S1900G

Activation Anticipated Q1 2023

A Randomized Phase II Study of Capmatinib plus Osimertinib with or without Ramucirumab in Participants with EGFR-Mutant, MET-Amplified Stage IV or Recurrent Non-Small Cell Lung Cancer (Lung-MAP Sub-Study)

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LUNG-MAP

S1900G Schema

KEY ELIGIBILITY

- **Advanced *EGFR*-mutant NSCLC**
- ***MET* amplification***
- **At least 1 prior EGFR TKI, including osimertinib as the most recent prior treatment (alone or in combination with other agents)**
- **Chemotherapy +/- immunotherapy is allowed but not required**
- **No prior MET or VEGF-pathway inhibitor**
- **Untreated, asymptomatic brain metastases allowed**

Randomize 1:1

→ **Capmatinib at 400 mg BID** plus osimertinib 80mg QD plus ramucirumab 10mg/kg Q2w**

→ **Capmatinib at 400 mg BID** plus osimertinib 80mg QD**

Primary Endpoints:

- **Progression-free survival**

Secondary Endpoints:

- **Toxicity by CTCAE**
- **Response**
- **Duration of response**
- **Overall survival**

N = 60 eligible (66 total)

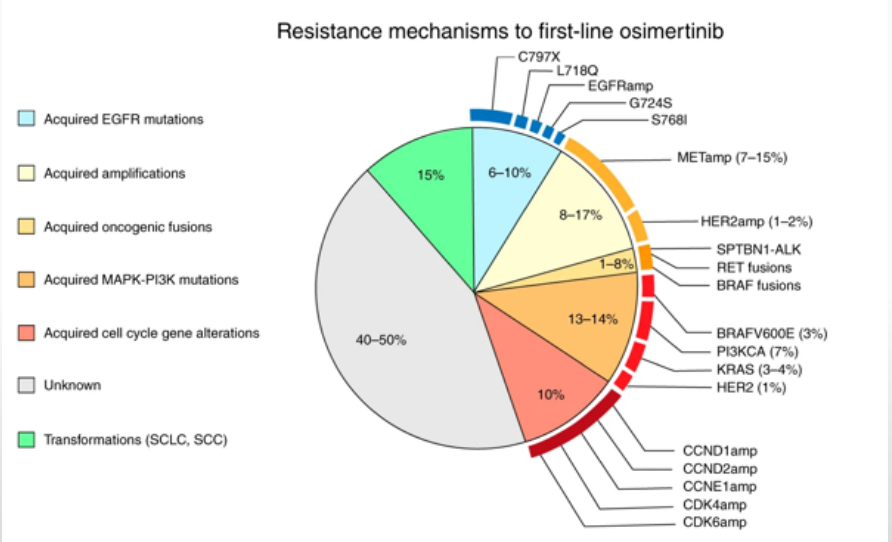
Stratification factors: Brain metastases and 2L vs 3+L prior lines of therapy

* *MET* amplification as determined by tissue-based or blood-based (ctDNA) NGS assay obtained at the time of progression on osimertinib. Tissue testing may be done by FMI through the LUNGMAP screening protocol or using testing results completed outside of the study.

** The study will include a safety run-in on the 1st 10 participants in each arm; if too toxic, regimen will include capmatinib at 200mg BID

Background/Overview

- Participants with advanced EGFR-mutant NSCLC often respond well to EGFR inhibitors but resistance eventually develops
- One mechanism of resistance to EGFR inhibitors is MET amplification
- Combining a MET inhibitor with an EGFR inhibitor can overcome resistance to EGFR TKIs driven by MET amplification



- The addition of a VEGF or VEGFR2 inhibitor can increase the progression-free survival when added to an EGFR TKI in EGFR-mutant lung cancer
- Preclinical data demonstrates the crosstalk between VEGF and MET signaling, and the dual inhibition of VEGFR and MET may be able to delay or overcome resistance to EGFR TKIs

Primary Objectives

- To compare investigator-assessed progression-free survival (IA-PFS) between participants with EGFR mutated, MET amplified NSCLC randomized to capmatinib and osimertinib with or without ramucirumab

Secondary Objectives

- To evaluate if the combination of capmatinib, osimertinib and ramucirumab or capmatinib and osimertinib during the first cycle of treatment has an acceptable toxicity rate.
- To evaluate the frequency and severity of toxicities within the arms.
- To compare IA-PFS between the arms, in the following subsets:
  - Participants with centrally-confirmed MET amplification in tissue
  - Participants with centrally-confirmed MET amplification based on ctDNA
  - Participants with and without history of brain metastases
  - Participants who have received only 1 prior line of therapy and those who have received 2 or more prior lines of therapy
- To compare the objective response rate between the arms among participants with measurable disease at baseline.
- To evaluate duration of response among responders within each arm.
- To compare overall survival between the arms.

Translational Medicine Objectives

- To collect, process, and bank cell-free deoxyribonucleic acid (ctDNA) prior to treatment and throughout treatment for future development of a proposal to evaluate comprehensive next-generation sequencing of circulating tumor deoxyribonucleic acid (ctDNA).
- To establish a tissue/blood repository from participants with refractory non-small cell lung cancer (NSCLC).

Overview of Treatments

- Osimertinib is an EGFR tyrosine kinase inhibitor.
  - Approved for first-line treatment of participants with EGFR-mutant NSCLC.
- Capmatinib is a kinase inhibitor that targets MET.
  - FDA-approved for participants with MET exon 14 skipping mutations.
- Ramucirumab is a VEGFR2 antagonist that results in inhibition of angiogenesis.
  - FDA-approved in combination with erlotinib or docetaxel.
- Concomitant therapy:
  - No concomitant systemic cancer therapies are permitted while on trial.
  - Radiation for symptomatic metastases (e.g. bone) is permitted.
- Recommended pre-medication:
  - Pre-medication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics, growth factors, or other medications) may be given as indicated by the current ASCO guidelines.
  - Pre-medication with a histamine H1 antagonist such as diphenhydramine hydrochloride is recommended prior to infusion of ramucirumab.

Treatment Administration

	Osimertinib	Capmatinib	Ramucirumab
Route:	PO	PO	IV
Dose:	80mg	400mg	10 mg/kg
Cycle duration:	28 days	28 days	28 days
Administration:	Daily	Twice daily	Day 1 and 15
Premedication:	None	None	Histamine H1 antagonist recommended
Supportive care:	See Section 8 of the protocol		
Disease assessment:	CT scans +/- brain MRI every 8 weeks		
Prohibited medications:	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.		

Key Eligibility (1)

- 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.
- 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. Tissue or blood must be obtained after disease progression on osimertinib. The testing must be done within a laboratory with CLIA, ISO/IEC, CAP, or similar certification.
- Participants must have either measurable disease or non-measurable disease documented by CT or MRI.
- 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.

Key Eligibility (2)

- Participants must not have received an anti-VEGF or VEGFR inhibitor or MET inhibitor.
- Zubrod performance status must be 0-1.
- ECG performed, with a QTcF ≤ 470 msec.
- Participant must have a urinary protein ≤1+ on dipstick or routine urinalysis (UA).
- Participants must have adequate cardiac function.
- 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.
- Participants must not have uncontrolled blood pressure and hypertension.

Anticipated Adverse Events/ Serious Adverse Events

- All study drugs are FDA-approved and not anticipated to result in toxicity outside of what is typically expected.

Dose Modifications/Interruptions

- Dose reductions of ramucirumab are allowed for proteinuria only.
- Osimertinib and capmatinib may be dose-reduced as necessary.
- The maximum dose delay for any treatment-related toxicity or unforeseen circumstance unrelated to toxicity is 28 days.
- Missed doses will not be made up.
- Dose interruptions and discontinuations are allowed to manage toxicity.
- If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.
- Reductions are based on the dose being given at the end of the preceding cycle and are based on toxicities observed since the prior toxicity evaluation.
- If osimertinib or capmatinib must be permanently discontinued, the participant must be removed from protocol therapy. If ramucirumab must be discontinued the participant may remain on osimertinib and capmatinib as long as they are well tolerated and according to the treatment physician, the participant is still deriving clinical benefit.

Dose Modifications Table

DRUG	DOSE LEVEL	DOSE
osimertinib		
	Full	80 mg
	-1 Level	40 mg
INC280 (capmatinib)		
	Full	400 mg BID
	-1 Level	300 mg BID
	-2 Level	200 mg BID
Ramucirumab		
	Full	10 mg/kg
	-1 Level	6 mg/kg

Criteria for Removal from Treatment

- Progression of disease or symptomatic deterioration. However, a participant may continue protocol treatment as long as the participant is continuing to clinically benefit form treatment in the opinion of the treating investigator.
- Unacceptable toxicity.
- Treatment delay > 28 days.
- Participants may withdraw from protocol treatment at any time for any reason.

LUNGMAP Registration (Screening Step): Identification of MET amplification

This will occur during **LUNGMAP** screening prior to sub-study assignment to **S1900G**:

THREE POSSIBLE SCENARIOS:

- Note: The specimen that identifies MET amplification must have been obtained after radiographic or clinical progression on osimertinib as the most recent line of therapy.

1. Participant with EGFR-mutant NSCLC progressing on osimertinib (alone or in combination with another therapy) and repeat molecular testing at progression has not yet been performed:

    - Submit new biopsy material for on-study biomarker profiling on **LUNGMAP** *(standard **LUNGMAP** procedure)*

LUNGMAP Registration (Screening Step): Identification of MET amplification cont.

2. Participant with EGFR-mutant NSCLC progressing on osimertinib (alone or in combination with another therapy) and MET amplification was **detected at the time of progression** using commercial FoundationOne CDx tissue-based (not liquid) tumor testing:

   - Submit request for reanalysis of commercial FoundationOne CDx results via the SWOG Specimen Tracking System *(standard **LUNGMAP** procedure)*

   - Additional submission of tissue on **LUNGMAP** is not needed.

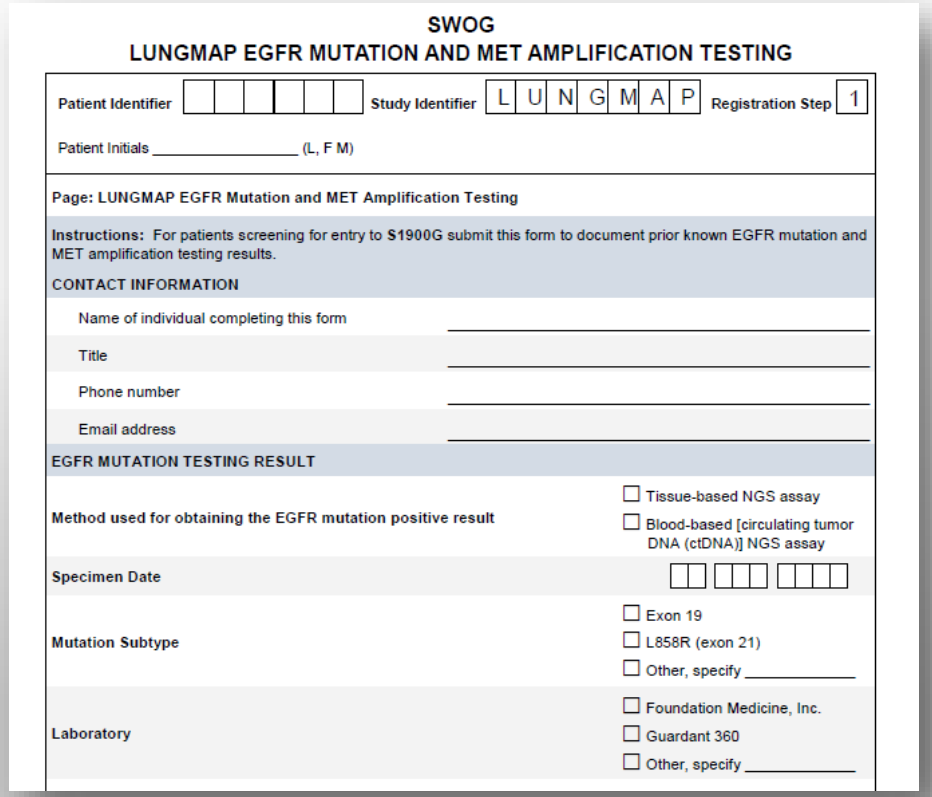
LUNGMAP Registration (Screening Step): Identification of MET amplification cont.

3. Participant with EGFR-mutant NSCLC progressing on osimertinib (alone or in combination with another therapy) and MET amplification was **detected at the time of progression** using other tissue OR blood-based assay results

   - Acceptable assays:
     - Tissue-based: Any assay performed in a laboratory with CLIA, ISO/IEC, CAP or similar certification

       Note: If results are from commercial FoundationOne CDx (tissue) assay, refer to #2 on the previous slide.
     - Blood-based: Foundation Medicine or Guardant 360 cfDNA assays only
   - Indicate this during **LUNGMAP** registration and then submit results in **LUNGMAP** Rave EDC on the EGFR Mutation and MET Amplification Testing Form (new with activation of S1900G)
   - Submit tissue if available (not required)

Email LungMAPquestion@crab.org or call 206-652-2267 with questions



SWOG
LUNGMAP EGFR MUTATION AND MET AMPLIFICATION TESTING

Patient Identifier ☐☐☐☐☐☐ Study Identifier L U N G M A P Registration Step 1

Patient Initials _____ (L, F M)

Page: LUNGMAP EGFR Mutation and MET Amplification Testing

Instructions: For patients screening for entry to S1900G submit this form to document prior known EGFR mutation and MET amplification testing results.

CONTACT INFORMATION

Name of individual completing this form _____

Title _____

Phone number _____

Email address _____

EGFR MUTATION TESTING RESULT

Method used for obtaining the EGFR mutation positive result
☐ Tissue-based NGS assay
☐ Blood-based [circulating tumor DNA (ctDNA)] NGS assay

Specimen Date ☐☐/☐☐☐/☐☐☐☐

Mutation Subtype
☐ Exon 19
☐ L858R (exon 21)
☐ Other, specify _____

Laboratory
☐ Foundation Medicine, Inc.
☐ Guardant 360
☐ Other, specify _____

Has patient been tested for and determined to have EGFR-mutated, MET-amplified NSCLC? ☐Yes ☐No

LUNG-MAP

Tissue Submission for LUNGMAP – if using known test results

- Participants must submit tumor tissue if available when screening on the LUNGMAP protocol with known test results.
- The tissue must be from a biopsy performed at the time of disease progression on the most recent line of therapy.
- An additional biopsy is not required to obtain this tissue if it is not already available.
- Participants with prior commercial FoundationOne CDx tissue-based (not liquid) tumor test results [obtained after radiographic or clinical disease progression on osimertinib] do not need to submit tumor tissue

Registration for **S1900G**

- The **LUNGMAP** screening protocol has a Protocol Specific Requirement (PSR) as noted in Section 13.2 of **LUNGMAP**.
- The **S1900G** sub-study has additional optional training materials available through the Compliance, Learning, and SOP Solutions (CLASS) website. Online training is not required to register participants to **S1900G**.
- A Delegation Task Log is required for this sub-study.

Data Submission

- Data must be submitted according to the protocol requirements for ALL participants registered, whether or not assigned treatment is administered, including participants deemed to be ineligible. Participants for whom documentation is inadequate to determine eligibility will generally be deemed ineligible. See Protocol Section 14.0 for Data Submission Requirements, Procedures and Timepoints.

Specimen Submission on S1900G

- **ctDNA Assay – Peripheral Whole Blood (Required for Participants)**
  - Sites must contact Foundation Medicine, Inc. – Blood Samples, Lab #232, to order kits
    - Kits include: two Roche Cell-Free DNA blood collection tubes, collection instructions, FedEx return bags, and pre-printed FedEx airway bills.
  - Collection timepoints: Cycle 1 Day 1 (prior to treatment); Cycle 1 Day 15; Cycle 3 Day 1; First Progression
  - The translational medicine proposal to use these specimens will be submitted as a revision to CTEP for approval, prior to the SWOG Statistical and Data Management Center review of assay results.
- **Buffy Coat and Plasma Banking (Required If Participant Consents)**
  - Participants must be offered the opportunity to participate in banking of specimens for future research.
  - Collection timepoints: Pre-treatment, Cycles 2-4 (same day as other labs), first progression.
  - Collect approximately 8-10 mL of blood in EDTA tubes.
  - See Protocol Section 15.5 for additional specimen processing instructions.
  - Frozen plasma and buffy coat specimens must be shipped to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201.
  - Specimen collection kits are not being provided for this submission; sites must use institutional supplies.

Quality Control – Routine Data Monitoring

S1900G includes routine SWOG Centralized Data Coordinator Monitoring and Safety-specific monitoring (standard for all SWOG trials, Lung-MAP and Lung-MAP substudies), including:

- Data submission review for missing data, submission errors and protocol deviations.
- Institutional Performance Review processes.
- Source data (pathology, radiology and lab reports) review for confirmation of disease classification and response assessment.
- Routine monitoring of SAE reporting.

S1900G substudy does NOT have potential to be utilized for FDA registration.
Herein, S1900G does NOT require:

1) Participating site maintenance of a Trial Master File,
2) Upload of documents into the Source Document Portal (SDP), or
3) Central Monitoring Review by the SDMC Monitors
4) Blinded independent central review of response and Progression-Free Survival (PFS) Endpoint.

Quality Control – Additional On-Site Monitoring

Consistent with Lung-MAP Protocol Section 18.2 and all Lung-MAP substudies, S1900G includes On-Site Monitoring, as follows:

- First on-site monitoring visit at each institution within 3 months of first patient registration to a LUNGMAP sub-study.
- Subsequent on-site visits for all sites with patients registered to a sub-study twice per year. Additional visits may be scheduled in response to several factors such as high rate of accrual, previous monitoring visit results, centralized monitoring outcome, change in staff, etc.
- An exception to the onsite audit requirement may be allowed in the following circumstances:
  - Sites that use a centralized pharmacy and data management team may be monitored at this central location.
  - Sites that had an acceptable on-site pharmacy audit in the last year may be audited off site.
  - Covid visitor restrictions

Funding

- Capmatinib and ramucirumab will be provided; osimertinib is commercially available and should be purchased by a third party.
- Available site payments are included in the table below. Payments to offset the cost of research-directed laboratory tests are pending. Complete and detailed funding information, including Study-Specific Notes, will be available in the approved funding memorandum posted via CTSU.org at time of activation.

Funding Source and Study Component		Collect Type	Enter Date in Open?	NCTN Funding per Patient Std/HP LAPS	NCORP Funding per Patient Std/HP
Federal	Base Intervention – Standard / High Performance LAPS & NCORP	Mandatory	No	$2,500/$4,100	$2,500/$4,100
Federal	Biospecimen – Whole Blood Whole blood for ctDNA at multiple timepoints	Mandatory	Yes	$200	$200
Federal	Biospecimen – Blood (Multiple) Buffy coat and plasma collections at multiple timepoints	Mandatory Request	Yes	$200	$200
Total Potential Federal Funds				**$2,900/$4,500**	**$2,900/$4,500**
Non-Federal	Additional capitation resources from industry partners	Mandatory	No	$2,610/$1,010	$2,610/$1,010
Total Potential Non-Federal Funds				**$2,610/$1,010**	**$2,610/$1,010**
Total Potential Funds				**$5,510/$5,510**	**$5,510/$5,510**
Additional Support for Site Auditing					
Non-Federal	Additional capitation resources from industry partners for additional site auditing /monitoring.	Mandatory Event	No	$1,333 (per audit)	**$1,333 (per audit)**
All sites will be audited a minimum of twice per year as recommended by the FDA for this study. Sites will be reimbursed for any extra effort associated with increased auditing at $1,333 per additional audit above the FDA recommendation.					

Resources and Materials

- **S1900G** patient-friendly plain language trial summary and accompanying social media toolkit (tweets and graphics).
  - The patient-friendly trial summary and social media toolkit will be available for participating site use on SWOG.org and via the S1900G protocol abstract page on CTSU.org.

S1900G Contacts

Study Chairs:

- Dr. Sarah Goldberg (SWOG)
  Yale School of Medicine
- Dr. Ross Camidge (SWOG)
  University of Colorado School of Medicine

Questions:

Medical Questions for Study Chairs:

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Eligibility/Specimen/Data Submissions:
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General Protocol/Regulatory:
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