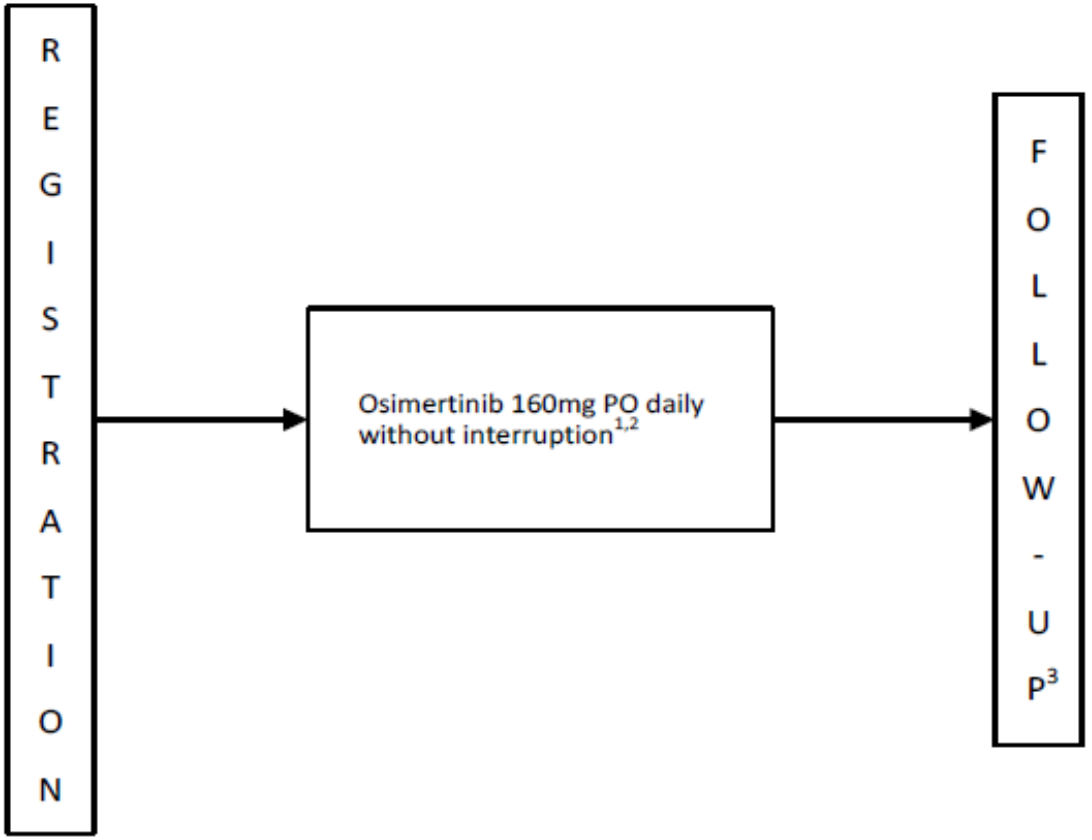
Schema



Cycle = 3 weeks (21 days)
Accrual = 20 patients

1. Until disease progression or unacceptable toxicities.
2. Restaging scans every 2 cycles (6 weeks).
3. Patients will be followed for 5 years from registration.

The primary endpoint is best objective response per RECIST 1.1, with confirmation of response required.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

Rev. Add4

3.1 Eligibility Criteria

_____3.1.1 Participants must have a pathologically-confirmed diagnosis of non-small cell lung cancer (NSCLC).

_____3.1.2 Participants must have advanced disease - either stage IV disease, stage IIIB disease not amenable to definitive multi-modality therapy, or recurrent disease after a prior diagnosis of stage I-III disease. All staging is via the American Joint Committee on Cancer (AJCC)/IASLC 7th edition staging criteria

_____3.1.3 An EGFR exon 20 insertion mutation must be detected in the tumor tissue. Patients may be enrolled in the study based on an exon 20 insertion EGFR mutation detected by any CLIA-certified tissue assay.

NOTE: Testing results are to be submitted via Medidata Rave and the study chair or delegate will review the reports.

Rev. Add5

_____ 3.1.4 Patients must have measurable disease as defined in Section 6.1.1. Baseline measurements and ALL sites of disease must be obtained within 4 weeks prior to registration.

_____3.1.5 Patients must have previously received at least one line of therapy for their advanced lung cancer. There are no restrictions on the maximum number of prior therapies allowed.

Rev. Add5 3.1.6 Participants must not have previously received osimertinib.

3.1.7 Participants must have not previously received therapies targeting PDL1, PD1 or CTLA4 within 6 months (180 days) prior to registration.

3.1.8 Age ≥ 18 years.

3.1.9 ECOG performance status ≤1

Rev. Add4
Rev. Add5 3.1.10 Participants must have normal organ and marrow function within 4 weeks before registration as defined below:

- Hemoglobin ≥ 9.0g/dL
- Leukocytes/White Blood Cells ≥ 3,000/mcL
- Absolute neutrophil count ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) if no liver metastases or ≤ 3 times ULN in the presence of documented Gilbert's Syndrome [unconjugated hyperbilirubinaemia] or liver metastases
- AST(SGOT)/ALT(SGPT) ≤ 3 × institutional upper limit of normal; for patients with known hepatic metastases AST and/or ALT ≤ 5x ULN
- Creatinine ≤ 1.5 × institutional upper limit of normal

3.1.11 Participants may not have clinically active or symptomatic interstitial lung disease or interstitial pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention), or a history of clinically significant interstitial lung disease or radiation pneumonitis

Rev. Add5 3.1.12 Participants may not have had radiation to the lung fields within four weeks (28 days) of starting treatment. For patients receiving palliative radiation to thoracic vertebrae, ribs or other sites where the radiation field includes the lungs, radiation must be completed at least two weeks before starting treatment. For all palliative radiation to all other sites, at least 7 days must have elapsed prior to starting treatment. At least six months (180 days) must have elapsed prior to starting treatment for radiation given with curative intent.

Palliative radiotherapy to control symptoms (including gamma knife technique) is permitted. For stereotactic radiosurgery (SRS) to CNS lesions, osimertinib can be held on the day of radiation only. For palliative RT to other sites of disease outside of the thorax, osi should be held for a minimum of 3 days before radiation and 3 days after RT is completed, but the duration of washout can be adjusted at the investigator's discretion with the approval of the study PI. For thoracic radiation, a 7-10 day washout period before the procedure and one week period after procedure before restarting osimertinib is advised to minimize the risk of pneumonitis. All radiotherapy related toxicities should be managed and ideally resolved before restarting osimertinib. Investigators should consider the radiotherapy when assessing causality if there are any localized AEs following the procedure.

3.1.13 Participants may not have clinically symptomatic brain metastases, leptomeningeal disease or spinal cord compression. Patients may be

on a stable dose of corticosteroids to control brain metastases if they have been on a stable dose for two weeks (14 days) prior to study treatment and are clinically asymptomatic.

Rev. Add4 ———3.1.14 Patients must have an ECHO or a nuclear study (MUGA or First Pass) within 4 weeks (28 days) prior to registration to treatment and must not have a left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN). If the LLN is not defined at a site, the LVEF must be ≥ 50% for the patient to be eligible.

Date of ECHO/Nuclear Study: _____

Rev. Add4 ———3.1.15 Participants may not have any of the following cardiac criteria:

- Mean resting corrected QT interval (QTc) ≥ 470 msec obtained from 3 electrocardiograms (ECGs) using the screening clinic ECG machine-derived QTc value.
- No history of QTc prolongation associated with other medications that required discontinuation of that medication
- Patient must not be receiving any concomitant medications that are known to be associated with Torsades de Pointes
- Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, third degree heart block, second degree heart block, any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, electrolyte abnormalities (including: Serum/plasma potassium < LLN; Serum/plasma magnesium < LLN; Serum/plasma calcium < LLN), congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medication known to prolong the QT interval
- Symptomatic heart failure – New York Heart Association (NYHA) grade II-IV

_____3.1.16 Participants may not have a second, clinically active, cancer. Patients with second cancers which have been treated with curative intent and/or are currently inactive are allowed

_____3.1.17 Participants may not be receiving any other investigational agents. Patients previously treated with investigational agents must complete a washout period of at least two weeks or five half-lives, whichever is longer, before starting treatment.

_____3.1.18 Participants may not have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

Rev. Add5 ———3.1.19 Patients must have no history of hypersensitivity to active or inactive excipients of AZD9291 (osimertinib) or drugs with a similar chemical structure or class to AZD9291 (osimertinib).

_____3.1.20 Patients must not currently be receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal

supplements known to be potent inducers of CYP3A4 (at least 3 weeks prior) (Appendix VIII). All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4.

_____3.1.21 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 or P-glycoprotein (Pgp) 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 AZD9291 (osimertinib).

NOTE: Use of St John's wort is a contra-indication for AZD9291 (osimertinib) use.

Rev. Add5 _____3.1.22 If applicable, it is recommended that the starting and maintenance dose of rosuvastatin (due to BCRP inhibition by AZD9291 [osimertinib]) should be as low as possible and should be guided by the statin label. Monitoring of low-density lipoprotein (LDL) cholesterol levels is advised. If the subject experiences any potentially relevant adverse events suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, the statin should be stopped, creatine kinase (CK) levels should be checked, and any appropriate further management should be taken.

_____3.1.23 Subjects taking warfarin should be monitored regularly for changes in prothrombin time or INR.

_____3.1.24 No unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of starting study treatment, with the exception of alopecia and grade 2, prior platinum-therapy–related neuropathy.

Rev. Add5 _____3.1.25 Patients with refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of AZD9291 (osimertinib) are ineligible.

Rev. Add4 _____3.1.26 Women must not be pregnant or breast-feeding because AZD9291 (osimertinib) has been shown to cause fetal harm in animal models.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Woman of Childbearing Potential?_____(Yes or No)

Date of blood test or urine study: _____

_____	3.1.27	Women of childbearing potential (WOCBP) and sexually active males must use an accepted and effective method of contraception while receiving protocol treatment or abstain from sexual intercourse for the duration of their participation in the study. WOCBP must use birth control two weeks prior to the start of the treatment and continue for 6 weeks after the last dose of the study drug. Sexually active male patients must use effective contraception from day 1 of treatment and continue for 4 months after the last dose of the study drug.
_____	3.1.28	Other anticancer agents and investigational agents should not be given while the subject is on study treatment.
_____	3.1.29	Supportive care and other medications that are considered necessary for the subject's wellbeing may be given at the discretion of the investigator.
_____	3.1.30	A guidance regarding potential interactions with concomitant medications is provided in Appendix VIII

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.