

# NSCLCs with *KRAS* mutations

**William N. William Jr., MD**

Líder de Oncologia Torácica e Co-Líder de Oncologia de Cabeça e Pescoço do Grupo Oncoclínicas  
Adjunct Associate Professor, The University of Texas MD Anderson Cancer Center  
Coordenador do Comitê de Tumores Torácicos da SBOC  
Chair, LACOG Head and Neck.

# Declaração de Conflitos de Interesse

## Dr. William Nassib William Junior CRM SP 104.421

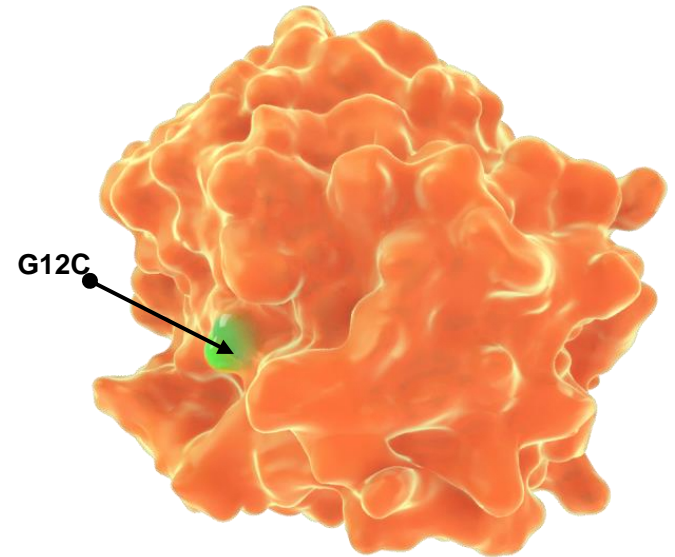
De acordo com a Norma 1595/2000 do Conselho Federal de Medicina e com a RDC 96/2008 da ANVISA, declaro que recebi compensação / financiamento como palestrante / consultor e/ou investigador das seguintes entidades:

- Amgen
- Astra Zeneca
- Genentech / Roche
- Astellas
- Boehringer Ingelheim
- Merck
- Eli Lilly
- BMS
- MSD
- Bayer
- Pfizer
- Janssen
- Sanofi-Aventis
- Takeda
- Novartis
- Ipsen
- United Medical

# Introduction

## ***KRAS* is an Oncogene in Human Cancers<sup>1</sup>**

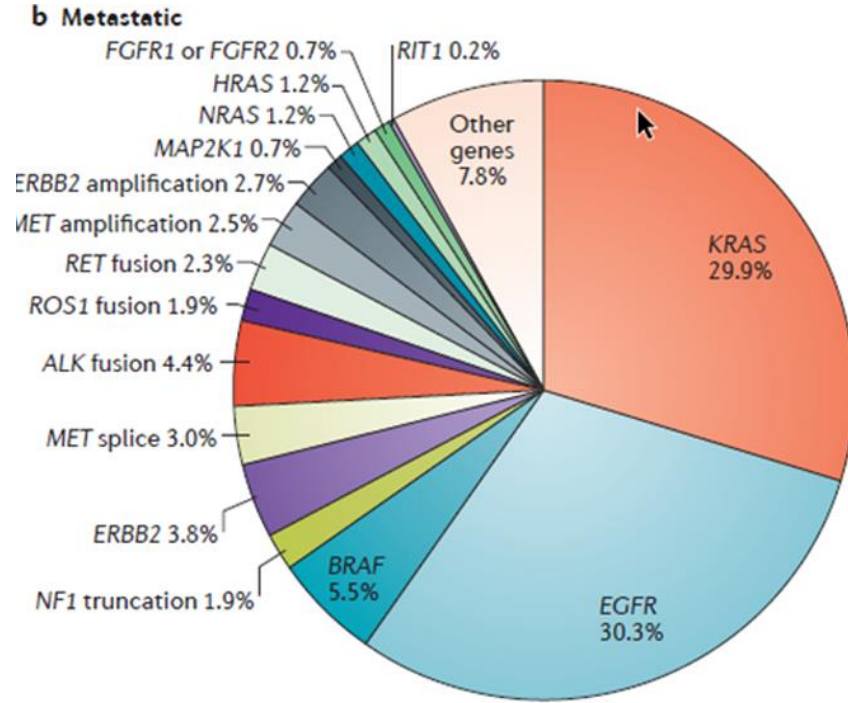
- Kirsten rat sarcoma viral oncogene homolog (*KRAS*) is one the most frequently mutated oncogenes in human cancers<sup>1</sup>
- *KRAS* G12C mutation (glycine to cysteine substitution at position 12) promotes tumorigenesis and is found in approximately 13% of patients with non-squamous non-small cell lung cancer (NSCLC) in Western countries and in approximately 5% of patients in Asian countries<sup>1-4</sup>
- *KRAS* G12C mutation also occurs in approximately 3% of colorectal cancer, and 1%–3% of other solid tumors<sup>5-9</sup>



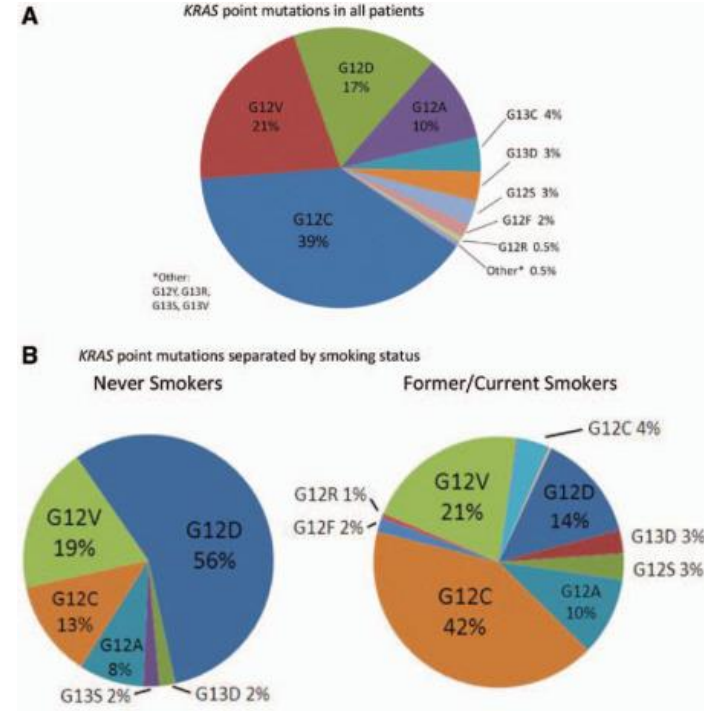
**KRAS<sup>G12C</sup>**

# Introduction

## KRAS in NSCLCs



Data from MSK-IMPACT (Jordan et al.<sup>59</sup>) and FoundationOne (Frampton et al.<sup>15</sup>) panels (n = 5262)

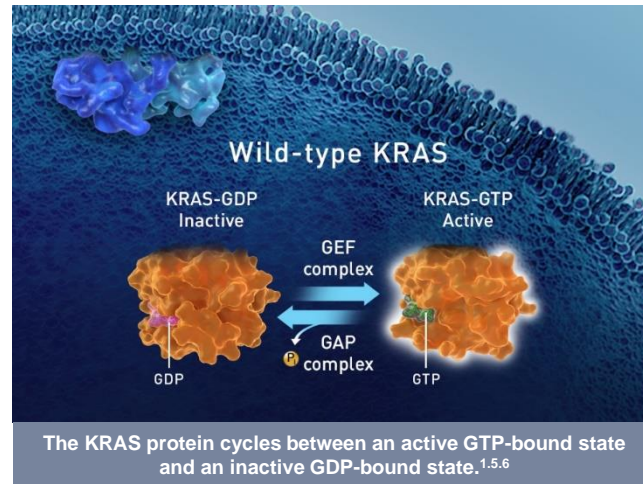


1. Skoulidis et al., *Nat Rev Cancer* 2020

2. Yu H, et al. *J Thorac Oncol.* 2015

# Introduction

## KRAS is a Regulator of Cellular Proliferation, Differentiation, and Survival<sup>1-6</sup>



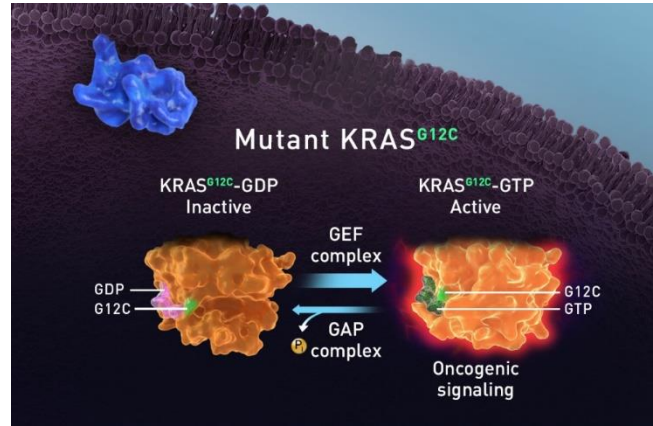
- KRAS serves as an on/off molecular switch to regulate downstream signaling<sup>1-3,6</sup>
- The KRAS protein is a GTPase<sup>7</sup>

**AKT**, protein kinase B; **EGFR**, epidermal growth factor receptor; **ERK**, extracellular signal-regulated kinase; **GAP**, GTPase-activating protein; **GDP**, guanosine diphosphate; **GEF**, guanine nucleotide exchange factor; **GTP**, guanosine triphosphate; **GTPase**, guanosine triphosphatase; **KRAS**, Kirsten rat sarcoma; **MEK**, mitogen-activated protein kinase; **mTOR**, mammalian target of rapamycin; **NF- $\kappa$ B**, nuclear factor kappa-light-chain-enhancer of activated B cells; **P<sub>i</sub>**, inorganic phosphate; **PI3K**, phosphoinositide 3-kinase; **RAF**, rapidly accelerated fibrosarcoma; **RAL**, Ras-like; **RTK**, receptor tyrosine kinase.

1. Barbacid M. *Annu Rev Biochem.* 1987;56:779-827. 2. Simanshu DK, et al. *Cell.* 2017;170:17-33. 3. Ryan MB, et al. *Nat Rev Clin Oncol.* 2018;15:709-720. 4. Neel NF, et al. *Genes Cancer.* 2011;2:275-287. 5. Ahmadzada T, et al. *J Clin Med.* 2018;7:153. 6. Ferrer I, et al. *Lung Cancer.* 2018;124:53-64. 7. Blair HA. *Drugs.* 2021. doi: 10.1007/s40265-021-01574-2.

# Introduction

## The KRAS<sup>G12C</sup> Mutation Favors the Active State, Promoting Cancer Growth and Survival<sup>1-4</sup>



The KRAS G12C mutation favors the active form of the KRAS-mutant protein, supporting tumorigenesis.<sup>1,5,6</sup>

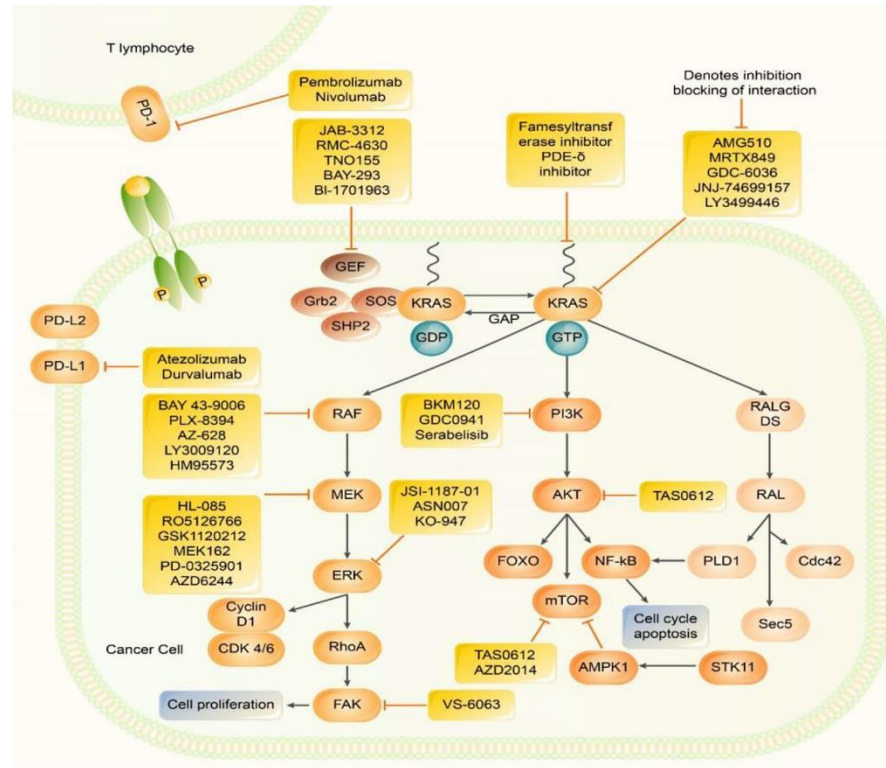
- **KRAS G12C is a single point mutation at codon 12 where a glycine is substituted with a cysteine<sup>1,2,5,7</sup>**

AKT, protein kinase B; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GAP, GTPase-activating protein; GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; Pi, inorganic phosphate; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAL, Ras-like; RTK, receptor tyrosine kinase.

1. Ryan MB, et al. *Nat Rev Clin Oncol*. 2018;15:709-720. 2. Simanshu DK, et al. *Cell*. 2017;170:17-33. 3. Ahmadzada T, et al. *J Clin Med*. 2018;7:153. 4. Ferrer I, et al. *Lung Cancer*. 2018;124:53-64. 5. Cox AD, et al. *Nat Rev Drug Discov*. 2014;13:828-851. 6. Neel NF, et al. *Genes Cancer*. 2011;2:275-287. 7. Ihle NT, et al. *J Natl Cancer Inst*. 2012;104:228-239.

# Introduction

**KRAS is associated with a complex intracellular signaling pathway**



# Introduction

## Characteristics of Patients with *KRAS* G12C-Mutated NSCLC<sup>1-3</sup>

	<i>KRAS</i> G12C mutant NSCLC			All NSCLC
	Flatiron <sup>a</sup> (n = 743)	AACR Genie <sup>b</sup> (n = 416)	CRISP <sup>c</sup> (n = 160)	Flatiron* (N = 7,069)
Median age at diagnosis, years	68	68 <sup>d</sup>	66	68
Female gender, %	61%	64%	44%	50%
Current/former smoker, %	97%	97%	93%	82%
Non-squamous NSCLC, %	91%	88%	99%	76%
Distant metastases at diagnosis, %	86%	NR	94%	84%
<i>STK11</i> Co-mutation, %	22%	24%	NR	12%
<i>KEAP1</i> Co-mutation, %	7%	10%	NR	6%

**Patients with advanced *KRAS* G12C-mutated NSCLC tend to be a current or former smoker with non-squamous histology; *STK11* co-mutation occurs in almost one-quarter of cases**

**AACR**, American Association for Cancer Research; **CRISP**, Clinical Research platform Into molecular testing, treatment and outcome of non-Small cell lung carcinoma Patients; **ECH**, erythroid cell-derived protein with cap and collar homology; **GENIE**, Genomics Evidence Neoplasia Information Exchange; **KEAP1**, Kelch-like ECH associated protein 1; **KRAS**, Kirsten rat sarcoma; **NR**, not reported; **NSCLC**, non-small cell lung cancer; **STK11**, serine/threonine kinase 11.

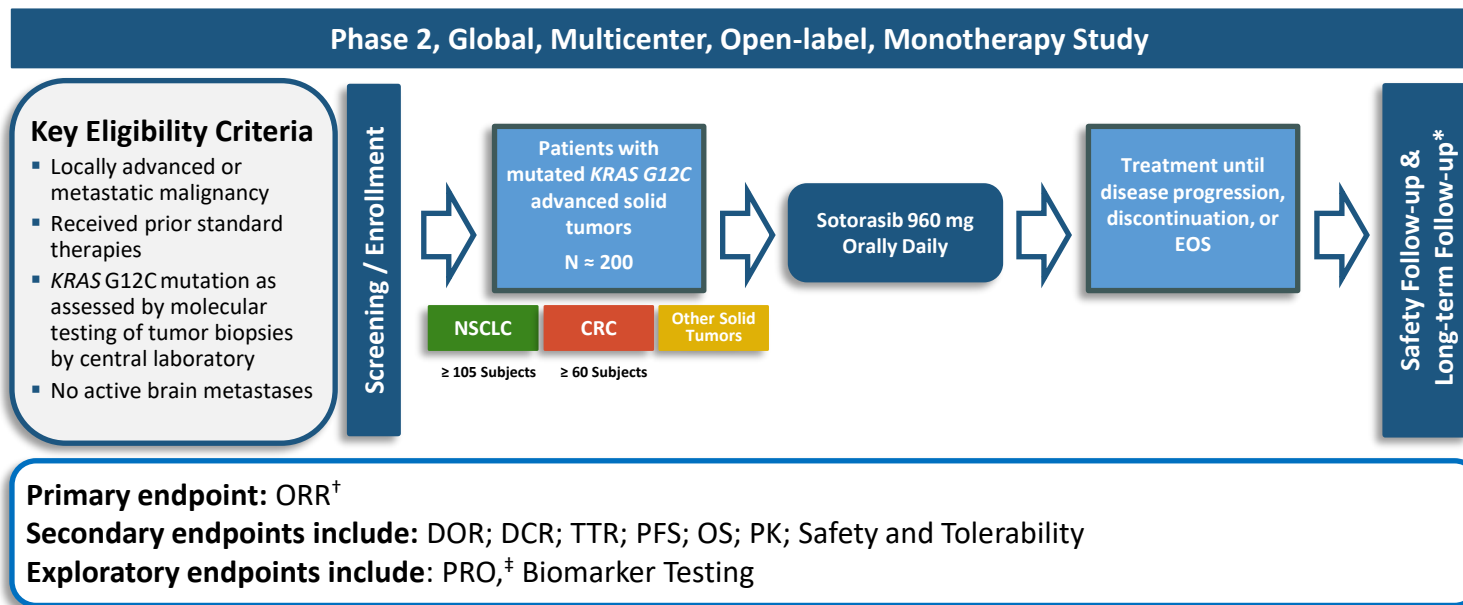
<sup>a</sup>Data from an analysis of the Flatiron Health-Foundation Medicine Clinic-Genomic Database among patients (N = 7,069) diagnosed with NSCLC between January 1, 2011, and March 31, 2019, with ≥ 6 months of follow-up, of whom 743 had the *KRAS* G12C mutation. <sup>b</sup>Data from an analysis of the AACR Project GENIE Database that included 416 patients with the *KRAS* G12C mutated NSCLC, of which 270 (65%) were diagnosed in 2015 or later. <sup>c</sup>Data from an analysis of the German prospective, observational, nationwide CRISP Registry among patients (N = 4,032) with advanced NSCLC between December 2015 and June 2019. <sup>d</sup>Median age at advanced diagnosis.

1. Spira AI, et al. *Lung Cancer*. 2021;159:1-9. 2. Ricciuti B, et al. Oral presentation at the AACR Annual Meeting 2021. Virtual Meeting April 10-15, 2021. Abstract #102. 3. Sebastian M, et al. *Lung Cancer*. 2021;154:51-61.



# CodeBreak 100

## Phase 2 Study Schema



\*30 (+7) days after end of treatment for safety follow-up; every 12 weeks for 3 years for long-term follow-up of OS.

<sup>†</sup>per RECIST 1.1; confirmatory assessment 4 weeks after first detection of response.

<sup>‡</sup>on disease-related symptoms and HRQOL.

**CRC**, colorectal cancer; **DCR**, disease control rate; **DOR**, duration of response; **EOS**, end of study; **HRQOL**, health-related quality of life;

**KRAS**, Kirsten rat sarcoma viral oncogene homolog; **NSCLC**, non-small cell lung cancer; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival;

**PK**, pharmacokinetic; **PRO**, patient-reported outcome; **RECIST**, response evaluation criteria in solid tumors; **TTR**, time to response.

Hong DS, et al. *N Engl J Med.* 2020;383:1207-1217. Supplementary material: Protocol.

# CodeBreak 100

## Tumor Response with Sotorasib: Patients With NSCLC

Response assessed by central review	Sotorasib 960 mg, N = 124*
<b>Confirmed objective response rate – % (95% CI)</b>	<b>37.1 (28.6, 46.2)</b>
<b>Best overall response – n (%)</b>	
Complete response	4 (3.2)
Partial response	42 (33.9)
Stable disease	54 (43.5)
Progressive disease	20 (16.1)
Not evaluable	2 (1.6)
Missing scan	2 (1.6)
<b>Disease control rate – % (95% CI)</b>	<b>80.6 (72.6, 87.2)</b>
<b>Kaplan-Meier estimate of response -- % (95% CI)</b>	
At 3 months	<b>90.5 (76.7 – 96.3)</b>
At 6 months	<b>70.8 (54.3 – 82.2)</b>
At 9 months	<b>57.3 (40.4 – 71.0)</b>

**Over 80% of patients achieved disease control, including 4 CRs and 42 PRs**

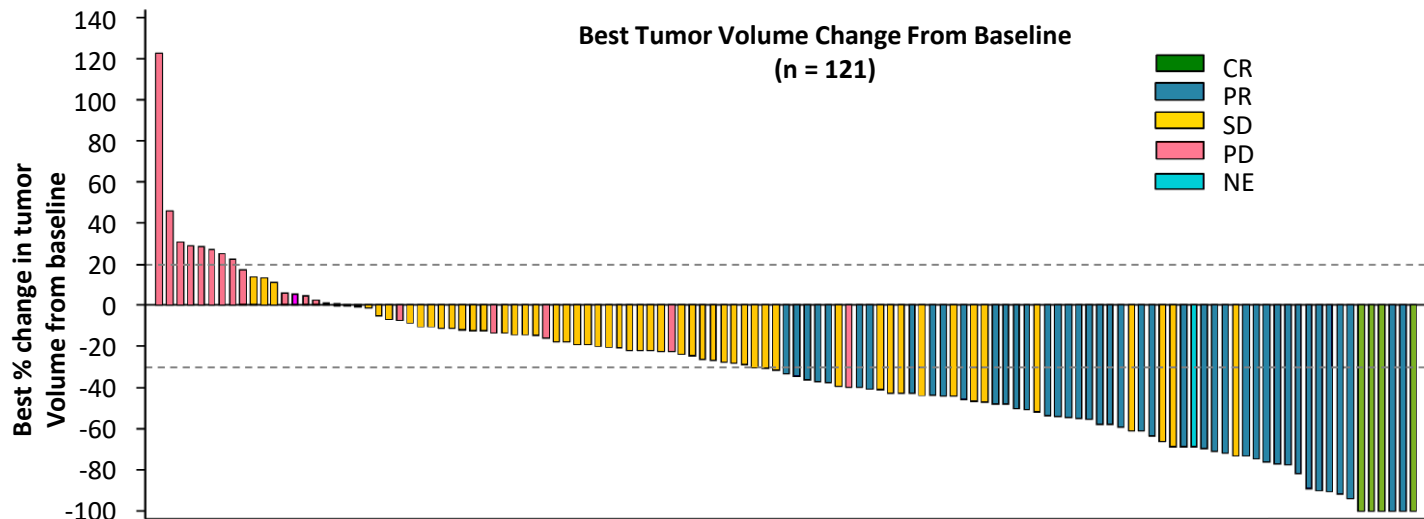
\*2 patients did not have measurable lesions at baseline and were ineligible for response assessment;

CI, confidence interval; CR, complete response; NSCLC, non-small cell lung cancer; PR, partial response.

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

# CodeBreak 100

## Depth of Tumor Response: Patients With NSCLC



**Tumor shrinkage of any magnitude was observed in 82% of patients (102/124)**  
**Median percentage of best tumor shrinkage among all responders was 60%**

Graph excluded 3 patients: 2 who had missing scans and 1 who had no measurement in target lesions.

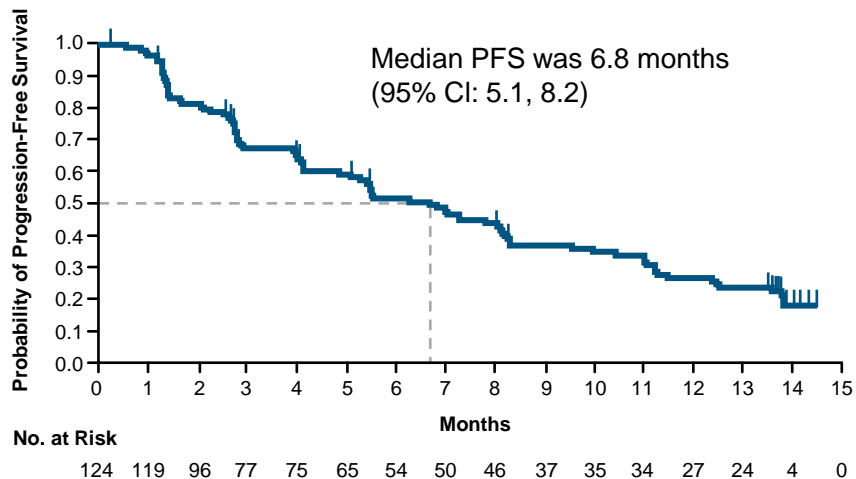
CR, complete response; NE, not evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

Adapted from: Skoulidis F, et al. *N Engl J Med.* 2021;384:2371-2381.

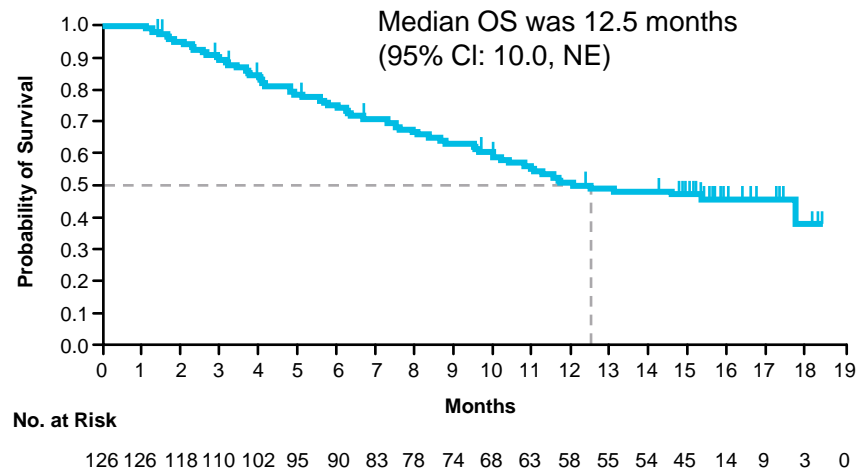
# CodeBreak 100

## Survival Outcomes with Sotorasib in Patients With Previously Treated Advanced or Metastatic NSCLC

### Progression-Free Survival



### Overall Survival



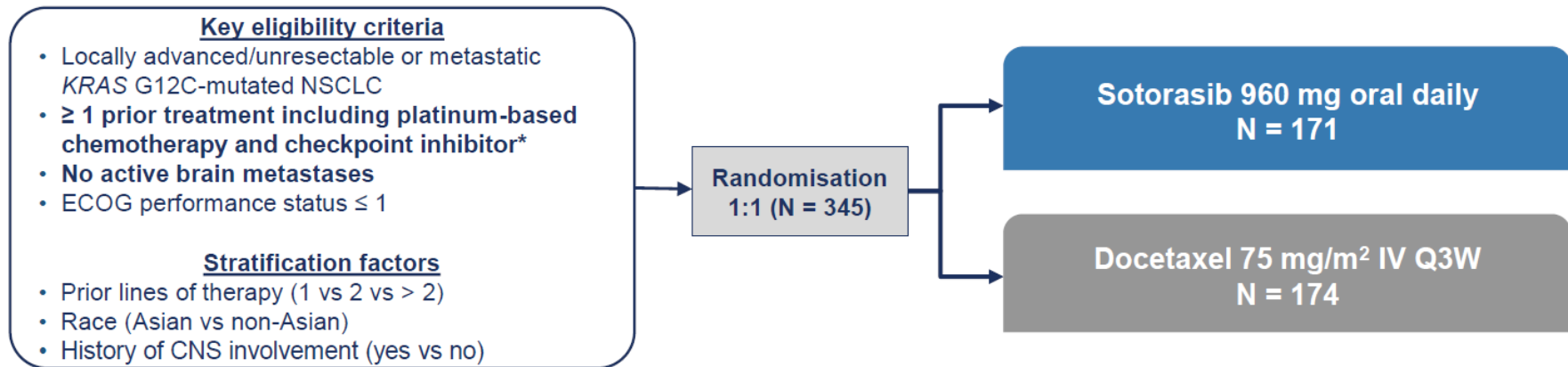
**Median PFS was 6.8 months (95% CI: 5.1, 8.2) and median OS was 12.5 months (95% CI: 10.0, NE)**

Censored data indicated by vertical bar. Data cutoff was March 15, 2021; median follow-up time was 15.3 months (range 1.1 to 18.4+ months); + indicates that the value includes data that were censored at data cutoff.

CI, confidence interval; NE, not evaluable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

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

# CodeBreak 200



## Primary Endpoint: PFS by BICR

**Secondary Endpoints: Efficacy (OS<sup>†</sup>, ORR, DOR, TTR, DCR), safety/tolerability, PRO**

ITT population analysis included all randomised patients

Per regulatory guidance, protocol was amended to reduce planned enrolment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted.

**Enrollment period: June 4, 2020 to April 26, 2021; protocol amendment: February 15, 2021; data cutoff: August 2, 2022.**

NCT04303780; EudraCT: 2019-003582-18.

\*Treatment with chemotherapy and checkpoint inhibitor could be concurrent or sequential; patients with medical contraindication to these therapies could be included with approval.

†Analysis of OS planned if PFS was found to be statistically significant and when at least 198 OS events have been reached.

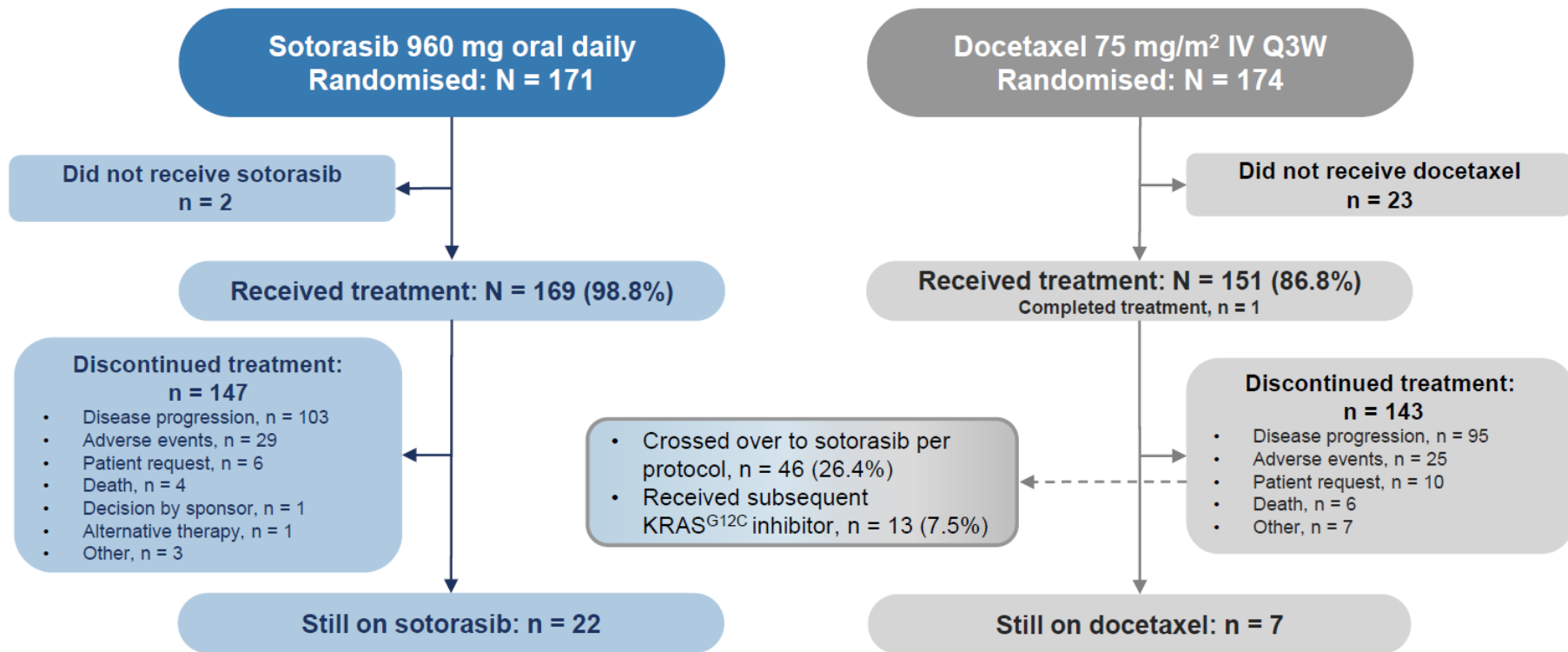
# CodeBreak 200

## Baseline Characteristics

	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m <sup>2</sup> IV Q3W (N = 174)
Age, median (range), years	64.0 (32, 88)	64.0 (35, 87)
Female, n (%)	62 (36.3)	79 (45.4)
North America/Europe/Other*, %	11.7 / 73.7 / 14.6	12.6 / 72.4 / 14.9
Race, Asian, n (%)	21 (12.3)	22 (12.6)
Smoking history (current or former), n (%)	166 (97.1)	166 (95.4)
ECOG performance status 1, n (%)	112 (65.5)	115 (66.1)
History of CNS involvement, n (%)	58 (33.9)	60 (34.5)
Liver metastasis, n (%)	30 (17.5)	35 (20.1)
Prior lines of therapy <sup>†</sup> , n (%)		
1	77 (45.0)	78 (44.8)
2	65 (38.0)	69 (39.7)
>2	29 (17.0)	27 (15.5)
PD-L1 expression, n (%)		
<1%	57 (33.3)	55 (31.6)
≥1–<50%	46 (26.9)	70 (40.2)
≥50%	60 (35.1)	40 (23.0)

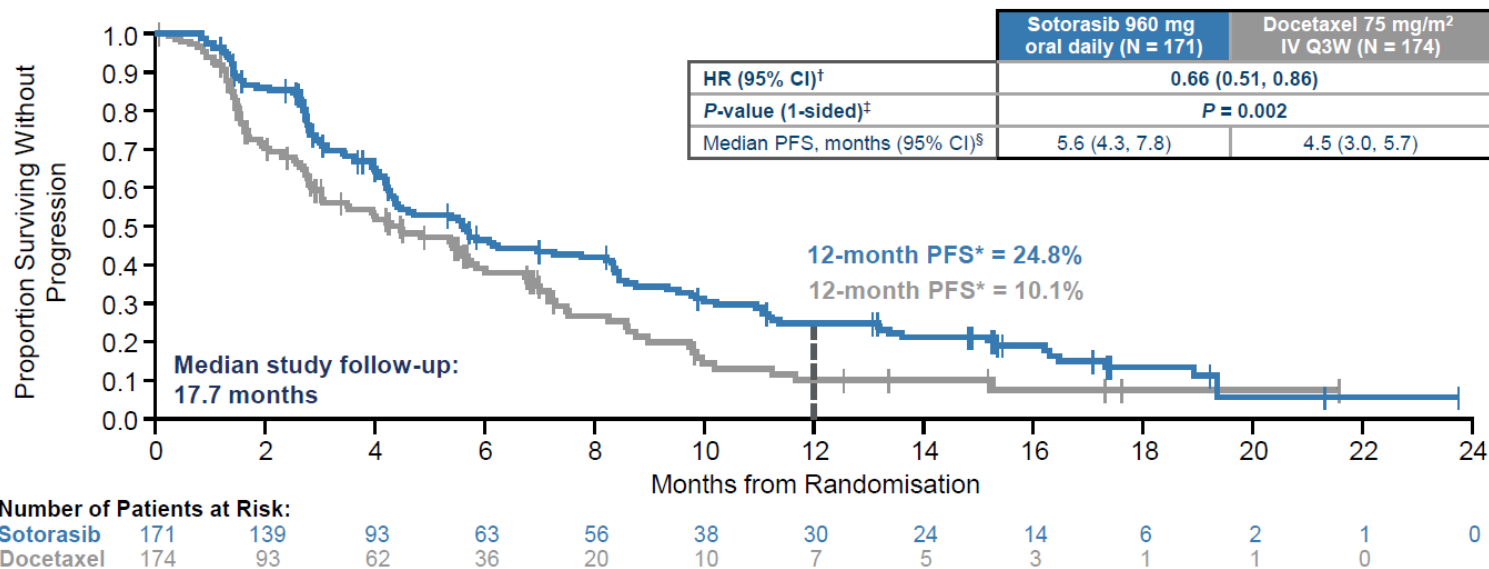
\*Other includes South America, Asia, and Australia. †Prior lines of therapy for advanced disease.

# CodeBreak 200



# CodeBreak 200

## Primary Endpoint: PFS by BICR



**CodeBreak 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, P = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel**

\*PFS rates estimated using Kaplan-Meier method; ITT population.

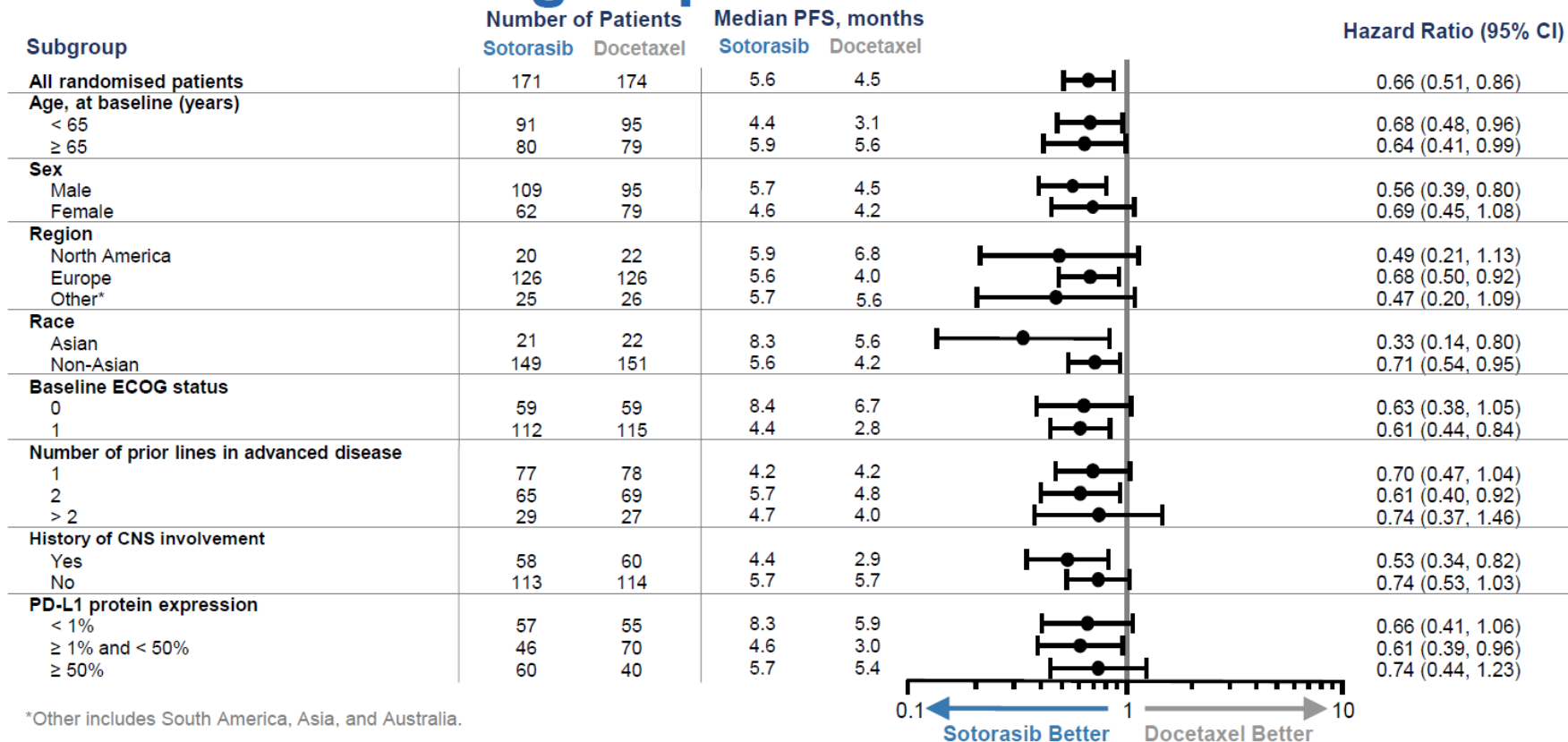
<sup>†</sup>HR and 95% CIs estimated using a stratified Cox proportional hazards model.

<sup>‡</sup>P-value calculated using a stratified log-rank test.

<sup>§</sup>Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

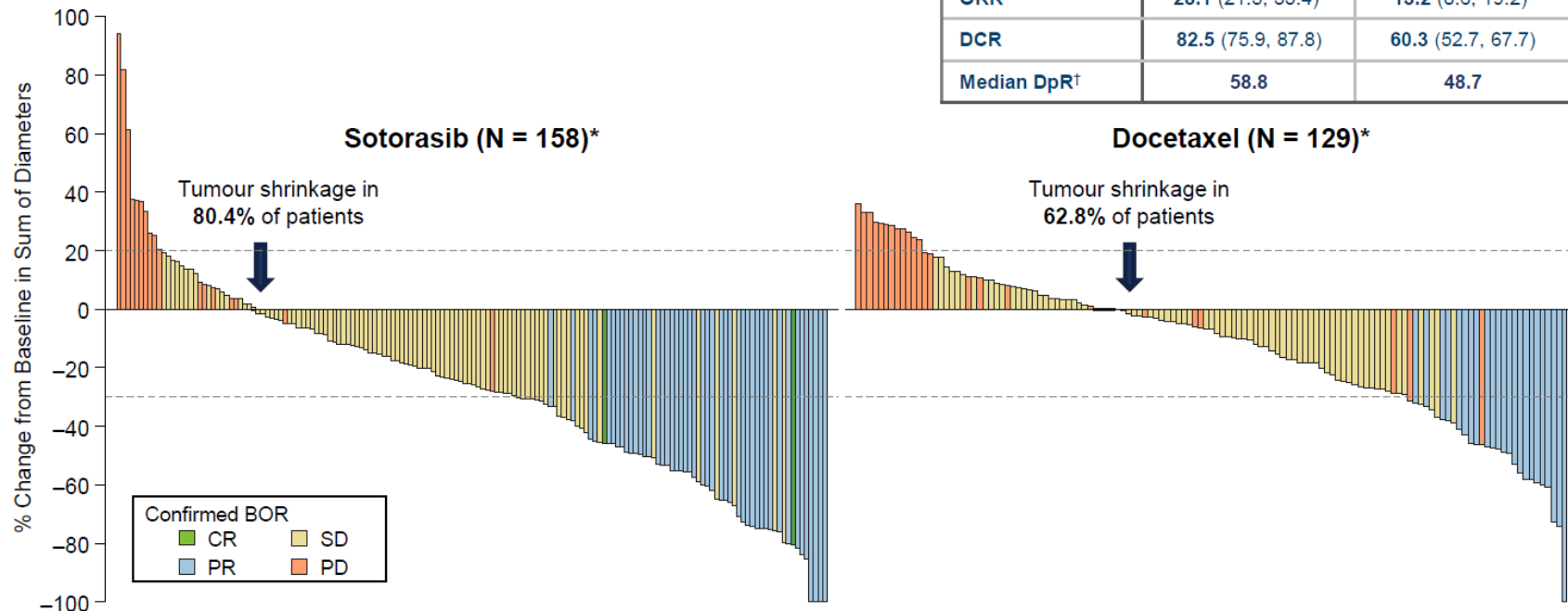


## PFS Across Subgroups



\*Other includes South America, Asia, and Australia.

# Tumour Response by BICR

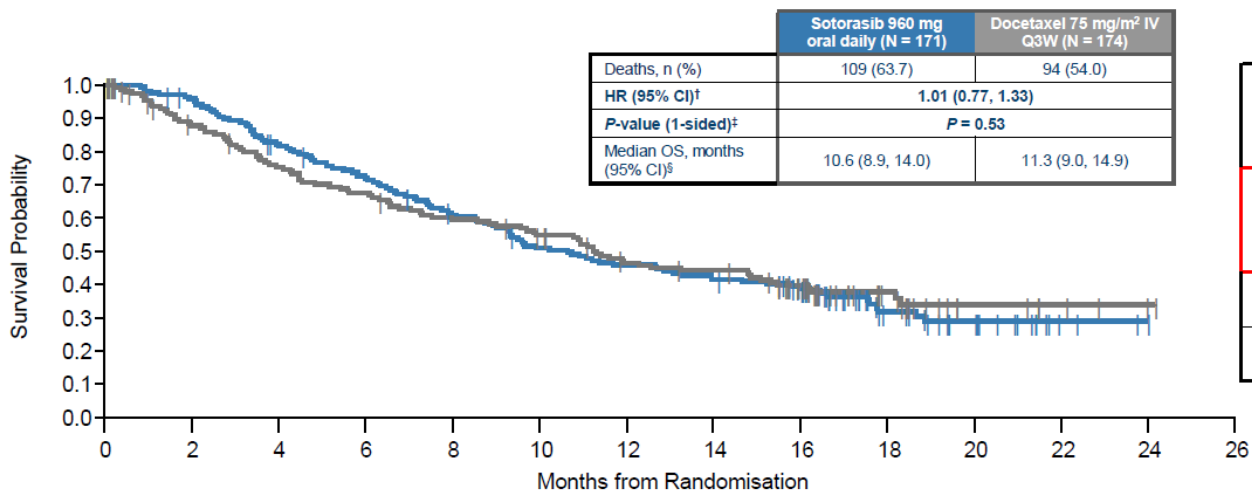


% (95% CI)	Sotorasib	Docetaxel
ORR	28.1 (21.5, 35.4)	13.2 (8.6, 19.2)
DCR	82.5 (75.9, 87.8)	60.3 (52.7, 67.7)
Median DpR <sup>†</sup>	58.8	48.7

Response rate was significantly higher with sotorasib versus docetaxel ( $P < 0.001$ )

# CodeBreak 200

## OS: Sotorasib vs Docetaxel\*



	Sotorasib	Docetaxel
Any subsequent treatment, including crossover**	36%	42%
Subsequent KRAS <sup>G12C</sup> inhibitor, including crossover	4%	34%
Subsequent chemo	21%	12%
Subsequent IO	9%	6%

### Number of Patients at Risk:

	171	162	137	119	98	81	73	66	56	25	15	3	0	
Sotorasib	171	162	137	119	98	81	73	66	56	25	15	3	0	
Docetaxel	174	135	115	103	90	81	65	61	44	20	7	4	1	0

\*OS rates estimated using Kaplan-Meier method; ITT population.

<sup>†</sup>HR and 95% CIs estimated using a stratified Cox proportional hazards model

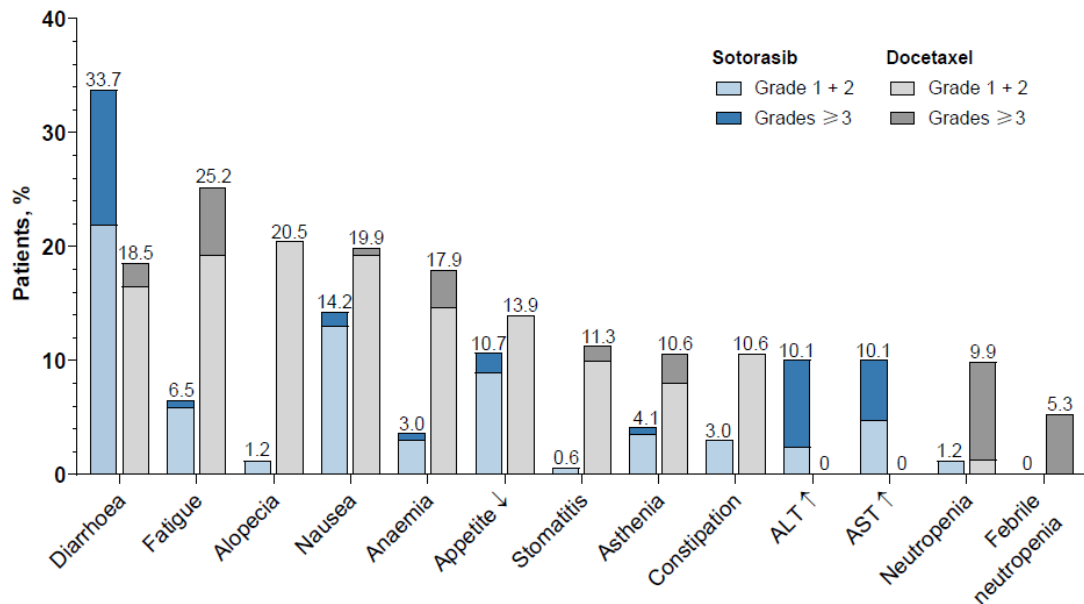
<sup>‡</sup>P-value calculated using a stratified log-rank test.

<sup>§</sup>Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

\*\*Patients (16.4% in sotorasib arm, 5.2% in docetaxel arm) were treated beyond progression

# CodeBreak 200

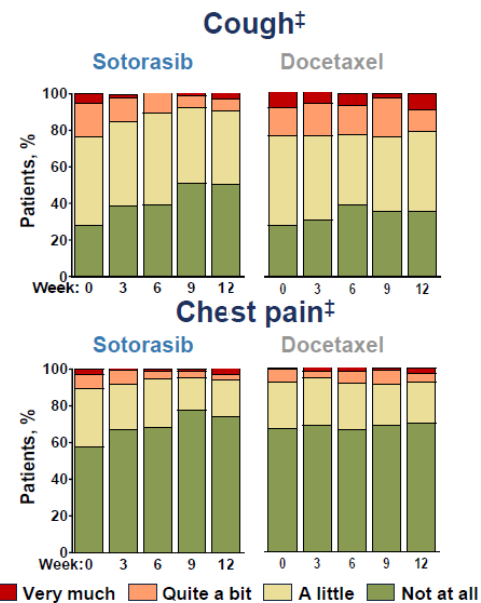
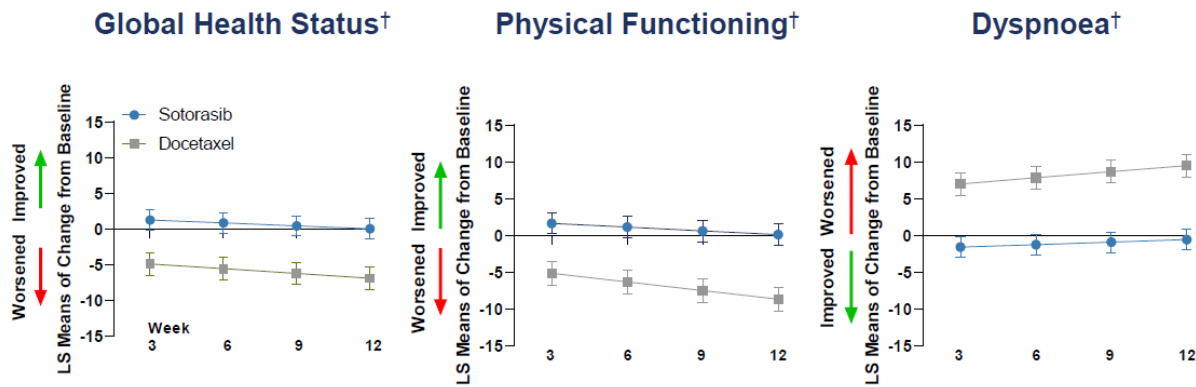
## Most Common TRAEs Any Grade TRAEs ( $\geq 10\%$ ) or Grade $\geq 3$ ( $\geq 5\%$ )



Most common Grade 3+ TRAEs with sotorasib were diarrhoea and elevated liver enzymes, and with docetaxel were neutropenia, fatigue, and febrile neutropenia

\*Highest-level TRAE per preferred term reported

## Patient-Reported Outcomes: Change from Baseline to Week 12\*



**Change over time in global health status, physical functioning, and dyspnoea favoured sotorasib  
Cough and chest pain did not show significant differences in symptom improvement**

\*Change from baseline to Week 12 was pre-specified as key secondary endpoint, time to deterioration as secondary endpoint. MMRM analysis for global health status, physical functioning (both from EORTC QLQ-C30) and dyspnea (composite score); GEE for cough and chest pain from EORTC QLQ-LC13 on an ordinal scale.

<sup>†</sup>Significant difference favouring sotorasib at each time point,  $P < 0.001$

<sup>‡</sup>Patient-reported response to questions: "During the past week, how much did you cough?" and "During the past week, have you had pain in the chest?"

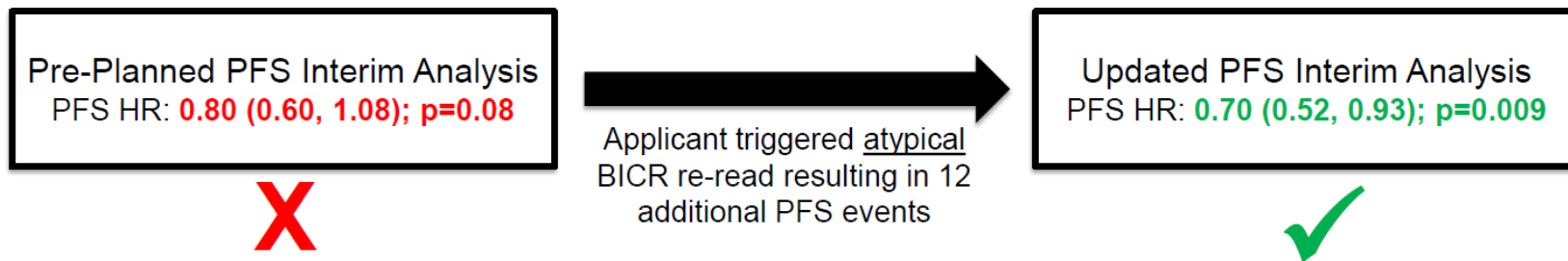
# Multiple Signals of Potential Systemic Bias and Study Conduct Issues



- Applicant triggered radiologic re-reads changing PFS interim results (based on 12 additional PFS events)
- Asymmetric dropout leading to potential loss of randomization
- Investigator imaging assessments favoring sotorasib arm

**Can we reliably interpret the primary endpoint,  
PFS per BICR, in CodeBreak 200?**

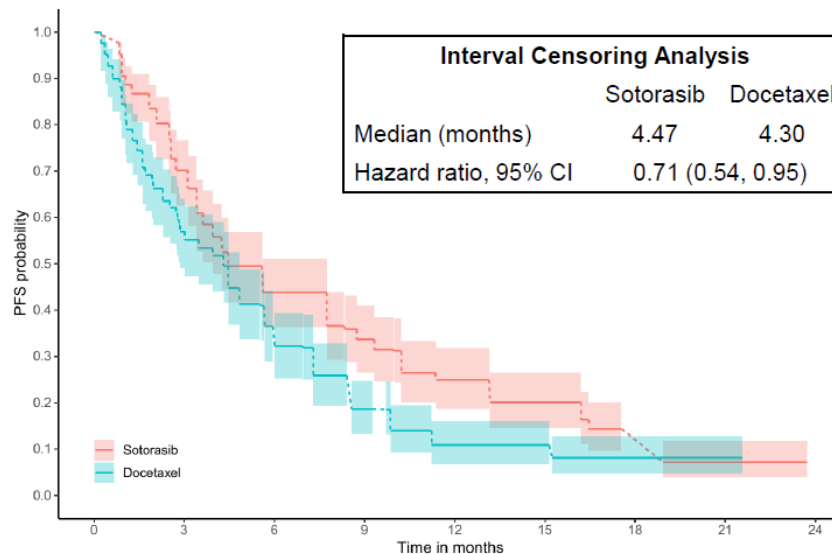
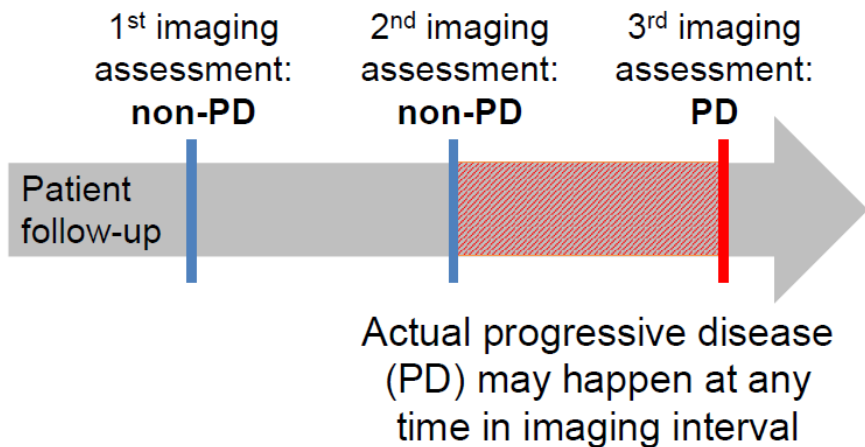
# Potential Misuse of COP Procedure



- Applicant observed “higher than expected discrepancy” between COP- and BICR-based events of progression and “raised concerns” with imaging vendor, triggering BICR re-read.
- Per imaging charter, “Response assessments performed by [imaging vendor] are not subject to input from [Applicant], its designees, or any site involved in this clinical trial.”

**FDA considers this a potential violation of imaging charter.**

# Impact of PFS Benefit Less than Imaging Interval



Although the hazard ratio is relatively consistent, median PFS difference could be as small as 5 days





## No Change in OS Results After Adjusting for Crossover

Analysis	HR (95% CI)
Primary analysis per protocol	1.01 (0.77, 1.33)
90-Day safety update	0.96 (0.74, 1.24)
RPSFTM adjusted analysis	0.96 (0.71, 1.43)
IPCW adjusted analysis	1.03 (0.78, 1.37)
Two-stage model	0.95 (0.63, 1.33)

Crossover is unlikely the reason for the observed lack of OS difference  
between sotorasib and docetaxel arms

RPSFTM: Rank Preserving Structural Failure Time Model

IPCW: Inverse-Probability-of-Censoring Weighting

# Adagrasib Accelerated Approval

KRYSTAL-1	Adagrasib 600 mg BID N = 112
Objective response rate per BICR, % (95% CI)	43 (34, 53)
Median duration of response, mos (95% CI)	8.5 (6.2, 13.8)

Source: KRIZATI (adagrasib) USPI

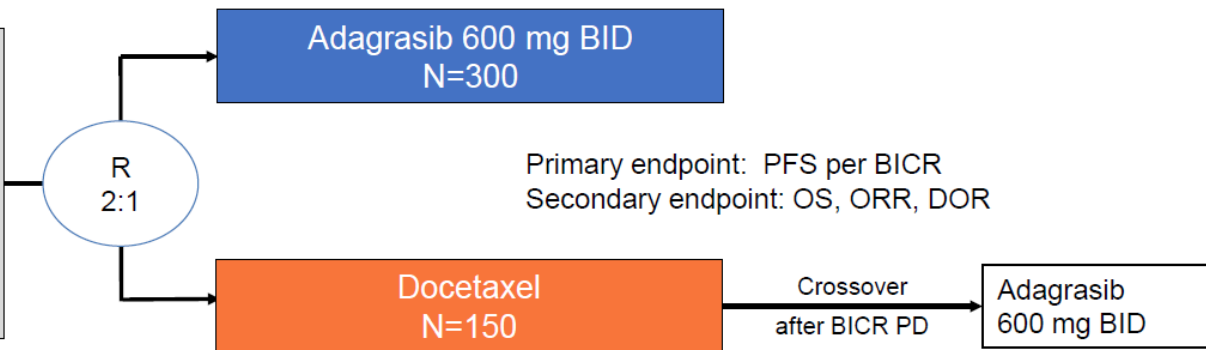
## Confirmatory Trial: KRYSTAL-12

**Key Eligibility Criteria**

- KRAS G12C mutation
- Advanced/ metastatic NSCLC
- Prior platinum chemo and IO

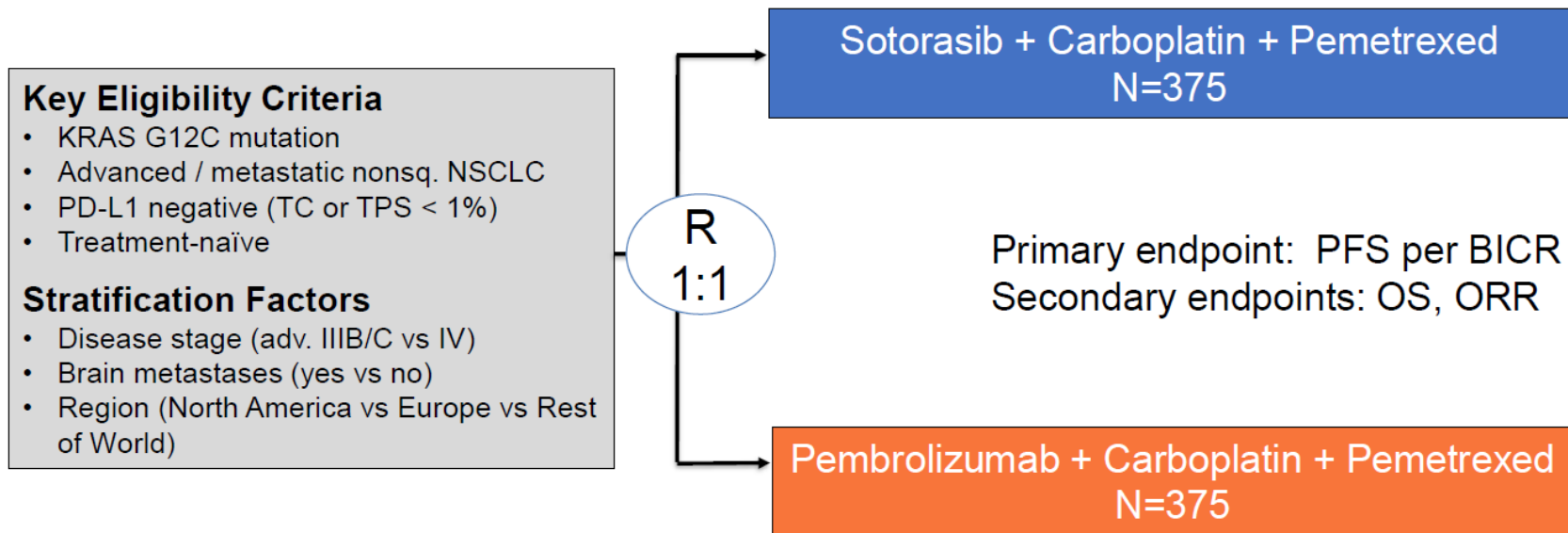
**Stratification Factors**

- Region: Non-Asia Pacific vs Asia Pacific
- Sequential vs concurrent platinum and anti-PD-(L)1 antibody



PD-(L)1: programmed cell death-1/programmed death ligand-1

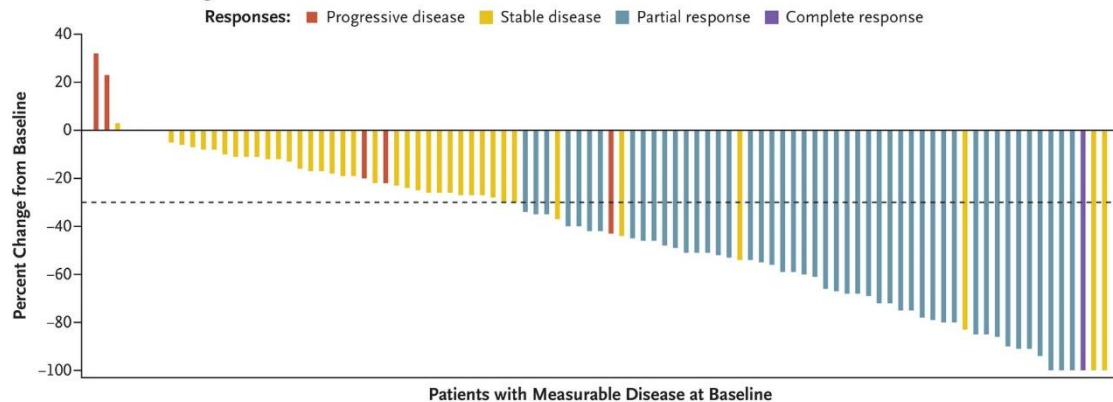
# First Line Trial of Sotorasib: CodeBreakK 202



Adv. = advanced; Nonsq: non-squamous; TC: tumor cells; TPS: tumor proportion score

# Adagrasib Krystal-1

**A Maximum Tumor Change from Baseline**

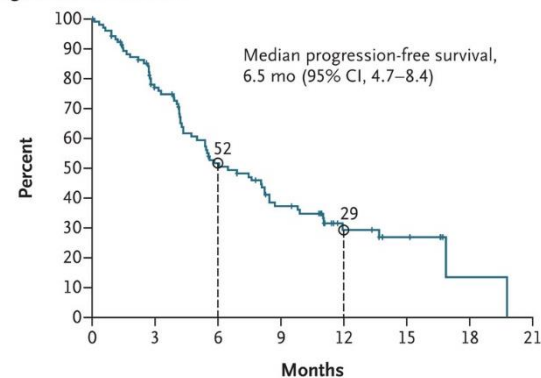


**Table 2. Overall Efficacy Summary According to Blinded Independent Central Review.\***

Variable	Cohort A (N=112)†
Objective response‡	
No. of patients	48
Percent (95% CI)	42.9 (33.5–52.6)
Best overall response — no. (%)	
Complete response	1 (0.9)
Partial response	47 (42.0)
Stable disease	41 (36.6)
Progressive disease	6 (5.4)
Not evaluable	17 (15.2)

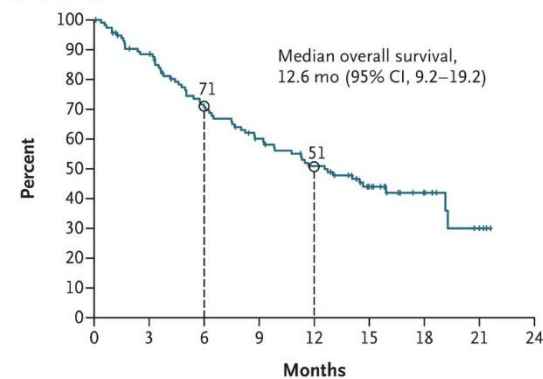
Janne et al., NEJM 2022

**C Progression-free Survival**



No. at Risk 112 72 45 30 13 6 1 0

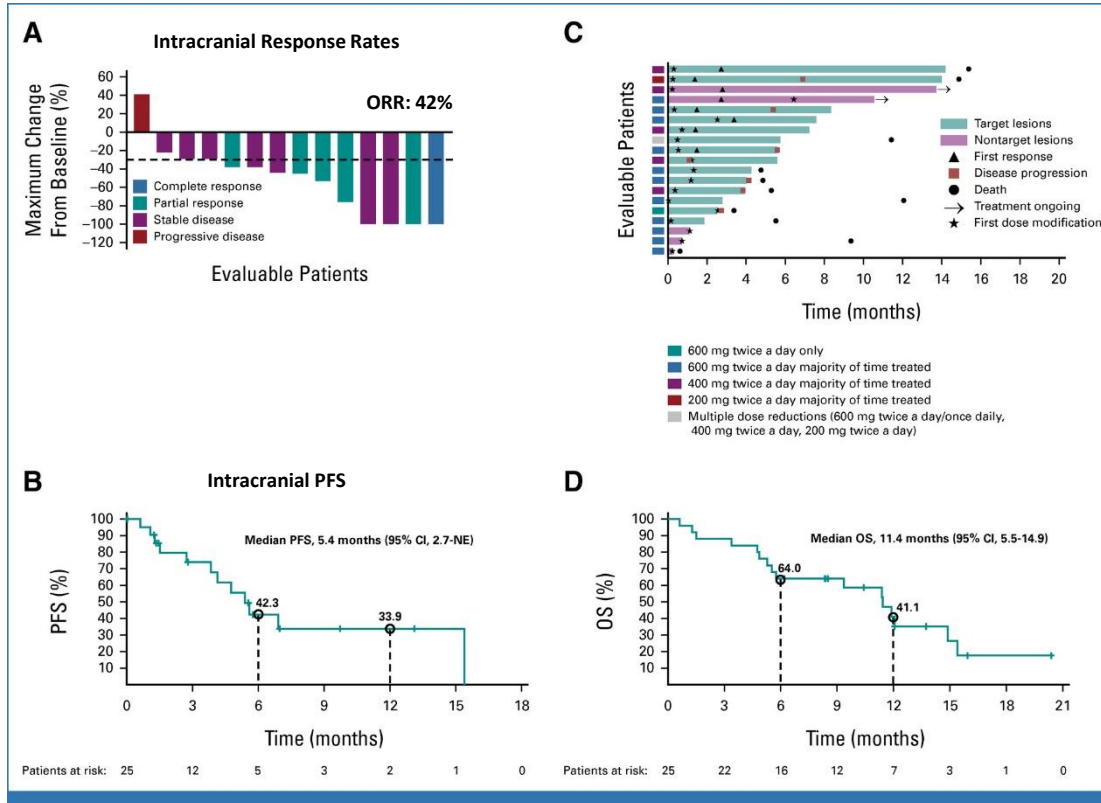
**D Overall Survival**



No. at Risk 116 98 74 60 49 29 10 3 0

# Adagrasib

## Krystal-1 – CNS Metastases



# Adagrasib Krystal-7

## KRYSTAL-7 (849-007) Phase 2 Cohorts

### Key Eligibility Criteria

- Advanced, unresectable or metastatic NSCLC with KRAS<sup>G12C</sup> mutation<sup>a</sup>
- No prior systemic therapy for locally advanced/ metastatic disease<sup>b</sup>
- Stable brain metastases allowed
- Known PD-L1 TPS score<sup>c</sup>

**Cohorts 1a and 2<sup>c</sup>**  
Adagrasib 400 mg BID +  
Pembrolizumab 200 mg Q3W  
N=148

### Key Study Objectives

- Primary endpoint: ORR (RECIST v1.1 per investigator assessment)
- Secondary endpoints: DOR and PFS (per investigator assessment), OS, safety, PK

- We report safety in all treated patients (N=148) and efficacy in patients with PD-L1 TPS  $\geq 50\%$  (n=51<sup>d</sup>) from the KRYSTAL-7 study evaluating adagrasib<sup>e</sup> + pembrolizumab (200 mg IV Q3W) in treatment-naïve patients with NSCLC harboring a KRAS<sup>G12C</sup> mutation
- Median follow-up for all treated patients, 8.7 months; PD-L1 TPS  $\geq 50\%$ , 10.1 months

<sup>a</sup>KRAS<sup>G12C</sup> mutation detected in tumor tissue and/or ctDNA by sponsor-approved local laboratory testing. <sup>b</sup>Prior systemic therapy or chemoradiation in the (neo)adjuvant setting were allowed if >1 year prior to the first dose of study treatment, and no TRAE of grade  $\geq 2$  while on (neo)adjuvant CPI (exceptions for clinically stable vitiligo and psoriasis regardless of grade, and hyper- or hypothyroidism that was adequately controlled). <sup>c</sup>Cohort 1a enrolled patients with PD-L1 TPS <1%; Cohort 2 enrolled patients with PD-L1 TPS  $\geq 1\%$ . Molecular testing for PD-L1 TPS was performed locally or centrally, with a sponsor-approved laboratory test (PD-L1 IHC 22C3 pharmDx, PD-L1 IHC 28-8 pharmDx or Ventana PD-L1 [SP142] assay). An additional cohort (1b) is enrolling patients with PD-L1 TPS <1% to receive adagrasib monotherapy, 600 mg BID. <sup>d</sup>Three patients excluded due to protocol deviations, including one each of atrial fibrillation, stroke within 6 months of enrollment, and presence of KRAS<sup>G12C</sup> mutation. <sup>e</sup>KRYSTAL-7 was initiated using the capsule (fasted) form of adagrasib but switched to the tablet (fed or fasted) form during study conduct.

# Adagrasib Krystal-7

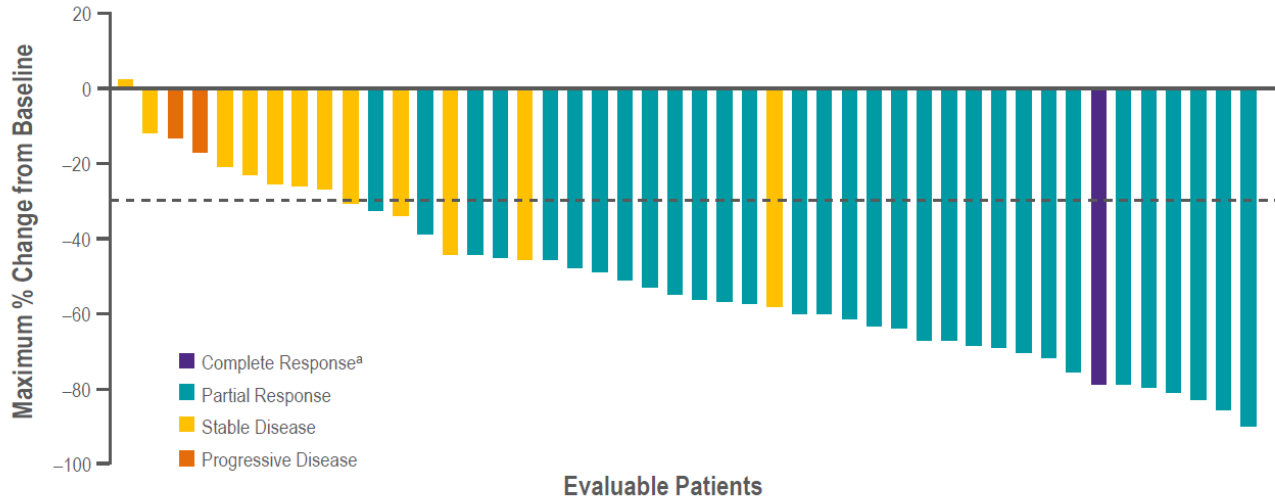
## Treatment-Related Adverse Events

Most Frequent TRAEs <sup>a</sup> , %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	51	28	20	3	0
Diarrhea	44	33	7	3	0
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Vomiting	29	17	11	1	0
Fatigue	26	12	10	4	0
Decreased appetite	24	14	9	1	0
Lipase increased	24	3	9	10	1

- There were two Grade 5 TRAEs, one each of pneumonitis and pneumonia
- Immune-related TRAEs<sup>b</sup> of any grade occurred in 18% of patients (26/148) and grade  $\geq 3$  occurred in 5% (8/148)
- TRAEs led to adagrasib dose reduction in 46% of patients (68/148) and temporary dose interruption in 59% of patients (88/148)
- TRAEs led to permanent discontinuation of adagrasib only in 6% of patients (9/148) and pembrolizumab only in 11% of patients (16/148); 4% of patients (6/148) discontinued both drugs due to TRAEs

# Adagrasib Krystal-7

## ORR and Best Tumor Change from Baseline in Patients With PD-L1 TPS $\geq 50\%$



- Confirmed ORR was 63% (32/51; 95% CI, 48–76) and DCR was 84% (43/51; 95% CI, 71–93)
- Of those patients who experienced any grade hepatotoxicity<sup>b</sup>, ORR was 70% (14/20; 95% CI, 46–88)

Response per investigator assessment (n=51; modified full analysis set). Waterfall plot excludes three patients without post-baseline measurement and one patient without confirmatory scan (only one assessment of PR on day 28, but minimum duration requirement for SD is 42 days). <sup>a</sup>One patient had CR without -100% change from baseline due to lymph node as target lesion. <sup>b</sup>Includes AST increase, ALT increase, mixed liver injury and liver function test increase; no grade 4 hepatotoxicity was observed in patients with PD-L1 TPS  $\geq 50\%$ . Data as of 19 June 2023. Median follow-up 10.1 months



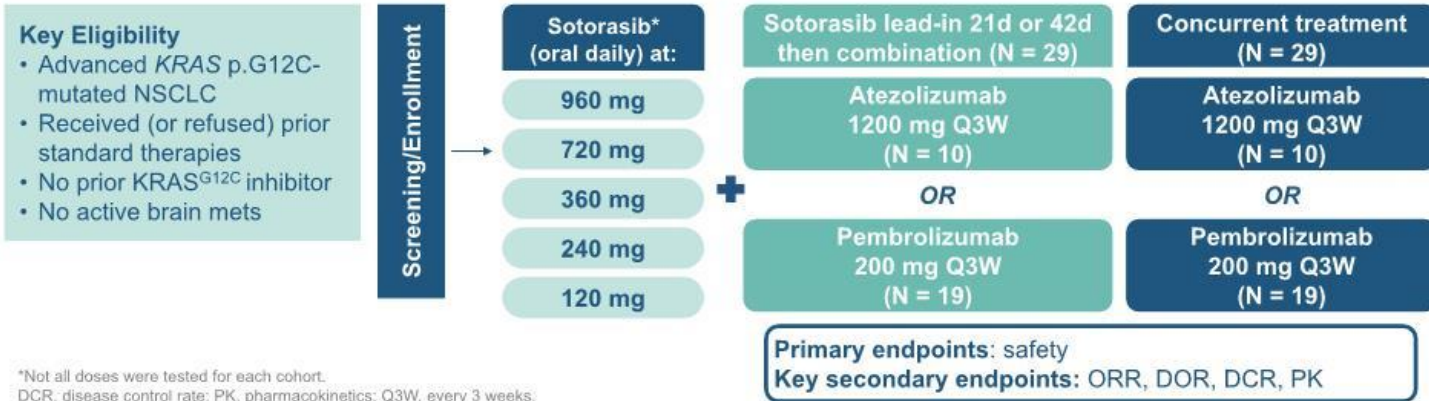
# Sotorasib

## CodeBreak 100/101



## CodeBreak 100/101 Study Design

- Phase 1b multicenter, open-label studies



\*Not all doses were tested for each cohort.  
DCR, disease control rate; PK, pharmacokinetics; Q3W, every 3 weeks.

Snapshot: April 15, 2022

Here we present first data of lead-in and concurrent sotorasib with pembrolizumab or atezolizumab from CodeBreak 100/101 with median follow-up time of 12.8 months (range: 1.6, 29.9)

# Sotorasib

## CodeBreak 100/101



### Safety Summary: Lead-in versus Concurrent

	Sotorasib + Atezolizumab Lead-In (N = 10)	Sotorasib + Atezolizumab Concurrent (N = 10)	Sotorasib + Pembrolizumab Lead-In (N = 19)	Sotorasib + Pembrolizumab Concurrent (N = 19)
TRAE, any grade, n (%)	10 (100)	9 (90)	15 (79)	17 (89)
Grade 3	3 (30)	5 (50)	10 (53)	14 (74)
Grade 4*	0	1 (10)	0	1 (5)
TRAE leading to sotorasib and/or IO discontinuation, n (%)	1 (10)	5 (50)	6 (32)	10 (53)
Median duration of sotorasib, months (min, max)	6.5 (1, 18)	4.4 (1, 14)	2.8 (1, 15)	4.9 (2, 30)
Median duration of combination, months (min, max) <sup>†</sup>	1.5 (0, 18)	2.5 (1, 14)	0.7 (1, 15)	2.3 (1, 9)
Hepatotoxicity grade ≥ 3, median onset, days (range)	50 (28, 93)	67 (36, 147)	73 (45, 127)	51 (29, 190)

- Lead-in had lower incidence of Grade 3-4 TRAEs and TRAEs leading to discontinuation than concurrent
- Grade 3-4 hepatotoxicity first occurrence was outside DLT window<sup>†</sup> in 88% of patients; 97% of events resolved with corticosteroids, treatment modification, and/or discontinuation
- The incidence of hepatotoxicity TRAEs was similar in IO-naïve versus IO-pretreated patients

Hepatotoxicity included ALT increased, AST increased, ALP increased, bilirubin increased, GGT increased; also hepatitis, liver function test increased, drug-induced liver injury, transaminases increased for sotorasib+atezolizumab; also hepatic enzyme increased, immune-mediated hepatitis for sotorasib lead-in+pembrolizumab; also autoimmune hepatitis for sotorasib+pembrolizumab concurrent.

\*Grade 4 TRAEs were ALT increased (n = 1; related to sotorasib and atezolizumab), and AST increased (n = 1; related to sotorasib).

<sup>†</sup>Duration of combination calculated for patients receiving both sotorasib and IO; one patient in a lead-in cohort did not receive IO and not included

<sup>‡</sup>DLT window was 21 days following initiation of combination treatment. IO, immune-oncology

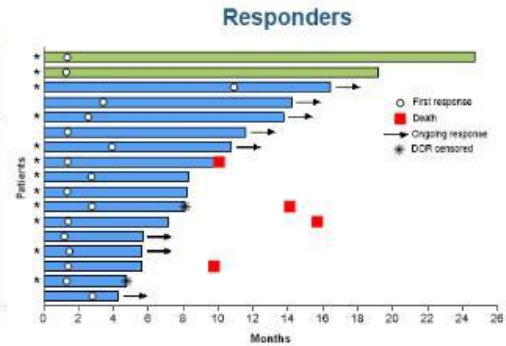
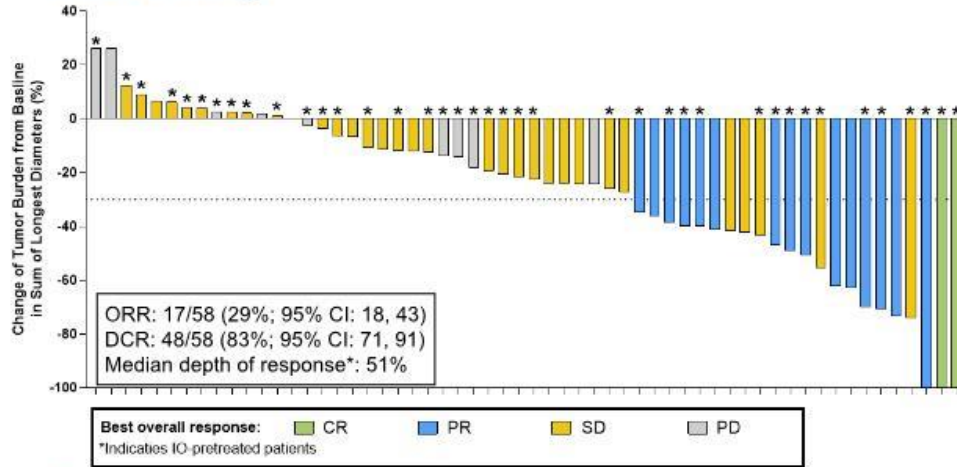
# Sotorasib

## CodeBreak 100/101

IASLC  2022 World Conference  
on Lung Cancer  
AUGUST 6-9, 2022 | VIENNA, AUSTRIA



### Efficacy



- Deep and durable responses were observed for this combination across all cohorts, including at low doses
- Among the 17 responders, median duration of response was 17.9 months (95% CI: 5.6, NE)
- Response was similar in IO-naïve and IO-pretreated patients

\*Median depth of response among responders. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

# Sotorasib SCARLET

## SCARLET: study schema

### Key inclusion criteria

- Advanced non-Sq, NSCLC
- With KRAS G12C
- Naïve for Cytotoxic chemotherapy and KRAS inhibitor
- With measurable lesion
- ECOG PS 0-1
- Asymptomatic CNS mets allowed

### Induction phase

Sotorasib 960mg  
+ CBDCA (AUC5)/ PEM 500 mg/m<sup>2</sup>  
[q3W, 4 cycles]  
(n = 30)

### Maintenance phase

Sotorasib + PEM  
[q3W, until PD]

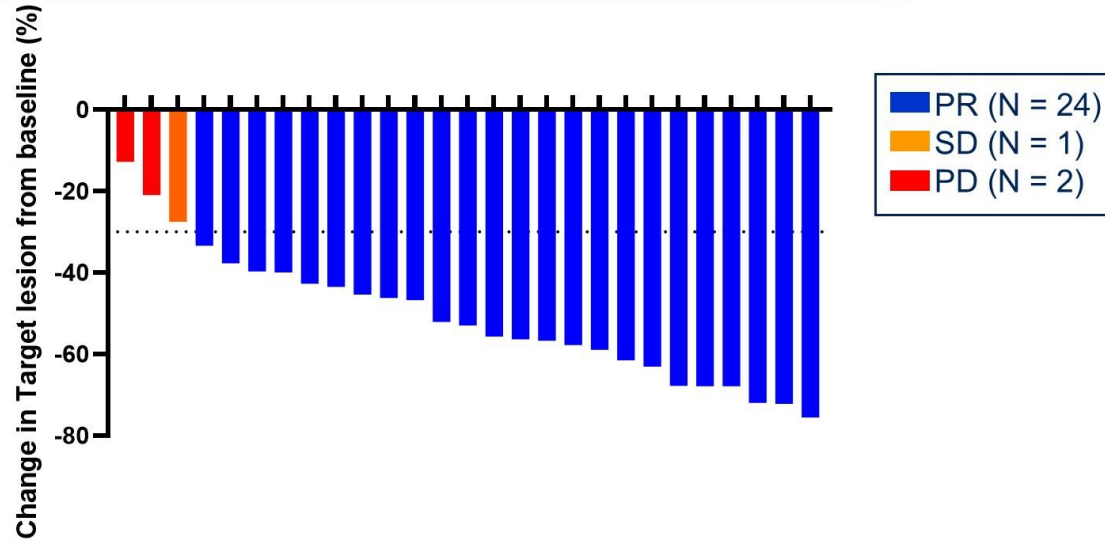
- Primary endpoint; ORR by blinded independent central review (BICR)
- Secondary endpoints; DCR, PFS, DOR, OS and AEs
- Translational research; NGS analysis (tissue and plasma [at baseline, 3 wks, and PD])

Trial identifier: jRCT2051210086

# Sotorasib SCARLET

## Primary endpoint: ORR by BICR

ORR 88.9% (80%CI 76.9-95.8%, 95%CI 70.8-97.6%)



# Sotorasib SCARLET

## Treatment-related AEs (≥ 15% or any severe cases)

	Any Grade		≥Grade 3		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
<b>Any adverse event</b>	29	100.0	21	72.4	1	3.4	7	24.1	14	48.3	6	20.7	1	3.4
Anaemia	21	72.4	11	37.9	2	6.9	8	27.6	10	34.5	1	3.4	0	0.0
PLT decreased	13	44.8	7	24.1	4	13.8	2	6.9	5	17.2	2	6.9	0	0.0
Neutrophil decreased	12	41.4	7	24.1	0	0.0	5	17.2	4	13.8	3	10.3	0	0.0
Decreased appetite	10	34.5	0	0.0	4	13.8	6	20.7	0	0.0	0	0.0	0	0.0
Nausea	10	34.5	0	0.0	3	10.3	7	24.1	0	0.0	0	0.0	0	0.0
WBC decreased	10	34.5	6	20.7	1	3.4	3	10.3	4	13.8	2	6.9	0	0.0
Malaise	8	27.6	0	0.0	5	17.2	3	10.3	0	0.0	0	0.0	0	0.0
Constipation	7	24.1	0	0.0	4	13.8	3	10.3	0	0.0	0	0.0	0	0.0
Diarrhoea	7	24.1	2	6.9	3	10.3	2	6.9	2	6.9	0	0.0	0	0.0
γ-GTP increased	6	20.7	1	3.4	4	13.8	1	3.4	1	3.4	0	0.0	0	0.0
Neutropenia	5	17.2	3	10.3	0	0.0	2	6.9	3	10.3	0	0.0	0	0.0
Hiccups	5	17.2	0	0.0	4	13.8	1	3.4	0	0.0	0	0.0	0	0.0
ALT increased	5	17.2	1	3.4	2	6.9	2	6.9	0	0.0	1	3.4	0	0.0
Blood Cre increased	5	17.2	0	0.0	4	13.8	1	3.4	0	0.0	0	0.0	0	0.0
AST increased	4	13.8	2	6.9	2	6.9	0	0.0	2	6.9	0	0.0	0	0.0
Hyperkalaemia	3	10.3	1	3.4	0	0.0	2	6.9	1	3.4	0	0.0	0	0.0
Lymph decreased	3	10.3	1	3.4	1	3.4	1	3.4	1	3.4	0	0.0	0	0.0
Cellulitis	2	6.9	1	3.4	0	0.0	1	3.4	1	3.4	0	0.0	0	0.0
Pneumonia	2	6.9	1	3.4	0	0.0	1	3.4	0	0.0	0	0.0	1	3.4
Thrombocytopenia	2	6.9	1	3.4	0	0.0	1	3.4	0	0.0	1	3.4	0	0.0
Anaphylactic reaction	1	3.4	1	3.4	0	0.0	0	0.0	1	3.4	0	0.0	0	0.0
Gastritis	1	3.4	1	3.4	0	0.0	0	0.0	1	3.4	0	0.0	0	0.0
Cholecystitis	1	3.4	1	3.4	0	0.0	0	0.0	1	3.4	0	0.0	0	0.0

# LY3537982 SUNRAY-01

 U.S. National Library of Medicine

*ClinicalTrials.gov*

[Find Studies](#) ▼

[About Studies](#) ▼

[Submit Studies](#) ▼

[Resources](#) ▼

[About Site](#) ▼

[PRS Login](#)

[Home](#) > [Search Results](#) > Study Record Detail

Save this study

**A Study of LY3537982 Plus Immunotherapy With or Without Chemotherapy in Participants With Non-Small Cell Lung Cancer (NSCLC) With a Change in a Gene Called KRAS G12C (SUNRAY-01)**

## Conclusions

- KRAS G12C mutations are found in a significant proportion of NSCLC patients and serve as driver events
- KRAS inhibitors (sotorasib and adagrasib) have demonstrated activity in pre-treated patients, including patients exposed to chemotherapy and immunotherapy, with a favorable toxicity profile as monotherapy
- Additional studies evaluating first-line therapy, combinations, and other KRAS inhibitors (KRAS G12D) under way