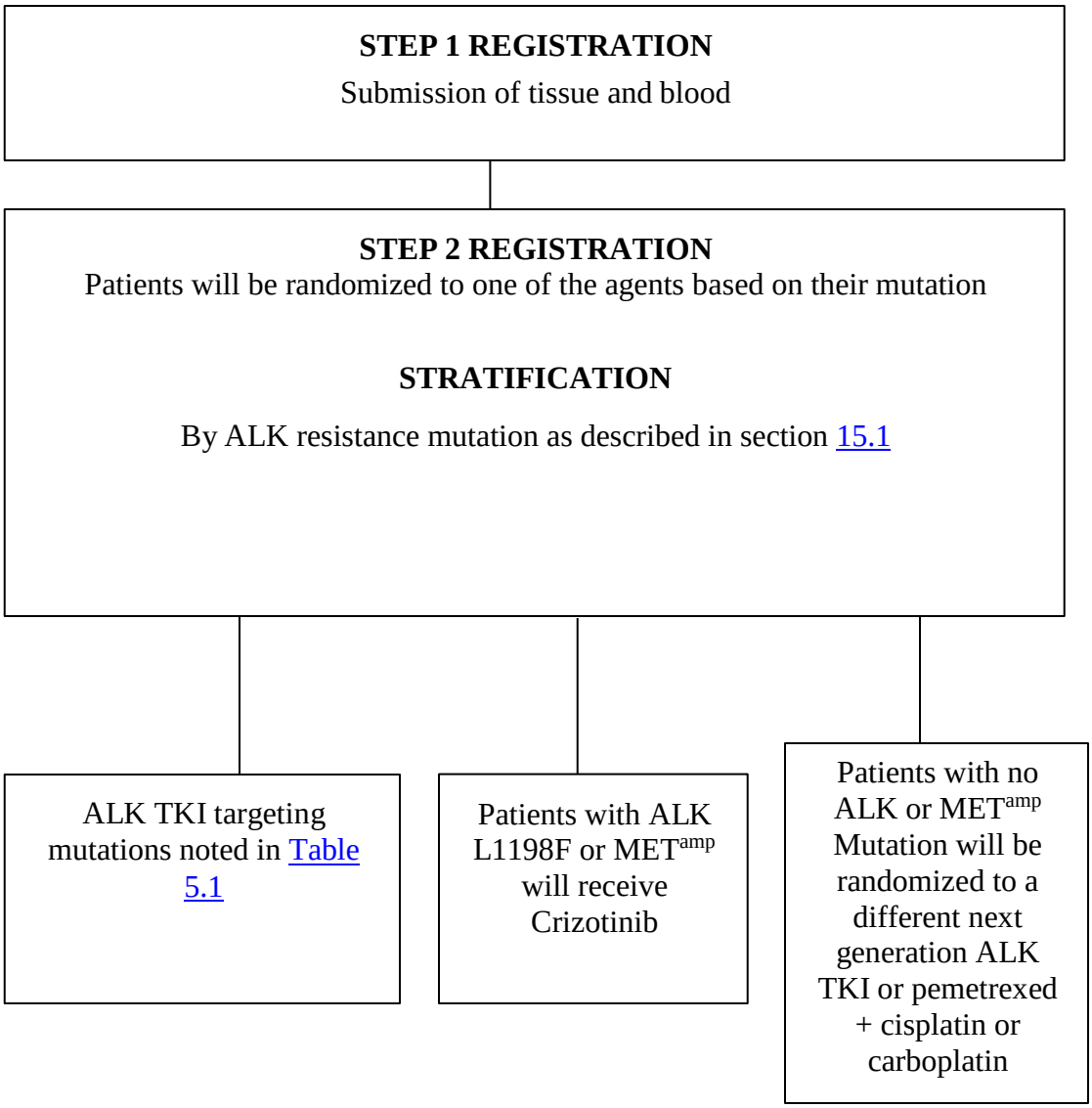
NRG-LU003
SCHEMA



Based on the identified ALK mutation(s), patients will be assigned to treatment with the indicated ALK inhibitors as described in Section 5.1 and Section 15.1. If no ALK-resistance mutations are identified, patients will be randomized to receive either a next-generation ALK inhibitor they have not received or pemetrexed based chemotherapy.

Next-generation ALK inhibitor = 2nd or 3rd generation

sampling for cfDNA analysis. The sensitivity of circulating-free (cf) DNA testing has not been established for routine clinical use in ALK positive non-squamous NSCLC. The implementation of cfDNA testing may be challenging given the multiple and heterogenous mechanisms of resistance to ALK inhibitors. Based on the results of tissue biopsy testing, patients will be assigned to a specific treatment group (see Table in Section 5.1). Treatments will be selected based on preclinical and in some cases, clinical data demonstrating activity of the treatment against the specific ALK mutation or resistance mechanism identified. If no ALK-resistance mutations are identified, patients will be randomized to receive either a next-generation ALK inhibitor they have not received or Pemetrexed based therapy with or without cisplatin or carboplatin. The response rate in the cohort receiving chemotherapy will be compared to the response rates of each of the second-generation ALK inhibitors among patients with no ALK-resistance mutations identified.

Patients whose tissue is insufficient will need to have a repeat biopsy if feasible, as per their treating physician; otherwise, they will not be eligible for this trial. We have anticipated about 10% of patients may have insufficient tissue from a tissue biopsy for mutational testing, and have taken this into consideration when calculating sample size. cfDNA will be collected on all cases.

After the first 200 patients are enrolled, we will analyze the concordance of cfDNA and tissue biopsy. If a high degree of concordance is found with confidence, we will amend the protocol and select patients based on cfDNA only. At that time, tumor biopsy will become optional, but recommend if possible. This will be decided with input from CTEP and the FDA.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page).

3.1 Patient Selection Guidelines

Investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of contraception during the trial.

3.1.3 Submission of blood and tumor tissue is required for all patients. This requirement may change to blood only after the first 200 patients have been analyzed. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. (See details of tissue and blood submissions in Section 10.)

3.1.4 Use of prohibited therapies listed in Appendix IX should be taken into consideration

when screening and enrolling patients in NRG-LU003. Sites will report at step 1 registration whether enrolling patients require the use of any CYP interacting agents, and any prohibited ALK inhibitors will be removed from assignment consideration for these patients

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to Step 1 Registration

3.2.1 Patients must have histologically or cytologically confirmed stage IV ALK-positive non-squamous NSCLC (includes M1a, M1b, M1c stage disease, AJCC 8th edition). ALK rearrangement must have been demonstrated by an FDA approved assay (Vysis FISH or Ventana IHC) or by next generation sequencing (NGS).

3.2.2 Patient must be willing and able to undergo a fresh biopsy or have sufficient tissue within the last 3 months while on the same TKI for central pathology

3.2.3 Age ≥ 18;

3.2.4 Patient must have progressive disease as defined by RECIST 1.1 after a second generation ALK inhibitor, including LDK378 (ceritinib), alectinib, ensartinib, and brigatinib or third generation ALK inhibitor referring to lorlatinib. The next generation ALK inhibitor must be the last ALK inhibitor given (prior crizotinib is allowed)

3.2.5 Patients who have received a cycle of chemotherapy at the time of original diagnosis of metastatic NSCLC are eligible as long as they have received a next generation ALK inhibitor

3.2.6 The patient or a legally authorized representative must provide study-specific informed consent prior to Step 1 Registration.

Prior to Step 2 Registration

3.2.7 Adequate hematologic function within 28 days prior to step 2 registration defined as follows:

- ANC ≥ 1500cells/mm3
- Platelets ≥ 100,000cells/mm3

3.2.8 Adequate renal function within 28 days prior to step 2 registration defined as follows:

- Serum creatinine ≤ 1.5 x upper limit of normal (ULN)

3.2.9 Adequate hepatic function within 28 days prior to step 2 registration defined as follows:

- Total Bilirubin ≤ 1.5 mg/dL
- SGOT (AST) ≤2.5X ULN, or ≤5X ULN in patients with liver metastasis SGPT (ALT) ≤2.5X ULN, or ≤5X ULN in patients with liver metastasis

3.2.10 Patients with asymptomatic treated or untreated brain metastases are eligible. Treated brain metastases are eligible as long as patients have measurable disease outside the brain according to RECIST 1.1. Patients must be on a stable or decreasing dose of steroids for at least 7 days prior to step 2 registration. Anticonvulsants are allowed as long as the patient is neurologically stable and not deteriorating.

3.2.11 Patients enrolled with asymptomatic brain mets must have at least one measurable target extracranial lesion according to RECIST 1.1.

3.2.12 ECOG performance status 0-2

3.2.13 Acute effects of any prior therapy resolved to baseline severity or to CTCAE Grade ≤1 (except for alopecia, hearing loss).

3.2.14 Not taking any medications identified in Section 5.4.2 that may interact with selected study medication based on stratification in Section 15.1

3.2.15 Patients must be able to take oral medications (i.e. swallow whole tablets/capsules)

3.2.16 All females of childbearing potential must have a blood test or urine study within 14 days prior to Step 2 Registration to rule out pregnancy. Refer to section 9 for requirements on the length of time patients should maintain adequate contraception for after the last dose of each medication. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- 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)
- Women must not be pregnant or breast-feeding due to potential harm to the fetus or infant from ALK inhibitors and the unknown risk. Women of childbearing potential and sexually active males must agree to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study.

3.3 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Major surgery within 2 weeks of study entry. Minor surgical procedures (eg, port insertion, pleurex catheter placement) are allowed and all wounds must not show signs of infection or draining.

3.3.2 Radiation therapy (except palliative RT to relieve bone pain) within 2 weeks of study entry. Palliative RT (<10 fractions) must have been completed at least 48 hours prior to study entry. Stereotactic or small field brain irradiation must have completed at least 1 week prior to study entry. Whole brain RT must have completed at least 2 weeks prior to study entry.

3.3.3 Prior dose of next generation ALK inhibitor (LDK378 (ceritinib), alectinib, ensartinib, lorlatinib] within 5 days prior to step 2 registration. Prior dose of brigatinib within 7 days prior to step 2 registration.

3.3.4 History of interstitial lung disease or interstitial fibrosis, including a history of pneumonitis, obliterative bronchiolitis, pulmonary fibrosis. Patients with a history of prior radiation pneumonitis are not excluded.

3.3.5 Active inflammatory gastrointestinal disease (such as Crohns, ulcerative colitis), chronic diarrhea, symptomatic diverticular disease, or any gastrointestinal disease that would affect the absorption of oral medications or increase the risk of toxicity.

3.3.6 Clinically significant cardiovascular abnormalities, as determined by the treating/registering physician, such as uncontrolled hypertension, congestive heart failure NYHA classification of 3, unstable angina or poorly controlled arrhythmia, or myocardial infarction within 6 months.

3.3.7 Active and clinically significant bacterial, fungal, or viral infection

3.3.8 Patients with active or chronic pancreatitis based on lipase elevation, symptoms, and radiographic findings

3.3.9 Other concomitant serious illness or organ system dysfunction that in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the study drug.

3.3.10 Patients must not plan to receive any other investigational agents during the course of therapy.

3.3.11 Patients with active malignancy other than ALK-positive non-squamous NSCLC within the last 2 years are excluded (note: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, papillary thyroid cancer treated with curative intent, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for 2 years are eligible).

3.3.12 No chemotherapy and/or immunotherapy allowed after step 1 registration.