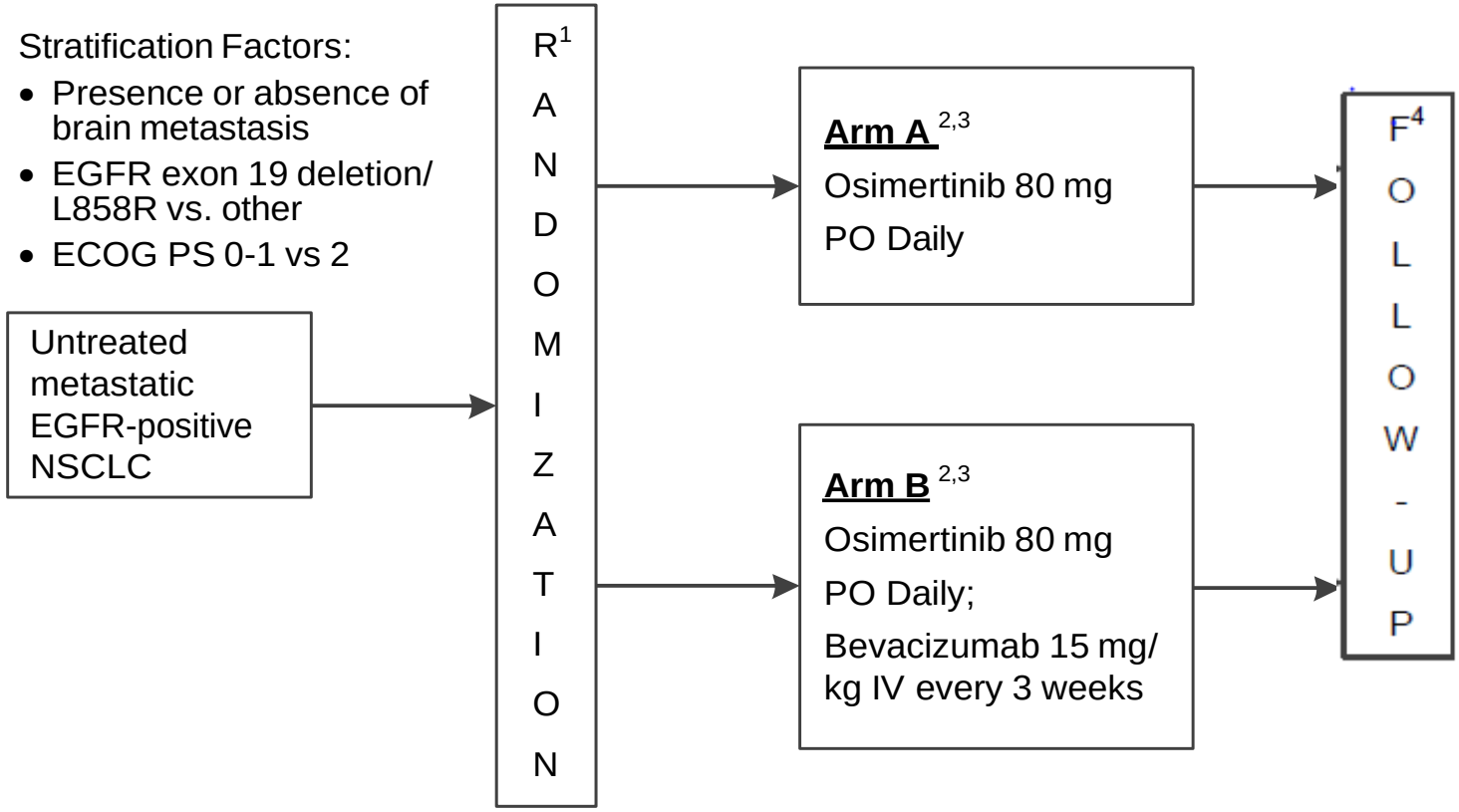
Schema



Accrual Goal = 300 patients
Cycle = 3 weeks (21 days)

1. Randomization is 1:1 for Arms A and B.
2. Systemic imaging will be obtained every 3 cycles (9 weeks) and CNS imaging will be obtained every 6 cycles (18 weeks).
3. Patients will continue on study treatment until progressive disease or unacceptable toxicity.
4. All patients, including those who discontinue protocol therapy early, will be followed until progression, even if non-protocol therapy is initiated, and for survival for 10 years from date of registration.

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.

3.1 Eligibility Criteria

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

_____3.1.2 Patient must have advanced disease, defined as - 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 8th edition staging criteria.

_____3.1.3 Patient must have somatic activating sensitizing mutation in EGFR (e.g. but not limited to Exon 19 deletion, L858R, G709X, G719X, exon 19 insertions, L861Q, S768I). Patients with non-sensitizing mutations in EGFR (EGFR exon 20 insertions) are not eligible. Test results originating from a CLIA-certified or similarly accredited laboratory are acceptable; no specific assay is mandated. If there is any question as to whether an EGFR mutation is sensitizing, please contact the primary study team.

_____3.1.4 Patient must not have received any prior treatment with an EGFR TKI or with an anti-VEGF agent.

_____ 3.1.5 Patients that have received prior radiation therapy are eligible. Radiation (WBRT or stereotactic radiation) must have been completed at least two weeks prior to study registration.

_____3.1.6 Patient must not have any risk factors for anti-VEGF administration, specifically, hemoptysis, active cardiovascular disease, uncontrolled hypertension, significant proteinuria (screening urine dipstick >3+) and tumor invading major blood vessels.

_____3.1.7 Patient must have measurable disease as defined in Section 6.1.2. Baseline measurements of sites of disease must be obtained within 4 weeks prior to study registration. If a potential target lesion is previously irradiated without subsequent growth and/or is radiated after the imaging from which baseline measurements are obtained, they cannot be included as target lesions, and additional target lesions are required to meet criteria for measurable disease.

_____ 3.1.8 Patient must not have had any prior systemic treatment for metastatic disease.

_____3.1.9 Patient must be ≥ 18 years of age.

_____3.1.10 Patient must have an ECOG Performance status of 0 to 2

_____3.1.11 Women must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.

All females of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy.

A female of childbearing potential is defined as any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of child bearing potential?_____(Yes or No)

Date of blood test or urine study: _____

_____3.1.12 Women of childbearing potential and sexually active males must not expect to conceive or father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse for 2 weeks prior to the start of treatment, while on study treatment, and for

- 6 weeks after the last dose of protocol treatment for female patients on the AZD9291 (osimertinib) alone arm
- 4 months after the last dose of protocol treatment for male patients on AZD9291 (osimertinib) alone arm
- 6 months after the last dose of protocol treatment for all patients on AZD9291 (osimertinib) plus bevacizumab combination arm

NOTE: Female patients should also not breastfeed while on treatment and for 6 months after the last dose bevacizumab.

_____3.1.13 Patient must have adequate organ and marrow function as defined below (must be obtained ≤14 days prior to registration):

_____Leukocytes ≥ 3,000/mcL

Leukocytes:_____Date of Test: _____

_____Absolute neutrophil count ≥ 1,500/mcL

Absolute neutrophil count:_____Date of Test: _____

_____Platelets ≥ 100,000/mcL

Platelets:_____Date of Test: _____

_____ Hemoglobin ≥ 9 g/dL

Hemoglobin:_____Date of Test: _____

_____Total bilirubin and creatinine ≤ 1.5 x institutional upper limit of normal (ULN)

Total Bilirubin:_____Institutional ULN:_____Date of Test: _____

Creatinine:_____Institutional ULN:_____Date of Test: _____

_____AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN

AST:_____Institutional ULN:_____Date of Test: _____

ALT:_____Institutional ULN:_____Date of Test: _____

_____3.1.14 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

_____3.1.15 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

_____3.1.16 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

_____3.1.17 Patients with treated brain metastases are eligible if neurologically stable without glucocorticoid therapy after the stated washout period from RT or surgery provided the metastatic lesions are non-hemorrhagic.

_____ 3.1.18 Patients with untreated brain metastases or leptomeningeal disease are eligible if the treating physician determines that immediate CNS specific treatment is not required provided the metastatic lesions are non-hemorrhagic and are neurologically stable without glucocorticoid therapy.

_____3.1.19 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or

efficacy assessment of the investigational regimen are eligible for this trial.

_____3.1.20 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

_____3.1.21 Patient must have the ability to understand and the willingness to sign a written informed consent document and comply with study requirements

_____3.1.22 Patient must not have had treatment with any investigational drug within five half-lives or 3 months (whichever is greater), prior to study initiation.

_____ 3.1.23 Patient must not be currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be strong inducers of CYP3A4 (see Appendix VII). For any patient currently receiving such inducers of CYP3A4, they must discontinue use prior to first dose of study treatment. All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4.

_____3.1.24 Patient must not have any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of registration, with the exception of alopecia and grade 2 prior platinum-therapy–related neuropathy.

_____ 3.1.25 Patient must not have any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it challenging for the patient to participate in the study. Screening for chronic conditions is not required.

_____3.1.26 Patient must not have refractory nausea and vomiting, chronic gastrointestinal diseases, the inability to swallow the osimertinib tablets or previous significant bowel resection that would preclude adequate absorption of osimertinib.

_____ 3.1.27 Patient must not have a 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.

_____ 3.1.28 Patient must not have a history of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib.

_____3.1.29 Patient must not have mean resting corrected QT interval (QTc) > 470 msec obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine derived QTc value.

_____ 3.1.30 Patient must not have any clinically important abnormalities in rhythm, conduction or morphology of resting ECG e.g. complete left bundle branch block, third degree heart block and second-degree heart block.

_____ 3.1.31 Patient must not have any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, electrolyte abnormalities (including: potassium < LLN; magnesium < LLN; 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 and cause Torsades de Pointes.

_____ _____

Physician Signature Date

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