sample size, the biomarker data analysis is for exploratory research only. The statistical analyses will be completed by either R 3.2.5 or SAS 9.4 statistical program in this project.

13.2 Sample Size/Accrual Rate

This trial will be available to all sites of the ETCTN, and we anticipate that 8-10 sites will participate. With an accrual rate of approximately 3 patients per month between the 8-10 sites, we will expect to fully enroll this trial in approximately 3 years.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	1	0	0	**2**
Asian	12	8	0	0	**20**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Native Hawaiian or Other Pacific Islander	1	1	0	0	**2**
Black or African American	6	5	0	0	**11**
White	35	23	5	3	**66**
More Than One Race	5	3	2	1	**11**
Total	**60**	**41**	**7**	**4**	**112**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

13.3 Stratification Factors

EGFR mutation status (exon 19 deltion vs L858R/other), number of untreated new or progressing brain metastases (≥4 or <4), and performance status (0-1 vs 2).

13.4 Analysis of Secondary Endpoints

13.4.1 Data analysis plan for secondary non-omics endpoints

Statistical data analysis for laboratory non-omics data and clinical data will utilize the following general strategies, as appropriate. For single time-point lab data, tests of hypotheses concerning within-group comparisons will be completed using the paired t-test or Wilcoxon signed-rank test for continuous parameters of interest, or McNemar's Chi-square test for categorical parameters of interest. Between-group comparisons will be assessed using either analysis of variance (ANOVA) with adjusted least squares means or Fisher's exact test, for continuous or categorical variables of interest, respectively. For count or binary multiple time-points or correlated data, tests of between-group comparisons will be completed using the generalized estimating equation (GEE) statistical procedure for longitudinal data analysis with multiple observable vectors for the same subject. For continuous multiple time points or correlated data, between-group comparisons will be tested using the restricted/residual maximum likelihood (REML)-based repeated measure model (mixed model analysis) with various variance-covariance structures For lifetime data analyses, possible risk factors for survival will be compared using Kaplan-Meier estimates and log-rank tests. The proportional hazards model will be used for adjusted tests of significance and estimates of odds ratios

13.4.2 Data analysis plan for secondary omics endpoints

The Omics biomarker data, e.g., RNA-seq, analysis will be completed using Lasso-based elastic net method. The elastic net method is a variable selection procedure by L1 and L2 penalized estimation that enforces variable selection and shrinkage simultaneously. The penalty parameter that controls the shrinkage of fixed terms and the variable selection will be determined by k-fold cross validation. Because of the limited sample size, other biomarker data analysis is for exploratory research only. The statistical analyses will be completed by either R 3.2.1 or SAS 9.4 statistical program in this project.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Osimertinib (AZD9291) with or without Bevacizumab.

13.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the exception of those who received no study medication) will be included in analysis of the response rate and other efficacy analyses. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. For PFS, OS, and other time-to-event endpoints, censoring is defined as (1) lost to follow-up or (2) event-free at the end of the study.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

REFERENCES

1. Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, Figg WD, Freidlin B, Halabi S, Hudes G, Hussain M, Kaplan R, Myers C, Oh W, Petrylak DP, Reed E, Roth B, Sartor O, Scher H, Simons J, Sinibaldi V, Small EJ, Smith MR, Trump DL, Wilding G, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol. 1999;17(11):3461-7. Epub 1999/11/05. PubMed PMID: 10550143.

2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11-30. Epub 2013/01/22. doi: 10.3322/caac.21166. PubMed PMID: 23335087.

3. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004;350(21):2129-39. Epub 2004/05/01. doi: 10.1056/NEJMoa040938. PubMed PMID: 15118073.

4. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;304(5676):1497-500. Epub 2004/05/01. doi: 10.1126/science.1099314. PubMed PMID: 15118125.

5. Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, Singh B, Heelan R, Rusch V, Fulton L, Mardis E, Kupfer D, Wilson R, Kris M, Varmus H. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A. 2004;101(36):13306-11. Epub 2004/08/27. doi: 10.1073/pnas.0405220101. PubMed PMID: 15329413; PMCID: PMC516528.

6. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947-57. Epub 2009/08/21. doi: 10.1056/NEJMoa0810699. PubMed PMID: 19692680.

7. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Milella M, Reguart N, Altavilla G, Jimenez U, Provencio M, Moreno MA, Terrasa J, Munoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baize N, Garcia-Campelo R, Robinet G, Rodriguez-Abreu D, Lopez-Vivanco G, Gebbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearz A, Artal A, Cortesi E, Rolfo C, Sanchez-Ronco M, Drozdowskyj A, Queralt C, de Aguirre I, Ramirez JL, Sanchez JJ, Molina MA, Taron M, Paz-Ares L. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer

(EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239-46. Epub 2012/01/31. doi: 10.1016/s1470-2045(11)70393-x. PubMed PMID: 22285168.

8. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, Zhou C, Hu CP, O'Byrne K, Feng J, Lu S, Huang Y, Geater SL, Lee KY, Tsai CM, Gorbunova V, Hirsh V, Bennouna J, Orlov S, Mok T, Boyer M, Su WC, Lee KH, Kato T, Massey D, Shahidi M, Zazulina V, Sequist LV. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol. 2015;16(2):141-51. Epub 2015/01/16. doi: 10.1016/s1470-2045(14)71173-8. PubMed PMID: 25589191.

9. P.A. Jänne M-JA, D.-W. Kim, S.-W. Kim, D. Planchard, S.S. Ramalingam, P. Frewer, M. Cantarini, S. Ghiorghiu, J.C.-H. Yang A PHASE I STUDY OF AZD9291 IN PATIENTS WITH EGFR-TKI-RESISTANT ADVANCED NSCLC – UPDATED PROGRESSION FREE SURVIVAL AND DURATION OF RESPONSE DATA, . Annals of Oncology 2015;26(suppl 1):Pp.i60.

10. S.S. Ramalingam YO, N. Nogami, J. Yang, C. Eberlein, S. Ashton, M. Mellor, P. Spitzler, C. Meador, E. Ichihara, D. Cross, W. Pao, P. Ballard, G. Hughes, M. Cantarini, P. Frewer, S. Ghiorghiu, P.A. Janne. Preclinical and clinical evaluation of AZD9291, a mutation-specific inhibitor, in treatment- naïve EGFR-mutated NSCLC Poster 454P. Annals of Oncology, Vol. 25, Sppl. 4. 34th Congress of the European Society for Medical Oncology: Annals of Oncology; 2014.

11. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, et al. Osimertinib in untreated EGFR-mutated advanced non-small cell lung cancer. N Enl J Med 2018; 378:113-125.

12. Cross DA, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, Orme JP, Finlay MR, Ward RA, Mellor MJ, Hughes G, Rahi A, Jacobs VN, Red Brewer M, Ichihara E, Sun J, Jin H, Ballard P, Al-Kadhimi K, Rowlinson R, Klinowska T, Richmond GH, Cantarini M, Kim DW, Ranson MR, Pao W. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov. 2014;4(9):1046-61. Epub 2014/06/05. doi: 10.1158/2159-8290.cd-14-0337. PubMed PMID: 24893891; PMCID: PMC4315625.

13. D. Kim JY, D. Cross, P. Ballard, P. Yang, J. Yates, L. Xie, M. Cantarini, S. Ghiorghiu, P.A. Janne. Preclinical evidence and clinical cases of AZD9291 activity in EGFR-mutant non-small cell lung cancer (NSCLC) brain metastases (BM). 39th European Society for Medical Oncology Congress; Annals of Oncology (2014) 25 (suppl_4): iv146-iv164 2014.

14. Porta R, Sanchez-Torres JM, Paz-Ares L, Massuti B, Reguart N, Mayo C, Lianes P, Queralt C, Guillem V, Salinas P, Catot S, Isla D, Pradas A, Gurpide A, de Castro J, Polo E, Puig T, Taron M, Colomer R, Rosell R. Brain metastases from lung cancer responding to erlotinib: the

importance of EGFR mutation. Eur Respir J. 2011;37(3):624-31. Epub 2010/07/03. doi: 10.1183/09031936.00195609. PubMed PMID: 20595147.

15. Bai H, Han B. The effectiveness of erlotinib against brain metastases in non-small cell lung cancer patients. Am J Clin Oncol. 2013;36(2):110-5. Epub 2012/03/07. doi: 10.1097/COC.0b013e3182438c91. PubMed PMID: 22391431.

16. Shimato S, Mitsudomi T, Kosaka T, Yatabe Y, Wakabayashi T, Mizuno M, Nakahara N, Hatano H, Natsume A, Ishii D, Yoshida J. EGFR mutations in patients with brain metastases from lung cancer: association with the efficacy of gefitinib. Neuro Oncol. 2006;8(2):137-44. Epub 2006/03/03. doi: 10.1215/15228517-2005-002. PubMed PMID: 16510849; PMCID: PMC1871943.

17. Ahn, MJ, Chiu CH, Cheng Y, Han JY, Goldberg SB, Greystoke A, Crawford J, Zhao Y, Huang X, Jonson M, Vishwanathan K, Mendoza-Naranjo A, Mok T. Osimertinib for patients with leptomeningeal metastases associated with EGFRm advanced NSCLC. Annals of Oncology (2018) 29 (Suppl_9):ix150-ix169.

18. Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, Winkler M, Ferrara N. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res. 1997;57(20):4593-9. Epub 1997/10/23. PubMed PMID: 9377574.

19. Genentech I. Avastin™ (bevacizumab) Investigator's Brochure. . 2008.

20. Kim KJ, Li B, Winer J, Armanini M, Gillett N, Phillips HS, Ferrara N. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature. 1993;362(6423):841-4. Epub 1993/04/29. doi: 10.1038/362841a0. PubMed PMID: 7683111.

21. Willett CG, Boucher Y, di Tomaso E, Duda DG, Munn LL, Tong RT, Chung DC, Sahani DV, Kalva SP, Kozin SV, Mino M, Cohen KS, Scadden DT, Hartford AC, Fischman AJ, Clark JW, Ryan DP, Zhu AX, Blaszkowsky LS, Chen HX, Shellito PC, Lauwers GY, Jain RK. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med. 2004;10(2):145-7. Epub 2004/01/28. doi: 10.1038/nm988. PubMed PMID: 14745444; PMCID: PMC2693485.

22. Borgstrom P, Gold DP, Hillan KJ, Ferrara N. Importance of VEGF for breast cancer angiogenesis in vivo: implications from intravital microscopy of combination treatments with an anti-VEGF neutralizing monoclonal antibody and doxorubicin. Anticancer Res. 1999;19(5B):4203-14. Epub 2000/01/11. PubMed PMID: 10628376.

23. Kabbinavar F, J.T. Wong, R.E. Ayala. The effect of antibody to vascular endothelial growth factor and cisplatin on the growth of lung tumors in nude mice. Proc Am Assoc Cancer Res 1995;36:A488.

24. Bergers G, Song S, Meyer-Morse N, Bergsland E, Hanahan D. Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. J Clin Invest. 2003;111(9):1287-95. Epub 2003/05/03. doi: 10.1172/jci17929. PubMed PMID: 12727920; PMCID: PMC154450.

25. Shaheen RM, Ahmad SA, Liu W, Reinmuth N, Jung YD, Tseng WW, Drazan KE, Bucana CD, Hicklin DJ, Ellis LM. Inhibited growth of colon cancer carcinomatosis by antibodies to vascular endothelial and epidermal growth factor receptors. Br J Cancer. 2001;85(4):584-9. Epub 2001/08/17. doi: 10.1054/bjoc.2001.1936. PubMed PMID: 11506500; PMCID: PMC2364099.

26. Cobleigh MA, Langmuir VK, Sledge GW, Miller KD, Haney L, Novotny WF, Reimann JD, Vassel A. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Semin Oncol. 2003;30(5 Suppl 16):117-24. Epub 2003/11/13. PubMed PMID: 14613032.

27. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB, 3rd. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25(12):1539-44. Epub 2007/04/20. doi: 10.1200/jco.2006.09.6305. PubMed PMID: 17442997.

28. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335-42. Epub 2004/06/04. doi: 10.1056/NEJMoa032691. PubMed PMID: 15175435.

29. [redacted], [redacted], [redacted], [redacted]. E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. . 41st Annual Meeting of the American Society of Clinical Oncology. 2005.

30. Miller K, H.S. Rugo, M.A. Cobleigh Phase III trial of capecitabine (Xeloda®) plus bevacizumab (Avastin™) versus capecitabine alone in women with metastatic breast cancer (MBC) previously treated with an anthracycline and a taxane. Breast Cancer Res Treat 76:S37. 2002.

31. HL Kindler DN, D Hollis, E Oraefo, D Schrag, H Hurwitz, HL McLeod, MF Mulcahy, RL Schilsky, RM Goldberg Cancer and Leukemia Group B A double-blind, placebo-controlled,

randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine plus placebo (P) in patients (pts) with advanced pancreatic cancer (PC): A preliminary analysis of Cancer and Leukemia Group B (CALGB) 80303. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings. 2007;Vol 25, No 18S (June 20 Supplement), 2007: 4508.

32. Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, Steinberg SM, Chen HX, Rosenberg SA. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med. 2003;349(5):427-34. Epub 2003/08/02. doi: 10.1056/NEJMoa021491. PubMed PMID: 12890841; PMCID: PMC2275324.

33. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355(24):2542-50. Epub 2006/12/15. doi: 10.1056/NEJMoa061884. PubMed PMID: 17167137.

34. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289(19):2560-72. Epub 2003/05/16. doi: 10.1001/jama.289.19.2560. PubMed PMID: 12748199.

35. Novotny W HE, Griffing S, et al. . Identification of squamous cell histology and central, cavitary tumors as possible risk factors for pulmonary hemorrhage in patients with advanced NSCLC receiving bevacizumab. . Proc Am Soc Clin Oncol 20:A1318. 2001.

36. JR Skillings DJ, K Miller. Arterial thromboembolic events (ATEs) in a pooled analysis of 5 randomized, controlled trials (RCTs) of bevacizumab (BV) with chemotherapy. Proc Am Soc Clin Oncol 24:A3019. 2005.

37. Scappaticci FA, Fehrenbacher L, Cartwright T, Hainsworth JD, Heim W, Berlin J, Kabbinavar F, Novotny W, Sarkar S, Hurwitz H. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J Surg Oncol. 2005;91(3):173-80. Epub 2005/08/25. doi: 10.1002/jso.20301. PubMed PMID: 16118771.

38. Wedam SB, Low JA, Yang SX, Chow CK, Choyke P, Danforth D, Hewitt SM, Berman A, Steinberg SM, Liewehr DJ, Plehn J, Doshi A, Thomasson D, McCarthy N, Koeppen H, Sherman M, Zujewski J, Camphausen K, Chen H, Swain SM. Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. J Clin Oncol. 2006;24(5):769-77. Epub 2006/01/05. doi: 10.1200/jco.2005.03.4645. PubMed PMID: 16391297.

39. D'Adamo DR, Anderson SE, Albritton K, Yamada J, Riedel E, Scheu K, Schwartz GK, Chen H, Maki RG. Phase II study of doxorubicin and bevacizumab for patients with metastatic

soft-tissue sarcomas. J Clin Oncol. 2005;23(28):7135-42. Epub 2005/09/30. doi: 10.1200/jco.2005.16.139. PubMed PMID: 16192597.

40. Glusker P, Recht L, Lane B. Reversible posterior leukoencephalopathy syndrome and bevacizumab. N Engl J Med. 2006;354(9):980-2; discussion -2. Epub 2006/03/03. doi: 10.1056/NEJMc052954. PubMed PMID: 16510760.

41. Ozcan C, Wong SJ, Hari P. Reversible posterior leukoencephalopathy syndrome and bevacizumab. N Engl J Med. 2006;354(9):980-2; discussion -2. Epub 2006/03/04. PubMed PMID: 16514715.

42. Smith AR, Hennessy JM, Kurth MA, Nelson SC. Reversible skeletal changes after treatment with bevacizumab in a child with cutaneovisceral angiomatosis with thrombocytopenia syndrome. Pediatr Blood Cancer. 2008;51(3):418-20. Epub 2008/05/22. doi: 10.1002/pbc.21597. PubMed PMID: 18493993.

43. Glade Bender JL, Adamson PC, Reid JM, Xu L, Baruchel S, Shaked Y, Kerbel RS, Cooney-Qualter EM, Stempak D, Chen HX, Nelson MD, Krailo MD, Ingle AM, Blaney SM, Kandel JJ, Yamashiro DJ. Phase I trial and pharmacokinetic study of bevacizumab in pediatric patients with refractory solid tumors: a Children's Oncology Group Study. J Clin Oncol. 2008;26(3):399-405. Epub 2008/01/19. doi: 10.1200/jco.2007.11.9230. PubMed PMID: 18202416.

44. Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, Kris MG, Varmus H. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med. 2005;2(3):e73. Epub 2005/03/02. doi: 10.1371/journal.pmed.0020073. PubMed PMID: 15737014; PMCID: PMC549606.

45. Oxnard GR, Arcila ME, Chmielecki J, Ladanyi M, Miller VA, Pao W. New strategies in overcoming acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in lung cancer. Clin Cancer Res. 2011;17(17):5530-7. Epub 2011/07/22. doi: 10.1158/1078-0432.ccr-10-2571. PubMed PMID: 21775534; PMCID: PMC3166976.

46. Janne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, Ahn MJ, Kim SW, Su WC, Horn L, Haggstrom D, Felip E, Kim JH, Frewer P, Cantarini M, Brown KH, Dickinson PA, Ghiorghiu S, Ranson M. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med. 2015;372(18):1689-99. Epub 2015/04/30. doi: 10.1056/NEJMoa1411817. PubMed PMID: 25923549.

47. Heon S, Yeap BY, Lindeman NI, Joshi VA, Butaney M, Britt GJ, Costa DB, Rabin MS, Jackman DM, Johnson BE. The impact of initial gefitinib or erlotinib versus chemotherapy on central nervous system progression in advanced non-small cell lung cancer with EGFR mutations. Clin Cancer Res. 2012;18(16):4406-14. Epub 2012/06/27. doi: 10.1158/1078-0432.ccr-12-0357. PubMed PMID: 22733536; PMCID: PMC3682221.

48. Wu YL, Zhou C, Cheng Y, Lu S, Chen GY, Huang C, Huang YS, Yan HH, Ren S, Liu Y, Yang JJ. Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: a phase II study (CTONG-0803). Ann Oncol. 2013;24(4):993-9. Epub 2012/11/07. doi: 10.1093/annonc/mds529. PubMed PMID: 23129122.

49. Gerber NK, Yamada Y, Rimner A, Shi W, Riely GJ, Beal K, Yu HA, Chan TA, Zhang Z, Wu AJ. Erlotinib versus radiation therapy for brain metastases in patients with EGFR-mutant lung adenocarcinoma. Int J Radiat Oncol Biol Phys. 2014;89(2):322-9. Epub 2014/04/01. doi: 10.1016/j.ijrobp.2014.02.022. PubMed PMID: 24679729.

50. Hata A, Katakami N, Yoshioka H, Takeshita J, Tanaka K, Masago K, Fujita S, Kaji R, Imai Y, Monden K, Matsumoto T, Nagata K, Otsuka K, Tachikawa R, Tomii K, Kunimasa K, Iwasaku M, Nishiyama A, Ishida T, Nishimura Y. Prognostic impact of central nervous system metastases after acquired resistance to EGFR-TKI: poorer prognosis associated with T790M-negative status and leptomeningeal metastases. Anticancer Res. 2015;35(2):1025-31. Epub 2015/02/11. PubMed PMID: 25667490.

51. Ballard P, Yates JW, Yang Z, Kim DW, Yang JC, Cantarini M, Pickup K, Jordan A, Hickey M, Grist M, Box M, Johnstrom P, Varnas K, Malmquist J, Thress KS, Janne PA, Cross D. Preclinical Comparison of Osimertinib with Other EGFR-TKIs in EGFR-Mutant NSCLC Brain Metastases Models, and Early Evidence of Clinical Brain Metastases Activity. Clin Cancer Res. 2016;22(20):5130-40. Epub 2016/07/21. doi: 10.1158/1078-0432.ccr-16-0399. PubMed PMID: 27435396.

52. Sequist LV, Piotrowska Z, Niederst MJ, Heist RS, Digumarthy S, Shaw AT, Engelman JA. Osimertinib Responses After Disease Progression in Patients Who Had Been Receiving Rociletinib. JAMA Oncol. 2016;2(4):541-3. Epub 2016/01/01. doi: 10.1001/jamaoncol.2015.5009. PubMed PMID: 26720284.

53. Lee DH KD-W, Ahn M-J, et al. AZD9291 activity in patients with leptomeningeal disease from non-small cell lung cancer: a Phase I study. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. Abstract PR07.2015.

54. Yang J C-H KD-W, Kim S-W, Cho BC, Lee J-S, Ye X, Yin X, Yang Z, Jiang H, Ahn M-J. Osimertinib activity in patients (pts) with leptomeningeal (LM) disease from non-small cell lung cancer (NSCLC): Updated results from BLOOM, a phase I study. 2016 ASCO Annual Meeting J Clin Oncol 34, 2016 (suppl; abstr 9002). 2016.

55. Besse B, Le Moulec S, Mazieres J, Senellart H, Barlesi F, Chouaid C, Dansin E, Berard H, Falchero L, Gervais R, Robinet G, Ruppert AM, Schott R, Lena H, Clement-Duchene C, Quantin X, Souquet PJ, Tredaniel J, Moro-Sibilot D, Perol M, Madroszyk AC, Soria JC. Bevacizumab in Patients with Nonsquamous Non-Small Cell Lung Cancer and Asymptomatic, Untreated Brain Metastases (BRAIN): A Nonrandomized, Phase II Study. Clin Cancer Res.

2015;21(8):1896-903. Epub 2015/01/24. doi: 10.1158/1078-0432.ccr-14-2082. PubMed PMID: 25614446.

56. Besse B, Lasserre SF, Compton P, Huang J, Augustus S, Rohr UP. Bevacizumab safety in patients with central nervous system metastases. Clin Cancer Res. 2010;16(1):269-78. Epub 2009/12/24. doi: 10.1158/1078-0432.ccr-09-2439. PubMed PMID: 20028762.

57. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, Carpentier AF, Hoang-Xuan K, Kavan P, Cernea D, Brandes AA, Hilton M, Abrey L, Cloughesy T. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med. 2014;370(8):709-22. Epub 2014/02/21. doi: 10.1056/NEJMoa1308345. PubMed PMID: 24552318.

58. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell. 1996;86(3):353-64. Epub 1996/08/09. PubMed PMID: 8756718.

59. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol. 2005;23(5):1011-27. Epub 2004/12/09. doi: 10.1200/jco.2005.06.081. PubMed PMID: 15585754.

60. Elamin YY, Rafee S, Toomey S, Hennessy BT. Immune effects of bevacizumab: killing two birds with one stone. Cancer Microenviron. 2015;8(1):15-21. Epub 2014/10/19. doi: 10.1007/s12307-014-0160-8. PubMed PMID: 25326055; PMCID: PMC4449343.

61. Naumov GN, Nilsson MB, Cascone T, Briggs A, Straume O, Akslen LA, Lifshits E, Byers LA, Xu L, Wu HK, Janne P, Kobayashi S, Halmos B, Tenen D, Tang XM, Engelman J, Yeap B, Folkman J, Johnson BE, Heymach JV. Combined vascular endothelial growth factor receptor and epidermal growth factor receptor (EGFR) blockade inhibits tumor growth in xenograft models of EGFR inhibitor resistance. Clin Cancer Res. 2009;15(10):3484-94. Epub 2009/05/19. doi: 10.1158/1078-0432.ccr-08-2904. PubMed PMID: 19447865; PMCID: PMC2893040.

62. Herbst RS, Ansari R, Bustin F, Flynn P, Hart L, Otterson GA, Vlahovic G, Soh CH, O'Connor P, Hainsworth J. Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): a double-blind, placebo-controlled, phase 3 trial. Lancet. 2011;377(9780):1846-54. Epub 2011/05/31. doi: 10.1016/s0140-6736(11)60545-x. PubMed PMID: 21621716; PMCID: PMC4134127.

63. Seto T, Kato T, Nishio M, Goto K, Atagi S, Hosomi Y, Yamamoto N, Hida T, Maemondo M, Nakagawa K, Nagase S, Okamoto I, Yamanaka T, Tajima K, Harada R, Fukuoka M, Yamamoto N. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an

open-label, randomised, multicentre, phase 2 study. Lancet Oncol. 2014;15(11):1236-44. Epub 2014/09/02. doi: 10.1016/s1470-2045(14)70381-x. PubMed PMID: 25175099.

64. Yu HA, Hayes SA, Young RJ, Ni A, Rodriguez C, Makhnin A, Riely GJ, Kris MG. A phase I study of osimertinib and bevacizumab as initial treatment for patients with EGFR-mutant lung cancers. J Clin Oncol 35, no.15_suppl (May 2017).

65. Tran HT, Liu Y, Zurita AJ, Lin Y, Baker-Neblett KL, Martin AM, Figlin RA, Hutson TE, Sternberg CN, Amado RG, Pandite LN, Heymach JV. Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis of phase 2 and phase 3 trials. Lancet Oncol. 2012;13:827-37. Epub 2012/07/05. doi: S1470-2045(12)70241-3 [pii]
10.1016/S1470-2045(12)70241-3. PubMed PMID: 22759480.

66. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, Bergethon K, Shaw AT, Gettinger S, Cosper AK, Akhavanfard S, Heist RS, Temel J, Christensen JG, Wain JC, Lynch TJ, Vernovsky K, Mark EJ, Lanuti M, Iafrate AJ, Mino-Kenudson M, Engelman JA. Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors. Science Translational Medicine. 2011;3(75):75ra26-75ra26. doi: 10.1126/scitranslmed.3002003.

67. Hrustanovic G, Olivas V, Pazarentzos E, Tulpule A, Asthana S, Blakely CM, Okimoto RA, Lin L, Neel DS, Sabnis A, Flanagan J, Chan E, Varella-Garcia M, Aisner DL, Vaishnavi A, Ou SH, Collisson EA, Ichihara E, Mack PC, Lovly CM, Karachaliou N, Rosell R, Riess JW, Doebele RC, Bivona TG. RAS-MAPK dependence underlies a rational polytherapy strategy in EML4-ALK-positive lung cancer. Nat Med. 2015;21(9):1038-47. Epub 2015/08/25. doi: 10.1038/nm.3930. PubMed PMID: 26301689; PMCID: PMC4734742.

68. Bean J, Brennan C, Shih JY, Riely G, Viale A, Wang L, Chitale D, Motoi N, Szoke J, Broderick S, Balak M, Chang WC, Yu CJ, Gazdar A, Pass H, Rusch V, Gerald W, Huang SF, Yang PC, Miller V, Ladanyi M, Yang CH, Pao W. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc Natl Acad Sci U S A. 2007;104(52):20932-7. Epub 2007/12/21. doi: 10.1073/pnas.0710370104. PubMed PMID: 18093943; PMCID: PMC2409244.

69. Velcheti V, Schalper KA, Carvajal DE, Anagnostou VK, Syrigos KN, Sznol M, Herbst RS, Gettinger SN, Chen L, Rimm DL. Programmed death ligand-1 expression in non-small cell lung cancer. Lab Invest. 2014;94(1):107-16. Epub 2013/11/13. doi: 10.1038/labinvest.2013.130. PubMed PMID: 24217091.

70. Schalper KA, Carvajal-Hausdorf D, McLaughlin J, Altan M, Velcheti V, Gaule P, Sanmamed MF, Chen L, Herbst RS, Rimm DL. Differential expression and significance of PD-L1, IDO-1 and B7-H4 in human lung cancer. Clin Cancer Res. 2016. Epub 2016/07/22. doi: 10.1158/1078-0432.ccr-16-0150. PubMed PMID: 27440266.

71. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47. Epub 2008/12/23. doi: 10.1016/j.ejca.2008.10.026. PubMed PMID: 19097774.

72. Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, Bendszus M, Brown PD, Camidge DR, Chang SM, Dancey J, de Vries EG, Gaspar LE, Harris GJ, Hodi FS, Kalkanis SN, Linskey ME, Macdonald DR, Margolin K, Mehta MP, Schiff D, Soffietti R, Suh JH, van den Bent MJ, Vogelbaum MA, Wen PY. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol. 2015;16(6):e270-8. Epub 2015/06/13. doi: 10.1016/s1470-2045(15)70057-4. PubMed PMID: 26065612.

73. Rustin GJ, Quinn M, Thigpen T, du Bois A, Pujade-Lauraine E, Jakobsen A, Eisenhauer E, Sagae S, Greven K, Vergote I, Cervantes A, Vermorken J. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Natl Cancer Inst. 2004;96(6):487-8. Epub 2004/03/18. PubMed PMID: 15026475.

74. Rolff J, Becker M, Merk J, Hoffmann J, Fichtner I. Preclinical Study of a Combination of Erlotinib and Bevacizumab in Early Stages of Unselected Non-Small Cell Lung Cancer Patient-Derived Xenografts. Target Oncol. 2016;11(4):507-14. Epub 2016/01/29. doi: 10.1007/s11523-015-0415-4. PubMed PMID: 26817645.

75. Camp RL, Chung GG, Rimm DL. Automated subcellular localization and quantification of protein expression in tissue microarrays. Nat Med. 2002;8(11):1323-7. doi: 10.1038/nm791. PubMed PMID: 12389040.

76. Bordeaux J, Welsh A, Agarwal S, Killiam E, Baquero M, Hanna J, Anagnostou V, Rimm D. Antibody validation. Biotechniques. 2010;48(3):197-209. doi: 10.2144/000113382. PubMed PMID: 20359301; PMCID: 3891910.

77. Narayan A, Carriero NJ, Gettinger SN, Kluytenaar J, Kozak KR, Yock TI, Muscato NE, Ugarelli P, Decker RH, Patel AA. Ultrasensitive measurement of hotspot mutations in tumor DNA in blood using error-suppressed multiplexed deep sequencing. Cancer Res. 2012;72(14):3492-8. Epub 2012/05/15. doi: 10.1158/0008-5472.can-11-4037. PubMed PMID: 22581825; PMCID: PMC3426449.

78. Narayan A, Bommakanti A, Patel AA. High-throughput RNA profiling via up-front sample parallelization. Nat Methods. 2015;12(4):343-6. Epub 2015/03/03. doi: 10.1038/nmeth.3311. PubMed PMID: 25730493; PMCID: PMC4451056.

79. Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, Xie M, Zhang Q, McMichael JF, Wyczalkowski MA, Leiserson MD, Miller CA, Welch JS, Walter MJ, Wendl MC, Ley TJ, Wilson RK, Raphael BJ, Ding L. Mutational landscape and significance across 12 major cancer

types. Nature. 2013;502(7471):333-9. Epub 2013/10/18. doi: 10.1038/nature12634. PubMed PMID: 24132290; PMCID: PMC3927368.

80. Nixon AB, Pang H, Starr MD, Friedman PN, Bertagnolli MM, Kindler HL, Goldberg RM, Venook AP, Hurwitz HI, Alliance for Clinical Trials In O. Prognostic and Predictive Blood-Based Biomarkers in Patients with Advanced Pancreatic Cancer: Results from CALGB80303 (Alliance). Clin Cancer Res. 2013;19(24):6957-66. doi: 10.1158/1078-0432.CCR-13-0926. PubMed PMID: 24097873.

81. Weickhardt AJ, Williams D, Lee C, Simes J, Murone C, Wilson K, Cummins M, Asadi K, Price TJ, Mariadason J, Tebbutt NC, Group AGT. Vascular endothelial growth factors (VEGF) and VEGF receptor expression as predictive biomarkers for benefit with bevacizumab in metastatic colorectal cancer (mCRC): Analysis of the phase III MAX study. J Clin Oncol. 2011;29:3531 (suppl; abstr).

82. Lieu CH, Tran H, Jiang ZQ, Mao M, Overman MJ, Lin E, Eng C, Morris J, Ellis L, Heymach JV, Kopetz S. The association of alternate VEGF ligands with resistance to anti-VEGF therapy in metastatic colorectal cancer. PLoS One. 2013;8(10):e77117. doi: 10.1371/journal.pone.0077117. PubMed PMID: 24143206; PMCID: 3797099.

83. Lambrechts D, Lenz HJ, de Haas S, Carmeliet P, Scherer SJ. Markers of response for the antiangiogenic agent bevacizumab. J Clin Oncol. 2013;31(9):1219-30. doi: 10.1200/JCO.2012.46.2762. PubMed PMID: 23401453.

84. Miles DW, de Haas SL, Dirix LY, Romieu G, Chan A, Pivot X, Tomczak P, Provencher L, Cortes J, Delmar PR, Scherer SJ. Biomarker results from the AVADO phase 3 trial of first-line bevacizumab plus docetaxel for HER2-negative metastatic breast cancer. Br J Cancer. 2013;108(5):1052-60. doi: 10.1038/bjc.2013.69. PubMed PMID: 23422754; PMCID: 3619079.

85. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, Zarba JJ, Chen M, McCann L, Pandite L, Roychowdhury DF, Hawkins RE. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010;28(6):1061-8. doi: 10.1200/JCO.2009.23.9764. PubMed PMID: 20100962.

86. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, Atkins JN, Picus J, Czaykowski P, Dutcher J, Small EJ. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. 2010;28(13):2137-43. doi: 10.1200/JCO.2009.26.5561. PubMed PMID: 20368558; PMCID: 2860433.

87. Nixon AB, Halabi S, Shterev I, Starr MD, Brady JC, Dutcher J, Hopkins J, Hurwitz HI, Small E, Rini B, Febbo PG, George D. Identification of predictive biomarkers of overall survival (OS) in patients (pts) with advanced renal cell carcinoma (RCC) treated with interferon alpha (I)

+/- bevacizumab (B): Results from CALGB 90206 (Alliance) J Clin Oncol. 2013;31:Suppl; abstr 4520.

88. Chung AS, Wu X, Zhuang G, Ngu H, Kasman I, Zhang J, Vernes JM, Jiang Z, Meng YG, Peale FV, Ouyang W, Ferrara N. An interleukin-17-mediated paracrine network promotes tumor resistance to anti-angiogenic therapy. Nat Med. 2013;19(9):1114-23. doi: 10.1038/nm.3291. PubMed PMID: 23913124.

89. Shojaei F, Wu X, Malik AK, Zhong C, Baldwin ME, Schanz S, Fuh G, Gerber HP, Ferrara N. Tumor refractoriness to anti-VEGF treatment is mediated by CD11b+Gr1+ myeloid cells. Nat Biotechnol. 2007;25(8):911-20. doi: 10.1038/nbt1323. PubMed PMID: 17664940.

90. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. N Engl J Med. 2011;364(7):656-65. doi: 10.1056/NEJMra0910283. PubMed PMID: 21323543.

91. Yu H, Jove R. The STATs of cancer--new molecular targets come of age. Nat Rev Cancer. 2004;4(2):97-105. doi: 10.1038/nrc1275. PubMed PMID: 14964307.

92. Yu H, Kortylewski M, Pardoll D. Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. Nat Rev Immunol. 2007;7(1):41-51. doi: 10.1038/nri1995. PubMed PMID: 17186030.

93. Addison CL, Ding K, Zhao H, Le Maitre A, Goss GD, Seymour L, Tsao MS, Shepherd FA, Bradbury PA. Plasma transforming growth factor alpha and amphiregulin protein levels in NCIC Clinical Trials Group BR.21. J Clin Oncol. 2010;28(36):5247-56. doi: 10.1200/JCO.2010.31.0805. PubMed PMID: 21079146.

94. Baker JB, Dutta D, Watson D, Maddala T, Munneke BM, Shak S, Rowinsky EK, Xu LA, Harbison CT, Clark EA, Mauro DJ, Khambata-Ford S. Tumour gene expression predicts response to cetuximab in patients with KRAS wild-type metastatic colorectal cancer. Br J Cancer. 2011;104(3):488-95. doi: 10.1038/sj.bjc.6606054. PubMed PMID: 21206494; PMCID: 3049558.

95. Cushman SM, Jiang C, Hatch AJ, Shterev I, Sibley AB, Niedzwiecki D, Venook AP, Owzar K, Hurwitz HI, Nixon AB. Gene expression markers of efficacy and resistance to cetuximab treatment in metastatic colorectal cancer: results from CALGB 80203 (Alliance). Clin Cancer Res. 2015;21(5):1078-86. doi: 10.1158/1078-0432.CCR-14-2313. PubMed PMID: 25520391.

96. Hatch AJ, Pang H, Starr MD, Brady JC, Jia J, Niedzwiecki D, Venook AP, Cushman SM, Hurwitz H, Nixon AB. Prognostic and predictive blood-based biomarkers of overall survival (OS) in patients (pts) with advanced colorectal cancer (CRC) treated with cetuximab (C): Results from CALGB 80203 (Alliance). J Clin Oncol. 2014;32(5):11022 (suppl; abstract).

97. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, Eisenberger MA, Higano C, Bubley GJ, Dreicer R, Petrylak D, Kantoff P, Basch E, Kelly WK, Figg WD, Small EJ, Beer TM, Wilding G, Martin A, Hussain M. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008;26(7):1148-59. Epub 2008/03/04. doi: 10.1200/jco.2007.12.4487. PubMed PMID: 18309951; PMCID: PMC4010133.

98. Vergote I, Rustin GJ, Eisenhauer EA, Kristensen GB, Pujade-Lauraine E, Parmar MK, Friedlander M, Jakobsen A, Vermorken JB. Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup. J Natl Cancer Inst. 2000;92(18):1534-5. Epub 2000/09/21. PubMed PMID: 10995813.

99. Wieand S SG, O'Fallon JR. Stopping when the experimental regimen does not appear to help. Stat Med 13:1453-1458. 1994.

APPENDIX A 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 B GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

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

DRUGS INDUCING CYP3A4 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMEND ARE NOT COMBINED WITH OSIMERTINIB (AZD9291)

Osimertinib (AZD9291) is metabolised by CYP3A4 and CYP3A5 enzymes.
A drug-drug interaction study of AZD9291 evaluated in patients showed that there is potential for Osimertinib (AZD9291) being a victim when co-administered with strong inducers of CYP3A4 Osimertinib (AZD9291) 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 (AZD9291).

Table 1 Drugs inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to Osimertinib (AZD9291) start
Carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentin	3 weeks
St John's Wort	
Phenobarbitone	5 weeks

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

MEDICINES WHOSE EXPOSURES MAY BE AFFECTED BY AZD9291 (OSIMERTINIB) THAT ASTRAZENECA CONSIDERS MAY BE ALLOWED WITH CAUTION

Osimertinib (AZD9291) 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 2 Exposure, pharmacological action and toxicity may be increased by Osimertinib (AZD9291)

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 (AZD9291).

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 website: https://www.crediblemeds.org/. The website characterizes 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 (AZD9291) 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 3 Drugs with a known risk of TdP

Drug name	Withdrawal period prior to Osimertinib (AZD9291) start
Anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansentron, papaverine, hydrochloride, procainamide, sulpiride, sulropride, terfenadine, terlipressin	2 days

Table 3 Drugs with a known risk of TdP

Drug name	Withdrawal period prior to Osimertinib (AZD9291) start
Cilostazol, Cisapride, disopyramide, dofetilide, domperidone, flecanide, gatifloxacine, 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
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.

APPENDIX C INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, Osimertinib (**AZD9291).** This clinical trial is sponsored by the National Cancer Institute (NCI). This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

Osimertinib (AZD9291) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- Osimertinib (AZD9291) is metabolized by CYP3A4 and CYP3A5 enzymes. A drug-drug interaction study of Osimertinib (AZD9291) evaluated in patients showed that there is potential for Osimertinib (AZD9291) being a victim when co-administered with strong inducers of CYP3A4
- Osimertinib (AZD9291) may increase the concentration of sensitive BCRP and Pgp substrates

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

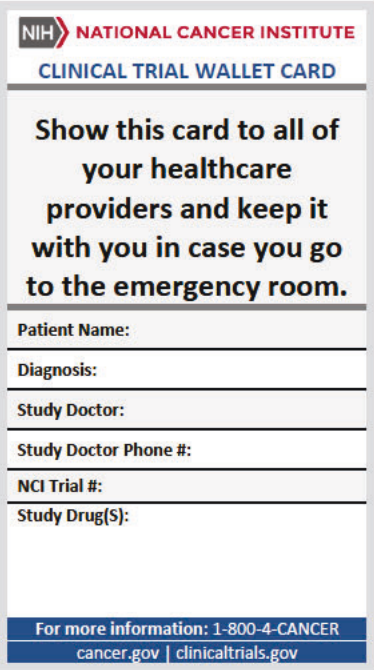
Osimertinib (AZD9291) interacts with many drugs which can cause side effects. Because of this, it is very important to tell your study doctors about all of your medicines before you enroll on this clinical trial. It is also very important to tell them if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care prescribers can write prescriptions. You must also tell your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Osimertinib (AZD9291) must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers of CYP 3A4 or substrates of P-gp and BCRP."

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctor or pharmacist to determine if there could be any side effects.
    - Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.


NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX D FORMALIN-FIXED, PARAFFIN EMBEDDED (FFPE) TUMOR TISSUE COLLECTION, HANDLING AND SHIPMENT

The purpose of this Standard Operating Procedure (SOP) is to outline the process for formalin-fixing and paraffin embedding tissue for processing and shipping to the laboratory of Dr. [redacted] at Yale. Tissue samples will be collected from participants who have been properly consented and who have agreed to participate in the research study. Tumor tissues are only suitable for molecular studies if fixed in a timely and appropriate manner. The purpose of this document is to outline standardized procedures for collection sites to follow for formalin fixing/paraffin embedding tissue.

The tumor tissue will be obtained by surgical resection or biopsy procedure. Tissue will be obtained prior to the start of trial therapy. Patients with only CNS progression are not required to undergo a tissue biopsy. Immediately after acquisition, tissue cores (preferably three) will be placed into separate pre-labeled 30mL tubes of 10% neutral buffered formalin (NBF). Let fix for 16-24 hours. Pathology at the site will paraffin block the core biopsies.

Ship FFPE blocks, once embedded, for overnight delivery (Mon-Thur). If blocks are not available, 15-20 unstained slides are acceptable alternatives (15 slides minimum, 20 slides strongly encouraged). Once slides are cut, they should be shipped within 7 days.

Shipping Instructions

1. Label the samples with the following information:

   CTEP Protocol Number (NCI#10020)
   Description (FFPE block)
   Patient Study ID Number
   Date of Collection
   Time of Collection

2. Place the FFPE blocks or unstained slides in a ziplock bag and wrap in bubble wrap or another type of padded material prior to shipping. The zip lock bag can be placed into a FedEx envelope or small shipping box.
3. Verify that the FedEx air bill is marked **Standard Overnight Shipping.**
4. Call Courier Service to pick up specimens.
5. Ship overnight (Mon-Thur). No shipments will occur over weekends or holidays. Prior to any shipment, please notify [redacted] via email and/or telephone. The samples will be shipped to the following address:

   [redacted]
   C/O [redacted] Lab
   Yale School of Medicine
   Yale Comprehensive Cancer Center
   333 Cedar Street, NSB 287B
   New Haven, CT 06510
   lab: [redacted]
   fax: 203-785-7531
   Email: [redacted]

APPENDIX E PLASMA COLLECTION AND SHIPMENT

At each required timepoint, one 10 mL purple-top tube is to be sent to the [redacted] Laboratory and one 10 mL purple-top tube is to be sent to the [redacted] Laboratory as per instructions below.

Plasma Collection/Processing/Storage SOP – [redacted] Laboratory

1. Collect blood in 10 mL purple-top EDTA-containing Vacutainer tubes and gently turn tubes end over end 3-4 times upon collection to dissolve the EDTA and prevent coagulation. If blood is collected from a port-a-cath instead of by venipuncture, an appropriate volume should first be discarded as waste to avoid contamination with saline and/or heparin.

2. Tubes should be kept at room temperature and transported to the laboratory without excessive agitation (preferably not via hospital's pneumatic tube system).

3. Spin tubes at 1000 x g for 15 minutes in a clinical centrifuge ideally within 1 hour of collection, and not more than 4 hours. Tubes should be carefully balanced in the centrifuge to avoid vibrations, which might disrupt WBCs and increase background DNA in the plasma. The centrifuge should be stopped in "brake off" mode. It is important to handle tube very gently to avoid bringing cells back into the plasma when transporting the tube from the centrifuge back to the lab bench and when opening the rubber plug at the top of the tube.

4. Plasma should be dispensed into cryovials in 1mL aliquots (the final aliquot can be less than 1mL). From a 10 mL tube, we typically obtain about 4.5 mL of plasma. Care should be taken to avoid any white blood cells by not pipetting the last ~0.5 mL of plasma above the buffy coat layer. Plasma should be frozen at -70ºC to -80ºC for long-term storage

5. The buffy coat layer should be preserved in a separate cryovial as a source of germline DNA. It is acceptable for some plasma and RBCs to be taken up by the pipette along with the buffy coat. This can be kept in long-term storage at -70ºC to -80ºC.

6. Once the plasma is frozen, it should not be thawed until it is ready to be processed for sequencing.

7. Samples should be shipped on dry ice overnight to the analyzing lab. Samples can be stored locally for several months and shipped in batches once several samples have been collected. Please email Dr. [redacted] prior to shipping so that we know to expect the shipment. The shipping address is:
   [redacted] Lab

Yale School of Medicine
15 York Street, Room HRT 210
New Haven, CT 06510

Plasma Collection/Processing/Storage SOP – [redacted] Laboratory

- ***Biomarker assays are time sensitive. Samples must be processed within 90 minutes of collection. Complete the Biomarker Flowsheet, insert a copy of the flowsheet with shipment, and fax to ATTN: BIOMARKER LABORATORY at 919-668-3925.***
- ***For any questions regarding biomarker processing, supplies and shipping, please call 919-681-2239***

For plasma samples:

1. *Draw one 10ml purple-top (K_2EDTA) tube (BD Vacutainer, Catalog no. 366643)*
2. *Invert tubes 10 times to mix blood*
3. *Centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)*
4. *Remove plasma from each tube and transfer equally into two separate clean 15ml polypropylene tubes*
5. *Repeat centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)*
6. *Aliquot approximately 1.0ml of plasma from each tube into each 2.0ml cryovial. For the EDTA, aliquot into pink capped cryovial. Total of 4 pink capped cryovials needed for EDTA plasma.*
7. *Label and freeze at -80°C* (see labeling instructions below)*

***Please note**: If your site does not have a -80°C freezer, samples should be shipped on dry ice on the day of collection. If unable to ship samples on the day of collection, please place the samples on dry ice until they can be shipped. Samples can be stored on dry ice for no more than 48 hours prior to shipping. Please replenish dry ice as needed to ensure samples stay frozen and there is enough to last throughout shipment.

LABELING INSTRUCTIONS:

- ***Plasma-containing tubes need to be labeled with the following information (using a Sharpie or Cryopen):***

1. Protocol Name
2. Subject Study Number
3. Subject Initials
4. Sample Date and Time
5. Sample Type (ie. whole blood, EDTA plasma, citrate plasma, serum, urine)

SHIPPING INSTRUCTIONS:

- ***Ship biomarker samples within 48 to 72 hours of completed processing.***
- ***Please include complete the Biomarker Flowsheet with shipment.***
- ***All biomarker samples (whole blood, plasma, serum and urine) must be shipped on dry ice by overnight delivery Monday through Thursday (no holidays) to the following address:***

Attention: Phase I Biomarker Laboratory
ATTN: [redacted], PhD
Duke University Medical Center
395 MSRB, Research Drive
Durham, NC 27710

CTEP-assigned Protocol # 10042
Local Protocol # _____

APPENDIX F PATIENT MEDICATION DIARY

Today's date _____**Cycle Number:** _____ **Agent:** Osimertinib (AZD9291)

Patient Name_____(*initials acceptable)*

Patient Study ID _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take **Osimertinib (AZD9291)** tablets **daily.** Take tablets with or without food and take with 8 ounces of water. Tablets should be swallowed whole, do not chew or crush. Take _____ mg tablet at the same time each day. If you miss a dose (i.e. if you do not take it within 12 hours of scheduled time), skip the dose and resume taking Osimertinib (AZD9291) at the next scheduled time on the next day. If you vomit after taking Osimertinib, do not retake the dose; you should take Osimertinib (AZD9291) at the next scheduled time on the next day.
4. Record the date, and when you took the tablet.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please bring this form and your bottles of Osimertinib (AZD9291) tablets when you return for each appointment.
7. Please store Osimertinib (AZD9291) tablets at room temperature.

Day	Date	Time of dose	AM/PM	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				

Patient's signature _____

Physician's Office will complete this section:
1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose

_____
3. Total number of tablets taken this cycle **of Osimertinib (AZD9291)**_____
4. Physician/Nurse/Data Manager's Signature

_____