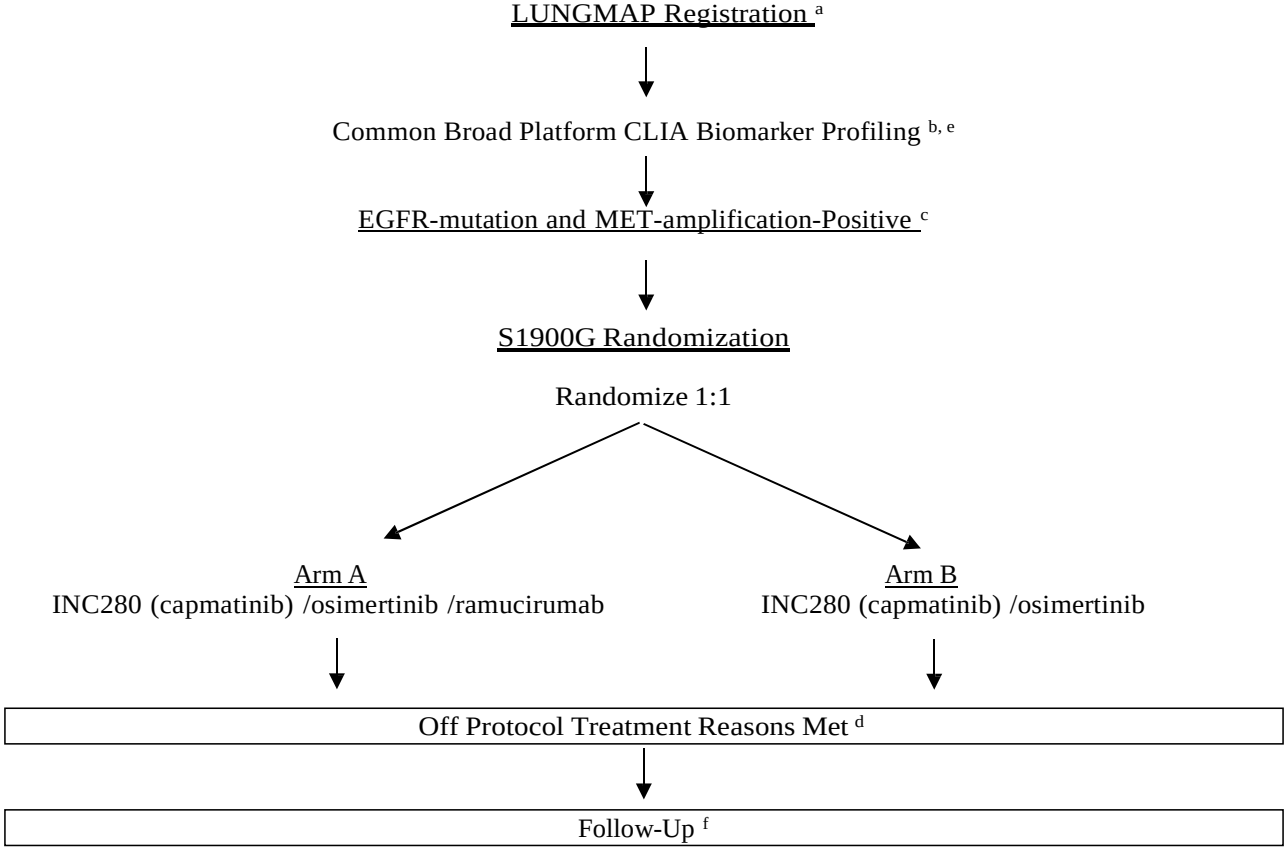
SCHEMA



a. See LUNGMAP Section 5.1 for registration information. Participants must be screened on LUNGMAP at the time of radiographic or clinical disease progression on osimertinib, in order to capture MET amplification.
b. See S1900G Section 5.1. Participants must submit either tissue for biomarker profiling, commercial FoundationOne CDx test results, or tissue or blood (ctDNA) test results from an accepted CLIA laboratory (see LUNGMAP Section 5.1 and 18.7 for details). Tissue or blood sample must be obtained after radiographic or clinical disease progression on osimertinib, alone or in combination with other agent(s), as their most recent line of therapy (See Section 5.2b). Participants with MET amplification results detected outside of the Lung-MAP study, are required to submit documentation as outlined in LUNGMAP Section 18.7.
c. See Section 5.0 for the criteria of MET amplification.
d. See Section 7.7 for criteria for removal from protocol treatment.
e. Notification of sub-study assignment will be provided by the SWOG Statistics and Data Management Center (SDMC) (see LUNGMAP Section 11.0 for details).
f. See Section 7.9 for follow up period details.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a participant to be considered eligible for registration in OPEN. Section 5.0 may be printed and used to by the site, but is not to be uploaded in RAVE (unless specially stated). For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG SDMC in Seattle at 206/652-2267 or LUNGMAPQuestion@crab.org prior to randomization. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

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 4 weeks later would be considered Day 28. This allows for efficient participant scheduling without exceeding the guidelines. If Day 7, 14, 16, 28, or 42 falls on a weekend or holiday, the limit may be extended to the next working day.

5.1 Disease Related Criteria

a. Participants must have been assigned to S1900G by the SWOG Statistics and Data Management Center (SDMC). Assignment to S1900G is determined by the LUNGMAP protocol.

b. Participants must have documentation of NSCLC with a sensitizing EGFR mutation and have radiologically or clinically progressed (in the opinion of the treating physician) on osimertinib, alone or in combination with other agent(s), as their most recent line of therapy. Any number of prior lines of therapy is allowed.

c. Participants must have a MET amplification determined by tissue-based or blood-based (circulating tumor DNA [ctDNA]) NGS assay. MET amplifications may have been determined based on tissue submitted for testing by FMI through the LUNGMAP screening protocol or using test results completed outside of the study (see Section 5.1c and 18.6 of LUNGMAP). See Section 18.6 for a list of acceptable blood-based assays if using results from outside of LUNGMAP. Tissue or blood must be obtained after disease progression on osimertinib (alone or in combination with another agent(s)). The testing must be done within a laboratory with CLIA, ISO/IEC, CAP, or similar certification..

   Note: Participants previously tested for and determined to have MET amplified NSCLC, at the time of progression on osimertinib, outside of LUNGMAP, must also submit tissue for central FMI testing on the LUNGMAP screening protocol, if available. See LUNGMAP Section 18.7b

d. Participants must have either measurable disease or non-measurable disease (Section 10.1) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in Section 10.1c. Measurable disease must be assessed within 28 days prior to sub-study randomization. Non-measurable disease must be assessed within 42 days prior to sub-study randomization. All known sites of disease must be assessed and documented on the Baseline Tumor Assessment Form. Participants whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of the treating investigator) prior to sub-study randomization to be considered

measurable. See Section 15.6 for guidelines and submission instructions for required central radiology review.

e. Participants must have a CT with contrast or MRI scan of the brain to evaluate for CNS disease within 42 days prior to sub-study randomization.

f. Participants with symptomatic CNS metastasis (brain metastases or leptomeningeal disease) must be neurologically stable and have a stable or decreasing corticosteroid requirement for at least 5 days before sub-study randomization.

5.2 Prior/Concurrent Therapy Criteria

a. Participants must have recovered (≤ Grade 1) from any side effects of prior therapy, except for alopecia and vitiligo.

b. Participants must not have received an anti-VEGF or VEGFR inhibitor or MET inhibitor.

c. Participants must not have received any anti-cancer drug (investigational or standard of care drug, except osimertinib) within 21 days prior to sub-study randomization. Note: osimertinib may continue up to the day prior to study treatment initiation.

d. Participants must not have received any radiation therapy within 14 days prior to sub-study randomization.

e. Participants must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment while receiving treatment on this study.

f. Participants must not have had a major surgery within 14 days prior to sub-study randomization. Participants must have fully recovered from the effects of prior surgery in the opinion of the treating investigator.

g. Participants must not have received a live attenuated vaccination within 28 days prior to sub-study randomization (See Appendix 18.5). All COVID-19 vaccines that have received FDA approval or FDA emergency use authorization are acceptable.

5.3 Clinical/ Laboratory Criteria

a. Participants must be able to swallow tablets whole.

b. Participants must have adequate organ and marrow function as defined below within 28 days prior to sub-study randomization:

- absolute neutrophil count	≥1.5 x 10^3/uL
- hemoglobin	> 9.0 g/dL
- platelets	≥100 x 10^3/uL
- total bilirubin	≤ 1.5 x institutional upper limit of normal (ULN) unless history of Gilbert's disease. Participants with history of Gilbert's disease must have total bilirubin ≤ 5 x institutional ULN.
- AST and ALT	≤ 2.5 × institutional ULN. Participants with history of liver metastasis must have AST ≤ 5 x ULN

c. Participants must have a serum creatinine ≤ the IULN OR calculated creatinine clearance ≥ 50 mL/min using the following Cockcroft-Gault Formula. This specimen must have been drawn and processed within 28 days prior to sub-study randomization:

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{weight in kg}) \dagger}{72 \times \text{serum creatinine} *}$$ Multiply

this number by 0.85 if the participant is a female.

† The kilogram weight is the participant weight with an upper limit of 140%of the IBW.
* Actual lab serum creatinine value with a minimum of 0.7 mg/dL.

d. Participants' most recent Zubrod performance status must be 0-1 (Section 10.4) and be documented within 28 days prior to sub-study randomization.

e. Participants must have an ECG performed, with a QTcF ≤ 470 msec, within 28 days prior to sub-study randomization. It is suggested that a local cardiologist review the QTcF intervals.

f. Participants must have a completed medical history and physical exam within 28 days prior to sub-study randomization.

g. Participants must have a urinalysis performed 28 days prior to sub-study randomization. Participant must have a urinary protein ≤1+ on dipstick or routine urinalysis (UA). Random analysis of urine protein with a normal value is sufficient. If urine dipstick or routine analysis indicated proteinuria ≥2+, then a 24-hour urine is to be collected and demonstrate <1000 mg of protein in 24 hours to allow participation in the study.

h. Participants must have an International Normalized Ratio (INR) ≤ 1.5 seconds above the institutional upper limit of normal (IULN) (unless receiving anticoagulation therapy) documented within 28 days to sub-study randomization. Participants must have a partial thromboplastin time (PTT) ≤ 5 seconds above the `institutional upper limit of normal (IULN) (unless receiving anticoagulation therapy) documented within 28 days prior to sub-study randomization.

i. Participants with known human immunodeficiency virus (HIV) infection must be on effective anti-retroviral therapy at randomization and have undetectable viral load within 6 months prior to sub-study randomization.

j. Participants must have asymptomatic serum amylase ≤ 2 x ULN and serum lipase ≤ ULN obtained within 28 days prior to sub-study randomization. Asymptomatic is defined as having no signs and/ or symptoms suggesting pancreatitis or pancreatic injury (e.g. elevated P. amylase, abnormal imaging findings of pancreas, etc.).

k. Participants must have adequate cardiac function. Participants with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, must have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification (see Section 18.1). To be eligible for this trial, participants must be class 2B or better.

l. Participants must not have received strong inducers of CYP3A4 (including herbal supplements such as St. John's Wort); CYP3A4 inhibitors; CYP1A2 substrates; P- gp

and BCRP substrates; sensitive substrates of MATE1 and MATE2K; or drugs that are known to prolong QT interval within 7 days prior to sub-study registration and must not be planning to use any of these throughout protocol treatment. (See Section 7.1 for examples).

m. Participants must not have uncontrolled blood pressure and hypertension within 28 days prior to sub-study randomization. See Section 7.4 for definition of uncontrolled blood pressure and hypertension.

n. Participants must not have a prior or concurrent malignancy whose natural history or treatment (in the opinion of the treating physician) has the potential to interfere with the safety or efficacy assessment of the investigational regimen.

o. Participants must not be pregnant or breastfeeding (nursing includes breast milk fed to an infant by any means, including from the breast, milk expressed by hand, or pumped). Individuals who are of reproductive potential must have agreed to use an effective contraceptive method with details provided as a part of the consent process. A person who has had menses at any time in the preceding 12 consecutive months or who has semen likely to contain sperm is considered to be of "reproductive potential." In addition to routine contraceptive methods, "effective contraception" also includes refraining from sexual activity that might result in pregnancy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) including hysterectomy, bilateral oophorectomy, bilateral tubal ligation/occlusion, and vasectomy with testing showing no sperm in the semen.

5.4 Specimen Submission Criteria

a. Participants must agree to have blood specimens submitted for circulating tumor DNA (ctDNA) as outlined in Section 15.4.

b. Participants must also be offered participation in specimen banking as outlined in Section 15.4. With participant consent, specimens must be collected and submitted via the SWOG Specimen Tracking System as outlined in Section 15.2.

5.5 Regulatory Criteria

Note: As a part of the OPEN registration process (see Section 13.0 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

a. Participants must be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional and federal guidelines.

b. Participants with impaired decision-making capacity must not have a neurological or psychological condition that precludes their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator). For participants with impaired decision-making capabilities, legally authorized representatives may sign and give informed consent on behalf of study participants in accordance with applicable federal, local, and CIRB regulations.