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)

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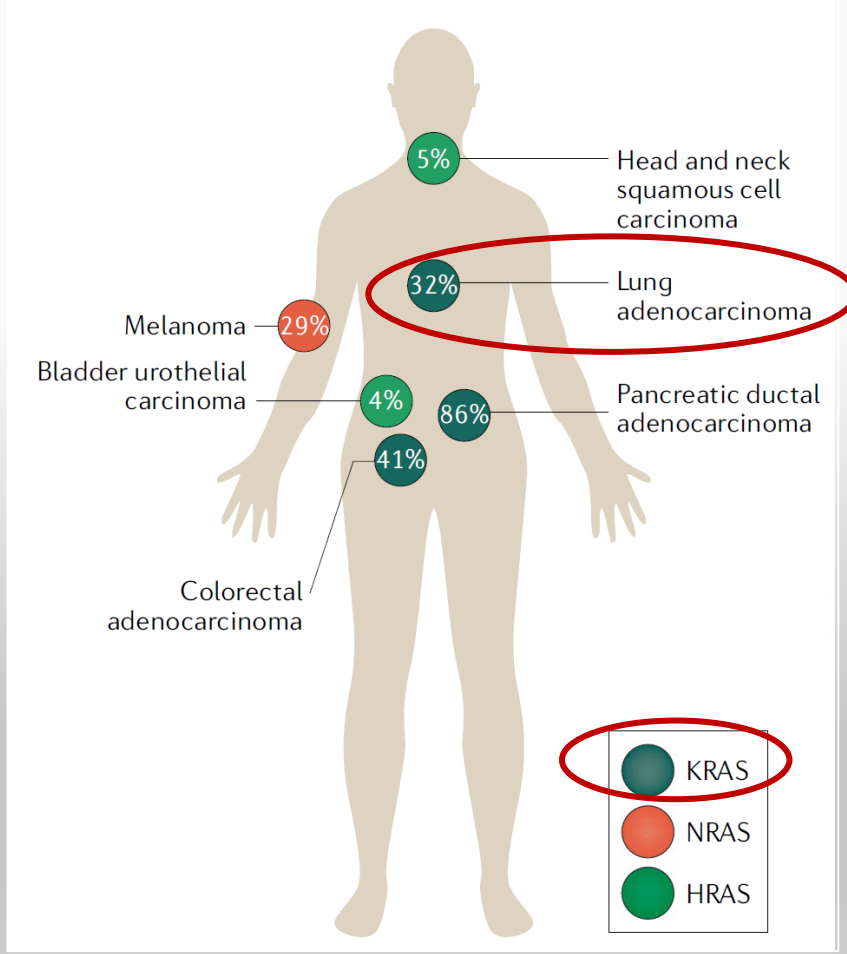
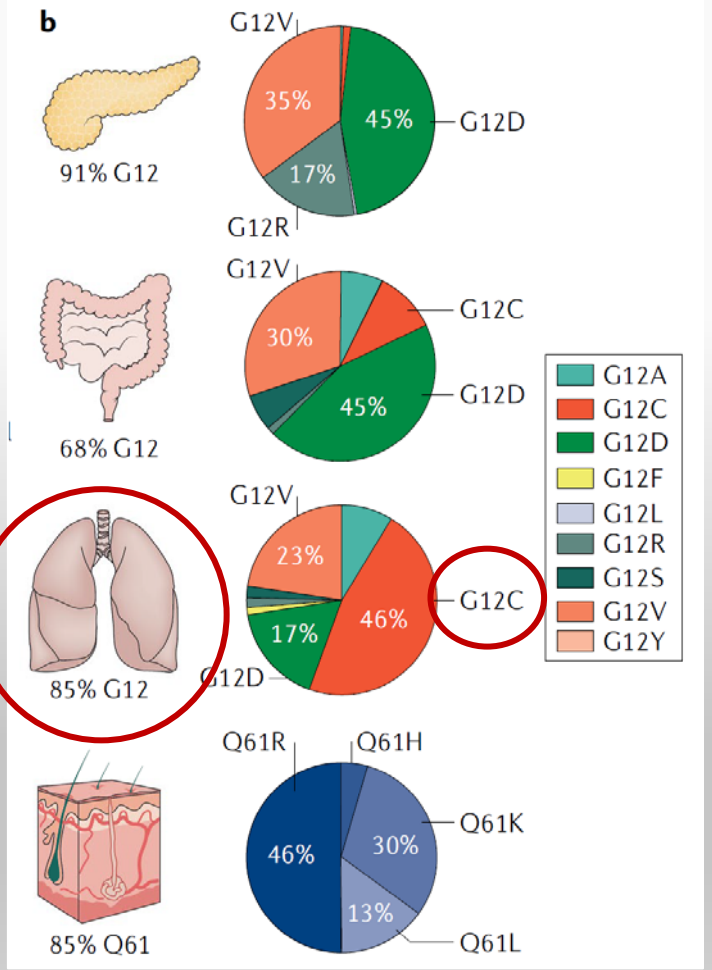
LUNG-MAP

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

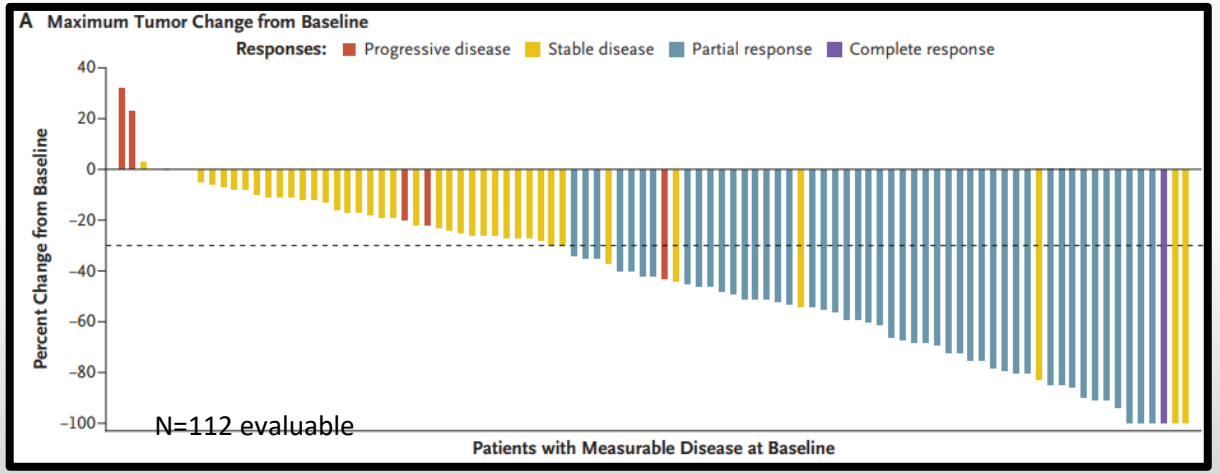
SOTORASIB – Approved 05/2021

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.

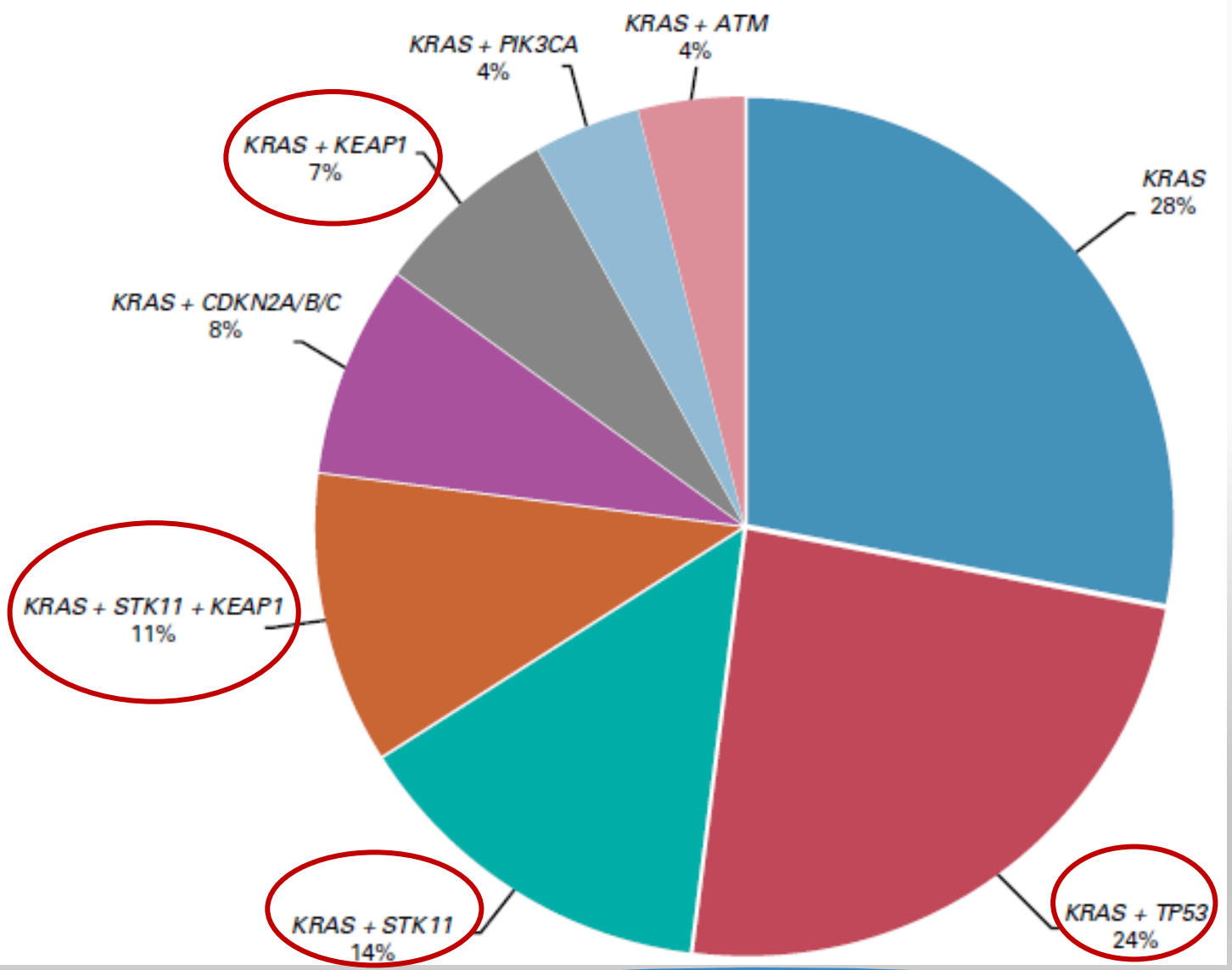
ADAGRASIB



- **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

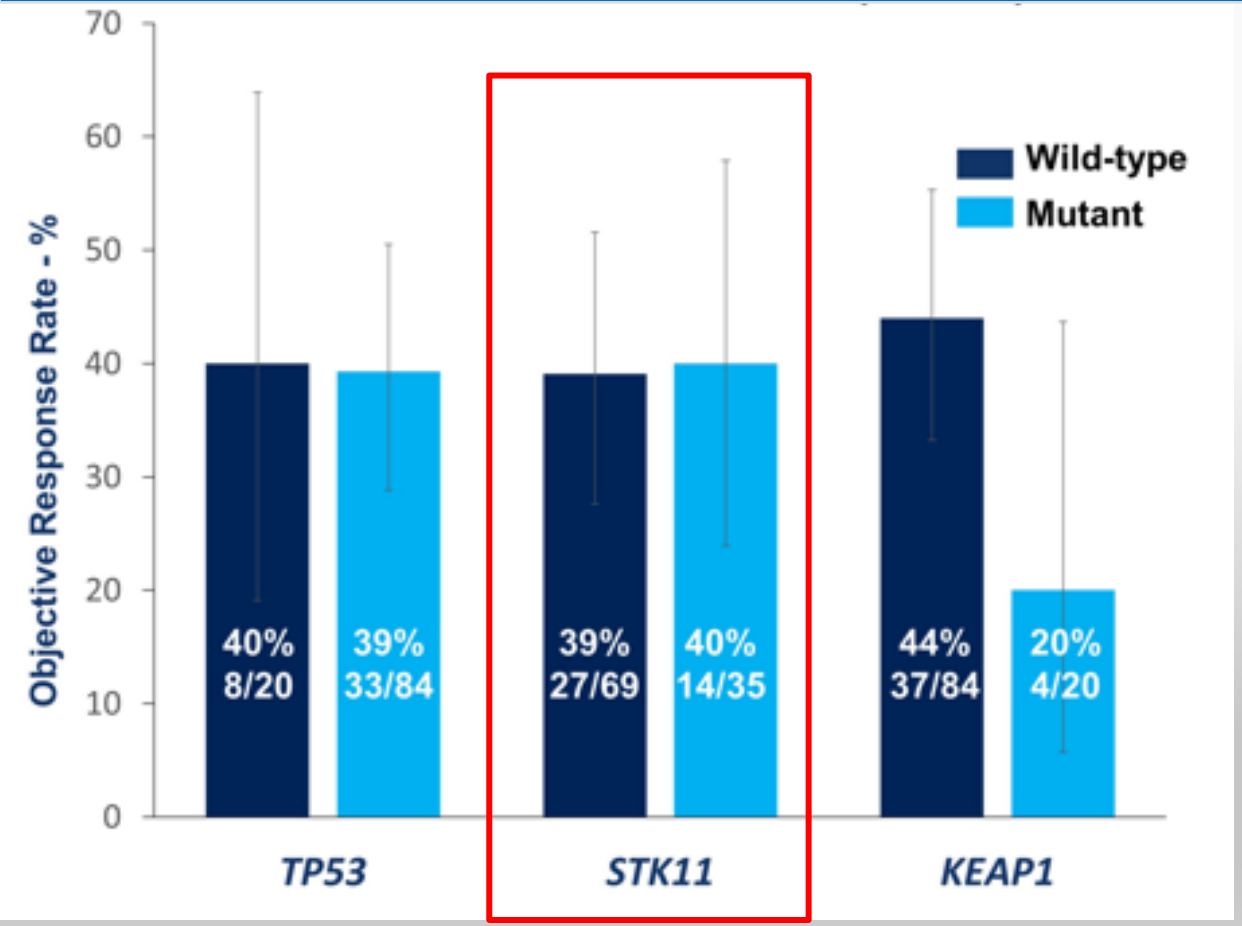
- Arbour et al (n=330): ***TP53* (42%), *STK11* (29%), *KEAP1* (24%),** *RBM10* (16%), and *PTPRD* (15%)
- Scheffler et al (n=1078): ***TP53* (39.4%);** additional identified in ***STK11* (19.8%), *KEAP1* (12.9%),** *ATM* (11.9%)
- Aredo et al (n=186): ***TP53* (38.7%)**, ***STK11* (11.8%), and *KEAP1*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

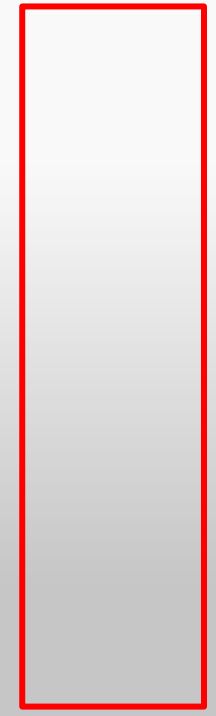
Aredo JV, Padda SK et al. *Lung Cancer*. 2019 Jul;133:144-150. Arbour KC et al. Clin Cancer Res. 2018 Jan 15;24(2):334-340. Scheffler M et al. J Thorac Oncol. 2019 Apr;14(4):606-616.

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

Are co-mutations predictive of KRAS G12C inhibitor efficacy?

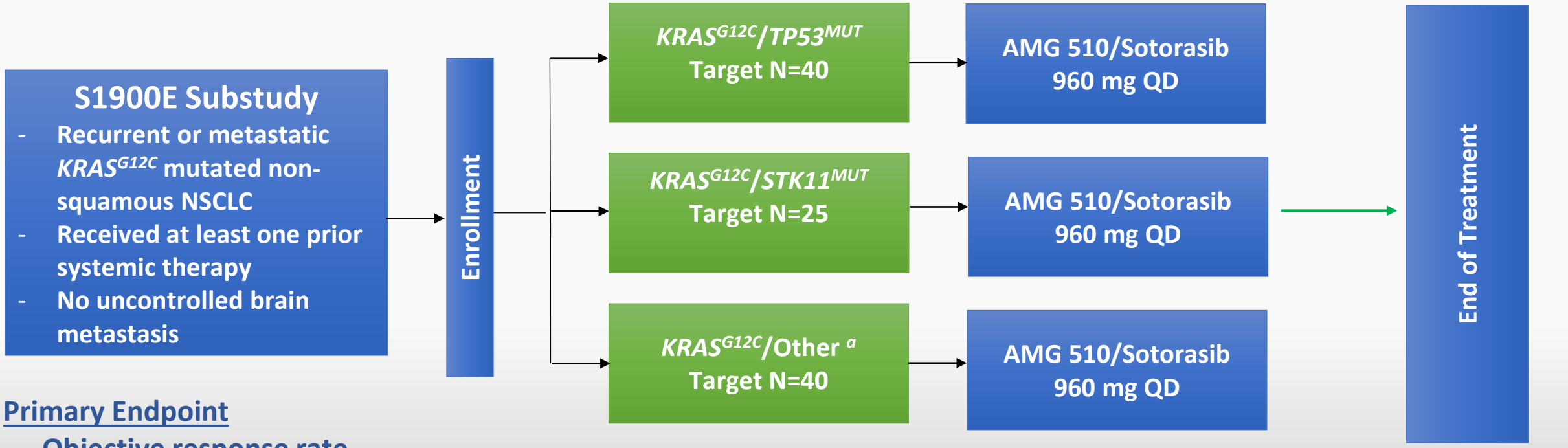
SOTORASIB (AMG 510)





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

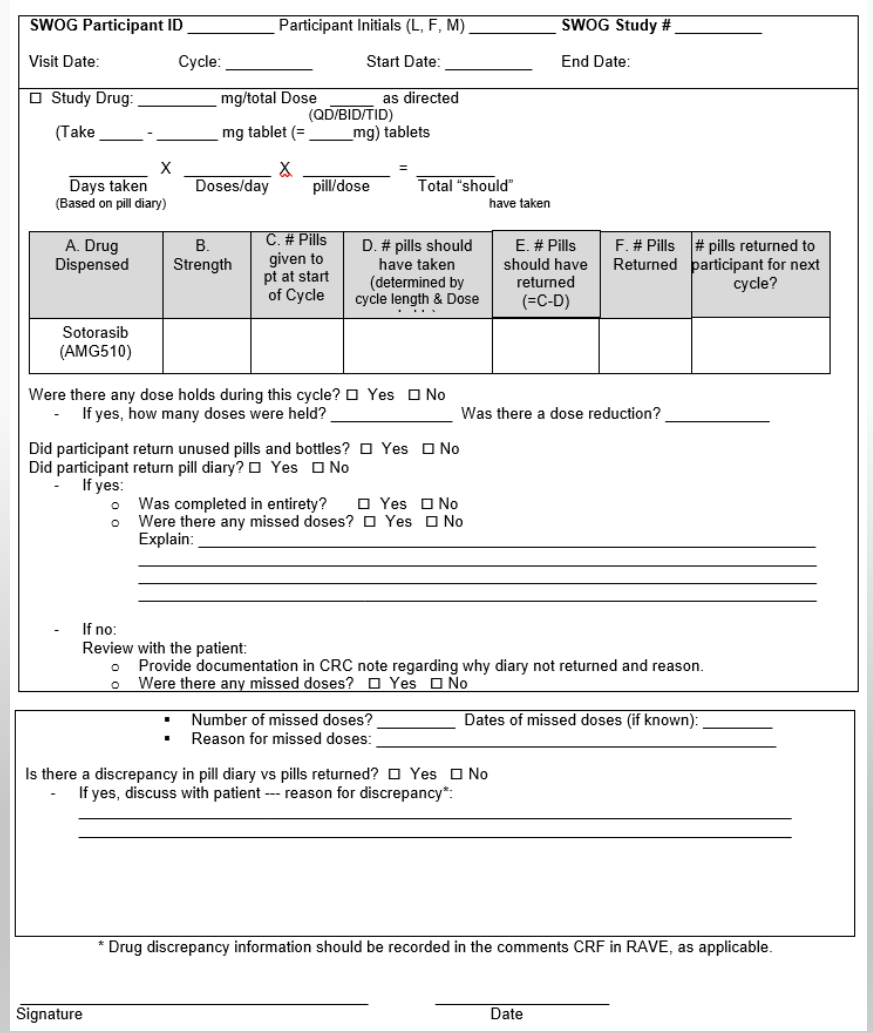
Revised site personnel instructions to clarify site's process for drug dispensation.

- 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

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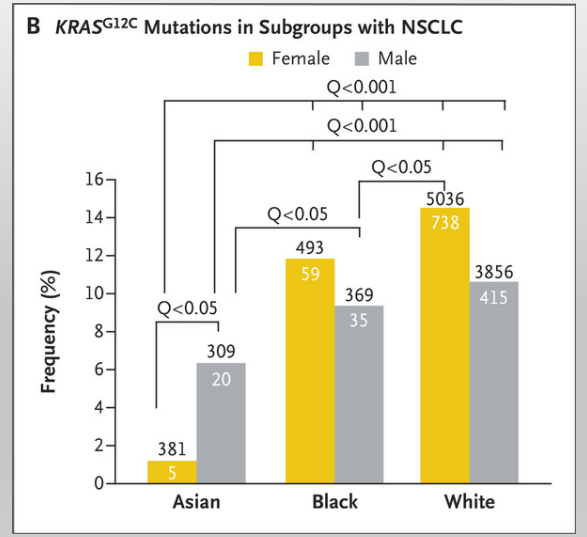
Underrepresentation of race/ethnicity in KRAS G12C trials –

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

Lung-MAP Contact Information

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It takes a village!

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Summary & Adjourn

Thank you for joining us!

The slides will be available on the SWOG & CTSU websites