GETTHI

Grupo Español de Oncología Transversal y Tumores Huérfanos e Infrecuentes

VII SIMPOSIO GETTHI

Sesión 4: Vías de desarrollo de la oncología transversal (II)

16 de diciembre de 2021

ALTERACIONES EN KRAS. IMPLICACIONES CLÍNICAS Y NUEVAS ALTERNATIVAS TERAPÉUTICAS

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DISCLOSURES

- Speaker: Rovi, Leo Pharma, Kyowa Kirin, Roche Pharma
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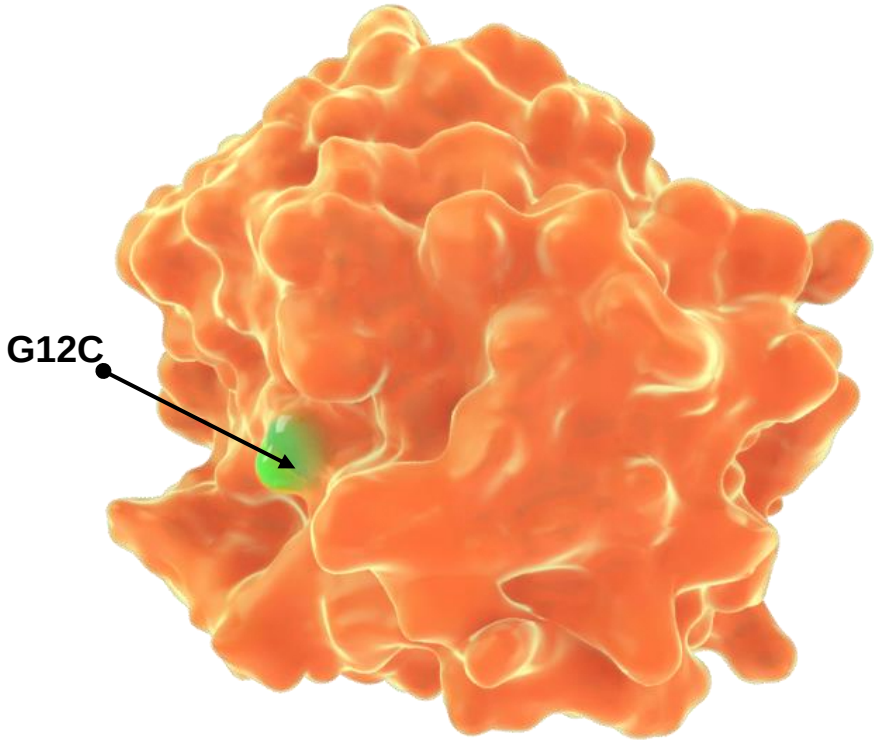
• VII SIMPOSIO GETTHI

Sesión 4: Vías de desarrollo de la oncología transversal (II)

1. IMPORTANCIA DE LA MUTACIÓN RAS
2. PREVALENCIA DE LA MUTACIÓN RAS EN TUMORES
3. INHIBICIÓN DE LA VÍA RAS G12C
4. MECANISMOS DE RESISTENCIA A LA INHIBICIÓN RAS G12C
5. CONCLUSIONES

KRAS in an Oncogene in human cancers

- Kirsten rat sarcoma viral oncogene homolog *(KRAS)* is one the most frequently mutated oncogenes in human cancers[1]
- Despite the discovery of *KRAS* almost 4 decades ago, there is currently no approved therapy targeting KRAS[1]
- *KRAS G12C* mutation (glycine to cysteine substitution at position 12) promotes tumorigenesis and is found in approximately 13% of NSCLC, **3–5% of colorectal cancer, and 1%–3% of other solid tumors[2–7]**



KRAS G12C

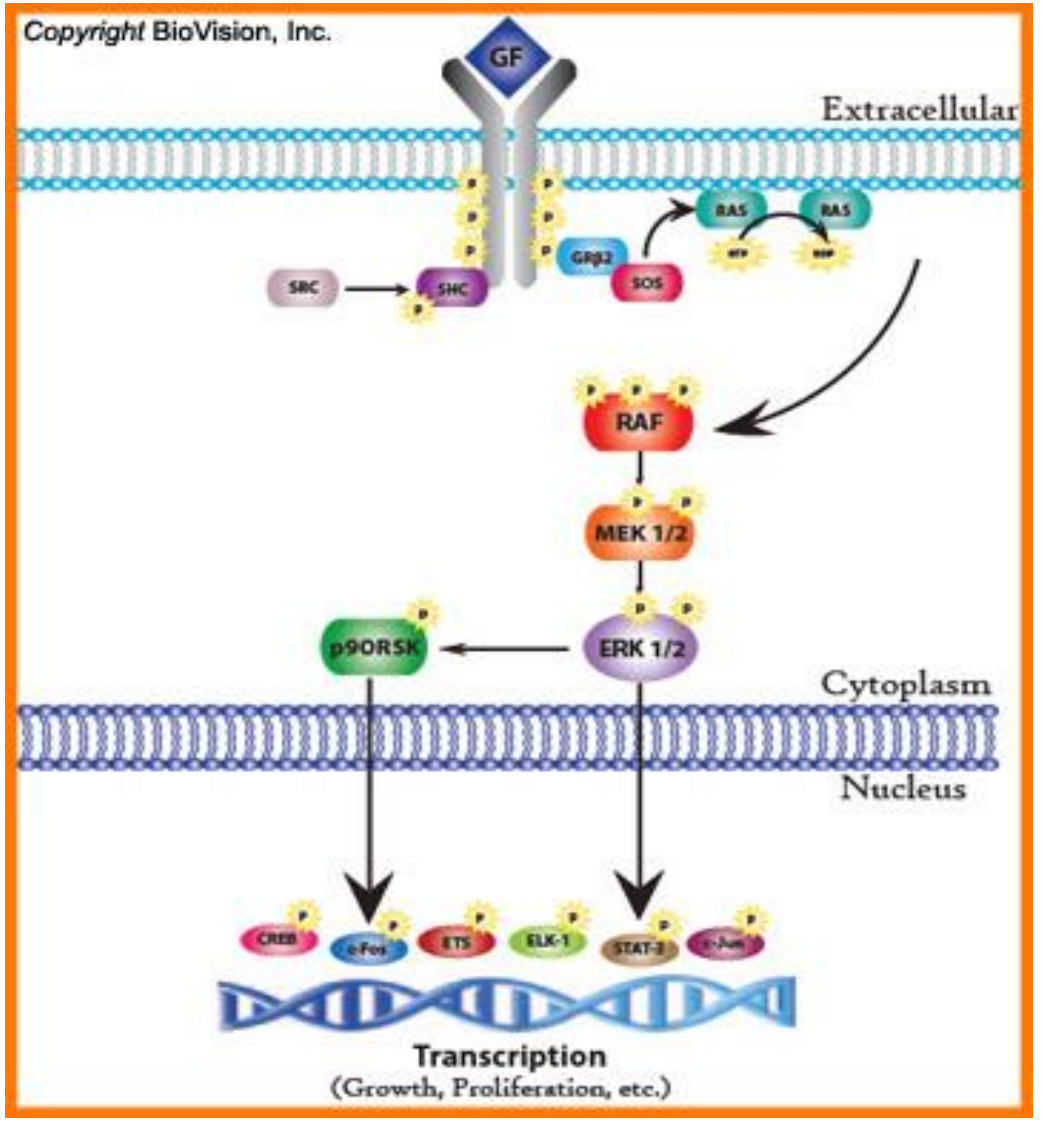
GDP, guanosine diphosphate; **H95,** histidine amino acid at position 95; **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **NSCLC,** non-small cell lung cancer; **Q99,** glutamine amino acid at position 99; **Y96,** tyrosine amino acid at position 96.

1. Cox AD, et al. *Nat Rev Drug Discov.* 2014;13:828-851. **2.** Biernacka A, et al. *Cancer Genet.* 2016;209:195-198. **3.** Neumann J, et al. *Pathol Res Pract.* 2009;205:858-862. **4.** Jones RP, et al. *Br J Cancer.* 2017;116:923-929. **5.** Wiesweg M, et al. *Oncogene.* 2019;38:2953-2966.
6. Zhou L, et al. *Med Oncol.* 2016;33:32. **7.** Canon J, et al. *Nature.* 2019;575:217-223.

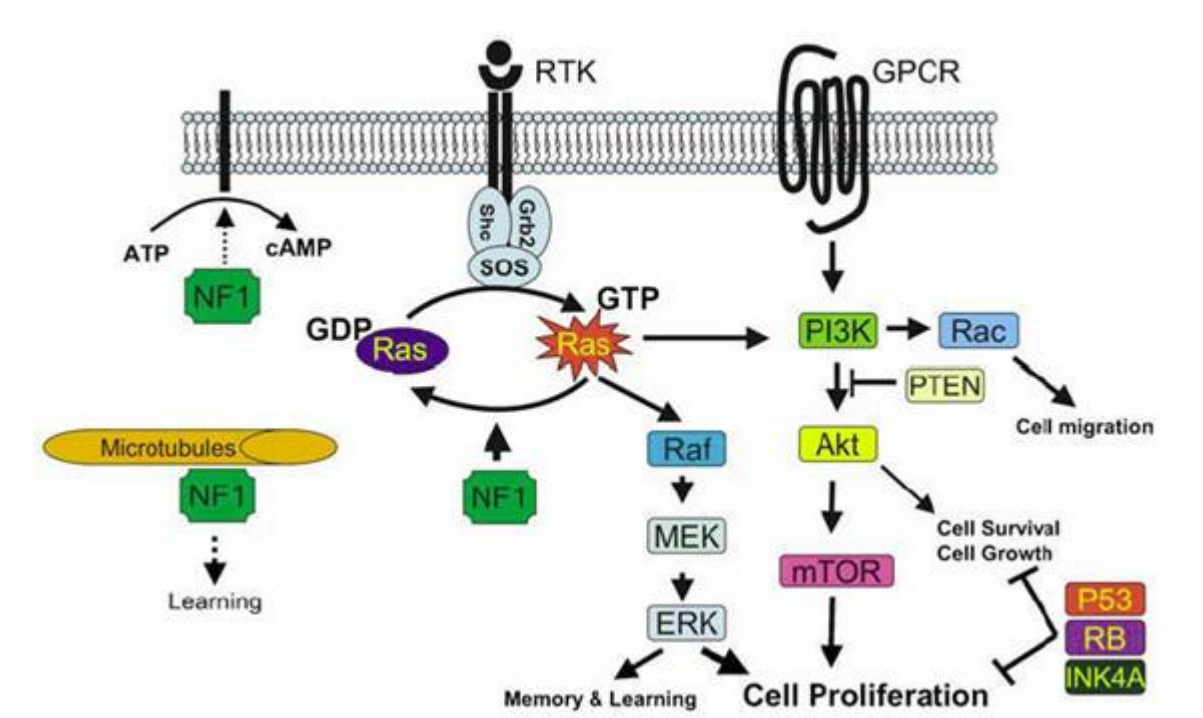
KRAS mutations impairing GTPase activity are well known to play pivotal role in oncogenic transformation

↳ *KRAS*-mutated tumors represents a genetically heterogenous subgroup

ONCOGENE RAS:
- Cytoskeletal integrity
- Cell proliferación
- Cell differentiation
- Cell adhesion
- Cell migration
- Apoptosis



Role of RAS mutated in cancer

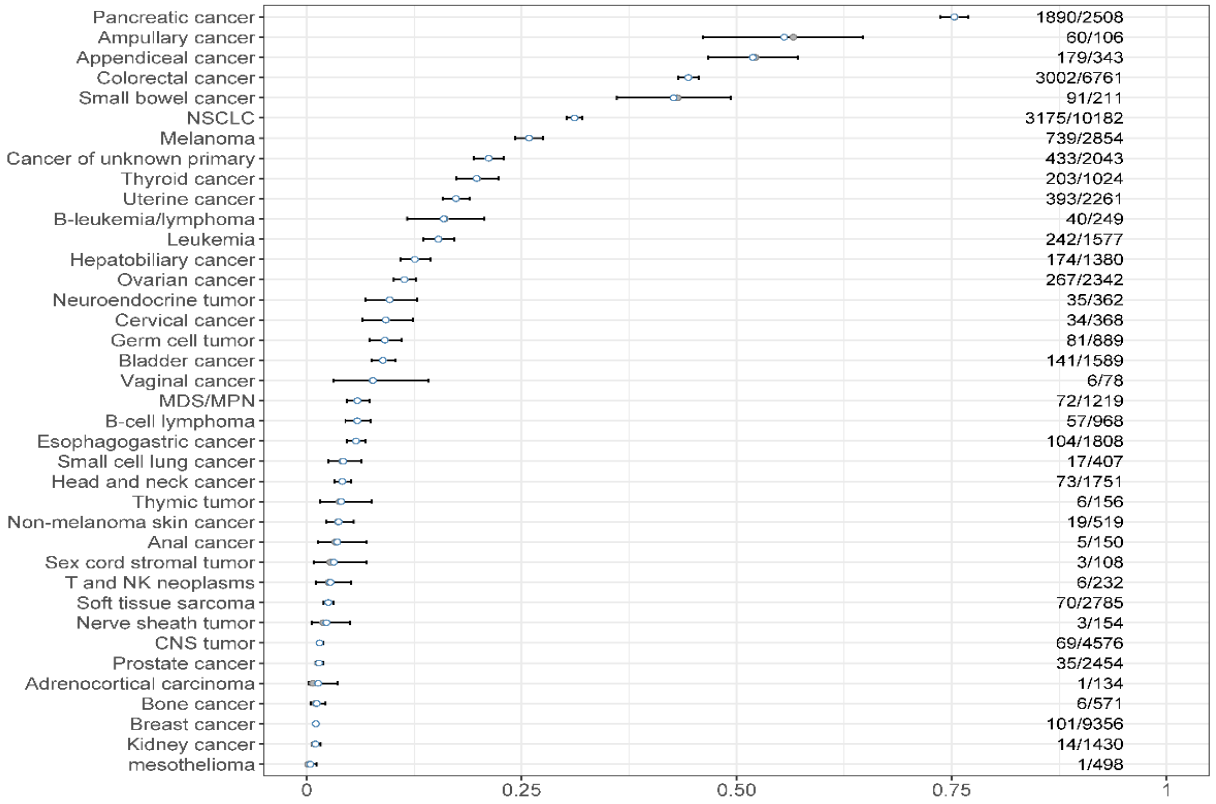


Ras activates several pathways, of which the mitogen-activated protein (MAP) kinase cascade has been well-studied.

This cascade transmits signals downstream and results in the transcription of genes involved in cell growth and division.

Another Ras-activated signaling pathway is the PI3K/AKT/mTOR pathway, which stimulates protein synthesis and cellular growth, and inhibits apoptosis.

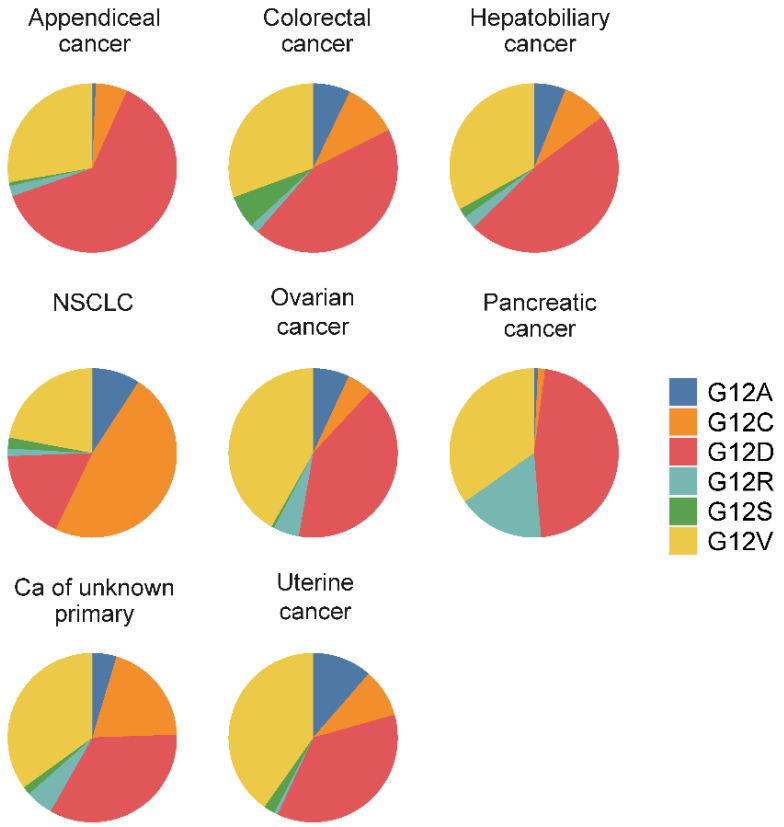
PREVALENCE OF RAS MUTATION RAS IN CANCER



- *RAS* codon 12, 13 and 61 mutation prevalence is cancer type-dependent.
  - 77.7% in pancreatic cancer
  - 44.8% in colorectal cancer
  - 31.2% in NSCLC
  - 1.1% in breast cancer
  - 0.5% in mesothelioma

Scharpf R, et al. Oral Presentation at American Association for Cancer Research (AACR), 2020. Virtual Meeting, April 27-28, 2020

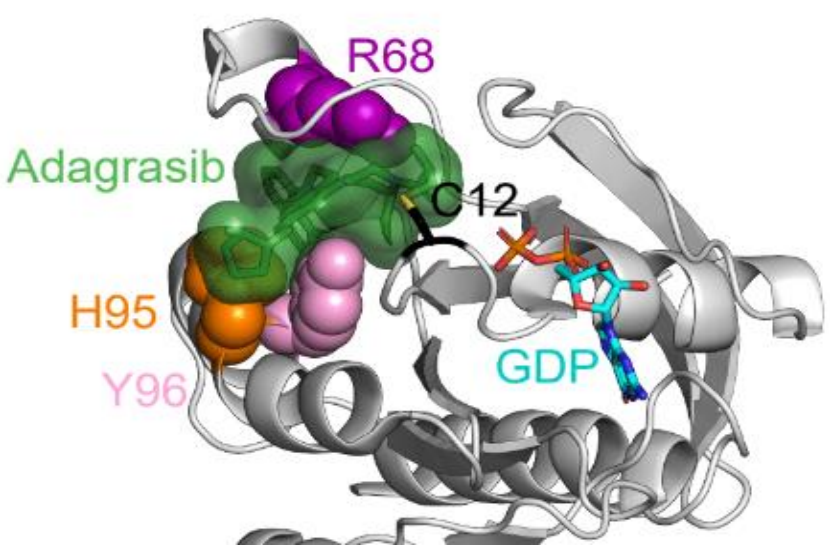
SEVERAL RAS MUTATIONS

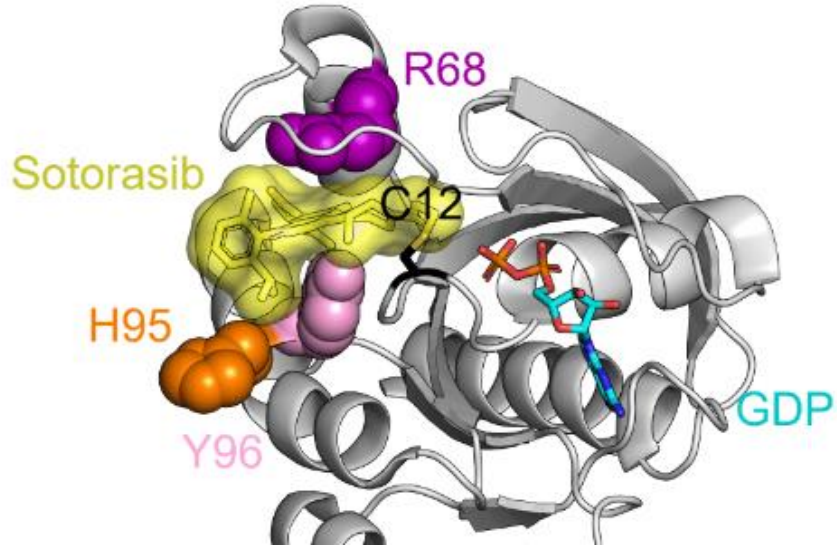


- The type of substitution at codon 12 is tissue-specific.
- 48% G12C in NSCLC vs. 10% in CRC and 1% in PAC.
- 47% G12D in PAC and 44% in CRC vs. 17% in NSCLC.
- 17% G12R in PAC vs. 1% in NSCLC and 2% in CRC.
- G12V comprises a third of codon 12 mutations.
- G12A and G12S less frequent among all tumor types.

Scharpf R, et al. Oral Presentation at American Association for Cancer Research (AACR), 2020. Virtual Meeting, April 27-28, 2020

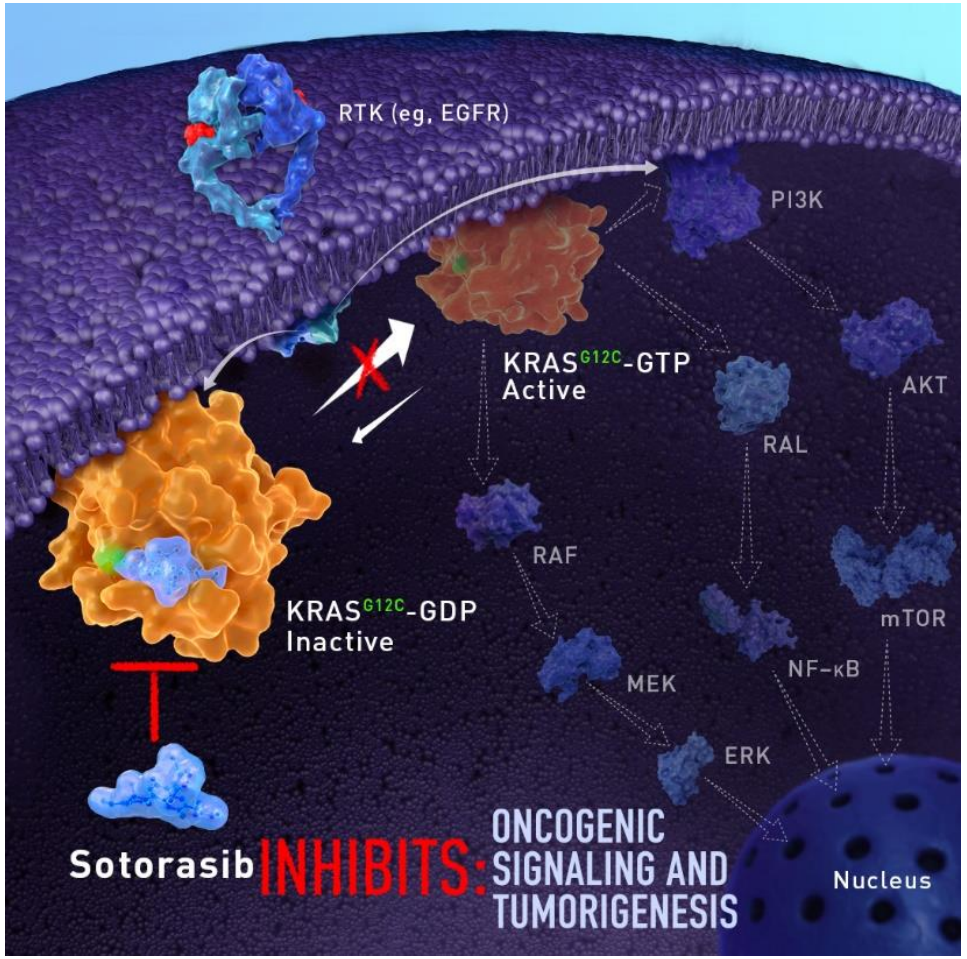
G12C RAS MUTATION INHIBITION





SOTORASIB

- **Sotorasib is a first-in-class, oral targeted therapy that selectively inhibits the KRAS^{G12C} protein[1]**
- **Sotorasib locks the KRAS^{G12C} mutant protein in an inactive state, preventing oncogenic signaling without affecting wild-type KRAS signaling[1-3]**



1. Canon J, et al. *Nature*. 2019; 575:217-223.
2. Hong DS, et al. *N Engl J Med.* 2020;383:1207-1217

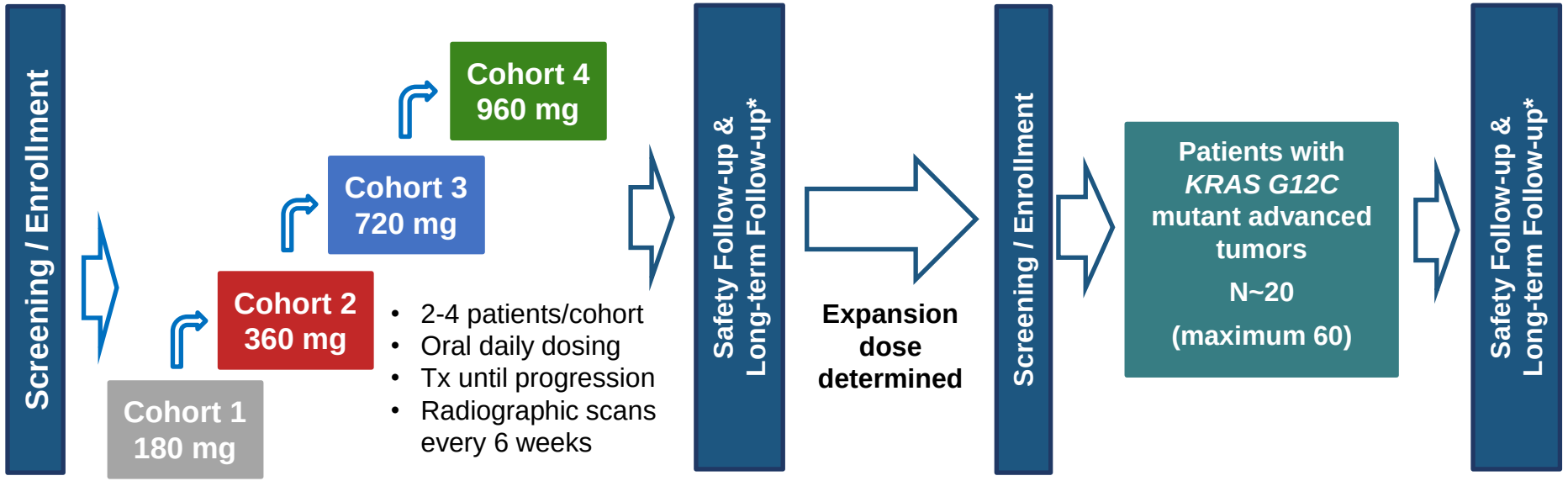
Phase 1 Study Design

Phase 1, Multicenter, Open-label Study – Dose Escalation

Dose Expansion

Key Eligibility

- Locally advanced or metastatic malignancy
- Received prior standard therapies
- *KRAS G12C* mutation as assessed by molecular testing of tumor biopsies
- No active brain metastases



Primary endpoint: Safety, including DLTs
Secondary endpoints include: PK; ORR; DOR; DCR; PFS; duration of SD

*30 (+7) days after end of treatment for safety follow-up; every 12 weeks for long-term follow-up.

DCR, disease control rate; **DOR,** duration of response; **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **ORR,** objective response rate; **PFS,** progression-free survival; **PK,** pharmacokinetic; **SD,** stable disease; **Tx,** treatment.

Hong DS. Oral presentation at European Society of Medical Oncology 2020 Virtual Congress, September 19-21, 2020.

CODEBREAK 100- Phase II

Screening / Enrollment

Key Eligibility:

- Locally advanced or metastatic NSCLC
- *KRAS G12C* mutation as assessed by central testing of tumor biopsies
- Progressed on prior standard therapies[a]
- No active brain metastases

Sotorasib was orally administered at 960 mg once daily until disease progression[b]

Radiographic scan every 6 weeks up to week 48 and once every 12 weeks thereafter

Primary endpoint: ORR (RECIST 1.1) by blinded independent central review

Key secondary endpoints: DoR; disease control rate; TTR; PFS; OS; safety

Exploratory endpoints: Evaluation of biomarkers (PD-L1, co-occurring mutations)

Safety and Long-term Follow-up[c]

a: no more than 3 prior lines of therapies were allowed; **b:** treatment beyond disease progression was allowed if certain criteria were met;
c: safety follow-up occurs 30 (+7) days after the last dose of sotorasib; long-term follow-up occurs every 12 (±2) weeks for up to 3 years.

DoR, duration of response; **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **NSCLC,** non-small cell lung cancer; **ORR,** objective response rate; **OS,** overall survival; **PD-L1,** programmed death-ligand 1; **PFS,** progression-free survival; **RECIST,** Response Evaluation Criteria in Solid Tumors; **TTR,** time to response.

Li BT, et al. Presentation at 2020 World Congress on Lung Cancer Singapore Worldwide Virtual Event, January 28-31, 2021. Abstract PS01.07.

Tumor Response with Sotorasib

Response assessed by central review	Sotorasib 960mg, N = 124[a]
Confirmed objective response rate – % (95% CI)	**37.1 (28.6, 46.2)**
Best overall response – n (%)	
Complete response	3 (2.4)
Partial response	43 (34.7)
Stable disease	54 (43.5)
Progressive disease	20 (16.1)
"Not evaluable" or "Missing scan"[b]	4 (3.2)
Disease control rate – % (95% CI)	**80.6 (72.6, 87.2)**

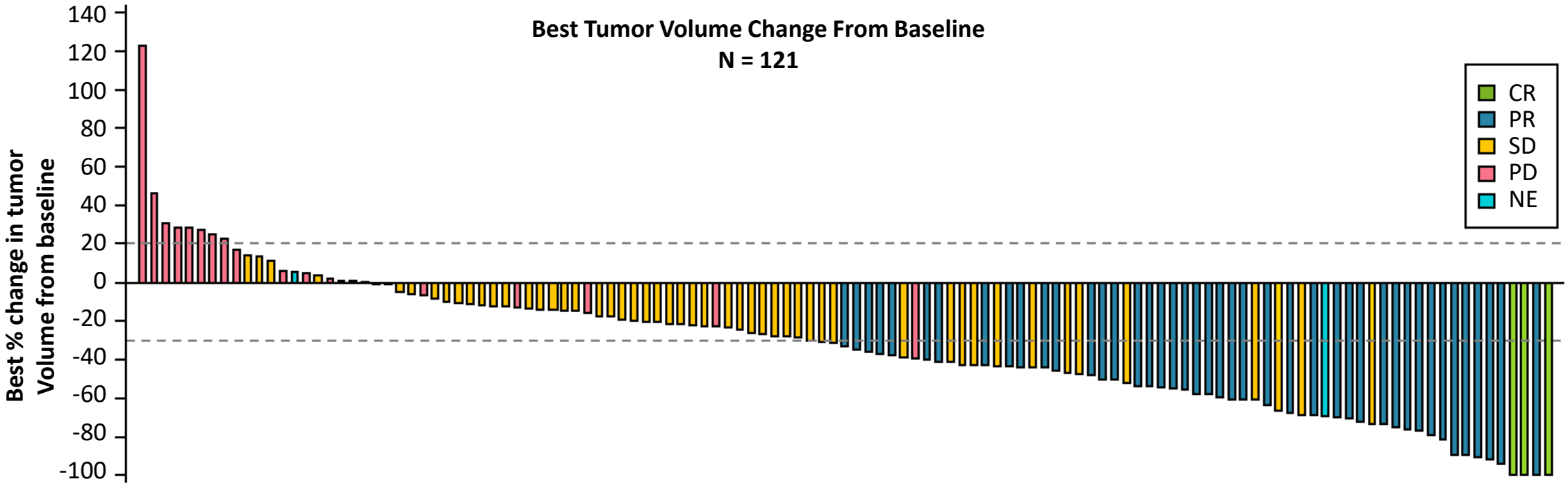
Over 80% of patients achieved disease control, including 3 CRs and 43 PRs

a: according to central review, 2 patients did not have measurable lesions at baseline per RECIST 1.1 and were excluded from response assessment;
b: 2 patients stopped treatment without post-baseline scans and were deemed as "missing scan"; 2 patients had 1 post-baseline scan and were assessed as "not evaluable" by central review.

CI, confidence interval; **CR,** complete response; **PR,** partial response.

Li BT, et al. Presentation at 2020 World Congress on Lung Cancer Singapore Worldwide Virtual Event, January 28-31, 2021. Abstract PS01.07.

Depth of Tumor Response



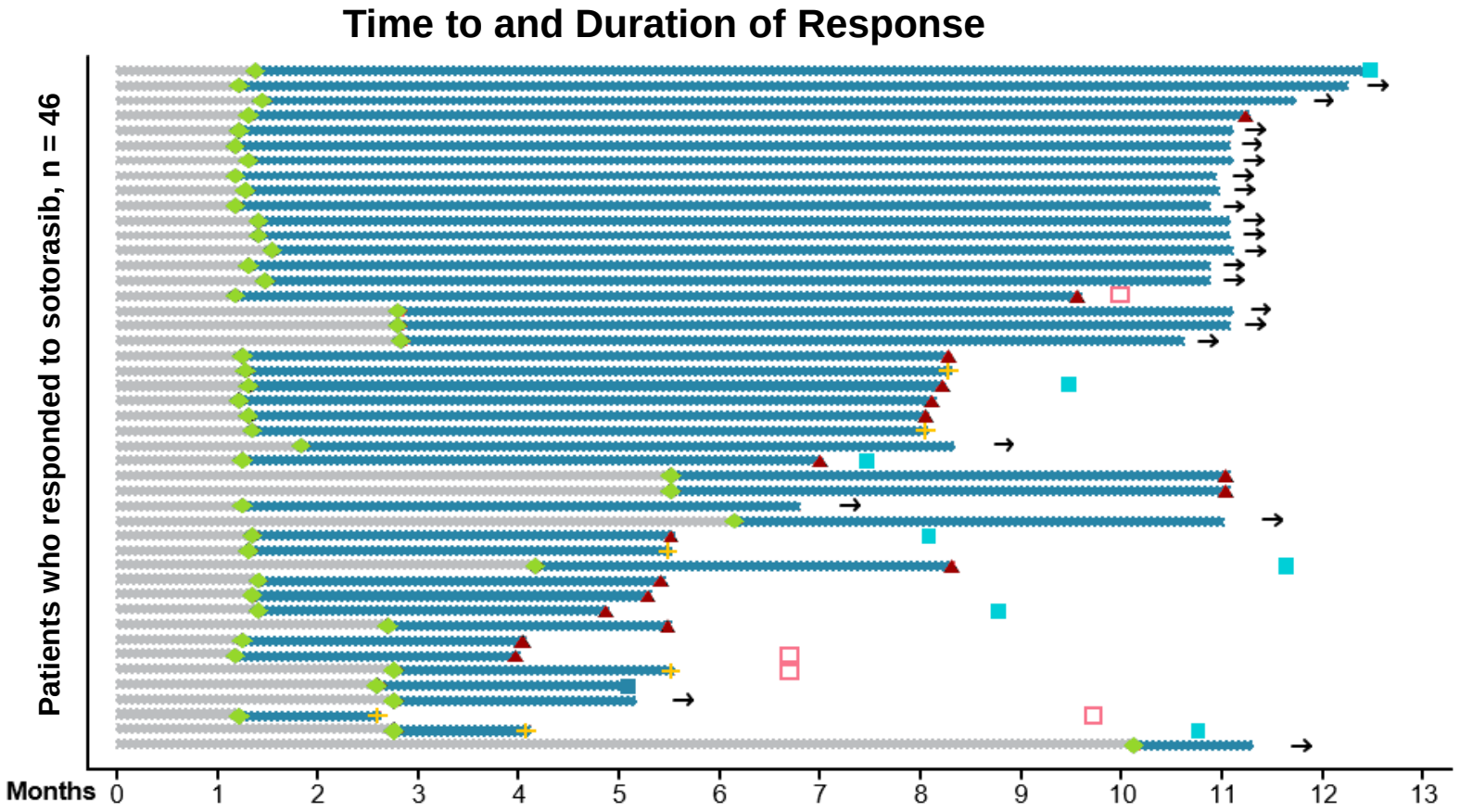
Tumor shrinkage of any magnitude was observed in 81% of patients (101/124)
Median percentage of best tumor shrinkage among all responders was 60%

Graph excluded 3 patients without post-baseline measurement in target lesions.

CR, complete response; **NE,** not evaluable; **PD,** progressive disease; **PR,** partial response; **SD,** stable disease.

Li BT, et al. Presentation at 2020 World Congress on Lung Cancer Singapore Worldwide Virtual Event, January 28-31, 2021. Abstract PS01.07.

Durability of Tumor Response



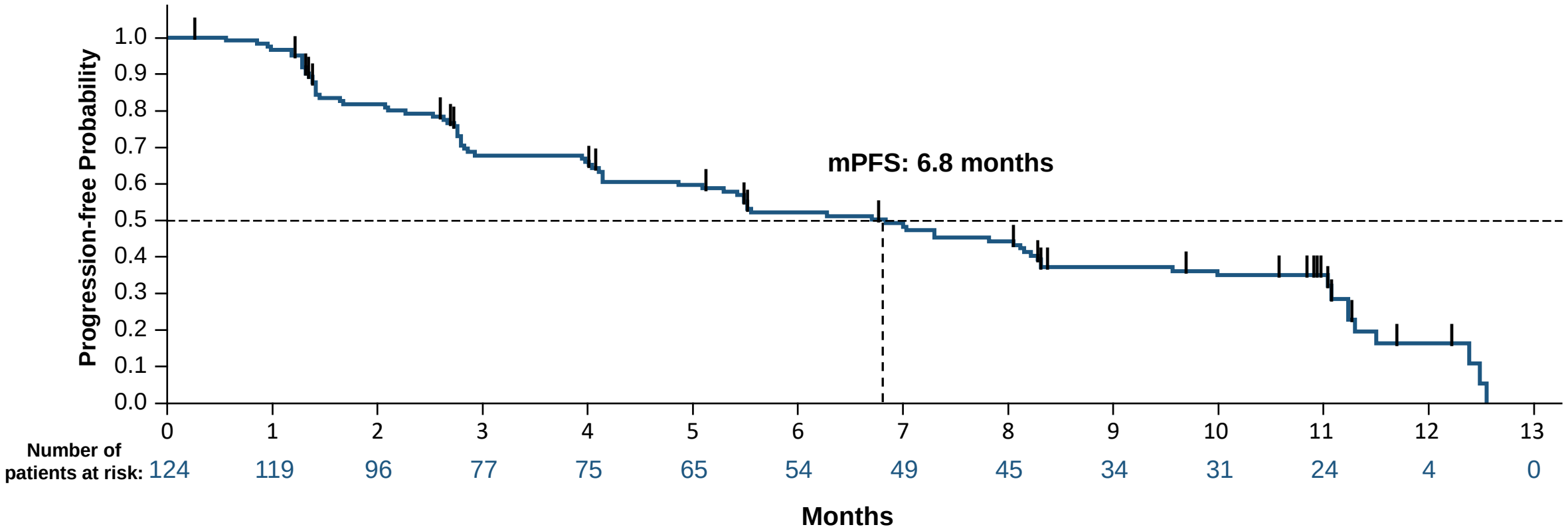
- Median duration of response:
  - **10.0 months** (95% CI: 6.9, 11.1)
- Median time to objective response:
  - **1.4 months**
- **43%** (20/46) of responders remained on treatment without progression as of the data cutoff

Responses to sotorasib were durable; 72% were seen at the first assessment

CI, confidence interval; **OS,** overall survival; **PFS,** progression-free survival.

Li BT, et al. Presentation at 2020 World Congress on Lung Cancer Singapore Worldwide Virtual Event, January 28-31, 2021. Abstract PS01.07.

Progression-Free Survival



Median progression-free survival was 6.8 months (95% CI: 5.1, 8.2)

CI, confidence interval; **mPFS,** median progression-free survival.

Li BT, et al. Presentation at 2020 World Congress on Lung Cancer Singapore Worldwide Virtual Event, January 28-31, 2021. Abstract PS01.07.

Treatment-Related Adverse Events

Treatment-related adverse events (TRAEs) occurring in > 5%, n (%)	Any Grade N = 126	Grade 3 N = 126
Any event	**88 (69.8)**	**25 (19.8)**
Diarrhea	39 (31.0)	5 (4.0)
Nausea	24 (19.0)	0
ALT increase	19 (15.1)	8 (6.3)
AST increase	19 (15.1)	7 (5.6)
Fatigue	14 (11.1)	0
Vomiting	10 (7.9)	0
Blood alkaline phosphatase increase	9 (7.1)	1 (0.8)
Maculopapular rash	7 (5.6)	0

1 patient (0.8%) reported grade 4 TRAEs (pneumonitis and dyspnea)

- Most TRAEs were grade 1 or 2
- No fatal TRAEs occurred
- TRAEs led to treatment discontinuation in 7.1% of patients
- TRAEs led to dose modification in 22.2% of patients

Treatment-related adverse events were generally mild and manageable

ALT, alanine aminotransferase; **AST,** aspartate aminotransferase.

Li BT, et al. Presentation at 2020 World Congress on Lung Cancer Singapore Worldwide Virtual Event, January 28-31, 2021. Abstract PS01.07.

CODEBREAK 100- SOTORASIB

- Sotorasib, the first-in-class $KRAS^{G12C}$ inhibitor administered as once daily oral therapy, demonstrated early, deep, and durable responses in the advanced NSCLC cohort from the phase 2 CodeBreaK 100 trial
  - ORR was 37.1%, with median DoR of 10.0 months and median PFS of 6.8 months, validating the phase 1 results
- Sotorasib was well tolerated with no deaths attributed to treatment and low incidence of grade 3 or 4 treatment-related adverse events, treatment discontinuation, and dose modification
- Tumor response to sotorasib was observed across a range of biomarker subgroups, including patients with negative or low PD-L1 expression level and those with mutant *STK11*
- Breakthrough therapy designation was granted by FDA; regulatory filings based on current data are underway
- Confirmatory phase 3 CodeBreaK 200 trial is currently enrolling (clinicaltrials.gov identifier: NCT04303780)

DoR, duration of response; FDA, Food and Drug Administration **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **NSCLC,** non-small cell lung cancer; **ORR,** objective response rate; **PD-L1,** programmed death ligand 1; **PFS,** progression-free survival; **STK11,** serine/threonine kinase 11; **TMB,** tumor mutational burden.

Li BT, et al. Presentation at 2020 World Congress on Lung Cancer Singapore Worldwide Virtual Event, January 28-31, 2021. Abstract PS01.07.

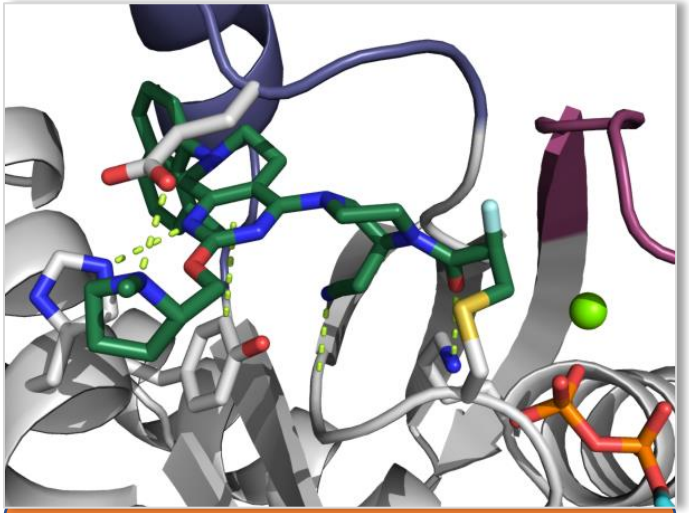
Clinical Trial	ClinicalTrials.gov NCT ID	Treatments	Advanced *KRAS G12C*-Mutated Cancers: NSCLC	CRC	Other Solid Tumors	Phase
CodeBreaK 200	NCT04303780	Monotherapy vs. docetaxel	●	●	●	3
CodeBreaK 100	NCT03600883	Monotherapy	●	●	●	2
		Monotherapy (240 mg)	●	●	●	2
		Monotherapy (treatment naïve)	●	●	●	1
		+ PD-1/PD-L1 inhibitor	●	●	●	1
CodeBreaK 101	NCT04185883	+ Oral EGFR inhibitor	●	●	●	1b
		+ PD-L1 inhibitor	●	●	●	1b
		+ Chemotherapy	●	●	●	1b
		+ EGFR Ab +/- Chemotherapy	●	●	●	1b
		+ VEGF Ab + Chemotherapy	●	●	●	1b
		+ PD-1 inhibitor	●	●	●	1b
		+ MEK inhibitor +/- EGFR Ab	●	●	●	1b
		+ SHP2 inhibitor	●	●	●	1b
		+ mTOR inhibitor	●	●	●	1b
		+ CDK inhibitor	●	●	●	1b
CodeBreaK 105	NCT04380753	Monotherapy*	●	●	●	1

ADAGRASIB

Adagrasib is a covalent inhibitor of $KRAS^{G12C}$ that irreversibly and selectively binds $KRAS^{G12C}$ in its inactive, GDP-bound state

Adagrasib was optimized for desired properties of a $KRAS^{G12C}$ inhibitor:

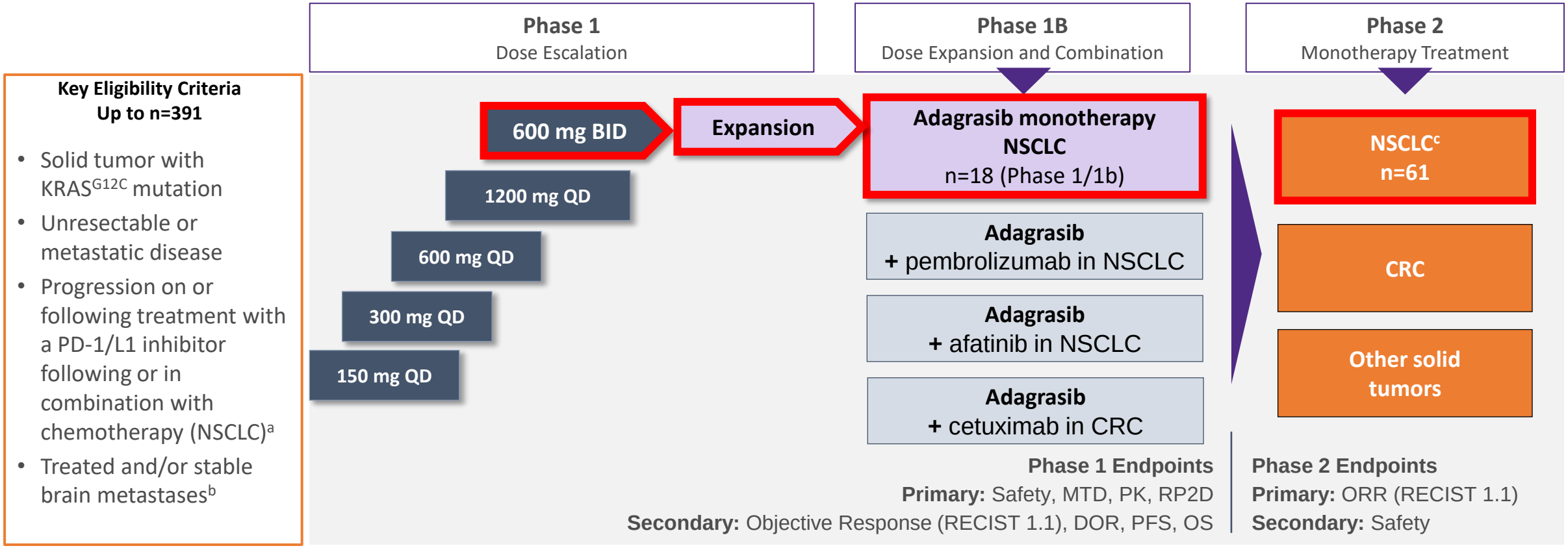
- Potent covalent inhibitor of $KRAS^{G12C}$ (cellular IC_{50}: ~5 nM)
- High selectivity (>1000X) for the mutant $KRAS^{G12C}$ protein vs wild-type KRAS
- Favorable PK properties, including oral bioavailability, long half-life (~24 h), and extensive tissue distribution



Adagrasib Crystal Structure

Hypothesis: Maintaining continuous exposure of adagrasib above a target threshold enables inhibition of KRAS-dependent signaling for the complete dose interval and maximizes depth and duration of antitumor activity

KRYSTAL-1 (849-001) Study Design



[a]Applies to the majority of NSCLC cohorts. [b]Most cohorts allow patients with brain metastases if adequately treated and stable; additional phase 1/1b cohort allows limited brain metastases. [c]Primary NSCLC cohort eligibility based on a tissue test; KRAS^{G12C} testing for entry was performed locally or centrally using a sponsor pre-approved test. ClinicalTrials.gov. NCT03785249.

Presented at the 32nd EORTC-NCI-AACR Symposium, October 24-25, 2020

	Phase 1/1b 600 mg BID (n=18)	Phase 1/1b and 2 600 mg BID (n=79)
Median age, y (range)	65 (40-76)	65 (25-85)
Female, n (%)	11 (61%)	45 (57%)
Race, n (%)		
White	15 (83%)	67 (85%)
Black	3 (17%)	5 (6%)
Asian	0 (0%)	5 (6%)
Other	0 (0%)	2 (3%)
ECOG PS, n (%)		
0	8 (44%)	17 (22%)
1	10 (56%)	62 (78%)
Current/former smokers	16 (89%)	75 (95%)
Nonsquamous histology, n (%)	18 (100%)	76 (96%)
Prior lines of anticancer therapy[a], median (range)	3 (1-9)	2 (1-9)
Prior anti-PD-1/L1 inhibitor, n (%)	16 (89%)	73 (92%)

[a]Phase 2 patients with NSCLC received prior treatment with platinum regimens.
Data as of 30 August 2020. Pooled includes NSCLC Phase 1/1b and Phase 2 600 mg BID.

Presented at the 32nd EORTC-NCI-AACR Symposium, October 24-25, 2020

Adagrasib in Patients With NSCLC: ORR in Pooled Dataset

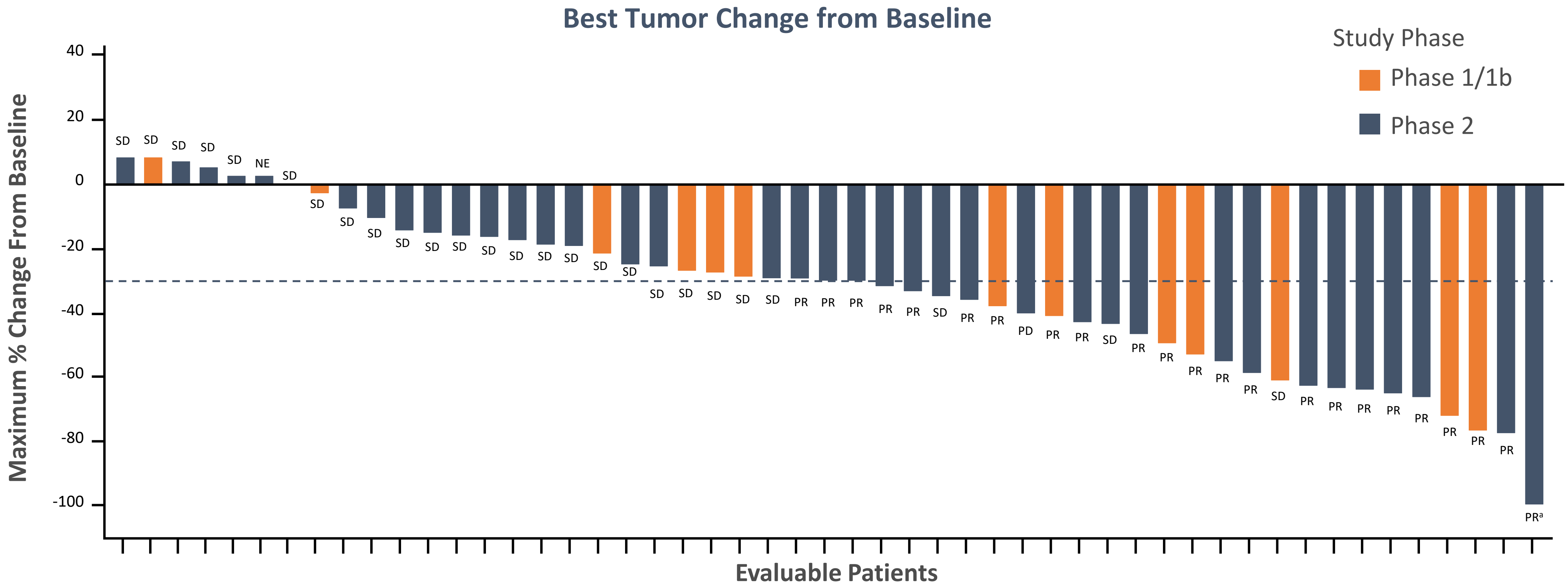
Efficacy Outcome[a], n (%)	Phase 1/1b, NSCLC 600 mg BID (n=14)	Phase 1/1b and 2, NSCLC 600 mg BID (n=51)
Objective Response Rate	6 (43%)	23 (45%)[b]
Best Overall Response		
Complete Response (CR)	0 (0%)	0 (0%)
Partial Response (PR)	6 (43%)	23 (45%)
Stable Disease (SD)	8 (57%)	26 (51%)
Progressive Disease (PD)	0 (0%)	1 (2%)
Not Evaluable (NE)	0 (0%)	1 (2%)[c]
Disease control	14 (100%)	49 (96%)

[a]Based on investigator assessment of the clinically evaluable patients (measurable disease with ≥1 on-study scan); 14/18 patients (Phase 1/1b) and 51/79 patients (Phase 1/1b and 2 pooled) met these criteria. [b]At the time of the 30 August 2020 data cut off, 5 patients had unconfirmed PRs. All 5 were confirmed by scans that were performed after the 30 August 2020 data cut off. [c]One patient had tumor reimaging too early for response assessment.

Data as of 30 August 2020. Pooled includes NSCLC Phase 1/1b and Phase 2 600 mg BID.

Presented at the 32nd EORTC-NCI-AACR Symposium, October 24-25, 2020

Adagrasib 600 mg BID in Patients With NSCLC: Best Tumor Change From Baseline



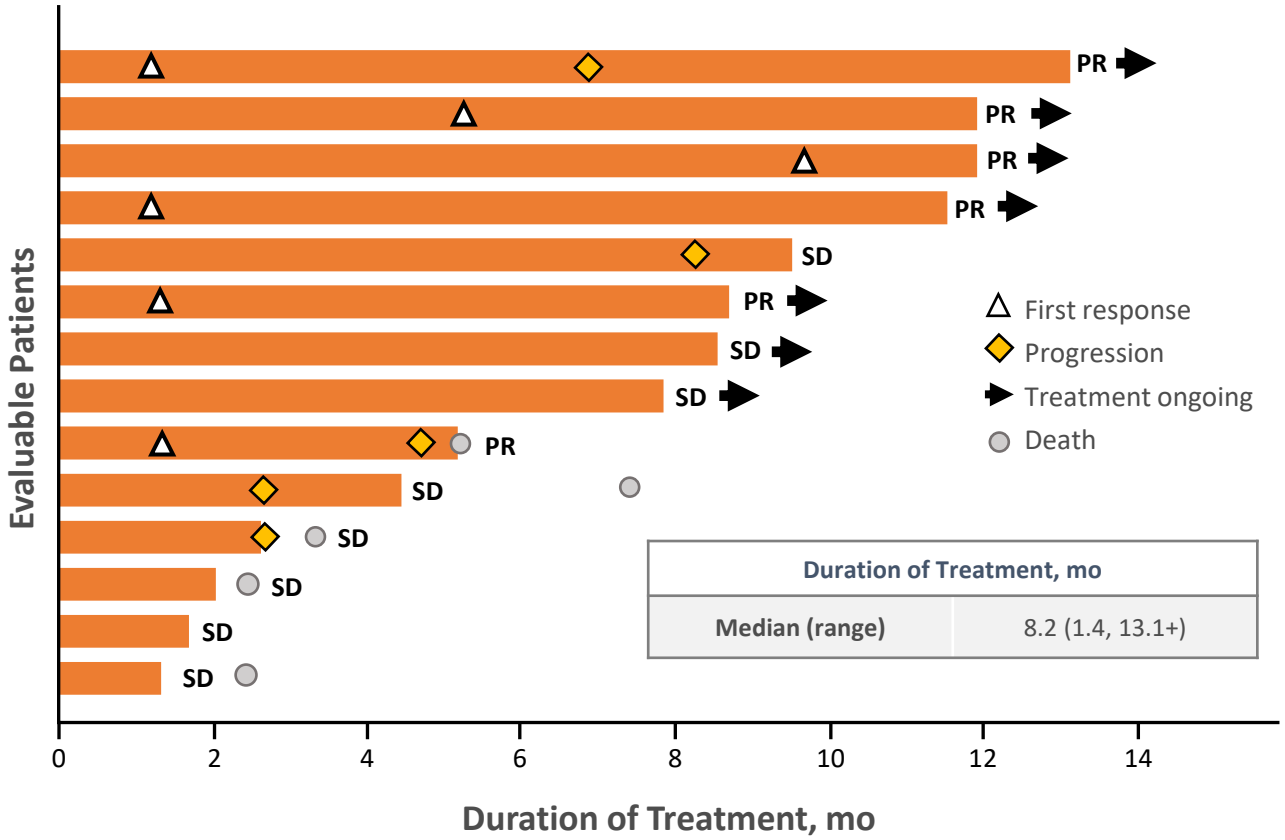
- Clinical benefit (DCR) observed in 96.1% (49/51) of patients

[a]Two timepoint assessments of CR were separated by recurrent disease associated with treatment interruption due to hypoxia; this patient remains on treatment and in two consecutive scans (1 after August 30 data cutoff) demonstrated 100% tumor regression in target and non-target lesions after resuming treatment.

Data as of 30 August 2020. Pooled includes NSCLC Phase 1/1b and Phase 2 600 mg BID.

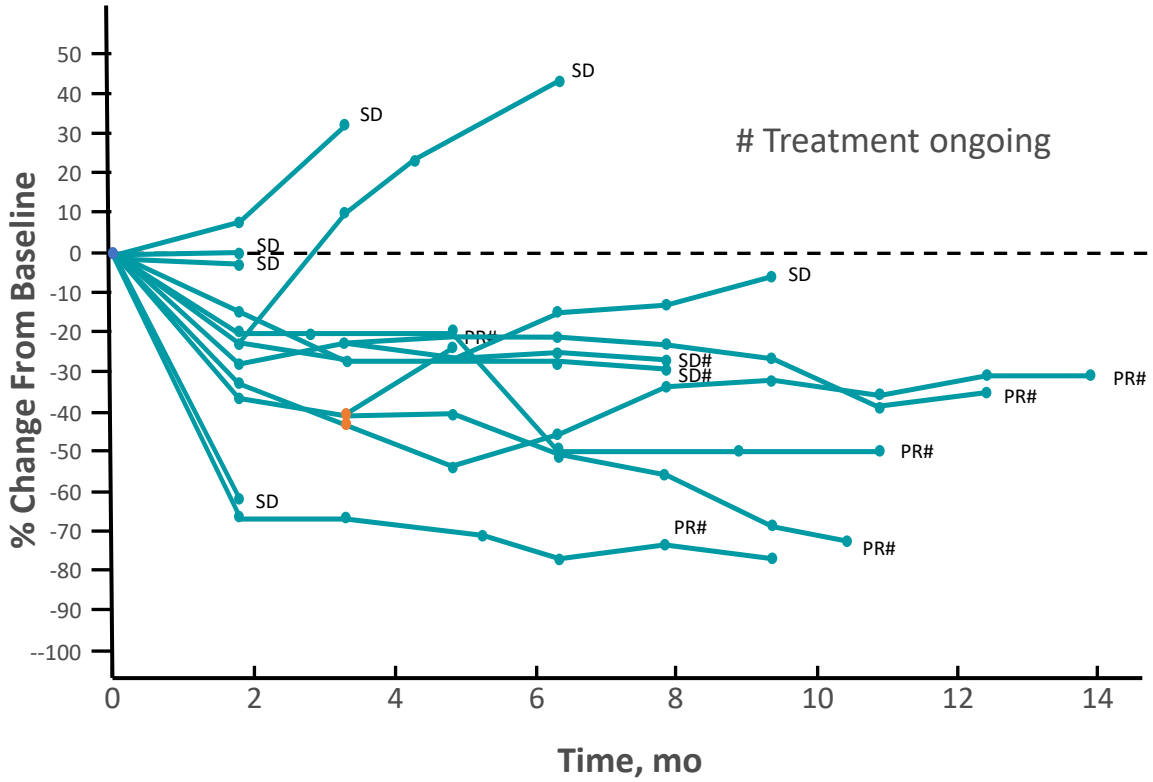
Adagrasib 600 mg BID in Patients With NSCLC: Treatment Duration and Change in Tumor Burden

Duration of Treatment, n=14



Duration of Treatment, mo	
Median (range)	8.2 (1.4, 13.1+)

Change in Tumor Burden Over Time, n=14



- Median follow-up, 9.6 mo
- 5 of the 6 responders remain on treatment; treatment ongoing >11 mo for the majority of patients with responses (4/6)
- Median time to response, 1.5 mo

Data as of 30 August 2020

Presented at the 32nd EORTC-NCI-AACR Symposium, October 24-25, 2020

The Oncologist®
Gastrointestinal Cancer

The Prognostic Impact of *KRAS* G12C Mutation in Patients with Metastatic Colorectal Cancer: A Multicenter Retrospective Observational Study

We demonstrate that, compared with non- G12C mutations, KRAS G12C mutation is significantly correlated with shorter first-line PFS and OS.

These findings indicate the relevance of a stratified treatment targeting KRAS G12C mutation in mCRC.

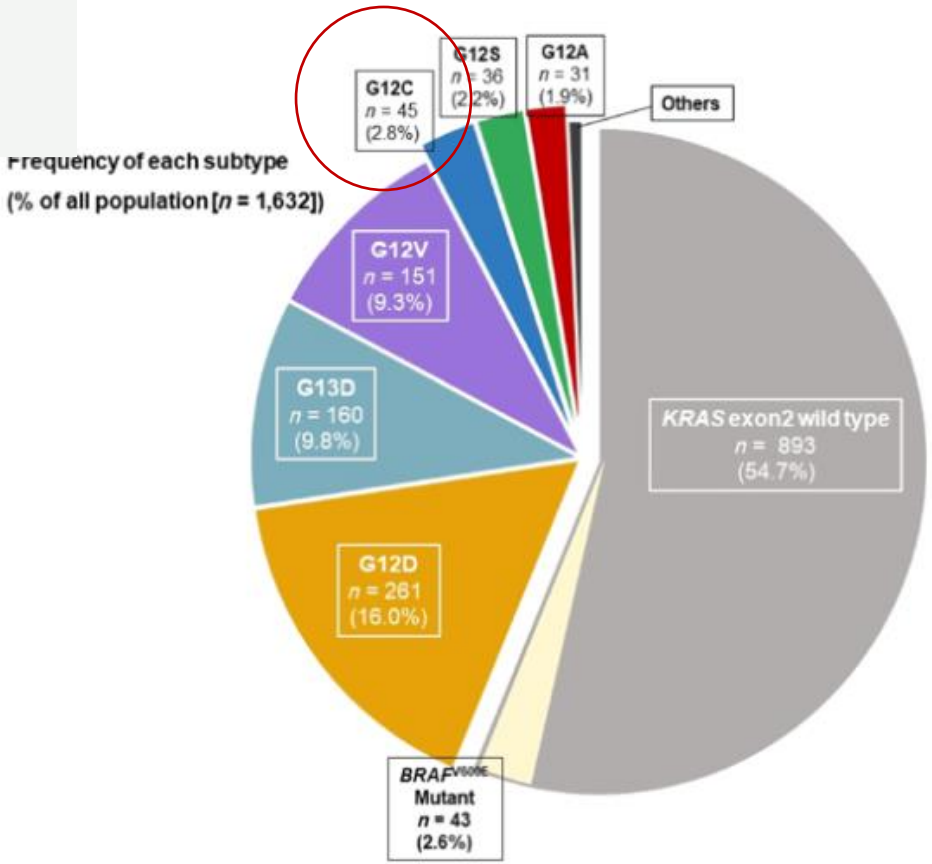


Figure 2. Frequency of each subtype (% of all population). *KRAS* exon 2 wild-type was 56.3%, and the most prevalent mutations in *KRAS* exon 2 were G12D (16.3%), followed by G13D (10.1%), G12V (9.5%), G12C (2.8%), G12S (2.3%), and G12A (1.9%).
Abbreviations: *KRAS*, Kirsten rat sarcoma.

The NEW ENGLAND JOURNAL of MEDICINE

KRAS^{G12C} Inhibition with Sotorasib in Advanced Solid Tumors

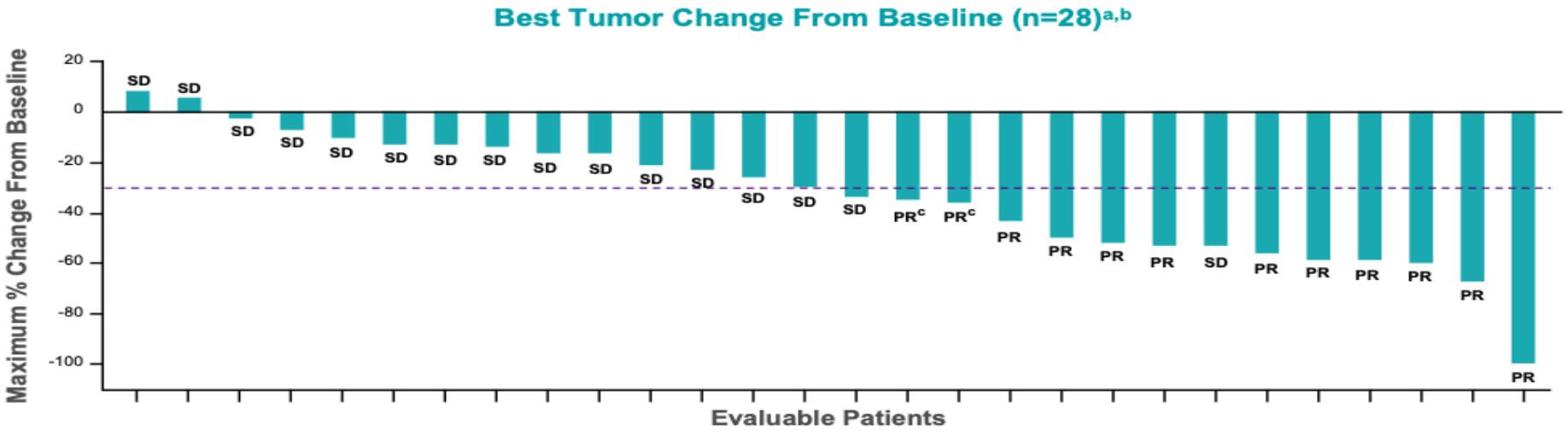
Table 3. Efficacy of Sotorasib in All Tumor Types.

	NSCLC (N=59)	Colorectal Cancer (N=42)	Other (N=28)
Best overall response — no. (%)			
Confirmed complete response	0	0	0
Confirmed partial response	19 (32.2)	3 (7.1)	4 (14.3)
Stable disease	33 (55.9)	28 (66.7)	17 (60.7)
Progressive disease	5 (8.5)	10 (23.8)	4 (14.3)
Could not be evaluated	1 (1.7)	0	1 (3.6)
No assessment*	1 (1.7)	1 (2.4)	2 (7.1)
Objective response — % (95% CI)†	32.2 (20.62–45.64)	7.1 (1.50–19.48)	14.3 (4.03–32.67)
Disease control — % (95% CI)‡	88.1 (77.07–95.09)	73.8 (57.96–86.14)	75.0 (55.13–89.31)

* One patient with NSCLC withdrew consent before tumor assessment. One patient with colorectal cancer and 2 patients with other tumor types had clinical progression.
† Objective response was defined as a complete or partial response.
‡ Disease control was defined as a complete response, a partial response, or stable disease.

ADAGRASIB COLORECTAL CANCER - ESMO 2021

LBA6 - KRYSTAL-1: Adagrasib (MRTX849) as Monotherapy or in Combination With Cetuximab in Patients (Pts) With Colorectal Cancer (CRC) Harboring a KRASG12C Mutation



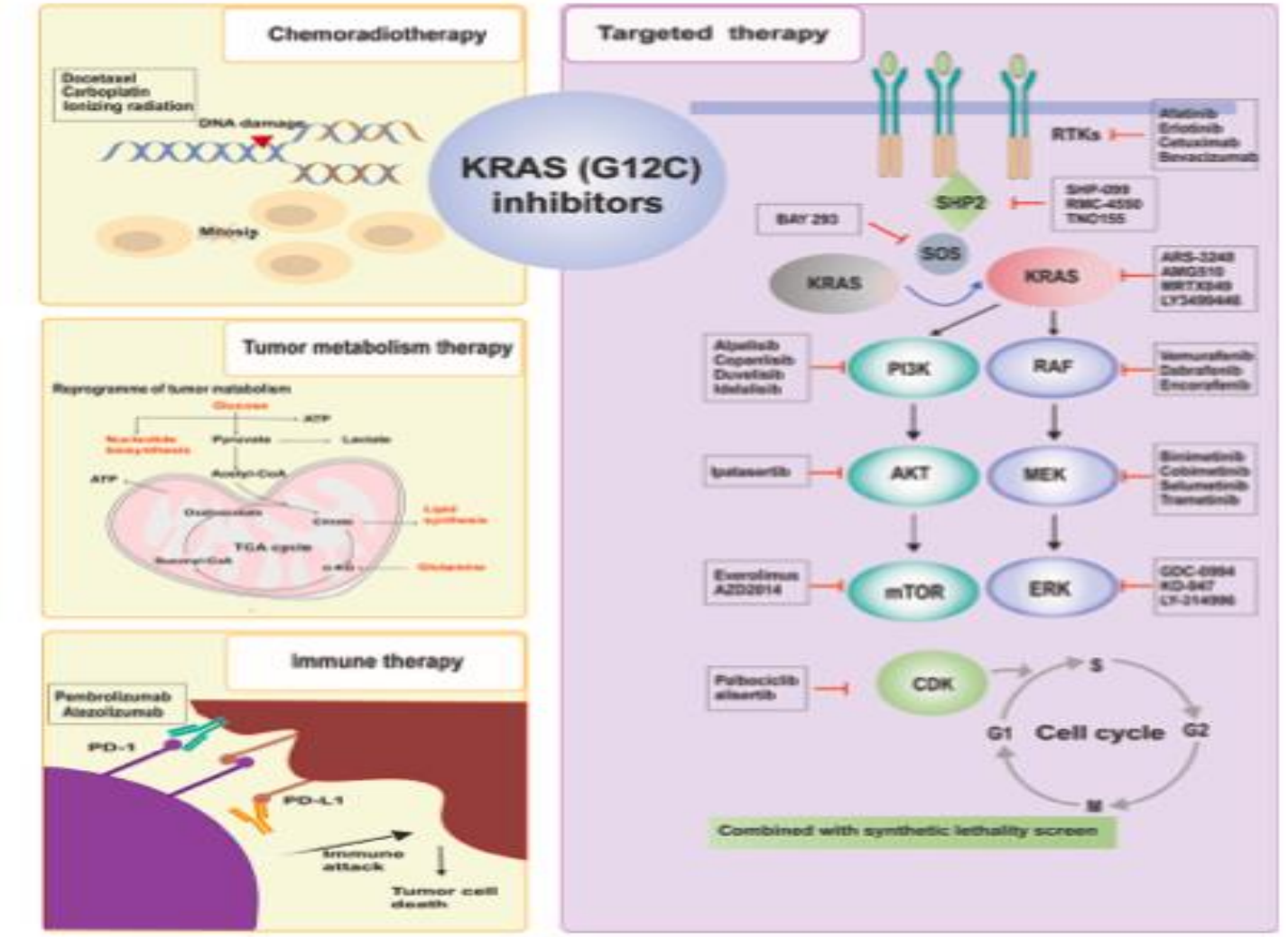
- Response rate was 43% (12/28), including 2 unconfirmed PRs
- SD was observed in 57% (16/28) of patients
- Clinical benefit (DCR) was observed in 100% (28/28) of patients
- No apparent association between response rate and molecular status was shown in an exploratory analysis[e]

REVIEW ARTICLE OPEN

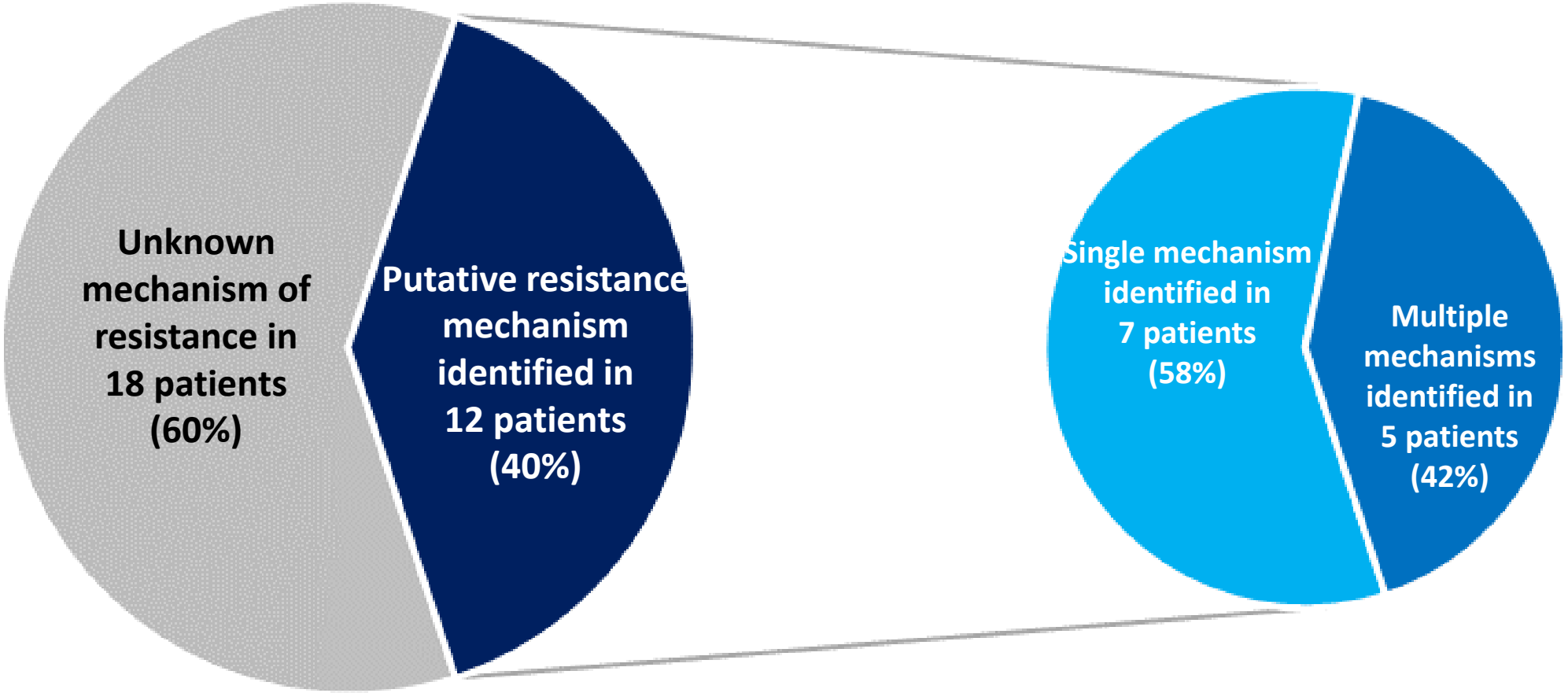
KRAS mutation: from undruggable to druggable in cancer

Lamei Huang[1], Zhixing Guo[1], Fang Wang[1] and Liwu Fu[1]✉

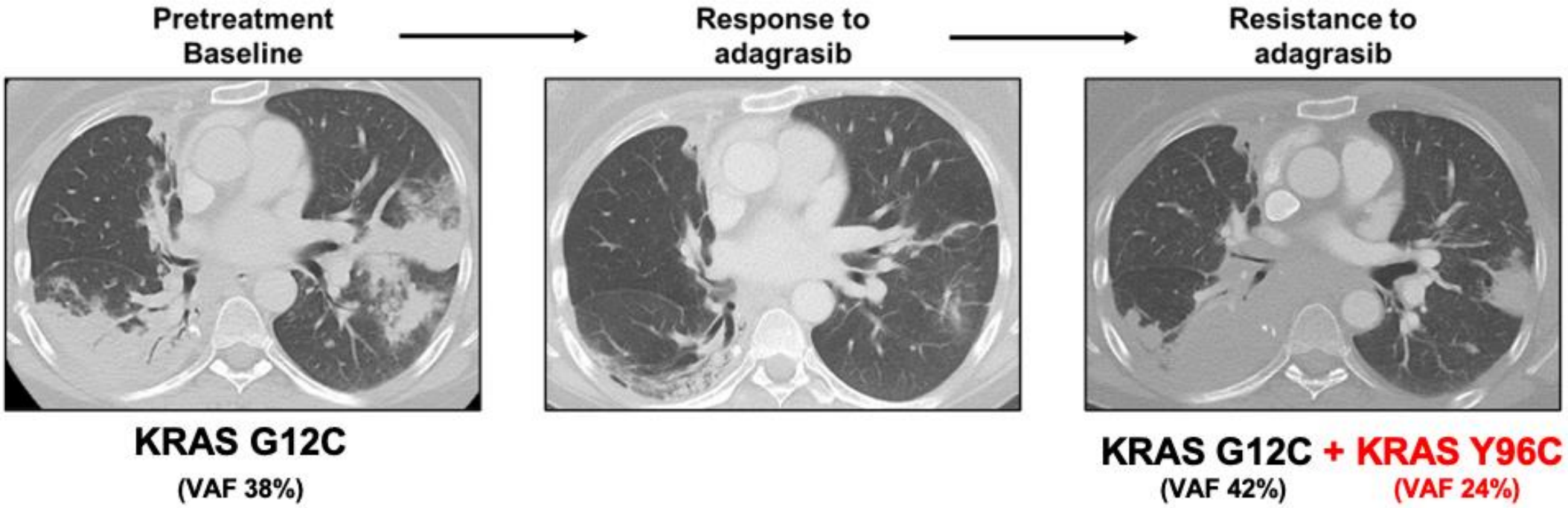
Ongoing



RESISTANCE MECHANISMS



AACR ANNUAL MEETING 2021: APRIL 10-15, 2021 AND MAY 17-21, 2021


Pretreatment
Baseline
Response to
adagrasib
Resistance to
adagrasib
KRAS G12C
(VAF 38%)
KRAS G12C + KRAS Y96C
(VAF 42%)
(VAF 24%)

Sesión 4: Vías de desarrollo de la oncología transversal (II)

Novel *KRAS* R68S, H95R/Q/D mutations with multiple concurrent alterations

Additional acquired fusions and MAPK pathway alterations

Secondary *KRAS* mutations in cis/trans

Acquired amplifications in *KRAS* (G12C allele) and *MET*

Histologic transformation

TAKE-HOME MESSAGES

More knowledge, more options.
What RAS mutation, now is a crucial issue in cancer
KRAS G12C: Agnostic molecular alteration
At least two drugs in motion: SOTORASIB and ADAGRASIB
Next year, a major milestone

GETTHI

Grupo Español de Oncología Transversal y Tumores Huérfanos e Infrecuentes

VII SIMPOSIO GETTHI

Sesión 4: Vías de desarrollo de la oncología transversal (II)

16 de diciembre de 2021

ALTERACIONES EN KRAS. IMPLICACIONES CLÍNICAS Y NUEVAS ALTERNATIVAS TERAPÉUTICAS

Elena María Brozos Vázquez

Servicio de Oncología Médica - EOXI Santiago de Compostela e Barbanza

• VII SIMPOSIO GETTHI

Sesión 4: Vías de desarrollo de la oncología transversal (II)

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