Welcome to the S1900F Training Webinar & S1900E Refresher!

Instructions to Attendees:

Thank you for your patience as we give everyone time to join before we begin at:

11:00 AM Pacific Time / 1:00 PM Central Time / 2:00 PM Eastern Time.

- Please use the “call me” audio option. This works best to avoid audio feedback from computers.
- Please mute your line and turn off your video if you are not speaking. Video can slow down WebEx.
- We will have a **Q & A session** at the end of the S1900F training and the end of the webinar, in which you will have time to **“raise your hand”** in WebEx to ask a question or place your question in the **chat box**.
- This meeting will be recorded. Slides and a recording will be posted to CTSU & SWOG websites.

We will begin shortly!

LUNG-MAP

S1900F Training Webinar & S1900E Refresher

WELCOME BY

DAVID GANDARA, MD, LUNGMAP MEDICAL ONCOLOGY CHAIR/CHAMPION (SWOG)

ON BEHALF OF THE LUNG-MAP TEAM

JULY 21, 2022

Agenda

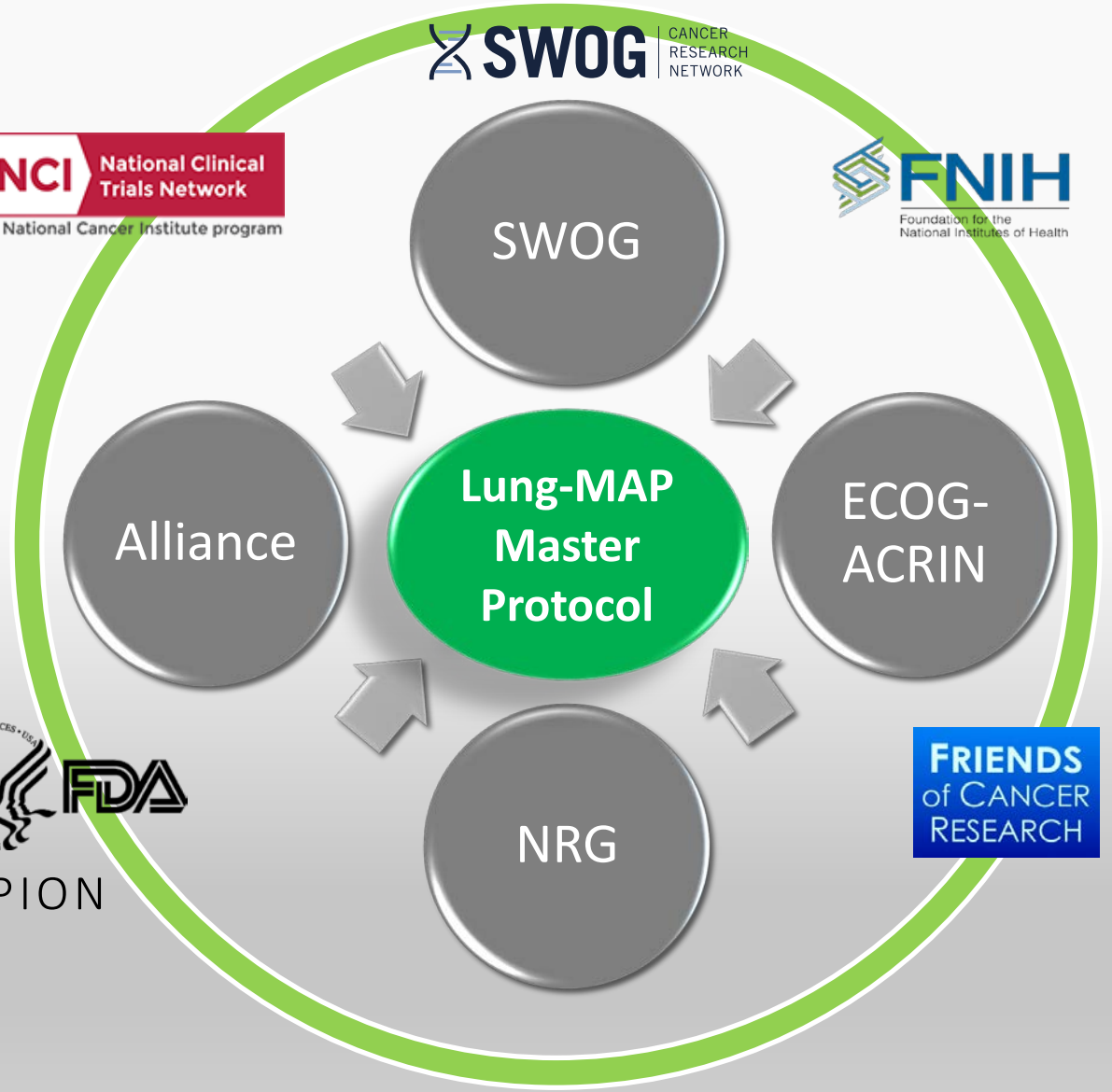
There will be a Q & A session at the end of the presentations.

- Study Updates
  - David Gandara, MD, LUNGMAP Medical Oncology Chair/Champion (SWOG)
- S1900F Training
  - Yasir Elamin, MD, S1900F Co-Chair (SWOG)
- LUNGMAP Revisions #5 & #6
  - David Gandara, MD, LUNGMAP Medical Oncology Chair/Champion (SWOG)
- Lung-MAP Central Monitoring Refresher
  - Cassie Villasin, SWOG Statistics & Data Management Center
- S1900F, LUNGMAP Revisions #5 & #6, and Central Monitoring Q & A – All attendees
- S1900E Refresher
  - Sukhmani Padda, MD, S1900E Chair (ECOG-ACRIN)
- General Q & A – All attendees

Lung-MAP Study Updates

DAVID GANDARA, MD

LUNGMAP MEDICAL ONCOLOGY CHAIR/CHAMPION (SWOG)



Accrual as of 7/18/22

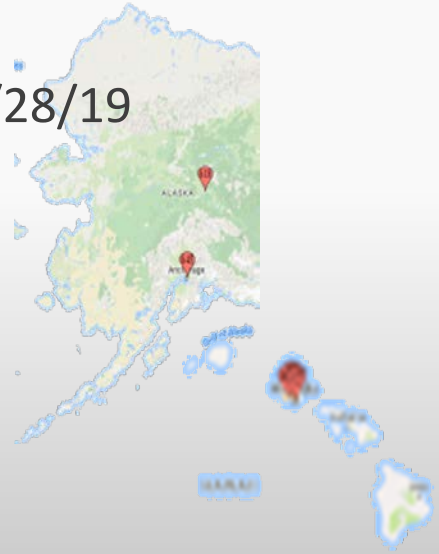
Where are we now?

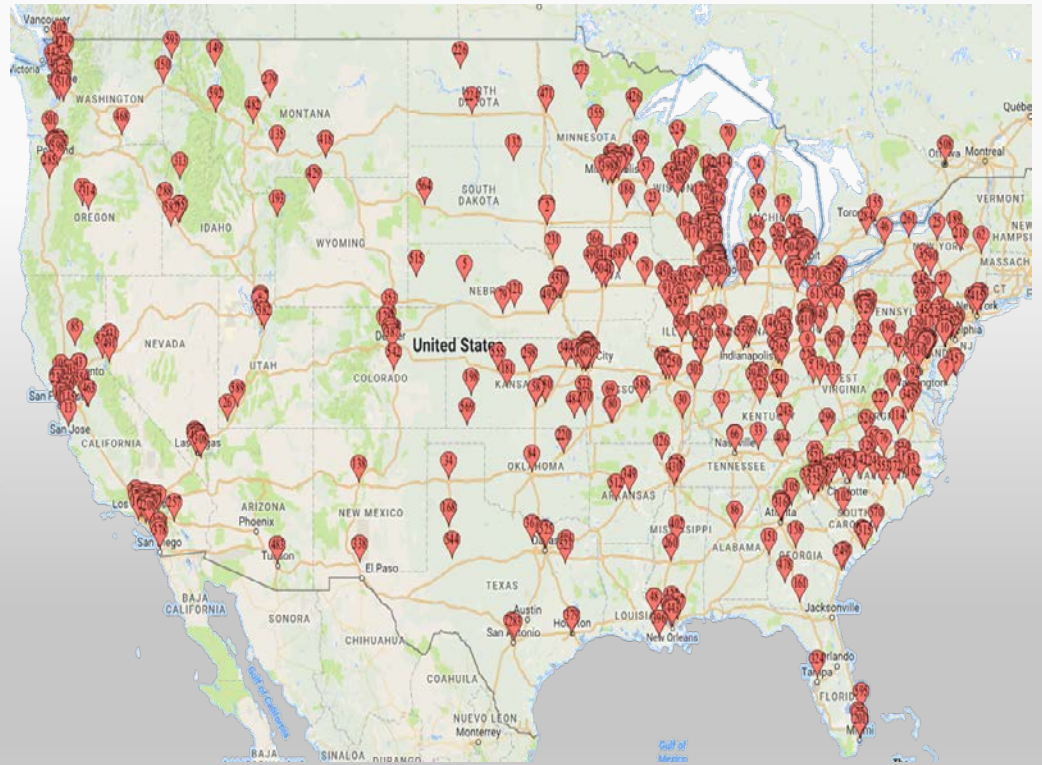
S1400 Screening Protocol - Opened 6/16/14. Closed 1/28/19 to expand to all histologies of NSCLC with the new LUNGMAP protocol.

- 1864 patients registered

LUNGMAP Screening Protocol - Opened 1/28/19

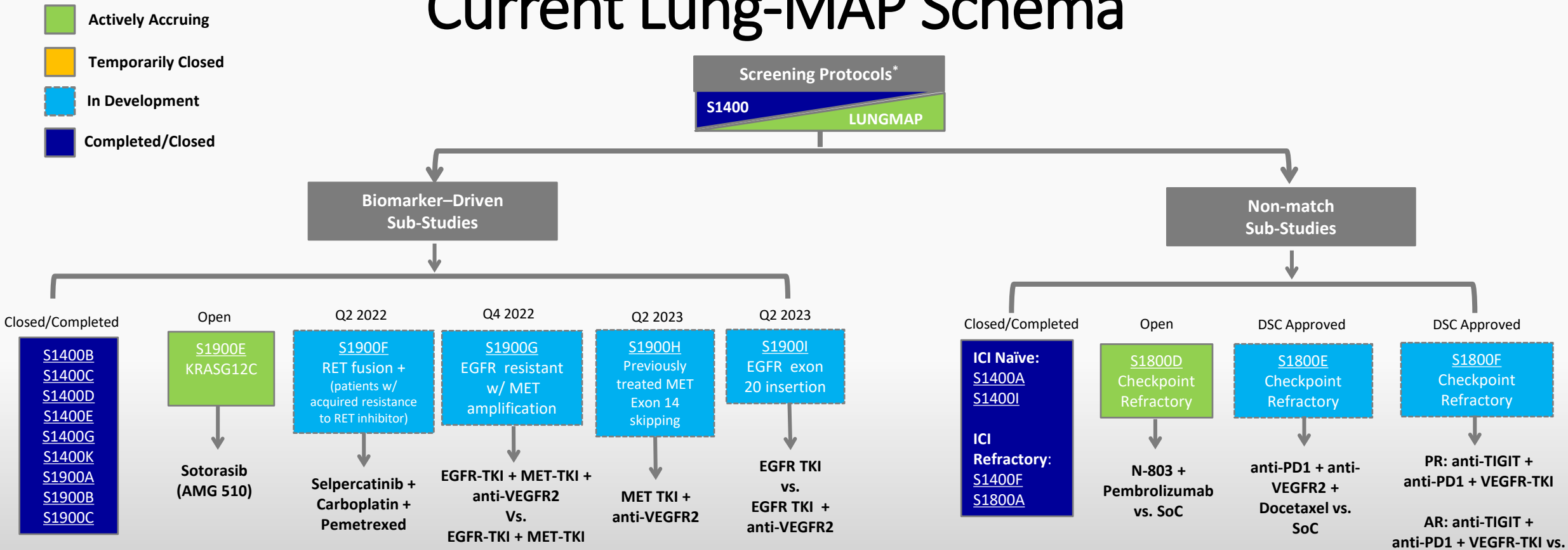
- 825 sites with LUNGMAP CIRB approval
- **2585** patients registered
  - 1638 pre-screening
  - 947 screening
  - 1821 non-squamous
  - 702 squamous
  - 62 mixed histology
- **1385** patients assigned to a sub-study
  - **369** patients have registered to sub-studies





LUNG-MAP

Current Lung-MAP Schema



*LUNGMAP screening protocol (activated 1/28/19) allows all histologic types of NSCLC. S1400, the original screening/umbrella protocol included only squamous lung cancer. S1400 accrued patients between 6/16/2014 and 1/28/2019. While S1400 is closed to accrual, patients enrolled to S1400 may participate in sub-studies they are eligible for.

TRIAL POINTS OF INTEREST:

- Each of sub-study operates independently of the others
- Prescreening can be performed while the patient is on any line of therapy for stage IV disease
- Repeat or fresh biopsy necessary for tissue screening is paid by the trial
- **#Biomarker-driven sub-studies may progress to Phase III if study meets endpoint and Phase III is feasible, at which point the standard of care arm will be determined.**

Accrual as of 7/18/22

Current Open Sub-Study Status

Biomarker-Driven

S1900E (AMG-510)

- Biomarker-Driven, non-squamous NSCLC
- *KRAS*^{G12C} & co-mutations in *TP53, STK11,* and others
- 66 patients enrolled
  - Cohort 1 (TP53): 30
  - Cohort 2 (STK11): 15
  - Cohort 3 (all others): 21
- Accrual goal:
  - 44 total (cohort 1 and 3)
  - 28 (cohort 2)

Non-Match

S1800D (N-803 + pembrolizumab v SOC)

- 29 patients enrolled
  - Primary Resistance: 2
  - Acquired Resistance: 27
- Accrual goal:
  - 334 acquired resistance cohort
  - 144 primary resistance cohort

Anticipated Future Studies

Sub-Study Protocols in Development

S1900G

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)

- MET amplification detected at progression on osimertinib as the most recent line of treatment.
- Targeting Activation in Q4 2022

Sub-Study Concepts in Development

(More information to come)

S1900H

- Biomarker-Driven, NSCLC

S1900I

- Biomarker-Driven, NSCLC

S1800E

- Non-Match

S1800F

- Non-Match

S1900F

Planned Activation Date: 7/25/2022

A Randomized Phase II Study of Carboplatin and Pemetrexed with or without Selpercatinib (LY3527723) in Participants with Non-Squamous RET Fusion-Positive Stage IV Non-Small Cell Lung Cancer and Progression of Disease on Prior RET Directed Therapy (Lung-MAP Sub-Study)

JHANELLE GRAY, MD

STUDY CHAIR (SWOG)

YASIR ELAMIN, MD

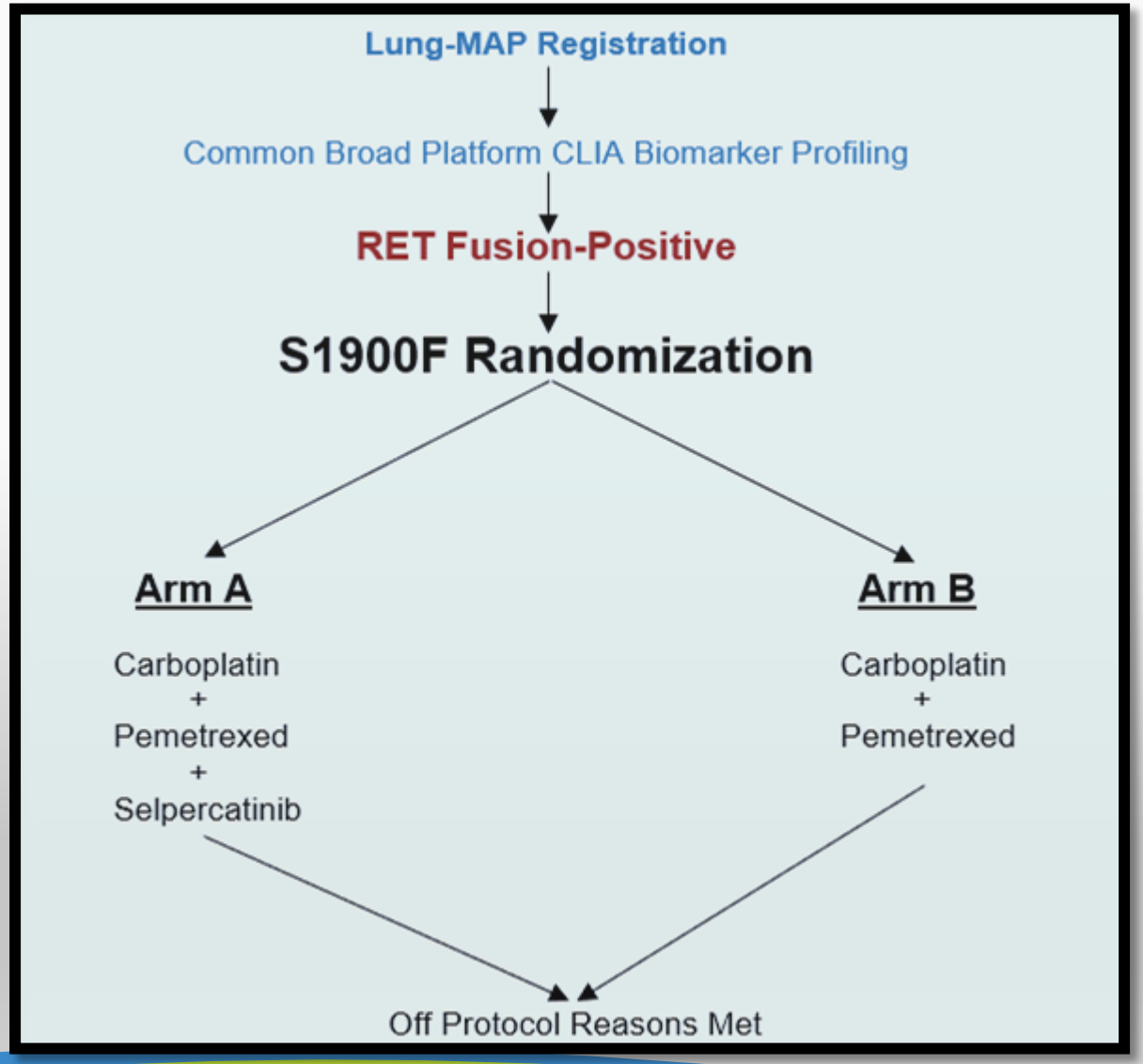
STUDY CO-CHAIR (SWOG)

LEAD GROUP: SWOG

DAVID GANDARA, MD

LUNGMAP MEDICAL ONCOLOGY CHAIR/CHAMPION (SWOG)

S1900F Schema



Lead Group: SWOG

Background/Overview

- The receptor tyrosine kinase RET can be oncogenically activated by gene fusions or point mutations
- RET fusions occur in a variety of malignancies, including 1-2% of lung cancers
- Selpercatinib is a novel, highly selective, FDA-approved ATP-competitive small molecule RET inhibitor
- In platinum-pretreated RET fusion-positive NSCLC, selpercatinib resulted in an ORR of 64%, mDoR of 17.5 months.
- For patients who progress on selpercatinib, there is no approved targeted therapy and the treatment paradigm is not well defined.

Study Objectives

- **Primary Objective:** To compare investigator-assessed progression-free survival (IA-PFS) in participants with RET fusion-positive NSCLC with acquired selective RET inhibitor resistance randomized to carboplatin and pemetrexed with or without selpercatinib.
- **Secondary Objectives**:
    a) To evaluate if the combination of selpercatinib combined with carboplatin and pemetrexed during the first cycle of treatment has an acceptable toxicity rate.
    b) To evaluate the frequency and severity of toxicities within the arms.
    c) To compare the investigator-assessed objective response rate (ORR) (complete or partial confirmed response) between the arms
    d) To compare overall survival (OS) between the arms.
    e) To evaluate duration of investigator-assessed response among responders within each treatment arm.
- **Translational Objective**: To collect, process, and bank cfDNA at baseline, progression, and end of treatment for future development of a proposal to evaluate comprehensive next-generation sequencing of ctDNA.

Overview of Treatment(s)

- Selpercatinib is a selective inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase (RTK). Selpercatinib competitively blocks the adenosine triphosphate (ATP) binding site of the RET RTK
- Arm A is selpercatinib given in combination with carboplatin and pemetrexed (per local institutional guidelines).
- Arm B is carboplatin and pemetrexed (per local guidelines).

Treatment Administration: Selpercatinib

Route:	PO
Dose:	160 mg BID if weight >50 Kg, 120 mg BID if <50kg
Cycle duration:	21 days
Administration:	Twice daily
Premedication:	None
Supportive care:	None
Disease assessment:	CT imaging every 6 weeks +/- 7 days
Prohibited medications:	Moderate and strong inducers of CYP1A2

Eligibility

- Participants must have RET fusion-positive NSCLC as determined by the FMI tissue-assay or other tumor-based assays such as NGS, PCR, or FISH, or by cfDNA blood assay. The testing must be done within a laboratory with CLIA, ISO/IEC, CAP, or similar certification.
- Participants must be negative for all additional validated oncogenic drivers that could cause resistance to selpercatinib treatment. This includes EGFR sensitizing mutations, EGFR T790M mutations, ALK gene fusions, ROS1 gene fusion, KRAS activating mutations, BRAF V600E mutation and MET exon 14 skipping mutations or high-level amplification and expression.
- Measurable disease by CT or MRI w/in 28 days prior to substudy randomization.
- For Stage IV or recurrent disease: Prior platinum-based chemotherapy regimen is not allowed.
- For prior systemic therapy for Stage I-III disease *only* (i.e., pt. had not yet received any treatment for Stage IV or recurrent disease): Pt. must not have had disease progression w/in 365 days from the last date of platinum-based chemo.
- Prior anti-PD-1/PD-L1 therapy, alone or in combination (e.g., Nivolumab, Pembrolizumab, or Durvalumab) is allowed.
- Participants must have received and developed disease progression during or after an anti-RET inhibitors treatment. The anti-RET inhibitor therapy must be the most recent therapy.

Anticipated Adverse Events to Selpercatinib

- Dry mouth
- Transaminitis
- Hypertension
- Allergic reactions

Dose Modifications/Interruptions

DRUG	DOSE LEVEL	DOSE	
Selpercatinib		(< 50 kg)	(≥50 kg)
	Full	120 mg BID	160 mg BID
	-1 Level	80 mg BID	120 mg BID
	-2 Level	40 mg BID	80 mg BID
	-3 Level	40 mg OD	40 mg BID
Permanently discontinue in participants unable to tolerate 3 dose reductions*			

Criteria for Removal from Treatment

- Progression of disease or symptomatic deterioration. However, the participant may continue protocol treatment after RECIST progression if the participant is continuing to clinically benefit in the opinion of the treating investigator and the participant is not exposed to unreasonable risk (including absence of symptoms and signs indicating clinically significant progressive disease; no decline in Zubrod performance status; absence of symptomatic rapid disease progression requiring urgent medical intervention [e.g., symptomatic pleural effusion, spinal cord compression]).
- Unacceptable toxicity.
- Treatment delay for any reason > 42 days.
- The participants may withdraw from the study at any time for any reason.

Registration

Delegation Task Log (DTL):

- Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling participants to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off.

Biomarker Review Panel for RET Fusions Detected Outside of LUNGMAP

- This will occur during **LUNGMAP** screening prior to sub-study assignment to **S1900F**:

  The biomarker review panel of translational medicine experts must review and confirm the study biomarker results/reports for those patients who have RET fusion-positive NSCLC detected outside of the Lung-MAP study. Patients must have RET fusion-positive NSCLC as determined by tumor-based assays such as NGS, PCR, or FISH or by cfDNA blood assay. The testing must be done within a laboratory with CLIA, ISO/IEC, CAP, or similar certification. The reviewers will also confirm that the outside reports do not include the presence of oncogenic drivers. The presence of oncogenic drivers will make the patient ineligible.

  Note: Patients previously tested for and determined to have RET-fusion-positive NSCLC outside of LUNGMAP, must also submit tissue for central FMI testing on the **LUNGMAP** screening protocol.

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 to FMI

- Kit Ordering: Immediately after identifying a participant for trial and prior to treatment initiation, sites must contact Foundation Medicine, Inc. – Blood Samples, Lab #232, to order kits. See protocol Section 15.5a for ordering instructions.
  - Kits will arrive approximately 3 business days after ordering.
  - Kits will read "Foundation Medicine Clinical Trials Kit," and include two Roche Cell- Free DNA blood collection tubes, collection instructions, FedEx return bags, and pre-printed FedEx airway bills. Blood collection tubes must be used before their expiration date.
- Collect two tubes (8.5 mL per tube) of peripheral whole blood required at following time points:
  - After sub-study randomization and prior to treatment initiation
    - Recommended to collect on Cycle 1 Day 1 (prior to treatment) during other labs to lessen participant visits.

      NOTE: This is a separate requirement for a ctDNA whole blood specimen for all participant registered to S1900F, regardless of whether or not there was a ctDNA blood collection for the LUNGMAP Screening Protocol.
  - First progression after study treatment
    - Collection must be within 14 days after site learns of progression and prior to starting non-protocol treatment.
  - Off treatment
- Ship (preferably on same day as collection) to FMI – Blood Samples, Lab #232 via FedEx overnight delivery at ambient temperature. Do not freeze or refrigerate blood samples. Keep at 43-99 degrees F (6-37 degrees C).
  - If shipping on a Friday, please overnight shipment and mark for Saturday delivery.

Buffy Coat and Plasma Specimen Submission to SWOG Biospecimen Bank

- With participant consent, collect 8-10 mL blood in EDTA at following time points:
  - Pre-study (after consenting and prior to treatment initiation on sub-study). NOTE: If a participant provided buffy coat and plasma at pre-screening or screening (see Section 15.0 of LUNGMAP) and the blood collection was within 42 days prior to the sub-study randomization, then no additional pre-study blood specimen is required.
  - Cycles 2, 3, and 4 (at the same time as lab collection, prior to the start of cycle treatment). Participants that go off protocol treatment are not required to continue to submit specimens.
  - First progression.
- Process for plasma and buffy coat, as indicated in Protocol Section 15.6a, within 1 hour after venipuncture. If processing, within 1 hour not possible, then refrigerate (4°C) in EDTA tube. Document time from collection to processing.
- Samples for multiple participants may be shipped in batches to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201, at least every 3 months (if not more frequently), with a maximum of 5 participants' samples included per batch.
- Refer to Protocol Section 15.6b and the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures) for labelling and shipping instructions.
- Specimen collection kits are not being provided for this submission; sites must use institutional supplies.

Imaging

- CT, PET/CT, and/or MRI images must be locally read and interpreted by the local site radiology service. Imaging exams must then be submitted (within 15 days after scans are performed) to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD Imaging Submission procedures for central data collection and quality control (QC) check as well as retrospective central review.
  - The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams.
- TRIAD Digital Image Submission: Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred

Funding

- Additional site payment for non-standard of care baseline EKG

  (pending approval)

- <u>SWOG Member Sites Only</u>:

  Sites will receive 1 membership credit per enrollment credited to SWOG

Funding Source and Study Component		Collect Type	Study Specific Notes	Enter Date in Open? (c)	NCTN Funding per Patient (a) Std/HP LAPS	NCORP Funding per Patient (b) Std/HP
Federal	Base Intervention – Standard / High Performance LAPS & NCORP	Mandatory	1	No	$2,500/$4,100	$2,500/$4,100
Federal	Biospecimen – Whole Blood Whole blood for ctDNA at multiple timepoints	Mandatory	2	Yes	$200	$200
Federal	Biospecimen – Blood (Multiple) Buffy coat and plasma collections at multiple timepoints	Mandatory Request	3	Yes	$200	$200
Total Potential Federal Funds					**$2,900/$4,500**	**$2,900/$4,500**
Non-Federal	Additional capitation resources from industry partners	Mandatory	4	No	$2,490/$890	$2,490/$890
Total Potential Non-Federal Funds (d)					**$2,490/$890**	**$2,490/$890**
Total Potential Funds					**$5,390/$5,390**	**$5,390/$5,390**
Additional Support for Site Auditing						
Non-Federal	Additional capitation resources from industry partners for additional site auditing /monitoring.	Mandatory Event	5	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 the extra effort associated with this increased auditing at $1,333 per audit.						

Acknowledgements

- Eli Lilly
- LUNG-MAP Operations Group
- LUNG-MAP leadership

S1900F Contacts

Study Chairs:

- Dr. Jhanelle E. Gray (SWOG)
  - Moffit Cancer Center

- Dr. Yasir Y. Elamin (SWOG)
  - UT/MD Anderson Cancer Center

Questions:

Medical Questions for Study Chairs:

S1900FMedicalQuery@swog.org

Eligibility/Specimen/Data Submissions:
LUNGMAPquestion@crab.org

General Protocol/Regulatory:
jbeeler@swog.org

LUNGMAP Revisions #5 & #6

DAVID GANDARA, M.D.

LUNGMAP MEDICAL ONCOLOGY CHAIR/CHAMPION (SWOG)

LUNG-MAP

Prior Lines of Therapy for S1900F participants

LUNGMAP Revisions #5 & #6 include updates to eligibility**.**

- For patients with known *RET fusion* and which are planning to register to **S1900F** the eligibility criterion 5.1c1 has been updated.
  - Patients must have received and developed disease progression following on or after anti-RET inhibitor treatment.
  - Patients must not have received platinum-based chemotherapy for Stage IV or recurrent disease.
    - For Stage I—III disease progression on platinum-based chemotherapy must not have occurred in 1 year.
- Patients with known RET are allowed to pre-screen for **LUNGMAP**.

c. Patients must either have progression on prior systemic treatment or have received at least one dose of systemic treatment as defined below:

These criteria are:

1. Screening at progression on prior treatment:

To be eligible for screening at progression, patients must have received at least one line of systemic therapy for any stage of disease (Stages I-IV) and must have progressed during or following their most recent line of therapy.

- For patients whose prior therapy was for Stage IV or recurrent disease, the patient must have received at least one line of a platinum-based chemotherapy regimen and/or anti-PD-1/PD-L1 therapy, alone or in combination.
- For patients whose prior systemic therapy was for Stage I-III disease only (i.e. patient has not received any systemic treatment for Stage IV or recurrent/progressive disease), disease progression on platinum-based chemotherapy must have occurred within **one year** from the last date that patient received that therapy. For patients treated with anti-PD-1 or anti-PD-L1 therapy for Stage I-III disease, disease progression on consolidation anti-PD-1 or anti-PD-L1 therapy must have occurred within **one year** from the date of initiation of such therapy. If disease progression was greater than one year after prior therapy, patients must receive subsequent systemic therapy to be eligible.
- For patients with a known RET fusion and which are planning to register to **S1900F**:
  - Patients must have received and developed disease progression during or after an anti-RET inhibitor treatment. The anti-RET inhibitor therapy must be the most recent therapy.
  - For patients with Stage IV or recurrent disease, the patient must not have received a platinum-based chemotherapy regimen.
  - For patients whose prior systemic therapy was for Stage I-III disease only (i.e., patient has not received any treatment for Stage IV or recurrent disease), disease progression on platinum-based chemotherapy must not have occurred within one year (**365 days**) from the last date that the patient received that therapy. Prior anti-PD-1/PD-L1 therapy, alone or in combination (e.g., Nivolumab, Pembrolizumab, or Durvalumab) is allowed.

S1900F Outside RET Testing Logistics

Purpose: To allow participants screened at progression who have a known RET fusion based on outside testing to proceed to treatment on S1900F as soon as possible.

Note: All patients registered to LUNGMAP will still submit tissue for the FMI NGS testing. OR submit a commercial FoundationOne CDx report for reanalysis

Participant registered to LUNGMAP and registration question “Has patient been tested and determined to have RET-fusion-positive NSCLC?” answered “Yes.”

- **RET Fusion Testing for S1900F Assignment** electronic form completed in Rave, including upload of at least one molecular report.
  - *Upload all pages of the molecular report, not just the page with the results.*
- Review of molecular report performed by the S1900F RET Fusion Review Panel
  - *RET Fusion Reviewer may contact site for additional information if needed*
  - *RET Fusion Panel Review Form completed in Rave documenting Approval or Rejection*

S1900F Outside RET Testing Logistics

- Patients **screened at progression**:
  - Approval of outside testing RET fusion result: sub-study assignment to S1900F will be sent immediately the next morning.
  - Disapproval of outside testing RET fusion result: site will be notified of the rejection and sub-study assignment will proceed based on LUNGMAP FMI testing.
- Patients **pre-screened prior to progression, upon submission of Notice of Progression**:
  - If LUNGMAP FMI testing successfully completed: sub-study assignment based on LUNGMAP FMI results (regardless of outside testing result).
  - If LUNGMAP FMI testing is not yet completed, or was unsuccessful AND patient has an approved outside testing RET fusion result: sub-study assignment to S1900F will be sent immediately the next morning.

Lung-MAP
Central Monitoring Refresher

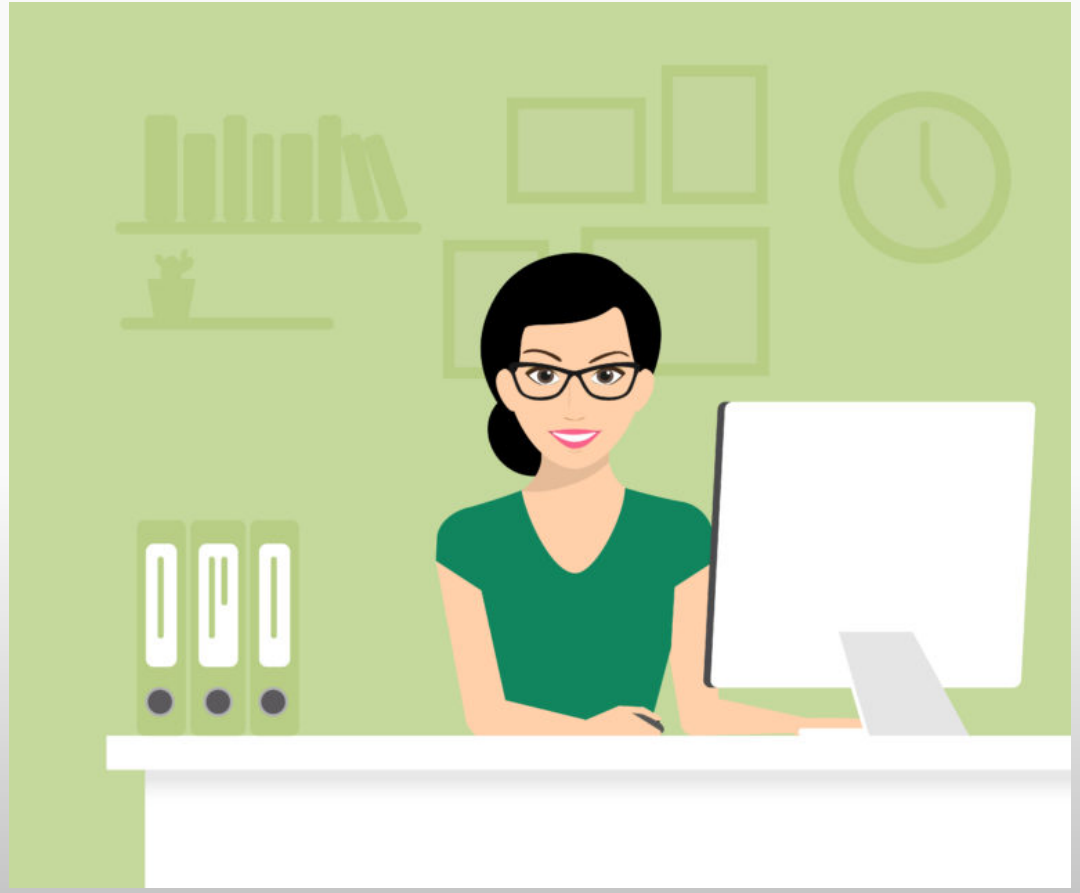
CASSIE VILLASIN

SWOG STATISTICS & DATA MANAGEMENT CENTER

LUNG-MAP

The FDA requires extra monitoring for all protocols that have FDA intent. Protocol Section *18.2.d Central Monitoring Review by the SDMC Monitors* provides the monitoring plan for Lung-MAP.

Central Monitoring for S1900E & S1900F is NOT required.



Current source document upload process

Off-site monitoring includes auditable elements for the Registration for the first two patients registered to the Lung-MAP Screening Study at each new study site or sites where an on-site Lung-MAP screening audit has not occurred.

Site staff are to **upload source documents** to support the Eligibility Criteria (Section 5.0) and applicable forms that have been submitted in Rave® for the **Lung-MAP** Registration.

All source documents for Central Monitoring review are to be uploaded to the Source Document Portal (SDP) which can be accessed directly through CTSU.org by going to the Auditing and Monitoring tab and selecting Source Document Portal. The SDP can also be accessed through Medidata Rave on the Central Monitoring Alert page. The review will also consist of timeliness of data submission, specimen collection and specimen submission.

New Platform for Uploading Source Documents

CTSU has now created a standalone, modernized SDP for the purpose of maintaining the application and implementing enhancements independently from the CTSU website. This is part of a larger effort to move towards a CTSU Portal approach to applications, which focuses on more role-based access. The modernized SDP has additional filters available to narrow search results when navigating the application which should aide in locating patients, documents etc.

Sites will continue to upload expected source documents via the CTSU website until the modernized SDP's planned release in late 2022.

As of July 8, 2022, the implementation of the NCI CTEP-IAM and ID.me credentials will be required for new users. Previous CTEP-IAM accounts will continue to be supported for one year after the go-live date. More details can be found on the CTEP Website: NCI CTEP IAM User Access Update | CTEP (cancer.gov)

* For questions regarding the SDMC monitoring or issues with , please contact centralmonitorquestion@crab.org.

Q & A

Please
“raise your hand”
in WebEx or place
questions in the
chat box.

ALL ATTENDEES

- S1900F,
- LUNGMAP Revisions #5 & #6, and
- Central Monitoring

S1900E Refresher

A PHASE II STUDY OF AMG 510 (SOTORASIB) IN PATIENTS WITH PREVIOUSLY TREATED STAGE IV OR RECURRENT KRAS G12C MUTATED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (ECOG-ACRIN LUNG-MAP SUB-STUDY)

SUKHMANI K. PADDA, MD

S1900E CHAIR (ECOG-ACRIN)

DAVID GERBER, MD

S1900E CO-CHAIR (ECOG-ACRIN)

LEAD GROUP: ECOG-ACRIN

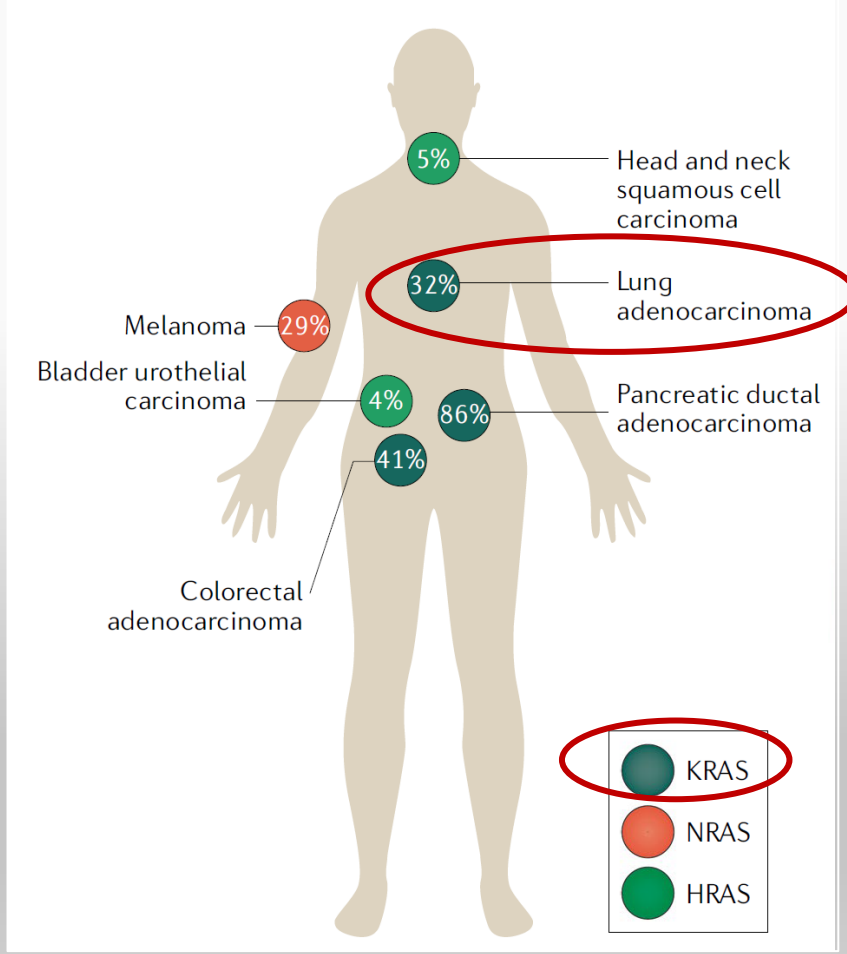
JOEL W. NEAL, MD, PHD

LUNGMAP STUDY CHAMPION (ECOG-ACRIN)

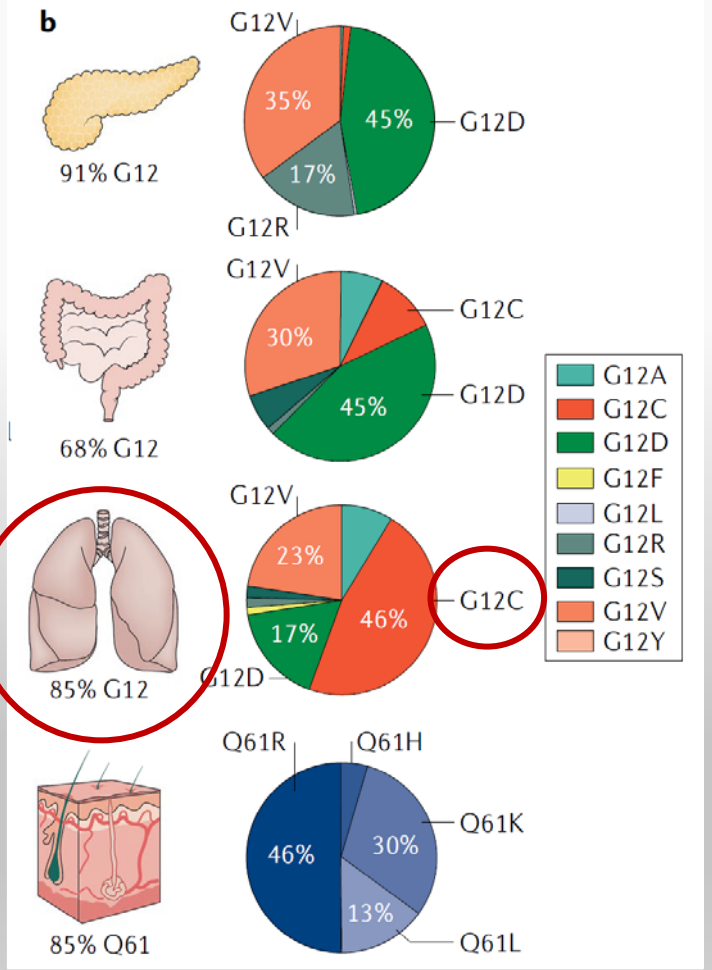
LUNG-MAP

KRAS mutations are the most common "driver" molecular alterations in non-small cell lung cancer (NSCLC)

KRAS Mutations



KRAS Mutation Subtypes



Figures from Moore AR et al. Nat Rev Drug Discov. 2020 Aug;19(8):533-552.

KRAS G12C allosteric inhibitors in previously treated metastatic *KRAS* G12C NSCLC

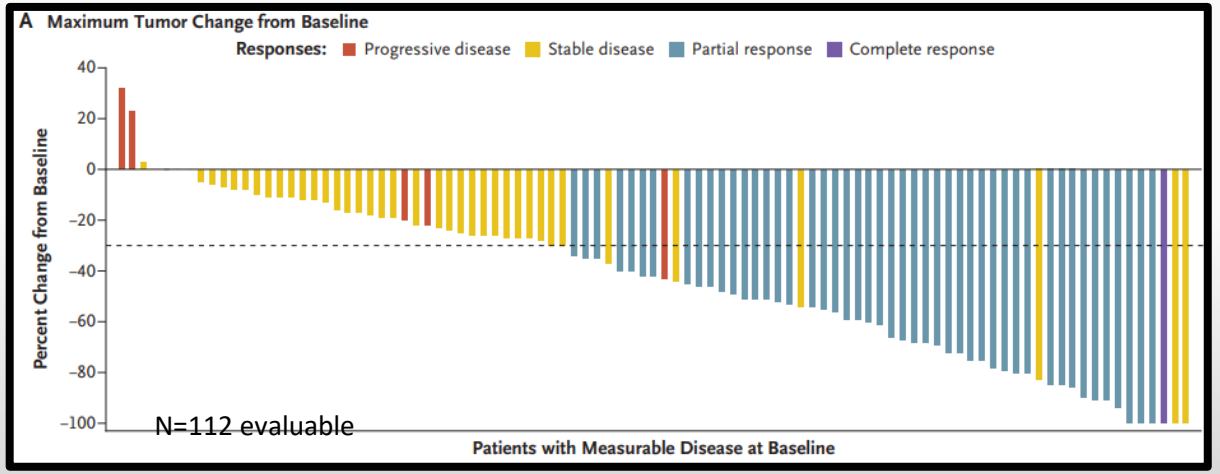
SOTORASIB – Approved 05/2021

N=124 evaluable

- **ORR 37.1%** (95% CI 28.6-46.2)
- **DCR 80.6%** (95% CI 72.6-87.2)
- **mDOR 11.1 mo** (95% CI 6.9-NE)
- **mPFS 6.8 mo** (95% CI 5.1-8.2)
- **mOS 12.5 mo** (95% CI 10.0-NE)

Skoulidis et al. N Engl J Med 2021;384:2371-2381.

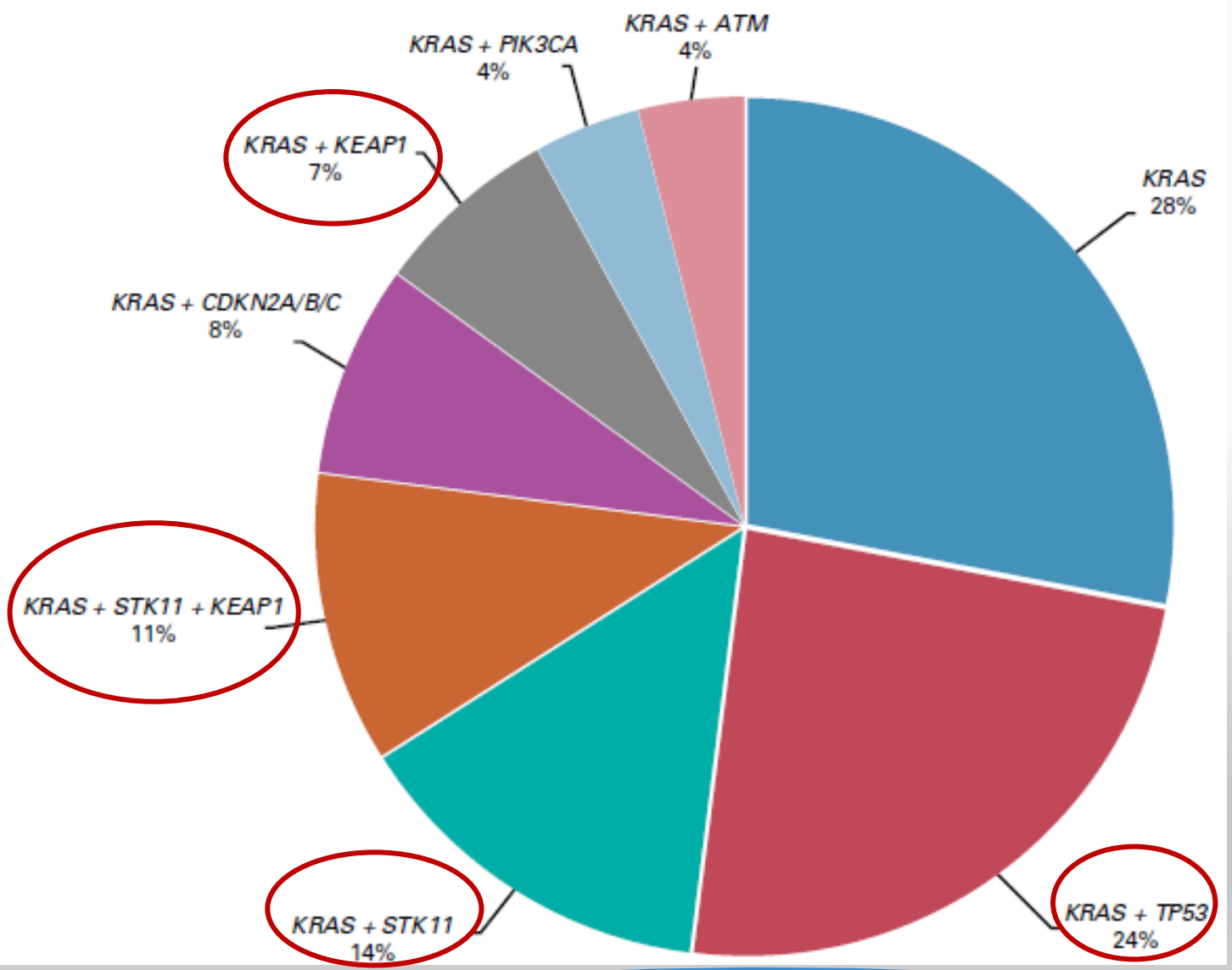
ADAGRASIB



- **ORR 43%** (95% CI 33.5-52.6)
- **DCR 80%** (95% CI 70.8-86.5)
- **mDOR 8.5 mo** (95% CI 6.2-13.8)
- **mPFS 6.5 mo** (95% CI 4.7-8.4)
- **mOS 12.6 mo** (95% CI 9.2-19.2)

Spira A et al. ASCO 2021. Janne et al. N Engl J Med. 2022 Jun 3. Epub

KRAS MUT NSCLC heterogeneity defined by co-mutations



CLINICAL DATASET CO-MUTATIONS

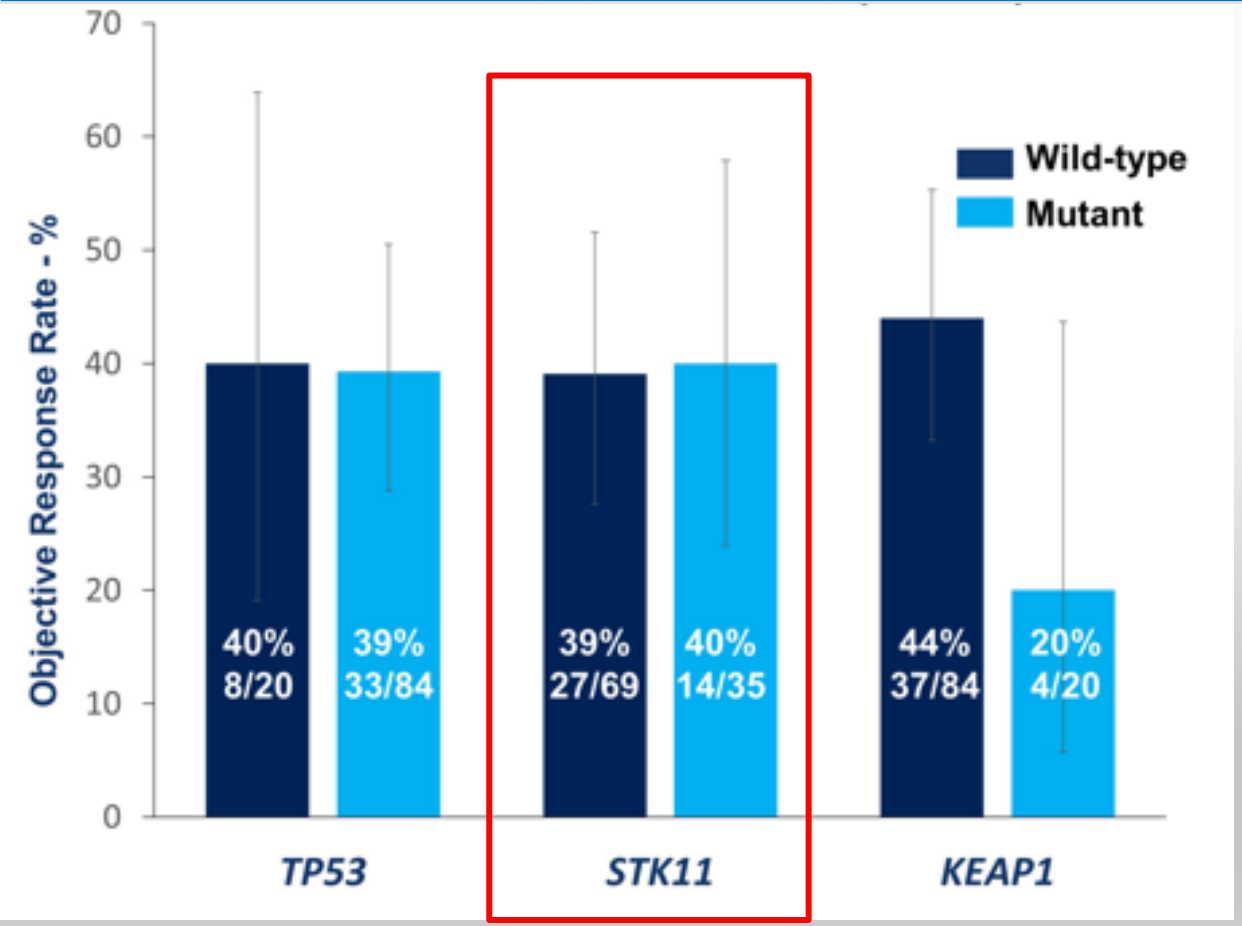
- Arbour et al (n=330): ***TP53* (42%), *STK11* (29%), *KEAP1* (24%),** *RBM10* (16%), and *PTPRD* (15%)
- Scheffler et al (n=1078): ***TP53* (39.4%);** additional identified in ***STK11* (19.8%), *KEAP1* (12.9%),** *ATM* (11.9%)
- Aredo et al (n=186): ***TP53* (38.7%)**, ***STK11* (11.8%), and *KEAP1* (8.1%),** *NKX2.1* (8.3%) and *ARID1A* (7.3%)

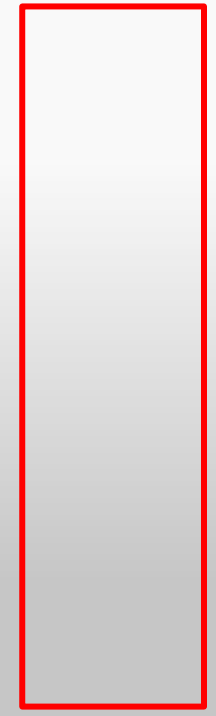
Aredo JV, Padda SK et al. *Lung Cancer*. 2019 Jul;133:144-150. Arbour KC et al. Clin Cancer Res. 2018 Jan 15;24(2):334-340. Scheffler M et al. J Thorac Oncol. 2019 Apr;14(4):606-616.

Figure from Padda SK, Aredo J et al. JCO Precision Oncology 2021

Are co-mutations predictive of KRAS G12C inhibitor efficacy?

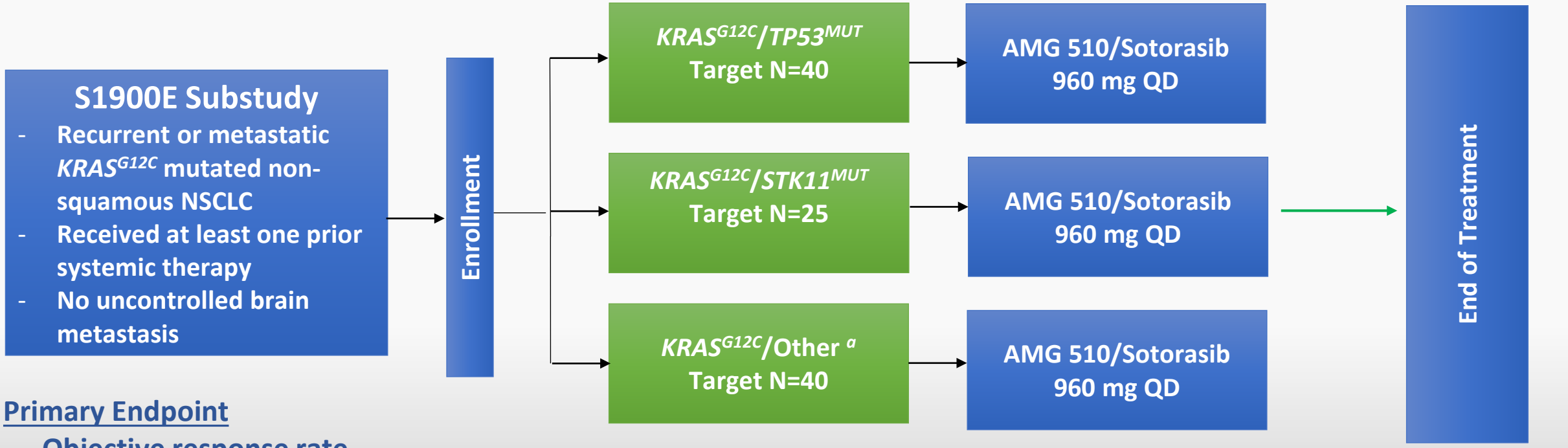
SOTORASIB (AMG 510)





Skoulidis et al. N Engl J Med 2021;384:2371-2381. Spira A et al. ASCO 2021. Jann et al. N Engl J Med. 2022 Jun 3. Epub

S1900E Schema



Primary Endpoint

- **Objective response rate**

Secondary Endpoints

- Duration of response
- Progression free survival
- Overall survival
- Safety

[a]other co-mutations (e.g., *KEAP1, NFE2L2, CUL3*), double or triple co-mutations (e.g., *STK11/TP53, STK11/TP53/KEAP1*), or no co-mutations

Lead Group: ECOG-ACRIN

LUNG-MAP

S1900E Revision #3 Updates

1. Removal of interim analysis.
2. Clinical/laboratory eligibility criteria more inclusive.
3. Updated risk information for sotorasib (AMG 510) based on Investigator Brochure version 6.0.
4. Updated information regarding drug dispensing guidelines.

More inclusive brain metastases eligibility criteria

Section 5.1g

Participants with untreated asymptomatic brain metastases are eligible.

Participants with spinal cord compression or symptomatic brain metastases must have received local treatment to these metastases and remained clinically controlled and asymptomatic for at least 3 **days following stereotactic radiation and/or 14 days following whole brain radiation,** and prior to sub-study registration. Participants with untreated asymptomatic brain metastases are eligible.

Decreased washouts for prior therapy eligibility criteria

Section 5.2d

Revised prior systemic therapy and radiation therapy washouts

d. Participants must not have received any prior systemic therapy within the following windows.

1. Chemotherapy administered in an every 3-week schedule, anti-cancer monoclonal antibody (mAb) therapy, or investigational agent must not have been received within **21 days** prior to sub-study registration
2. Chemotherapy administered in a daily or weekly schedule must not have been received within **7 days** prior to sub-study registration
3. Chemotherapy administered in an every 2-week schedule must not have been received within **14 days** prior to sub-study registration
4. Targeted small molecule therapy must not have been received within **7 days** prior to sub-study registration

e. Participants must not have received any radiation therapy within **7 days** prior to sub-study registration, with the exceptions of

(i) stereotactic radiation to CNS metastases which must have been completed at least 3 days prior to sub-study registration. (See Section 5.1g for criteria regarding therapy for CNS metastases) and

(ii) palliative radiotherapy to bone metastases which must have been completed at least **1 day** prior to sub-study registration

Updated risk information for sotorasib (AMG 510)

Section 3 is based on sotorasib (AMG 510) Investigator Brochure version 6.0

PHARMACOKINETICS

1. Absorption: sotorasib (AMG 510) is rapidly absorbed, with the median T_{max} occurring 1 hour after oral administration. A high-fat, high-calorie meal increased AUC by 25% compared to fasted conditions; sotorasib (AMG 510) may be taken with or without food. In non-human studies, bioavailability ranged from 3.3% to 47% across the species tested.

2. Distribution: *In vitro*, sotorasib (AMG 510) plasma protein binding is 89%. The mean volume of distribution at steady state is 211 L.

3. Metabolism: In *in vitro* studies, sotorasib (AMG 510) appeared to be metabolized by CYP2C8, CYP3A4, and CYP3A5, with CYP3A enzymes being primarily responsible for metabolism. The primary metabolite, M24, is >1000-fold less potent than sotorasib (AMG 510).

4. Elimination: The mean terminal elimination half-life is 5 hours. After a single dose of radiolabeled sotorasib (AMG 510), 74% of the dose was recovered in feces (53% unchanged) and 6% (1% unchanged) in urine.

ADVERSE EFFECTS

Adverse Effects:

AE >20%

Adverse effects reported in > 20% of participants treated with sotorasib (AMG 510) include: cough (includes cough, productive cough, and upper-airway cough syndrome), diarrhea (serious cases reported), fatigue (includes fatigue and asthenia), hepatotoxicity (includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatitis, hepatotoxicity, increased aspartate aminotransferase, increased alkaline phosphatase; serious cases of hepatotoxicity reported), musculoskeletal pain (includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, and pain in extremity), and nausea. The most common laboratory abnormalities were decreased lymphocytes, decreased hemoglobin, decreased calcium, increased urine protein, decreased sodium, decreased albumin, and increased activated partial thromboplastin time.

AE 4-20%

Adverse effects reported in 4% to 20% of participants include: abdominal pain (includes abdominal pain, abdominal pain upper, and abdominal pain lower), anorexia, arthralgia, constipation, dyspnea (includes dyspnea and dyspnea exertional), edema (includes generalized edema, localized edema, edema, edema peripheral, periorbital edema, and testicular edema), pneumonia (includes pneumonia, pneumonia aspiration, pneumonia bacterial, and pneumonia staphylococcal; serious cases reported), rash (includes dermatitis, dermatitis acneiform, rash, rash-maculopapular, and rash pustular), and vomiting

SAE ≤ 3%

Serious adverse effects reported in ≤ 3% of participants include: cardiac arrest, cardiac failure, gastric ulcer, pneumonitis, and respiratory failure

Updated Drug Dispensing Guidelines

Section 3.1e.4 & Section 18.4

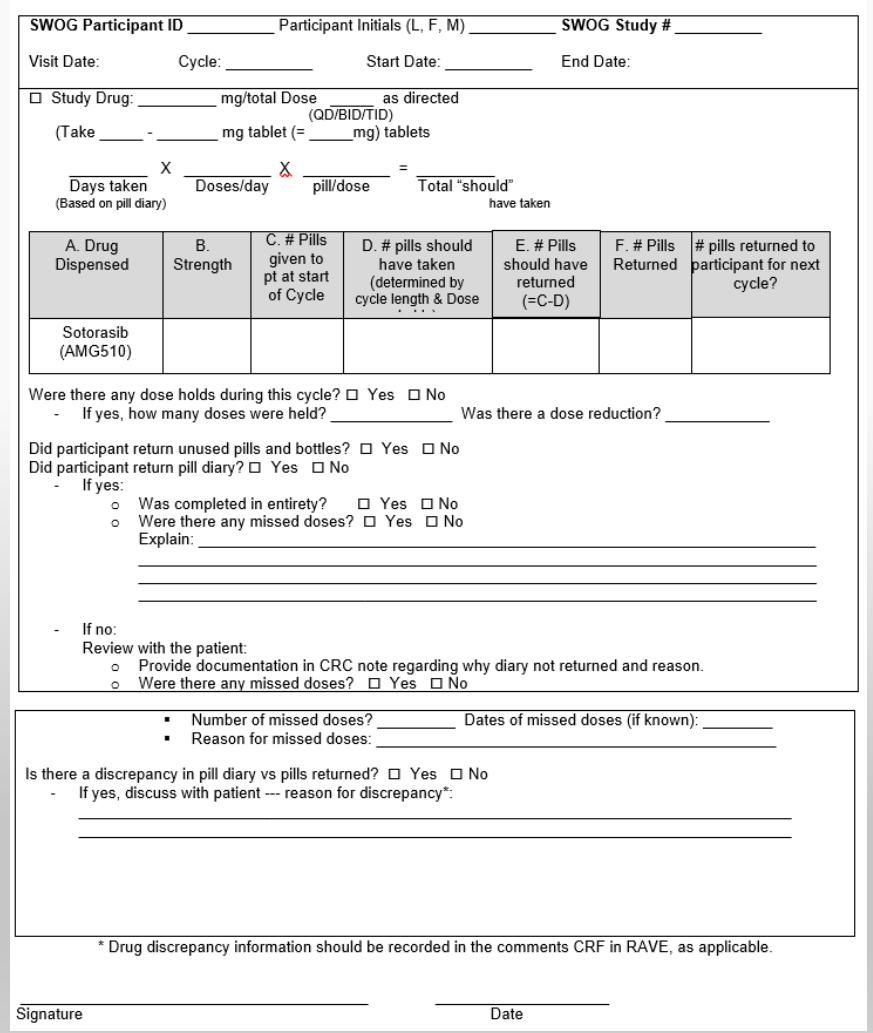
Revised site personnel instructions to clarify site's process for drug dispensation.

- The site should follow the following participant adherence procedures:
  - Site should confirm participant adherence by conducting a pill count and reviewing the Participant Diary.
  - Study participants may continue taking excess tablets from the previous 21-day cycle. The site may provide the counted excess tablets, in the original bottle, back to the same participant.
  - Any additional unopened bottle(s) should be provided to that study participant, to ensure enough supply to last until the next study visit. **NOTE:** Some cycles may require dispensing of two unopened bottles (in addition to the counted tablets).
  - **NOTE:** Do not repackage sotorasib (AMG 510). Sotorasib (AMG 510) must be stored in the original bottle.
- Unused drug and/or empty bottles should be returned to the site at the next study visit.
  - Participants should return empty bottle and/or unused drug (in the original bottle) to the site at each study visit.

Pill Count Reconciliation Worksheet

Section 18.6

A new Pill Count Reconciliation Worksheet has been added to assist sites with dispensing drug.



SWOG Participant ID _____ Participant Initials (L, F, M) _____ **SWOG Study #** _____

Visit Date: Cycle: _____ Start Date: _____ End Date:

☐ Study Drug: _____ mg/total Dose _____ as directed
(QD/BID/TID)

(Take _____ - _____ mg tablet (= _____mg) tablets

_____ X _____ X _____ = _____
Days taken (Based on pill diary) | Doses/day | pill/dose | Total "should" have taken

A. Drug Dispensed	B. Strength	C. # Pills given to pt at start of Cycle	D. # pills should have taken (determined by cycle length & Dose	E. # Pills should have returned (=C-D)	F. # Pills Returned	# pills returned to participant for next cycle?
Sotorasib (AMG510)						

Were there any dose holds during this cycle? ☐ Yes ☐ No
- If yes, how many doses were held? _____ Was there a dose reduction? _____

Did participant return unused pills and bottles? ☐ Yes ☐ No
Did participant return pill diary? ☐ Yes ☐ No
- If yes:
  - Was completed in entirety? ☐ Yes ☐ No
  - Were there any missed doses? ☐ Yes ☐ No
    Explain: _____
- If no:
  Review with the patient:
  - Provide documentation in CRC note regarding why diary not returned and reason.
  - Were there any missed doses? ☐ Yes ☐ No
    - Number of missed doses? _____ Dates of missed doses (if known): _____
    - Reason for missed doses: _____

Is there a discrepancy in pill diary vs pills returned? ☐ Yes ☐ No
- If yes, discuss with patient --- reason for discrepancy*:
  _____

* Drug discrepancy information should be recorded in the comments CRF in RAVE, as applicable.

_____ _____
Signature Date

LUNG-MAP

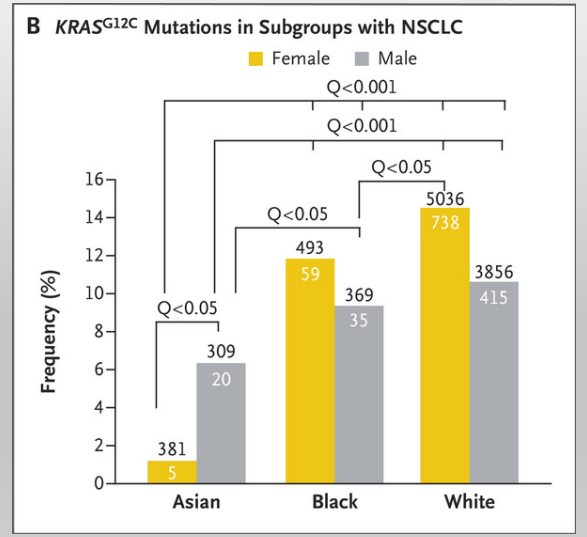
Underrepresentation of race/ethnicity in KRAS G12C trials –

ASCO & ACCC develop recommendation to increase racial & ethnic diversity in clinical trials[1]

	SOTORASIB – KRAS G12C NSCLC *N Engl J Med. 2021* N=126	ADAGRASIB- KRAS G12C NSCLC *N Engl J Med. 2022* N=116
Race		
White	81.7%	83.6%
Black	1.6%	7.8%
Asian	15.1%	4.3%
Native American or Alaska Native	---	0.9%
Other	1.6%	3.4%

US census 2021[2]

- 76.3% White / 60.1% White Non-Hispanic or Latinx
- **13.4%** Black or African American
- 5.9% Asian
- 1.3% Native American & Alaska Native
- 0.2% Native Hawaiian and Pacific Islander
- 2.8% Multi-racial
- **18.5%** Hispanic/Latinx



Registry of American Association for Cancer Research Project GENIE version 8 NSCLC – *KRAS* G12C by race[3]

- 13% White (1153/8892)
- **10.9%** Black (94/862)
- 3.6% Asian (25/690)

1=Oyer A et al. J Clin Oncol. 2022 May 19: Epub;
2= https://www.census.gov/quickfacts/fact/table/US/PST045221; accessed 05/21/2022;
3=Nassar AH et al. N Engl J Med. 2021 Jan 14;384(2):185-187.

Accrual Update

- 66/116 participants enrolled (**30**/40 *TP53*, **15**/25 *STK11*, **21**/40)
  - 2 in last 30 days; 0 in last 7 days as of 07/13/2022
  - Opened April 2021 (~accruing over 15 months)
  - *TP53* & *STK11* cohorts are meeting *conservative* accrual estimates
  - Cohort 3 lagging behind: pt can enroll even if no co-mutation in *STK11* or *TP53,* presence of other co-mutations (e.g. *KEAP1/NFE2L2/CUL3*), or no identified co-mutations

- Adagrasib review by FDA expected by 12/2022 - unlikely to impact accrual

Ongoing Importance of S1900E

- Rigorous upfront co-mutation biomarker definitions - accounts for co-occurring mutations
- Given prospective design, expected 95% CI narrower around point estimates of ORR
- More diverse clinical trial population

Please
“raise your hand”
in WebEx or place
questions in the
chat box.

General Q & A Session

ALL ATTENDEES

LUNG-MAP

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It takes a village!

LUNG-MAP

Summary & Adjourn

Thank you for joining us!

The slides will be available on the SWOG & CTSU websites