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Terapia biológica dirigida a nuevas mutaciones (KRAS G12C)

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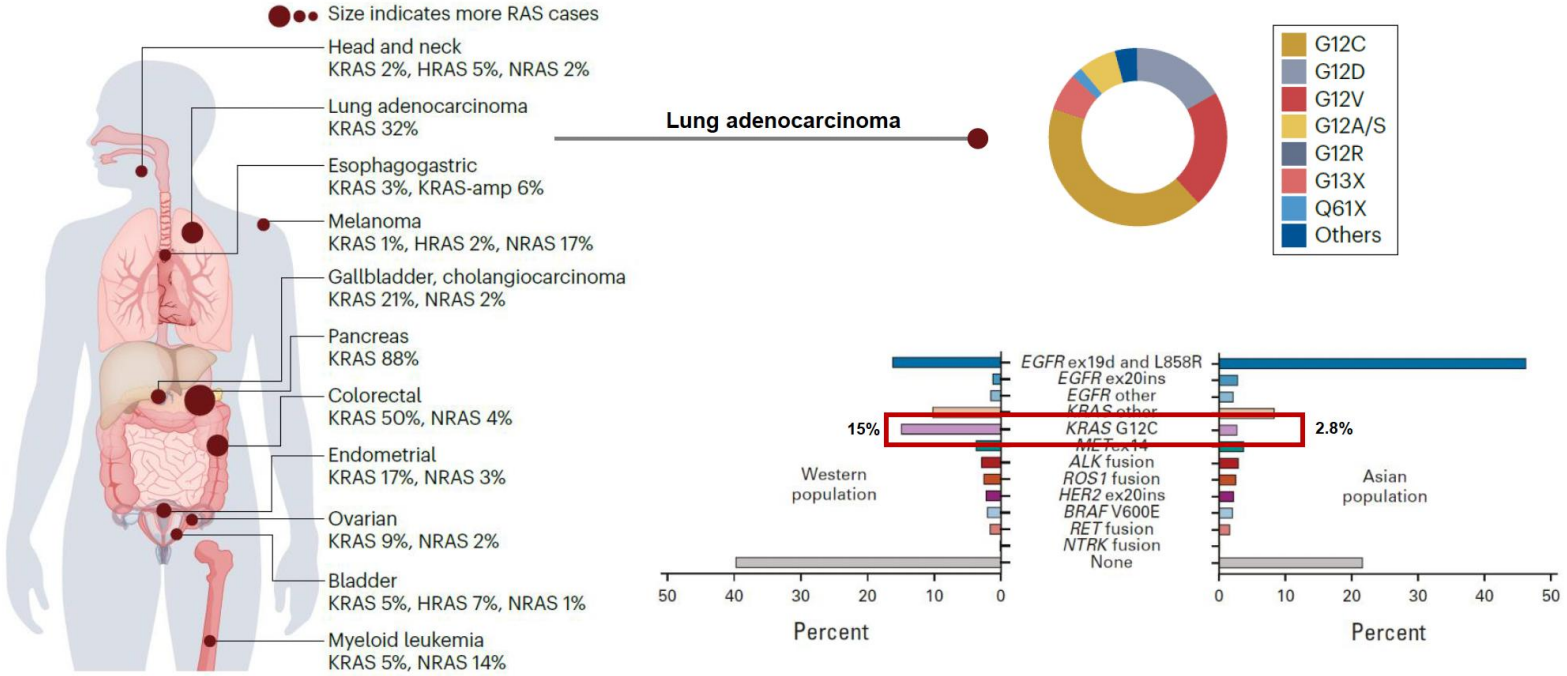
Disclosure

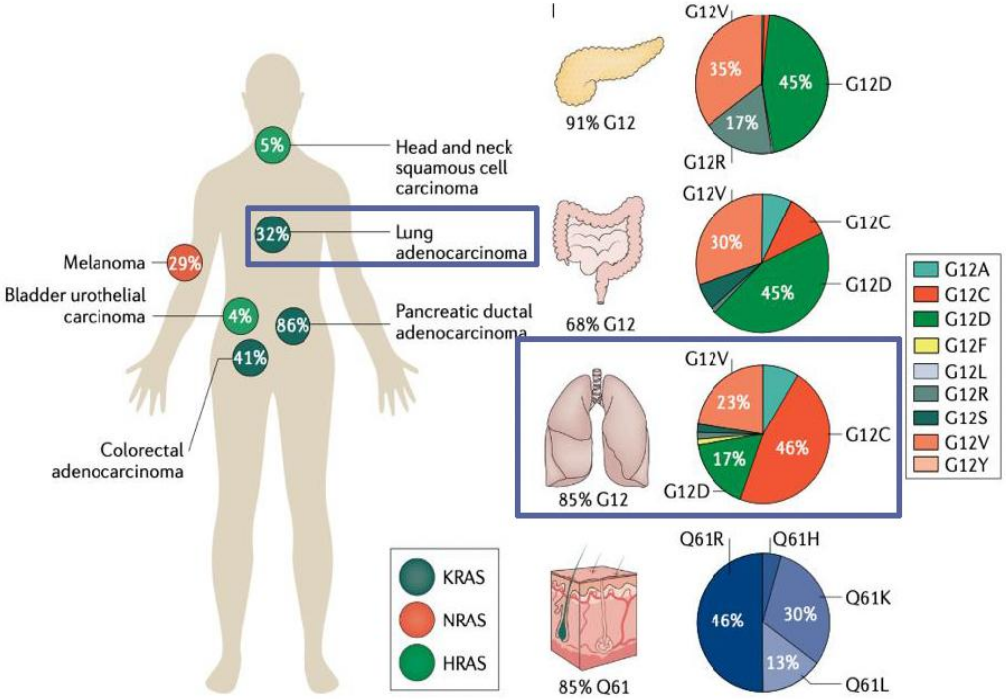
- Educational fees: Astra Zeneca, Bristol Myers Squibb, Merck Sharp and Dohme, and Roche.
- Consultancy/Advisory board: Astra Zeneca, Bayer, Beigene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Glaxosmithkline, Janssen, Lilly, Merck Sharp and Dohme, Novartis, Pfizer, Hoffmann- La Roche, Sanofi, Takeda
- Presenter/Speaker bureau: Astra Zeneca, Gilead, Hoffmann- La Roche, Merck Sharp and Dohme, Pfizer
- Employee: SERMAS
- Spanish Society of Medical Oncology, SEOM (Vicepresident)

KRAS MUTATIONS IN NSCLC



Nat Med. 2024 Apr;30(4):969-983 ; JCO 40, 611-625(2022).

KRAS G12C Mutated Lung Cancer: Epidemiology



Transversion Mutation:
Glycine→Cysteine

More common in smokers,
60% women, 95% adenocarcinoma

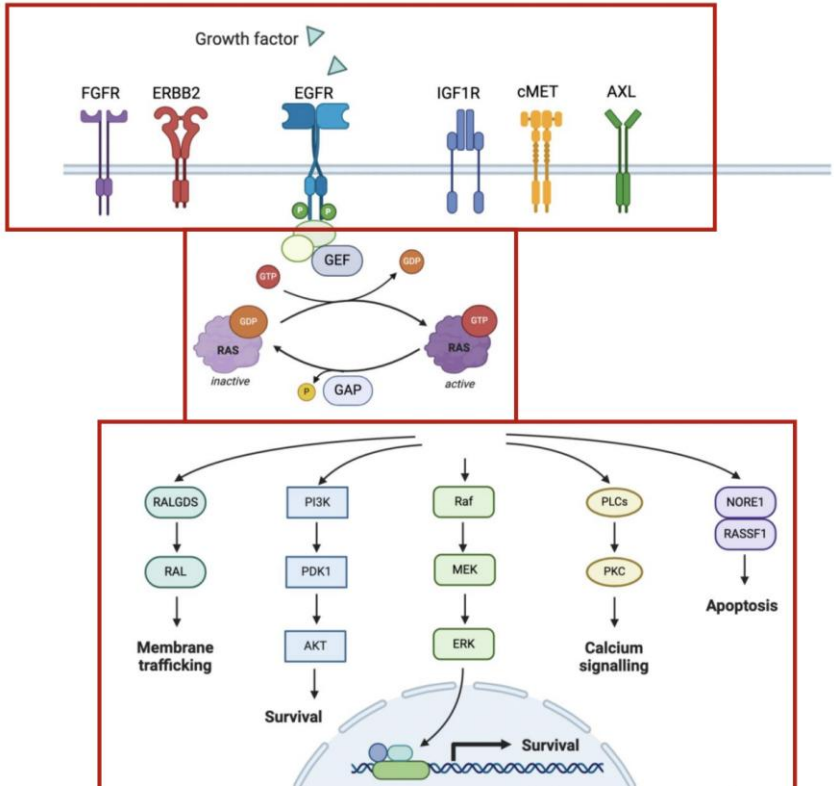
Associated with higher tumour PD-L1, TMB

Frequency ~15% West, 2.8% Asia

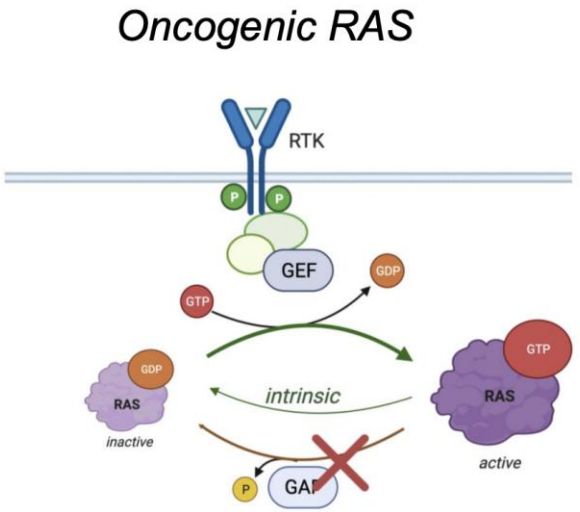
US Cohort (Foundation) N=68,297

Ancestry:	KRAS G12C Frequency
European	15.2%
African	11.9%
East Asian	4.0%
South Asian	6.2%
Admixed American	6.1%

Moore A et al Nat Rev 2020;; 19(8):533-552.Judd J et al. Mol Cancer Ther2021;20:2577–84; Arbour KC, et al. Clin Cancer Res 2021; 27(8):2209-2215; Tan & Tan J Clin Oncol 2022; SisoudiyaNPJ Precis Oncol 2024

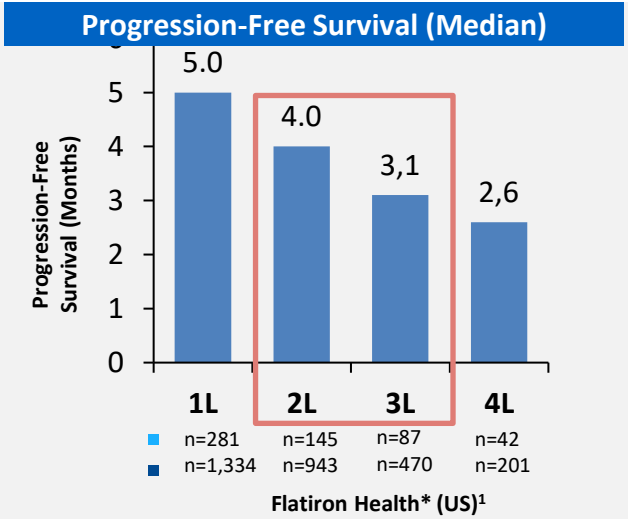


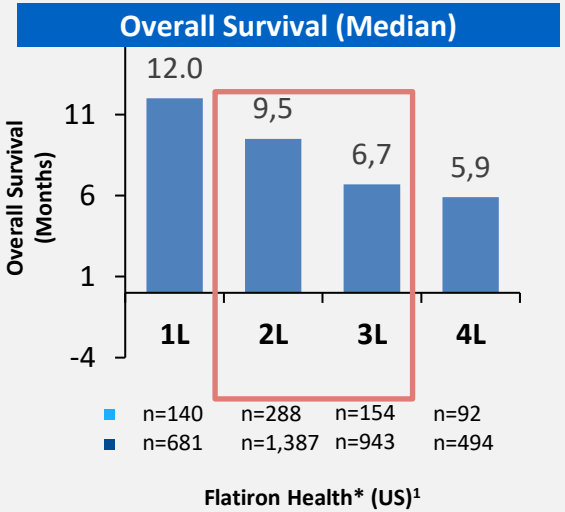
RAS pathway



Oncogenic RAS mutations impair GAP protein binding and therefore GTP hydrolysis

Patients With KRAS^{G12C} Mutated NSCLC



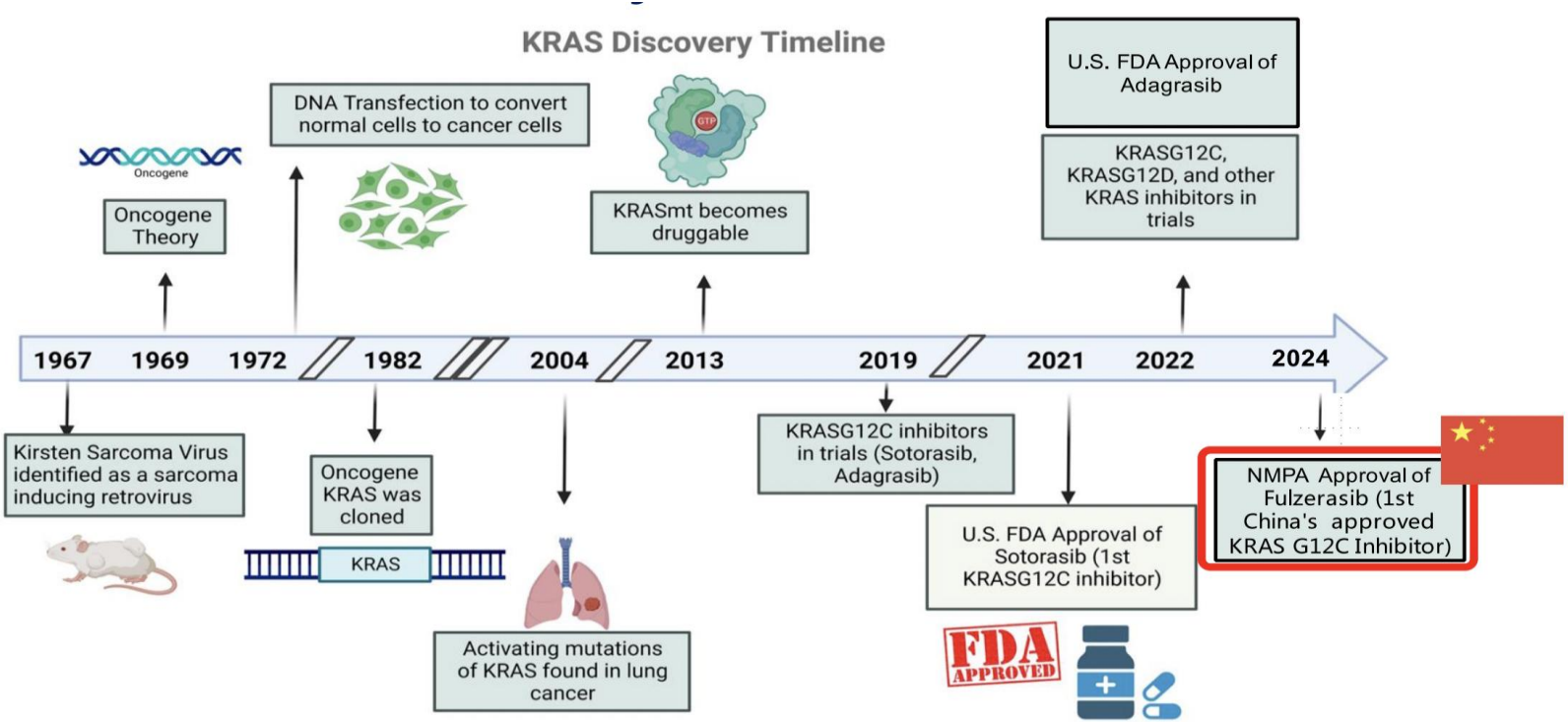


Real-world data obtained between 2011 and 2019 (prior to the approval of KRAS^{G12C} inhibitors) suggest that PFS and OS rates are poor for patients with KRAS^{G12C}–mutated NSCLC

*Data from an analysis of the Flatiron Health-Foundation Medicine Clinico-Genomic Database (FH-FMI CGDB). FH-FMI CGDB includes over 400,000 samples from approximately 280 oncology practices in the US and integrates broad genomic profiling results with clinical data from electronic health records (EHRs). The analysis identified 7,069 NSCLC patients of which 743 had the *KRAS* G12C mutation. Patient characteristics, treatment patterns, and clinical outcomes were documented for these patients from January 1, 2011, to September 30, 2019.[1] 1L, first line; 2L, second line; 3L, third line; 4L, fourth line

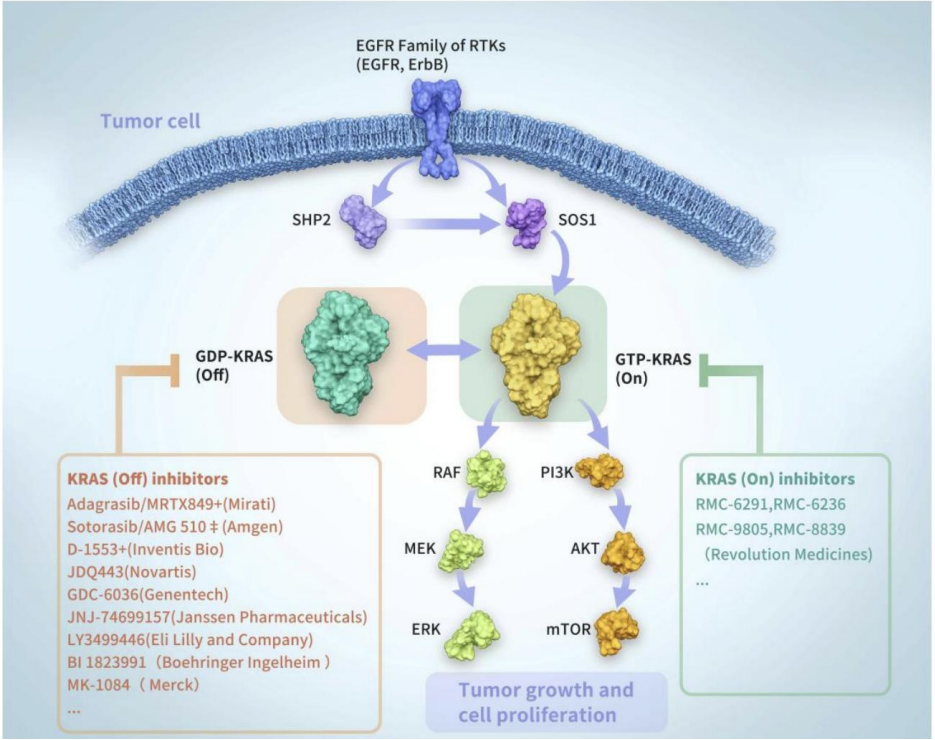
Spira AI, et al. *Lung Cancer*. 2021;159:1-9.

Timeline of KRAS discovery

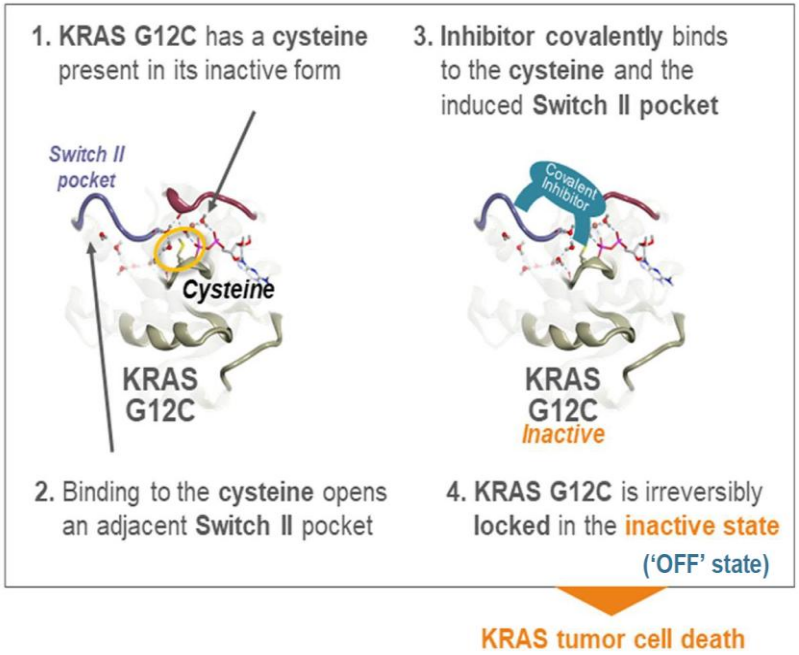


1.J Hematol Oncol. 2022 Oct 25;15(1):152.; 2. https://www.fda.gov/; 3. https://www.nmpa.gov.cn/; 4. Ostrem JM, et al. 2013. Nature; 503:543-551

Multiple approaches to target KRAS G12C mutations



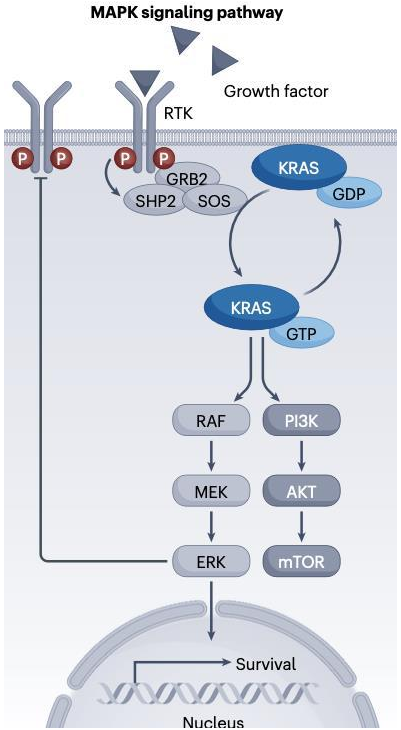
Most KRAS G12C inhibitors bind to the cysteine and the Switch II pocket, thus locking the mutant protein in the inactive (OFF) state irreversibly



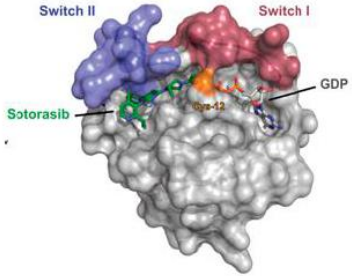
Judd, Mol Cancer Ther 2021; 2. Ostrem et al, Nature 2013

Cancer Cell. 2024 Mar 11;42(3):338-357; 2. Christensen JG, et al. J Intern Med. 2020

KRAS inhibitors

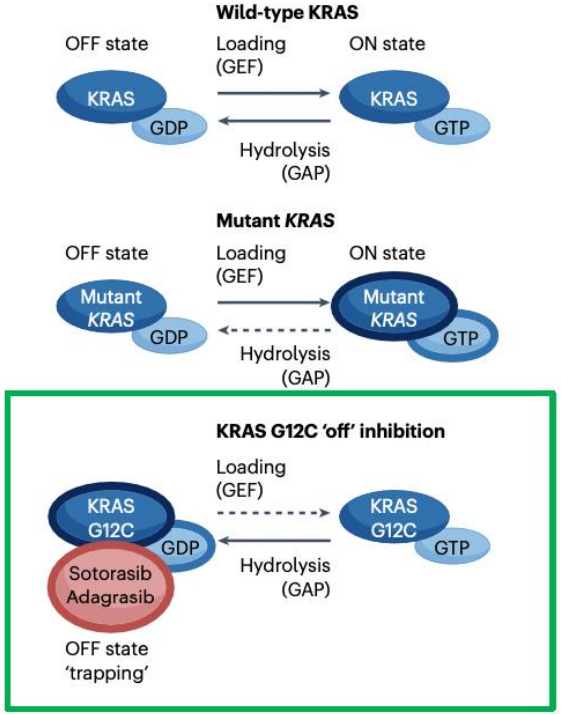


Allele specific inhibitors bind covalently to maintain KRAS in GDP-bound "inactive" state



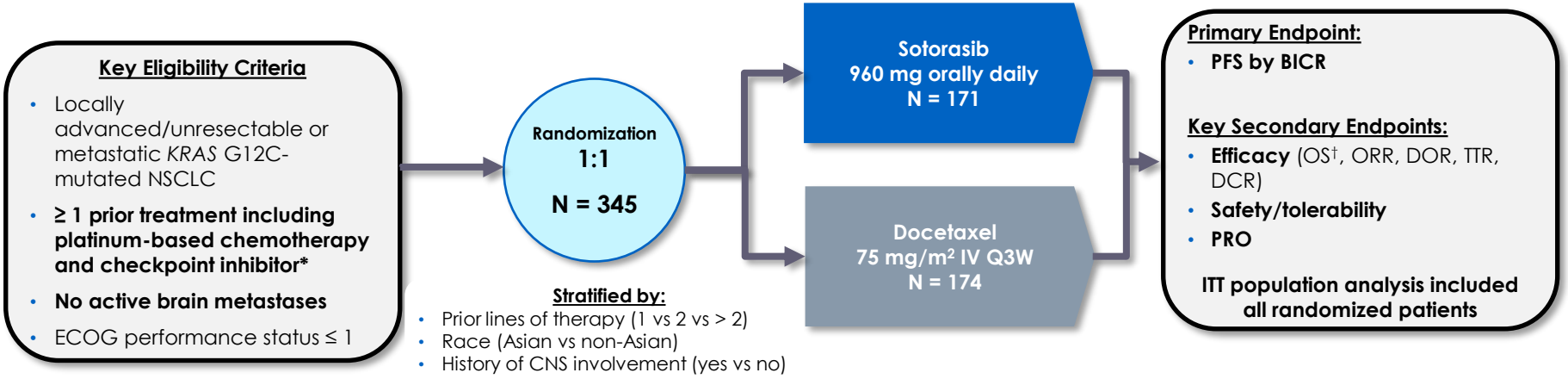
2013

Discovery of switch II "pocket"
With cysteine binding (G12C)



Singhal A et al Nature Med 2024;30:969-983; OstremJ et al Nature 2013

CodeBreaK 200
Phase 3 Study Design



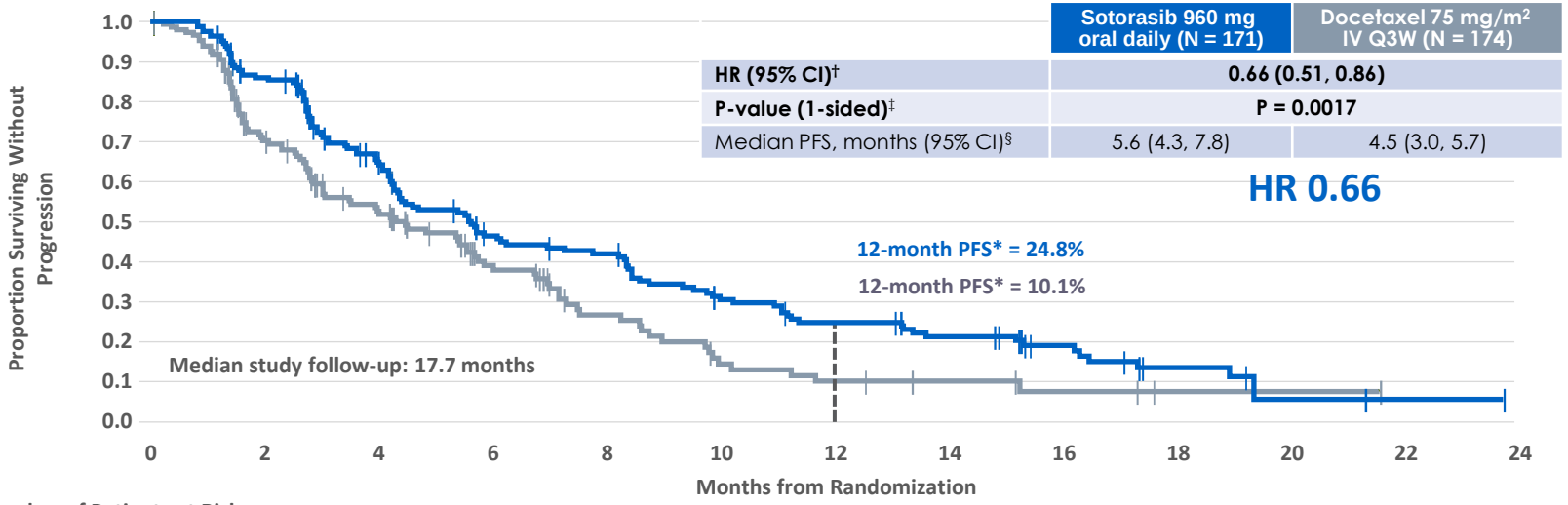
Per regulatory feedback following the observed clinical benefits of sotorasib in the CodeBreaK 100 phase 2 trial:
- **The protocol was amended to reduce planned enrollment from 650 to ~330 patients, to maximize the number of patients exposed to sotorasib**
- **Crossover from docetaxel to sotorasib was permitted upon disease progression**

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. **BICR**, blinded independent central review; **CNS**, central nervous system; **DCR**, disease control rate; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **ITT**, intent to treat; **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**, pharmacokinetics; **PRO**, patient-reported outcomes; **Q3W**, every 3 weeks; **TTR**, time to response.

de Langen AJ, et al. *Lancet*. 2023;401:733-746.

CodeBreaK 200 Primary Endpoint
PFS by BICR



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	P = 0.0017	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

Number of Patients at Risk:													
Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

Codebreak 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *p* = 0.0017); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

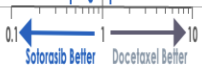
*PFS rates estimated using Kaplan-Meier method; ITT population. †HR and 95% CIs estimated using a stratified Cox proportional hazards model. ‡*P*-value calculated using a stratified log-rank test. §Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation. BICR, blinded independent central review; HR, hazard ratio; IV, intravenous; PFS, progression-free survival; Q3W, every 3 weeks

de Langen AJ, et al. *Lancet*. 2023;401:733-746.

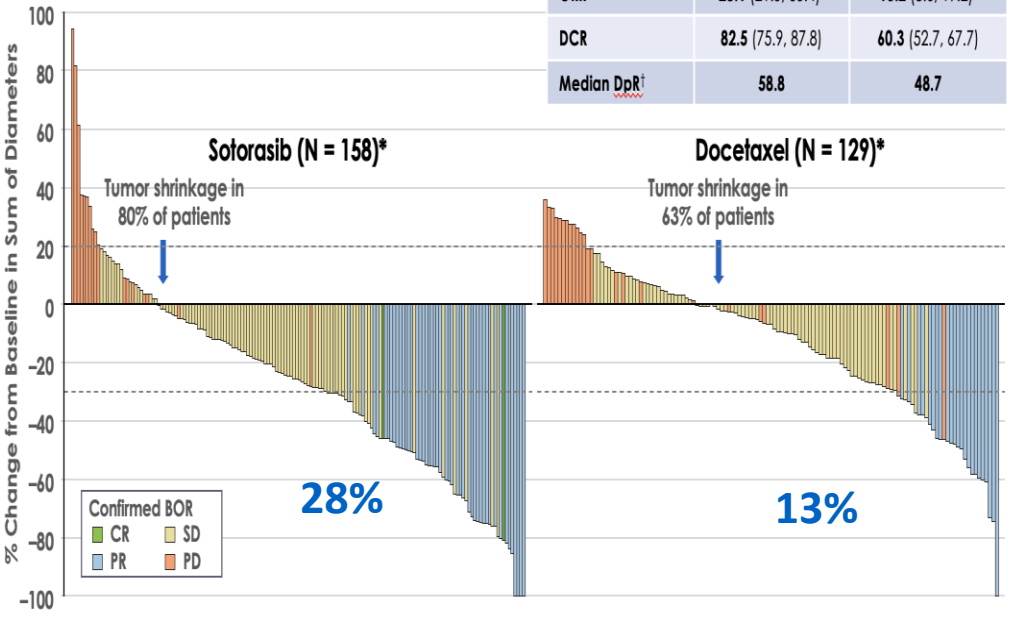
CodeBreaK 200

PFS Across Subgroups and Overall Response

Subgroup	Number of Patients: Sotorasib	Number of Patients: Docetaxel	Median PFS, months: Sotorasib	Median PFS, months: Docetaxel	Hazard Ratio (95% CI)
All randomized patients	171	174	5.6	4.5	0.66 (0.51, 0.86)
Age, at baseline (years)					
< 65	91	95	4.4	3.1	0.68 (0.48, 0.96)
≥ 65	80	79	5.9	5.6	0.64 (0.41, 0.99)
Sex					
Male	109	95	5.7	4.5	0.56 (0.39, 0.80)
Female	62	79	4.6	4.2	0.69 (0.45, 1.08)
Region					
North America	20	22	5.9	6.8	0.49 (0.21, 1.13)
Europe	126	126	5.6	4.0	0.68 (0.50, 0.92)
Other*	25	26	5.7	5.6	0.47 (0.20, 1.09)
Race					
Asian	21	22	8.3	5.6	0.33 (0.14, 0.80)
Non-Asian	149	151	5.6	4.2	0.71 (0.54, 0.95)
Baseline ECOG performance status					
0	59	59	8.4	6.7	0.63 (0.38, 1.05)
1	112	115	4.4	2.8	0.61 (0.44, 0.84)
Number of prior lines in advanced disease					
1	77	78	4.2	4.2	0.70 (0.47, 1.04)
2	65	69	5.7	4.8	0.61 (0.40, 0.92)
> 2	29	27	4.7	4.0	0.74 (0.37, 1.46)
History of CNS involvement					
Yes	58	60	4.4	2.9	0.53 (0.34, 0.82)
No	113	114	5.7	5.7	0.74 (0.53, 1.03)
PD-L1 protein expression					
< 1%	57	55	8.3	5.9	0.66 (0.41, 1.06)
≥ 1% and < 50%	46	70	4.6	3.0	0.61 (0.39, 0.96)
≥ 50%	60	40	5.7	5.4	0.74 (0.44, 1.23)



% (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†	**58.8**	**48.7**

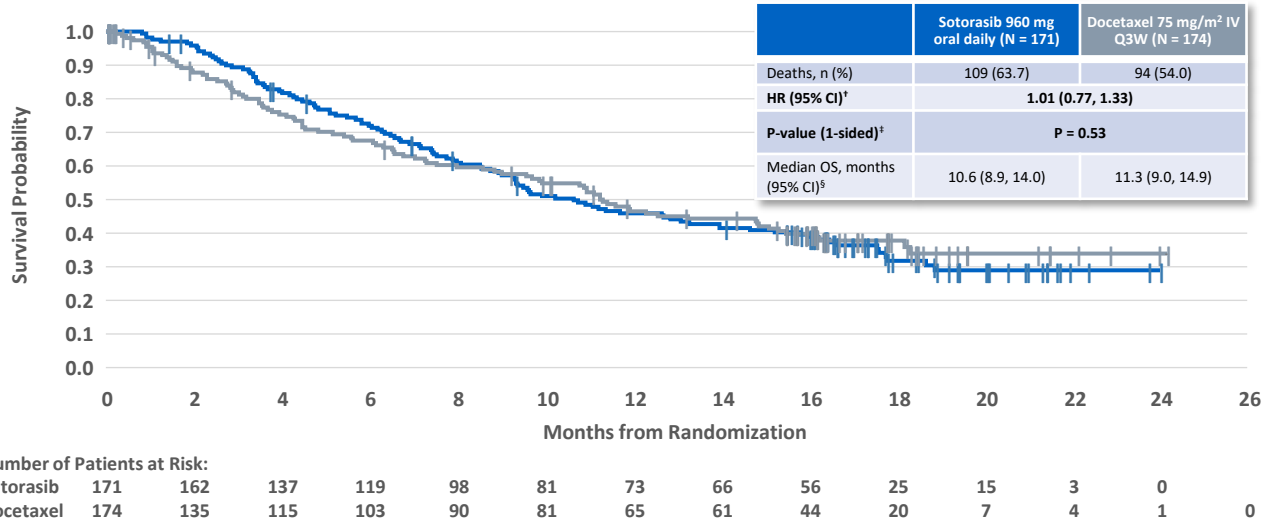


Response rate was significantly higher with sotorasib versus docetaxel (p < 0.001)

de Langen AJ, et al. *Lancet*. 2023;401:733-746.

CodeBreaK 200

OS: Sotorasib versus Docetaxel*



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	P = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

List of Subsequent Anti-cancer Treatment

Categories	Sotorasib (N = 171) n (%)	Docetaxel (N = 174) n (%)
Any subsequent anti-cancer therapy including crossover	62 (36.3)	73 (42.0)
Chemotherapy	36 (21.1)	21 (12.1)
KRAS^{G12C} inhibitor	6 (3.5)	59 (33.9)
Immunotherapy	16 (9.4)	10 (5.7)
Checkpoint inhibitor	14 (8.2)	10 (5.7)
Other	25 (14.6)	18 (10.3)

Overall survival was not different between the treatment groups; however, the study was not powered to detect a survival benefit and crossover from docetaxel at disease progression to sotorasib was permitted

*OS rates estimated using Kaplan-Meier method; ITT population. †HR and 95% CIs estimated using a stratified Cox proportional hazards model. ‡ *P*-value calculated using a stratified log-rank test. §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.

CI, confidence interval; ITT, intent to treat; IV, intravenous; KRAS, Kirsten rat sarcoma viral oncogene homolog; HR, hazard ratio; OS, overall survival; Q3W, every 3 weeks.

de Langen AJ, et al. *Lancet*. 2023;401:733-746.

CodeBreaK 200
Most Common TRAEs*

	Sotorasib 960 mg oral daily (N = 169)		Docetaxel 75 mg/m² IV Q3W (N = 151)	
	Any Grade, n (%)	Grade ≥ 3, n (%)	Any Grade, n (%)	Grade ≥ 3, n (%)
TRAEs	119 (70)	56 (33)	130 (86)	61 (40)
Diarrhea	57 (34)	20 (12)	28 (19)	3 (2)
Fatigue	11 (7)	1 (1)	38 (25)	9 (6)
Alopecia	2 (1)	0	31 (21)	0
Nausea	24 (14)	2 (1)	30 (20)	1 (1)
Anemia	5 (3)	1 (1)	27 (18)	5 (3)
ALT increased	17 (10)	13 (8)	0	0
AST increased	17 (10)	9 (5)	0	0
Neutropenia	2 (1)	0	20 (13)	18 (12)
Febrile neutropenia	0	0	8 (5)	8 (5)

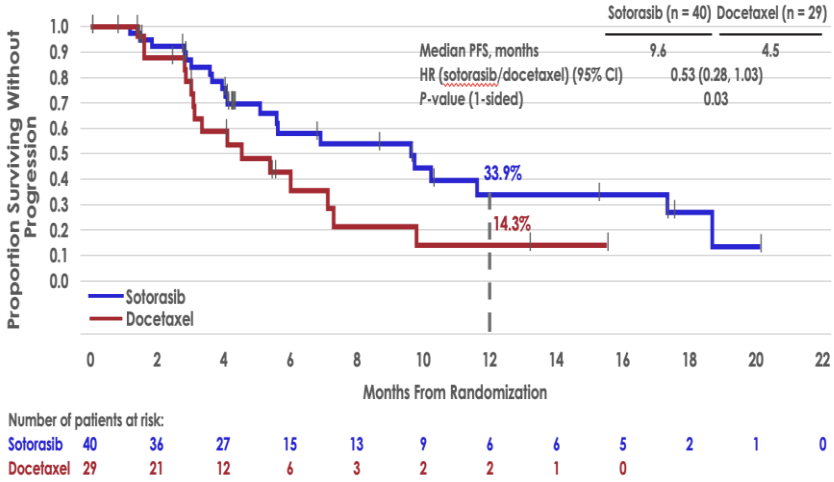
Most common grade ≥ 3 TRAEs with sotorasib were diarrhea and elevated liver enzymes, and with docetaxel were neutropenia, fatigue, and febrile neutropenia

*Incidence per arm: any grade TRAE > 15%; grade ≥ 3 TRAEs > 5%.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous; TRAE, treatment-related adverse event as per investigator.

de Langen AJ, et al. *Lancet*. 2023;401:733-746.

CodeBreaK 200: Retrospective, Exploratory CNS Analysis

CNS PFS and Intracranial Response in Patients With CNS Lesions at Baseline



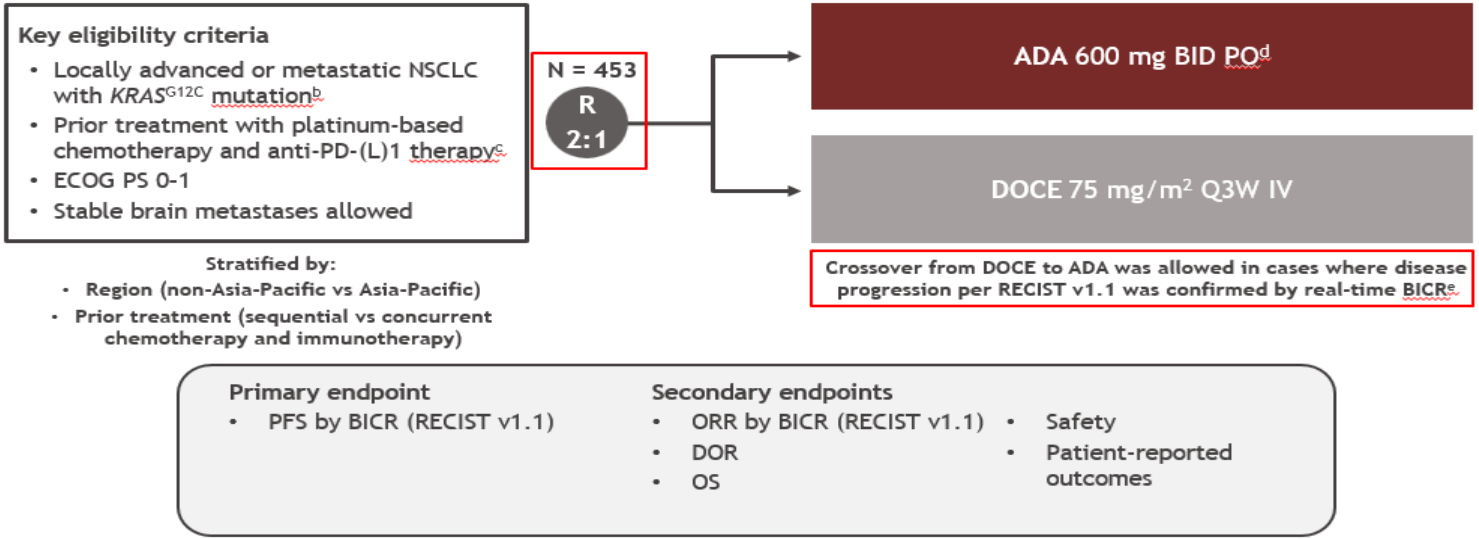
Median time to CNS progression or all-cause death was longer in patients treated with sotorasib compared to docetaxel

	Sotorasib n = 18	Docetaxel n = 13
Confirmed Objective Response, n (%)	6 (33.3)	2 (15.4)
CR	1 (5.6)	1 (7.7)
PR	5 (27.8)	1 (7.7)
Stable disease, n (%)	9 (50.0)	9 (69.2)
PD, n (%)	1 (5.6)	2 (15.4)
Not evaluable/Not done†, n (%)	2 (11.2)	0
Disease control, n (%)	15 (83.3)	11 (84.6)
Unconfirmed and confirmed ORR, n (%)	9 (50.0)	2 (15.4)

ORR was higher with sotorasib (33.3%) vs docetaxel (15.4%)

1. Dingemans AC, et al. Poster presented at: American Society of Clinical Oncology; June 2-6, 2023; Chicago, IL. Poster #LBA9016. **2.** de Langen AJ, et al. *Lancet*. 2023; 401: 733-746.

KRYSTAL 12
Study design



Database lock: March 19, 2024. Data cut-off: December 31, 2023.
[a]NCT04685135. [b]Detected in tumor tissue using sponsor-approved local or central testing. [c]No washout period was required between prior therapy and study treatment. [d]Tablet formulation, except for four patients who initially received the capsule formulation. [e]Other crossover criteria: ECOG PS 0-2, recovery from DOCE-related AEs to grade 1 or baseline (except peripheral neuropathy and alopecia for which grade 2 is acceptable).

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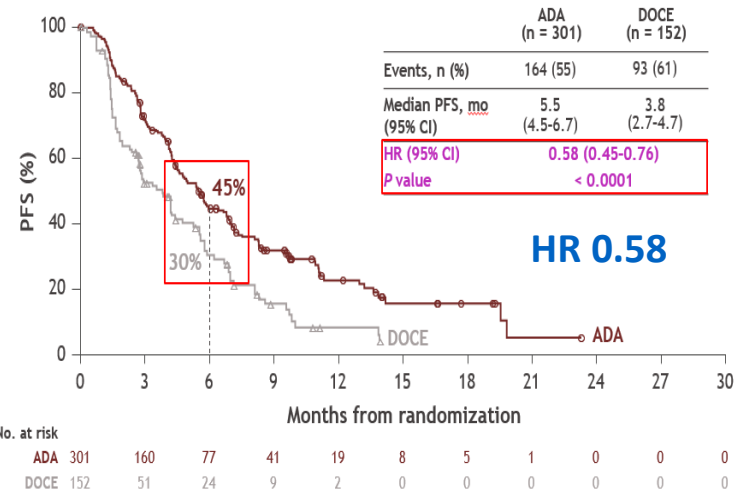
KRYSTAL 12

PFS and PFS subgroup analysis per BIRC

Primary endpoint: PFS[a] per BICR



	ADA (n = 301)	DOCE (n = 152)
Events, n (%)	164 (55)	93 (61)
Median PFS, mo (95% CI)	5.5 (4.5-6.7)	3.8 (2.7-4.7)
HR (95% CI)	0.58 (0.45-0.76)	
P value	< 0.0001	

HR 0.58

Median follow-up: 7.2 months.

[a]Time from randomization to the date of disease progression per BICR or death due to any cause, whichever occurs first. For patients who started a subsequent anticancer therapy prior to disease progression or death, PFS was censored at the date of the last tumor assessment prior to the start of the new therapy.

PFS subgroup analysis per BICR

	Median PFS, mo		Unstratified HR (95% CI)	Unstratified HR
	ADA (n = 301)	DOCE (n = 152)		
Overall (N = 453)	5.5	3.8		0.58
< 65 years (n = 234)	5.4	2.9		0.56
≥ 65 years (n = 219)	5.9	4.2		0.60
Male (n = 303)	5.4	2.9		0.55
Female (n = 150)	5.6	5.6		0.64
Non-Asia-Pacific (n = 335)	5.7	3.4		0.55
Asia-Pacific (n = 118)	5.4	3.9		0.66
ECOG PS 0 (n = 143)	11.1	5.8		0.44
ECOG PS 1 (n = 309)	4.6	2.8		0.61
Current smoker (n = 86)	4.2	4.4		0.89
Former smoker (n = 340)	5.8	3.6		0.51
Never smoker (n = 26)	5.5	6.2		0.70
Brain metastases at baseline (n = 80)[a]	4.1	4.2		0.71
No brain metastases at baseline (n = 373)[a]	5.8	3.6		0.55
Liver metastases at baseline (n = 64)[a]	4.5	1.4		0.43
No liver metastases at baseline (n = 389)[a]	5.6	4.2		0.59
Bone metastases at baseline (n = 107)[a]	4.4	2.8		0.56
No bone metastases at baseline (n = 346)[a]	5.8	4.2		0.58
PD-L1 < 1% (n = 95)	5.8	2.8		0.44
PD-L1 1-49% (n = 195)	5.9	3.6		0.56
PD-L1 ≥ 50% (n = 100)	5.0	3.9		0.62
Sequential chemo-immunotherapy (n = 121)	5.8	2.9		0.53
Concurrent chemo-immunotherapy (n = 332)	5.4	3.9		0.60

Median follow-up: 7.2 months.
Bold text indicates stratification factors. [a]In accordance with RECIST v1.1 per BICR.

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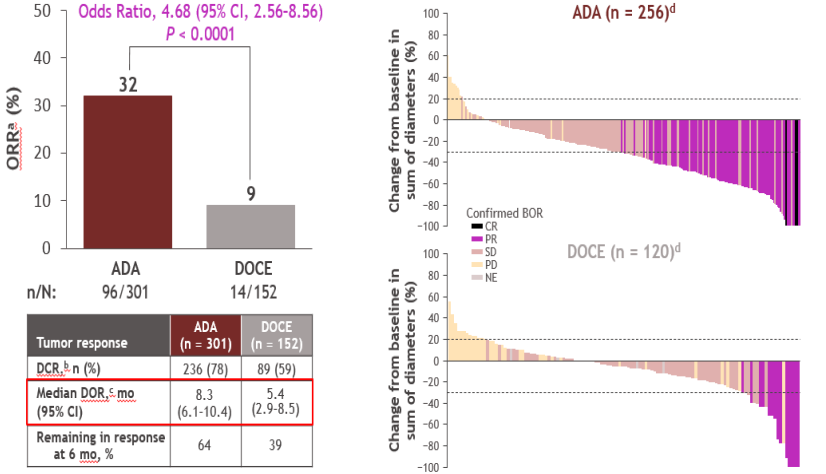
KRYSTAL 12

Tumor response and Intracranial response per BIRC

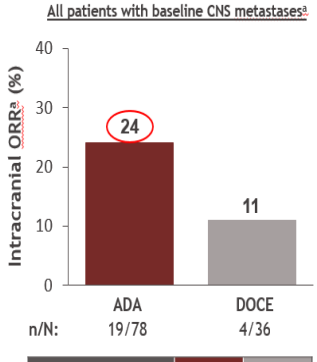
Tumor response per BICR 32% vs 9%



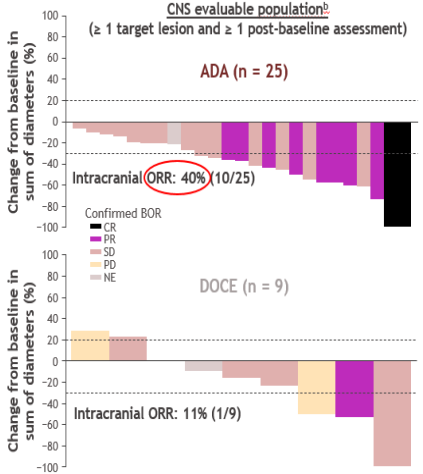
Tumor response	ADA (n = 301)	DOCE (n = 152)
DCR,[b] n (%)	236 (78)	89 (59)
Median DOR,[c] mo (95% CI)	8.3 (6.1-10.4)	5.4 (2.9-8.5)
Remaining in response at 6 mo, %	64	39

[a]ORR is defined as the percent of patients documented to have a confirmed CR/PR by BICR (per RECIST v1.1). [b]Disease control rate (DCR) is defined as the percent of patients documented to have a confirmed CR/PR/SD by BICR (per RECIST v1.1). [c]DOR is defined as the time from the date of first documentation of CR/PR to the first documentation of PD or death due to any cause in the absence of documented PD. DOR is only calculated for patients with confirmed CR/PR. [d]Waterfall plots include patients with at least one target lesion at baseline and at least one post-baseline tumor assessment.

Intracranial response per BICR[a] 24% vs 11%



Intracranial response[a]	ADA (n = 78)	DOCE (n = 36)
Intracranial DCR, n (%)	64 (82)	20 (56)



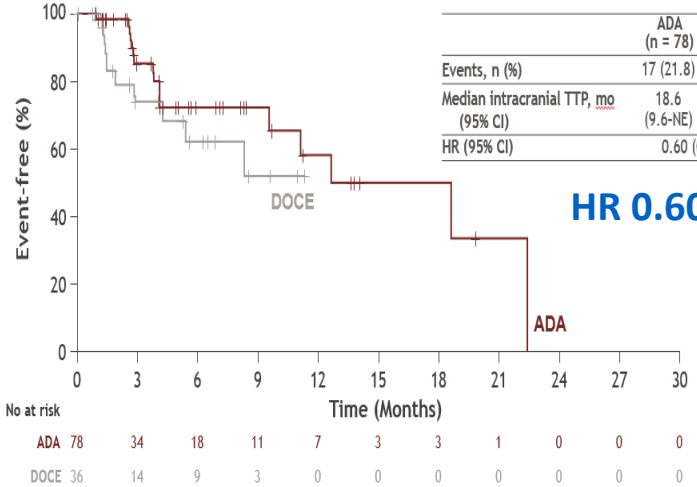
[a]In accordance with CNS-adapted RECIST v1.1. CNS RECIST data (including identification of patients with baseline CNS metastases) were based on a separate CNS imaging charter and neuroradiologist review. [b]Waterfall plots show CNS evaluable population including patients with at least one CNS target lesion at baseline and at least one post-baseline CNS tumor assessment. For lesions to be considered target lesions, they must have been measurable and either not previously treated with CNS-directed therapy or must have progressed after prior CNS-directed therapy.

Mok T, et al. ASCO 2024

Barlesi F, et al. ESMO 2024

KRYSTAL 12
Safety Summary

Intracranial TTP[a] in patients with baseline brain metastases[b]



	ADA (n = 78)	DOCE (n = 36)
Events, n (%)	17 (21.8)	9 (25.0)
Median intracranial TTP, mo (95% CI)	18.6 (9.6-NE)	NE (4.2-NE)
HR (95% CI)	0.60 (0.26-1.40)	

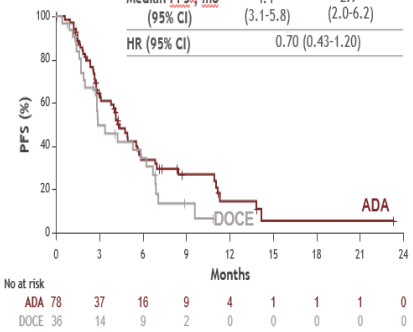
HR 0.60

- The HR for intracranial PFS[c] in patients with brain metastases was 0.93 (95% CI, 0.50-1.73)

Median follow-up for ITT population: 7.2 months. [a]Per BICR in accordance with CNS-adapted RECIST v1.1. TTP was defined as the time from randomization to the date of the first documentation of objective progression of intracranial disease, based on either new brain metastases or progression of existing brain metastases. [b]Identified using an independent CNS imaging charter and neuroradiologist review. [c]Per BICR in accordance with CNS-adapted RECIST v1.1. PFS was defined as the time from randomization to the date of intracranial progression of disease or death due to any cause, whichever occurred first.

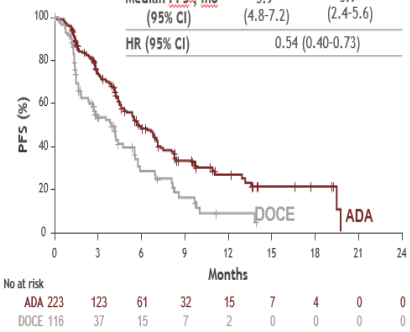
Systemic efficacy[a] according to presence of baseline brain metastases[b]

Patients with baseline brain metastases



	ADA (n = 78)	DOCE (n = 36)
Median PFS[c], mo (95% CI)	4.4[d] (3.1-5.8)	2.9[d] (2.0-6.2)
HR (95% CI)	0.70 (0.43-1.20)	

Patients without baseline brain metastases



	ADA (n = 223)	DOCE (n = 116)
Median PFS[c], mo (95% CI)	5.9[e] (4.8-7.2)	3.9[e] (2.4-5.6)
HR (95% CI)	0.54 (0.40-0.73)	

- ORR was higher in the ADA vs DOCE arm in patients with (26.9% vs 2.8%) and without (33.6% vs 11.2%) baseline brain metastases
- Median DOR[f] was higher in the ADA vs DOCE arm in patients with (7.4 vs 5.4 mo) and without (8.3 vs 5.4 mo) baseline brain metastases

Median follow-up: 7.2 months. [a]Per BICR in accordance with RECIST v1.1. [b]Identified using an independent CNS imaging charter and neuroradiologist review. [c]PFS was defined as the time from randomization to the date of disease progression per BICR or death due to any cause, whichever occurred first. For patients who started a subsequent anticancer therapy prior to disease progression or death, PFS was censored at the date of the last tumor assessment prior to the start of the new therapy. [d]PFS events occurred in 62.8% and 69.4% of patients in the ADA and DOCE arms, respectively. [e]PFS events occurred in 51.6% and 58.6% of patients in the ADA and DOCE arms, respectively. [f]DOR is defined as the time from the date of first documentation of CR/PR to the first documentation of PD or death due to any cause in the absence of documented PD. DOR is only calculated for patients with confirmed CR/PR.

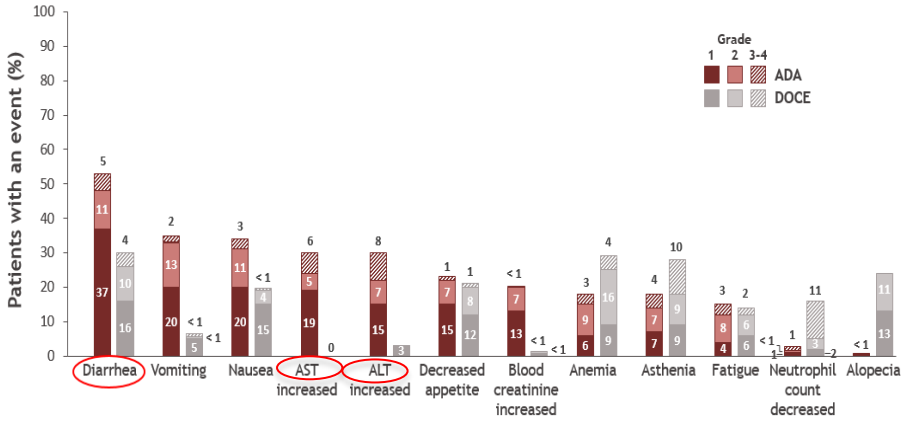
Barlesi F, et al. ESMO 2024

KRYSTAL 12
Safety Summary

Patients, %	ADA (n = 298)	DOCE (n = 140)
TRAEs	94	86
Grade ≥ 3 TRAEs	47	46
TRAEs leading to discontinuation[b]	8	14
TRAEs leading to dose reduction	48	24
TRAEs leading to dose interruption	59	19
Treatment-related SAEs	21	16
Treatment-related deaths[c]	1	< 1

[a]AEs per CTCAE v5.0 and MedDRA v26.0. Includes events reported between the first dose and 28 days after the last dose, and prior to the initiation of subsequent anticancer therapy. For each category, patients are included only once, even if they experienced multiple events in that category. [b]Most common TRAEs leading to treatment discontinuation were ALT increased (n = 3), neutropenia, diarrhea, and pneumonitis (n = 2 each) with ADA, and asthenia, fatigue, and peripheral neuropathy (n = 3 each) with DOCE. [c]Treatment-related deaths were due to epilepsy, hepatic failure, hepatic ischemia, and unknown cause with ADA, and sepsis with DOCE (n = 1 each).

Most frequent TRAEs (> 15% in either treatment arm[a])

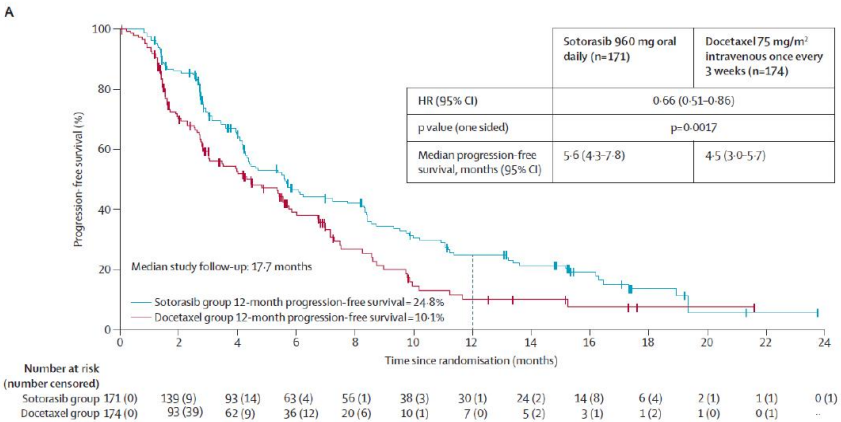


[a]For each TRAE, patients are included only once at the maximum severity.

Mok T, et al. ASCO 2024

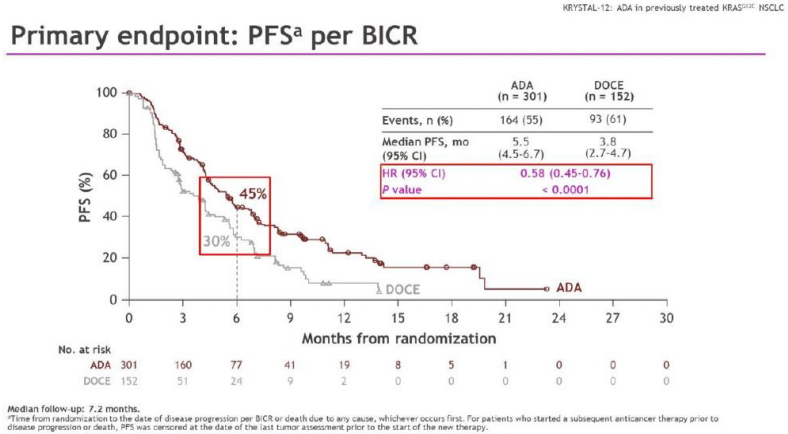
Can the promising response confirm superiority over the current SOC (docetaxel) in Phase III studies?

phase III CoreBreak200: Sotorasib vs Docetaxel



- ORR 28.1% (37.1% in phase II) vs 13.1%
- mPFS showed clinical marginal benefit (5.6 vs 4.5 months, HR 0.66)
- yet "cannot reliably be interpreted" due to early censoring and overperformance of control group?

phase III KRYSTAL-12: Adagrasib vs Docetaxel

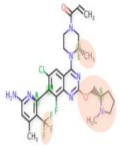


- ORR 32% (42.9% in phase II) vs 9%
- mPFS 5.5 vs 3.8 months, HR 0.58
- Potential CNS activity: intracranial response 24% (40% in CNS evaluable population)

1. Lancet 2023; 401: 733–46; 2.Tony Mok, et al. 2024 ASCO # LBA8509

New KRAS G12C inhibitors

Divarasib: single-agent long-term follow-up



Previous report (2023NEJM), NSCLC (n=60):

confirmed ORR 53.4% (95% CI, 39.9 to 66.7),

- Dose level 400 mg (n=39): 56.4% (95% CI, 39.6 to 72.2)

median DoR 14.0 months (95% CI, 8.3 to NE)

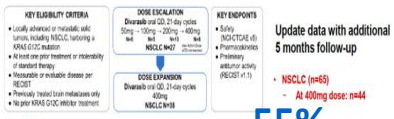
- 400mg: median DoR 11.9 months

median PFS 13.1 months (95% CI, 8.8 to NE)

- 400mg: median PFS 13.7 months

Data cut-off: Nov 21st, 2022;
Median treatment duration 8.3 months (range: 0 to 24.1)

N Engl J Med 2023;389:710-21.

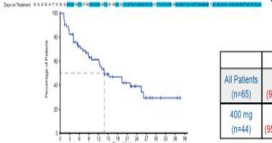


Update data with additional 5 months follow-up

- NSCLC (n=65)
  - At 400mg dose: n=44

55%

	Confirmed ORR
All Patients (n=65)	55.6% (n=63)*
400 mg (n=44)	59.1% (n=44)*



	Median PFS	Median DoR**
All Patients (n=65)	13.8 mo (95% CI 9.8, 25.4)	18.0 mo (95% CI 11.1, 24.9)
400 mg (n=44)	15.3 mo (95% CI 12.3, 26.1)	14.0 mo (95% CI 11.1, 24.9)

CCOD: Apr 1st, 2024; median Time on treatment, 11 months (range 0-40)

STUDY TREATMENT ACTION DUE TO TRAEs	NSCLC N=65
Patients with AEs resulting in divarasib modification (interruption/reduction/withdrawal)	25 (39%)
Patients with AEs resulting from divarasib reduction	15 (23%)
Patients with AEs resulting from divarasib withdrawal	3 (5%)

TRAEs OVERALL (≥10% PATIENTS) & CORRESPONDING GRADE 3-5 TRAEs	NSCLC N=65	
	All TRAEs	Grade 3-5 TRAEs
Patients with at least one AE	61 (94%)	11 (17%)
Nausea	51 (79%)	1 (2%)
Vomiting	43 (66%)	0
Diarrhea	40 (62%)	2 (3%)
Fatigue	16 (25%)	1 (2%)
Decreased appetite	15 (23%)	0
Amylase increased	11 (17%)	0
ALT increased	10 (15%)	4 (6%)
Lipase increased	10 (15%)	2 (3%)
AST increased	9 (14%)	3 (5%)

N Engl J Med 2023;389:710-21.

- Common treatment-related adverse events (TRAEs): nausea, vomiting, and diarrhea
  - Most events were Grade 1 and occurred early in study treatment
- No dose-limiting toxicities were reported
- Grade 5 events in 7 patients, all related to disease progression and none related to divarasib
- Among 31 patients who continued single-agent divarasib beyond one year, 17 (54.8%) experienced a new-onset TRAE after one year
  - No patients experienced new-onset Grade 3-5 TRAEs
  - No new-onset TRAEs led to dose reductions or divarasib withdrawal

Phase III studies including KRASCENDO-01

KontRASt-02: Phase 3, randomized, open-label trial of 2L JDQ443 vs docetaxel

Key eligibility criteria
- NSCLC with *KRAS* G12C mutation confirmed through central testing
- ECOG PS 0–1
- No active brain mets
- Prior treatment with platinum-based regimen and a checkpoint inhibitor
- No prior treatment with a $KRAS^{G12C}$ inhibitor

n=360 → R 1:1 → JDQ443 / Docetaxel

Primary endpoint: PFS

BFAST Cohort G: Randomized, open-label trial of 2L GDC-6036 vs docetaxel

Key eligibility criteria
- NSCLC with *KRAS* G12C mutation confirmed through central testing
- ECOG PS 0–1
- No active brain mets
- Prior treatment with platinum-based regimen and a checkpoint inhibitor
- No prior treatment with a $KRAS^{G12C}$ inhibitor

n=301 → R 1:1 → GDC-6036 / Docetaxel

Primary endpoint: PFS

- ≥18 years of age
- 2L/3L/4L unresectable advanced or metastatic *KRAS* G12C+ NSCLC
- ECOG performance status 0 or 1
- Prior platinum-based chemotherapy and PD-L1/PD-1 inhibitor
- Measurable disease per RECIST v1.1

R 1:1, N=320

Stratification factors:
- *KEAP1* mutation status* (detected vs not detected/unknown)
- History of CNS metastases (yes vs no)
- Intended choice of control arm drug (adagrasib or sotorasib)

Divarasib / Adagrasib or sotorasib†

Treatment discontinuation → Survival follow-up‡

P3.12D.07 WCLC 2024

Divarasib versus adagrasib or sotorasib in pretreated *KRAS G12C*+ advanced or metastatic non-small cell lung cancer (NSCLC)

Shirish M. Gadgeel,[1] Ahmadur Rahman,[2] Uyi Osaghae,[3] Tharu M. Fernando,[3] Mark T. Lin,[3] Kalpesh Koli,[3] Christoph Meyenberg,[4] Michael Mathisen,[3] Ferdinandos Skoulidis[5]

Primary endpoint	
Progression-free survival	Time from randomization to the first occurrence of disease progression or death from any cause
Secondary endpoints	
Key efficacy secondary endpoints	• Overall survival • Time to confirmed deterioration on the EORTC QLQ-C30 dyspnea item and the physical functioning scale, and the cough scale of the QLQ-LC13 scales
Other efficacy secondary endpoints	• Objective response rate • Duration of response
Safety and tolerability	• Incidence and severity of adverse events • Patient-reported outcomes, assessed by using the NCI PRO-CTCAE and the single-item EORTC IL46
Exploratory endpoints	
Biomarkers	Relationship between biomarkers in the blood, plasma, and tumor tissue, and efficacy, safety, and pharmacokinetics
Central nervous system activity, and pharmacokinetics and drug exposure	

Sacher A, et al WCLC 2024, OA14.06

NCT05132075; NCT03178552; Gadgeelet al WCLC 2024

New KRAS G12C inhibitors

Garsorasib: Updated Results from a Phase 2 Study

An open-label, multicenter, single-arm phase 2 study (NCT05383898)

Screening/ Enrollment → Garsorasib (600 mg, BID), continuous dosing 21 days per cycle → Tumor evaluation (every 6 weeks); Safety follow-up (30 days after last dose); OS follow-up (every 9 weeks)

Key Eligibility
- Locally advanced or metastatic NSCLC harboring KRAS G12C mutation
- Disease progression after prior anti-PD-(L)1 therapy and platinum-based chemotherapy or intolerance to the above regimens due to toxicity
- Measurable tumor lesions according to RECIST v1.1

Primary Endpoint
- ORR evaluated by IRC per RECIST v1.1.

Secondary Endpoints
- DOR, DCR, TTR, PFS, OS, and safety

Garsorasib (D-1553)

Previous Report (2024 Jan Lancet Respir Med):

IRC-confirmed ORR: 50% (61 / 123; 95% CI 41–59)

DCR 89% (109 / 123, 95% CI 82–94)

TTR 1.4 months, median DOR 12.8 months

Lancet Respir Med 2024; 12: 589–98

Updated data today: consistent response

IRC-confirmed ORR: 52% (64 / 123; 95% CI: 42.8, 61.1)
DCR 88.6% (95% CI: 81.6-93.6)

median DOR 12.5 months, DoR rate at 12mo: 51.7%

52%

Data cut-off: May 17th, 2024

Previous Report: DCO Nov 17th, 2023,
Median follow-up 7.9 months
Median PFS: 7.6 months (95% CI: 5.6-9.7)
Median OS: NR (95% CI: 11.4-NR)

Updated data today: With additional 6-month follow-up, more mature survival data

Median PFS: 9.1 months (95% CI: 5.6-10.3)

Median OS: 14.1 months (95% CI: 11.6-17.3)

Estimated 12mo OS rate: 57.2%

Data cut-off: May 17th, 2024

Updated safety summary with longer follow-up :

	n (%)
TRAEs leading to dose reduction	37 (30.1)
TRAEs leading to drug interruption	51 (41.5)
TRAEs leading to drug withdrawal	0

	Any Grade, n (%)	Grade ≥ 3, n (%)
Patients with at least one TRAE	118 (95.9)	63 (51.2)
TRAEs (frequency > 15%)		
Aspartate aminotransferase increased	65 (52.8)	21 (17.1)
Alanine aminotransferase increased	52 (42.3)	19 (15.4)
Gamma-glutamyltransferase increased	51 (41.5)	27 (22.0)
Anemia	42 (34.1)	5 (4.1)
Blood bilirubin increased	38 (30.9)	4 (3.3)
Blood alkaline phosphatase increased	33 (26.8)	6 (4.9)
Vomiting	29 (23.6)	2 (1.6)
Nausea	26 (21.1)	2 (1.6)
Diarrhoea	23 (18.7)	2 (1.6)
Conjugated bilirubin increased	23 (18.7)	8 (6.5)
Decreased appetite	22 (17.9)	3 (2.4)
Hypoalbuminaemia	21 (17.1)	0

ALT/AST increase : 5-6% in CB100 and K-1

Fulzerasib(IBI351, GFH925) : updated results

Key inclusion criteria:
- Advanced NSCLC patients with KRAS^{G12C} mutation
- Progression after standard treatment (≤ three lines)
- At least one measurable tumor lesion (per RECIST 1.1)

IBI351 monotherapy 600mg BID → progression or intolerable toxicity or other reasons to withdrawal

- Planned to enroll n=116~132
- Primary endpoint*: IRRC confirmed ORR per RECIST 1.1.
- Secondary endpoints: DCR, DoR, TTR, PFS, OS and Safety.

Previous report (2023ESMO Asia)
IRRC confirmed ORR 46.6%
Confirmed DCR 90.5%
Median PFS 8.3 month

Data cut-off: Jun 13th, 2023. Median follow-up 8.2 months
2023ESMO Asia, LBA12

Updated response

IRRC-Confirmed ORR 49.1%
DCR was 90.5%

Updated survival with addition 6-month follow-up

Median PFS: 9.7 months

12-month PFS rate: 37.9% (27.9, 47.9)

OS not mature, 12-month OS rate: 54.4% (44.9, 63.0)

median DoR not reached

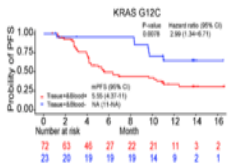
Data cutoff date: Dec 13, 2023
Median Follow-up: 13.7 months

CISION
China's First Approved KRAS G12C Inhibitor: Innovent Announces the Approval of Dupert® (Fulzerasib) by the National Medical Products Administration of China

Updated safety data with longer follow-up
- 48% (31/65) patients were treated beyond 1 year
- Grade ≥ 3 TRAE 41.4%
- 6.9% dose reduction, 6.0% discontinuation
- 2.6% (3/116) treatment related death

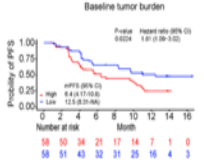
Common TRAEs (≥10% or G3 ≥5%)

KRAS G12C



- Shorter PFS in pts with blood+ *KRAS G12C*

Baseline tumor burden



- Shorter in pts with higher tumor burden at baseline

Li Z, et al WCLC 2024, OA14.03

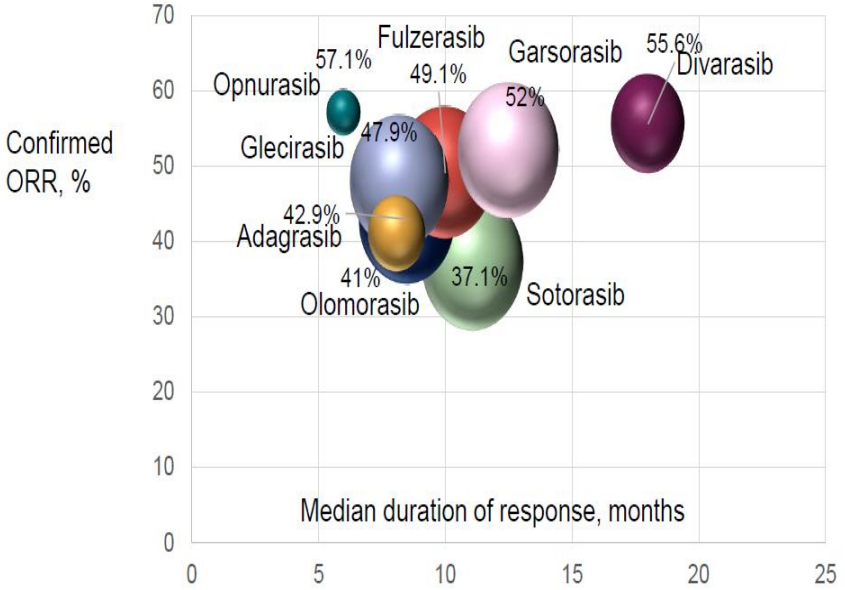
Zhou Q, et al WCLC 2024, OA14.05

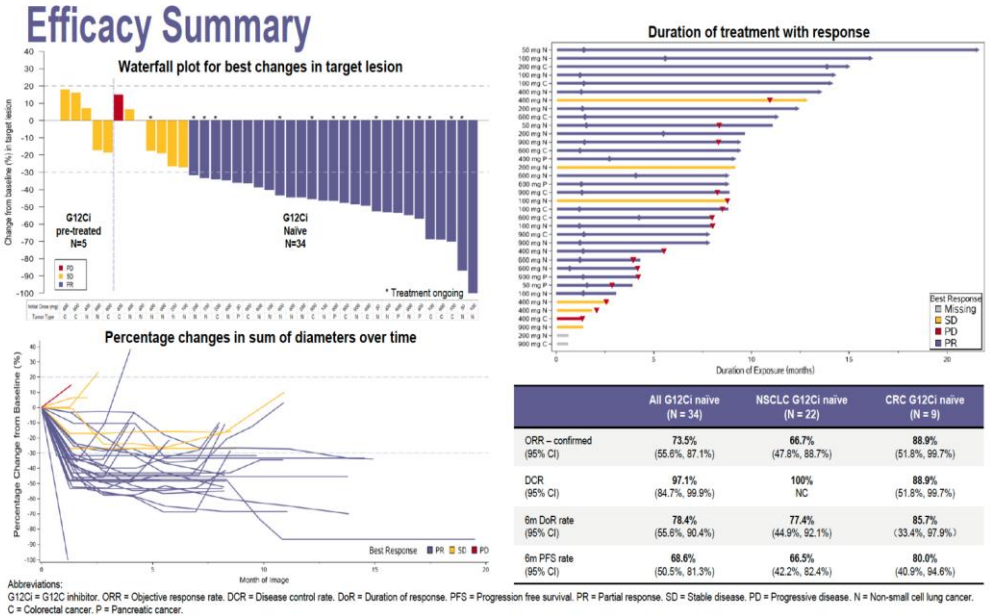
Data Summary of single agent KRAS G12C inhibitors in 2L+ NSCLC

Compound	Sotorasib		Adagrasib		Fulzerasib IBI351/GFH925	Divarasib GDC-6036		Garsorasib D-1553	Opnurasib JDQ443	Glecirasib JAB-21822	Olomorasib LY3537982
Approval / Highest study phase	FDA		FDA		NMPA	III		II	III	II	II
Study / Phase	CodeBreaK 100 / II	CodeBreaK 200 / III	KRYSTAL-1 / II	KRYSTAL-12 / III	II	I		II	KontRASt-01 / I-II	II	Ib
Patient Number	N=124	N=171	N=112	N=301	N=116	N=65	400mg N=44	N=123	200mg N=14	N=117	N=39
Confirmed ORR, %	37.1	28.1	42.9	32	**49.1**	**55.6**	**59.1**	**52.0**	**57.1**	47.9	41
DCR, %	80.6	82.5	79.5	78	**90.5**	-	-	**88.6**	**92.9**	86.3	88
Median DOR, months	11.1	8.6	8.5	8.3	**NC**	**18.0**	**14.0**	**12.5**	-	NE	-
Median PFS, months	6.8	5.6	6.5	5.5	**9.7**	**13.8**	**15.3**	**9.1**	-	8.2	8.1
Median OS, months	12.5	10.6 (vs11.3)	12.6	-	-	-	-	**14.1**	-	13.6	-
Safety population	N=126	N=169	N=116	N=298	**N=67**	**N=65**		**N=123**	N=68	N=119	N=184
Dose	960mg QD	960mg QD	600mg BID	600mg BID	600mg BID	50/100/200/400mg BID		600mg BID	200mg BID	800mg BID	50-200mg BID
Any grade TRAEs	69.8	70	97.4	94	**92.2**	**94**		**95.9**	**75**	97.5	**65**
Grade 3–4 TRAEs	20.6	33*	42.8	47	**33.6**	**17**		**51.2**	**5.9**	38.7	**7**
Dose reduction due to TRAE	-	15	51.7	48	**6.9**	**39****		**30.1**	**2.9**	-	**5**
Dose interruption due to TRAE	22.2	36	61.2	59	**33.6**	**23**		**41.5**	-	-	**13**
Dose discontinuation due to TRAE	7.1	10	6.9	8	**6.0**	**5**		**0**	-	5.0	**1**

1. N Engl J Med 2021;384:2371-81 ; 2. Lancet 2023; 401: 733–46 ; 3. N Engl J Med 2022;387:120-31; 4. 2024ASCO LBA8509; 5.2024WCLC OA14.03; 6.2024 WCLC OA14.05; 7.2024 WCLC OA14.06; 8.2023ASCO 9007 9.2024ASCO #468214;10.2024ASCO #3007

Phase 1/2 study of D3S-001, a second generation KRAS G12C inhibitor in advanced or metastatic solid tumors with KRAS G12C mutations





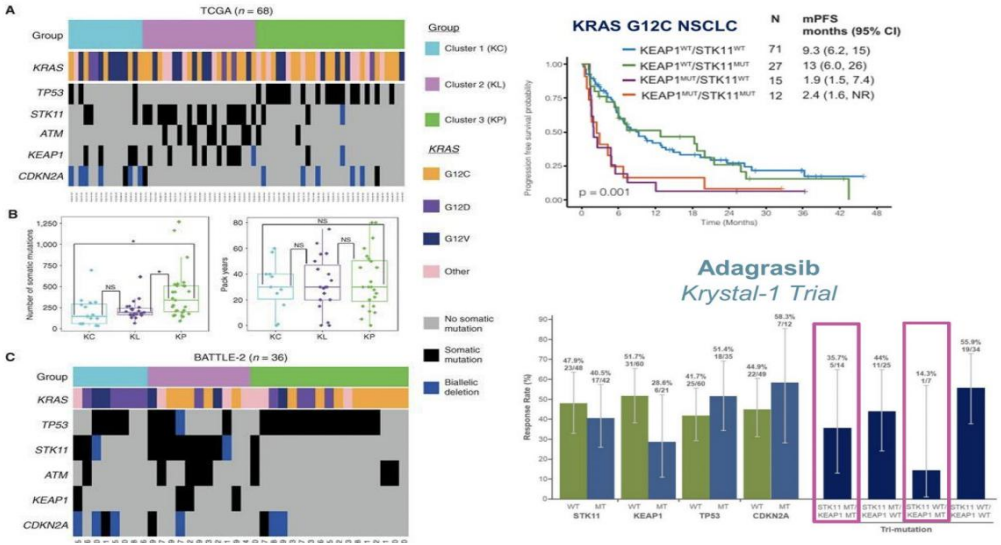
	All G12Ci naive (N = 34)	NSCLC G12Ci naive (N = 22)	CRC G12Ci naive (N = 9)
ORR – confirmed (95% CI)	**73.5%** (55.6%, 87.1%)	**66.7%** (47.8%, 88.7%)	**88.9%** (51.8%, 99.7%)
DCR (95% CI)	**97.1%** (84.7%, 99.9%)	**100%** NC	**88.9%** (51.8%, 99.7%)
6m DoR rate (95% CI)	**78.4%** (55.6%, 90.4%)	**77.4%** (44.9%, 92.1%)	**85.7%** (33.4%, 97.9%)
6m PFS rate (95% CI)	**68.6%** (50.5%, 81.3%)	**66.5%** (42.2%, 82.4%)	**80.0%** (40.9%, 94.6%)

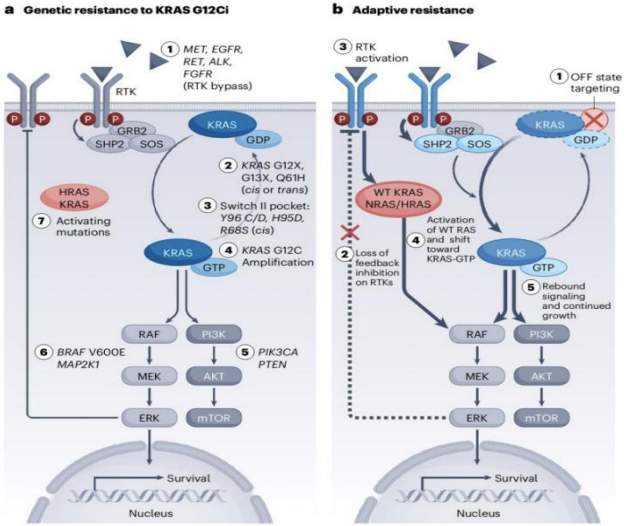
Abbreviations:
G12Ci = G12C inhibitor. ORR = Objective response rate. DCR = Disease control rate. DoR = Duration of response. PFS = Progression free survival. PR = Partial response. SD = Stable disease. PD = Progressive disease. N = Non-small cell lung cancer. C = Colorectal cancer. P = Pancreatic cancer.

Chul Cho B et al, ESMO 2024

Current challenges in KRASG12C management

- Heterogeneity of KRAS G12C: co-mutations indicate distinct subsets
  - TP53, STK11, and KEAP1 co-mutations are common in KRAS mut NSCLC
  - STK11 and KEAP1have been associated with poor outcomes.
- Multiple and complex resistant mechanisms

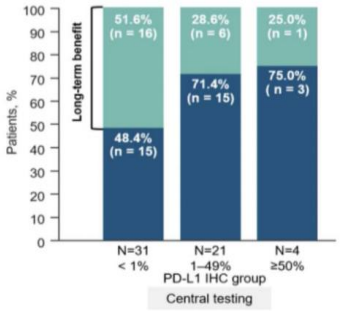


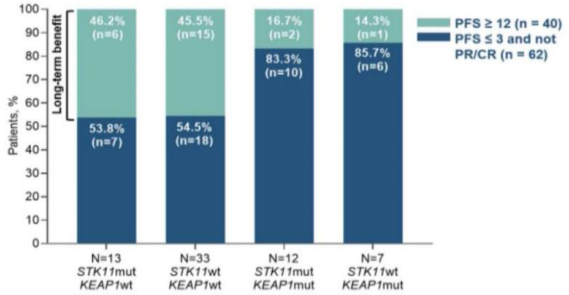


Nat Rev Drug Discov. 2020 Aug; 19(8): 533–552.Cancer Discov. 2015 Aug;5(8):860-77. Clin Cancer Res. 2018 Jan 15;24(2):334-340 ; Elkrief ef àl. Oncologist. 2017; Negrao et al. Cancer Discov. 2023; Anupriya Singhal et al, Nature, 2024

Biomarker of CodeBreak 100 and 200: PD-L1 and comutation

- Prolonged clinical benefit was observed across PD-L1 expression;
- Sotorasib Retained PFS Benefit Versus Docetaxel Across Key Co-alteration Subgroups





	Number of Patients		Median PFS (95% CI), months		Hazard Ratio (95% CI)	*P*-value
	Sotorasib (n = 171)	Docetaxel (n = 174)	Sotorasib (n = 171)	Docetaxel (n = 174)		
PD-L1 protein expression*						
< 1%	57	55	8.3 (4.1, 8.6)	5.9 (3.5, 7.2)	0.66 (0.41, 1.06)	0.06
≥ 1% and < 50%	46	70	4.6 (3.4, 7.8)	3.0 (2.1, 4.5)	0.61 (0.39, 0.96)	0.03
≥ 50%	60	40	5.7 (4.0, 10.0)	5.4 (2.0, 10.2)	0.74 (0.44, 1.23)	0.14

	Number of Patients		Hazard Ratio (95% CI)
	Sotorasib	Docetaxel	
All patients	164	154	0.68 (0.52, 0.88)
TP53			
Altered	89	92	0.83 (0.58, 1.18)
Wild-type	75	62	0.48 (0.30, 0.75)
STK11			
Altered	60	60	0.68 (0.45, 1.05)
Wild-type	104	94	0.65 (0.46, 0.92)
KEAP1			
Altered	46	36	0.84 (0.48, 1.47)
Wild-type	118	118	0.62 (0.45, 0.84)
EGFR			
Altered	31	35	0.86 (0.47, 1.58)
Wild-type	133	119	0.63 (0.46, 0.86)
BRAF			
Altered	7	9	–
Wild-type	157	145	0.63 (0.48, 0.83)
ALK			
Altered	19	15	0.72 (0.33, 1.57)
Wild-type	145	139	0.70 (0.53, 0.93)
MET			
Altered	18	21	0.52 (0.21, 1.29)
Wild-type	146	133	0.73 (0.55, 0.97)

1. 2022AACR.CT008; 2. JCO 41, 9008-9008(2023).

KRAS^{G12C} tumors develop fast resistance

Mechanisms of resistance

Secondary KRAS pathway mutations

Novel mutations or pre-existing?

Probably not enough to explain the rapid appearance of resistance

Increase of MAPK signalling (adaptive)

RKT upregulation and activation of wild-type RAS

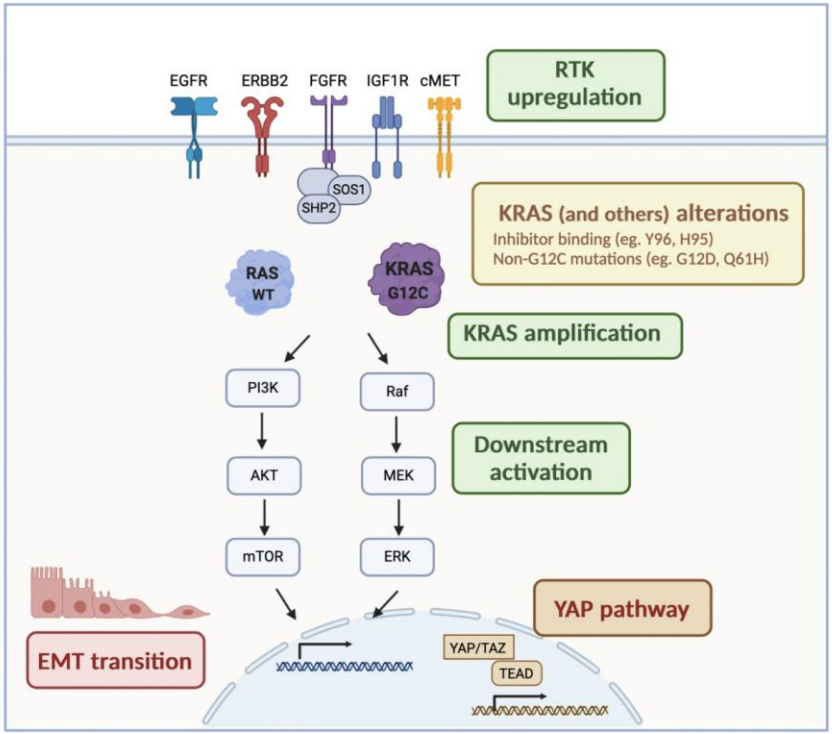
Downstream activation

KRAS amplification

Alternative

eg. YAP pa

Histologica

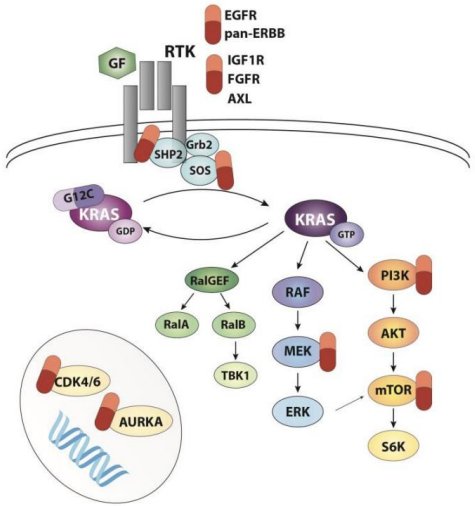


Targeting mechanisms of resistance

Identification of combination approaches for the use osf $KRAS^{G12C}$ inhibitors

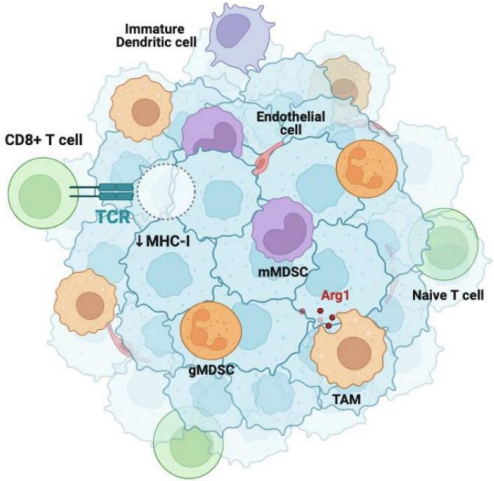
Tumour intrinsic

Targeting proliferative pathways driven by KRAS

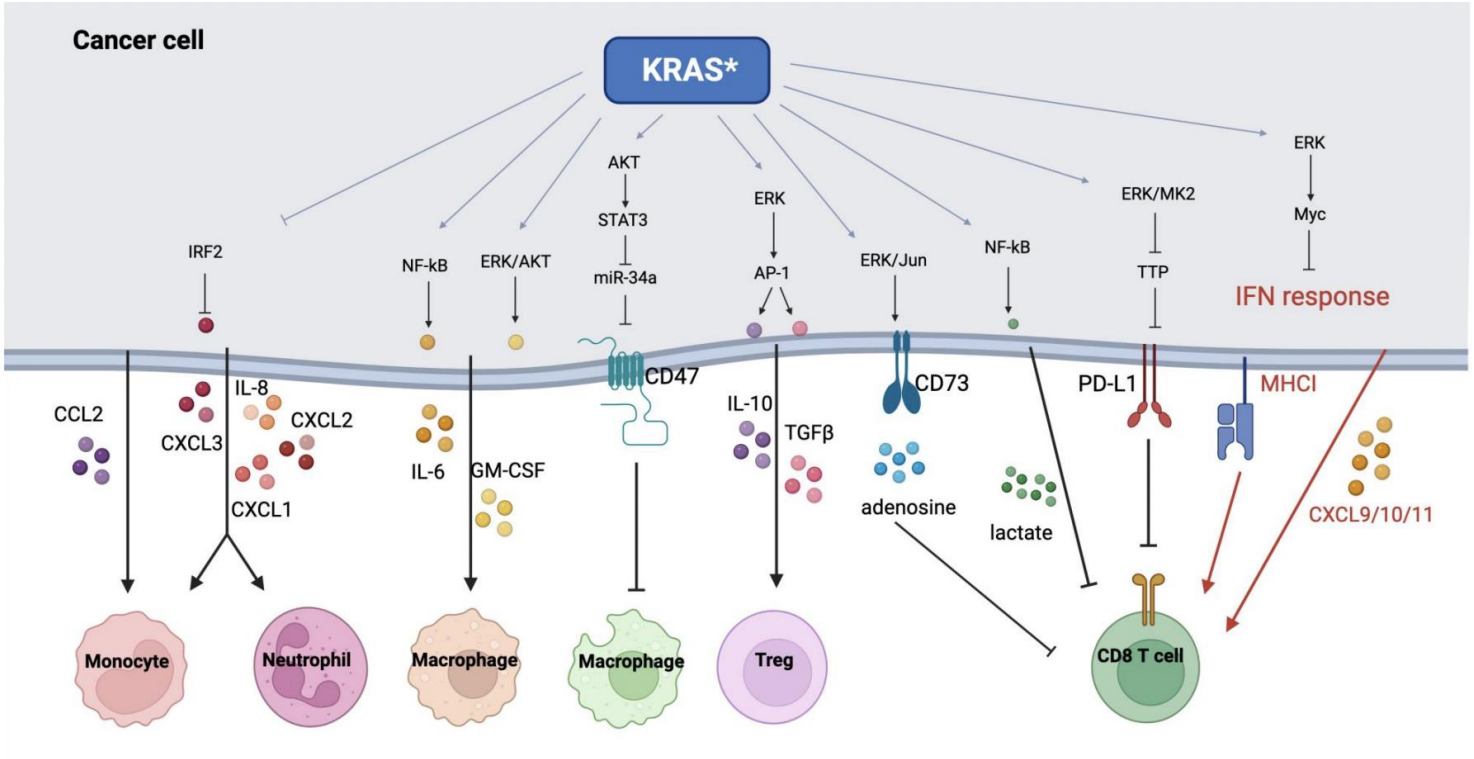


Tumour microenvironment

Targeting pathways driven by KRAS that promote tumour evasion of the immune system



Oncogenic KRAS modulates the immune TME



Augment G12C inhibitor-Optimal combination

- FDA summary analysis：Immunotherapy can be effective for KRAS NSCLC
- Patients with KRAS G12C NSCLC benefit from ICI+chemo similarly to those with KRAS-wt NSCLC;
- Optimal control arm for studies of 1L therapy may be **ICI+chemo;**
- Rapid emergence of drug resistance underscores the urgent need to synergize with other therapeutic approaches to improve outcomes.

Results: ORR according to *KRAS* status

Similar response rate between patients with *KRASwt* & *KRASm* NSCLC

	ORR (95% CI)		
	KRASwt N=875	***KRASm*** N=555	***KRAS G12C*** N=157
ICI+Chemo	**51%** (46, 57)	**46%** (39, 53)	**47%** (33, 60)
ICI alone	**33%** (27, 40)	**37%** (29, 46)	**33%** (20, 49)
Chemo alone	**32%** (33, 60)	**33%** (20, 49)	44% (31, 59)

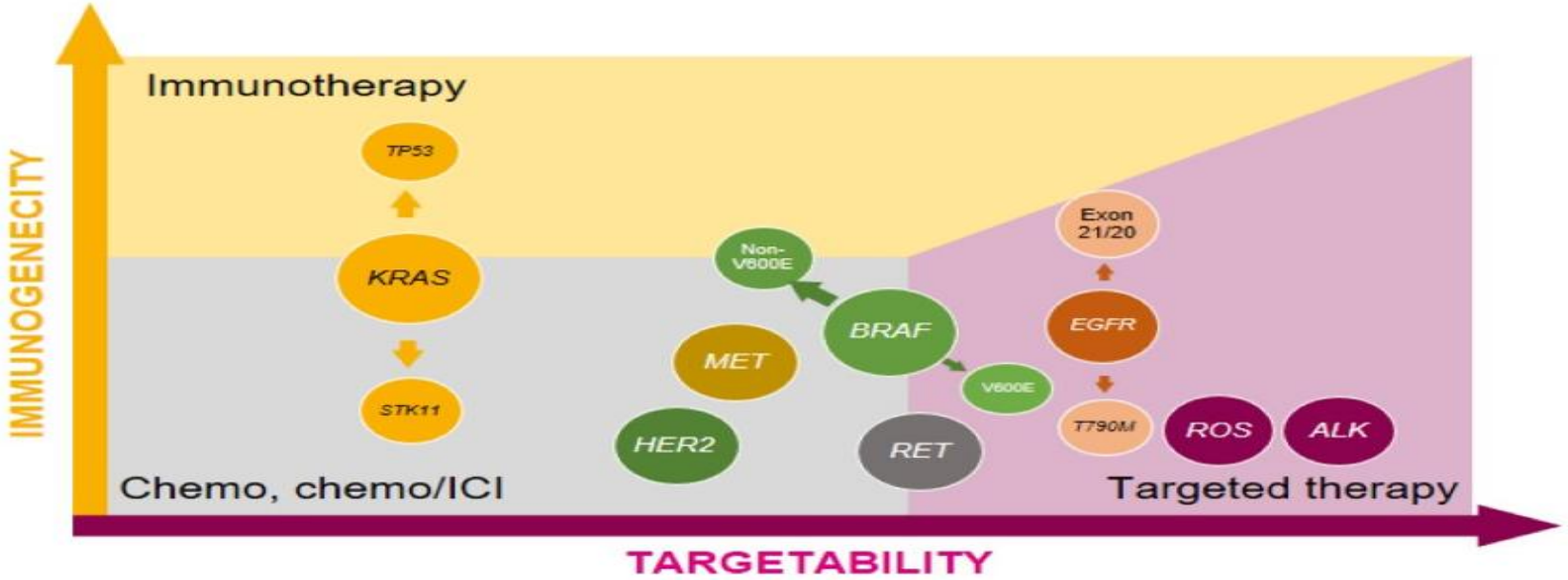
Results: Median OS according to *KRAS* status

Patients with *KRASm* NSCLC have similar OS to those with *KRASwt* NSCLC

Study Therapy	Median OS, mos (95% CI)		
	KRASwt	***KRASm***	***KRAS G12C***
ICI+chemo	**18.7** (16.0, 25.2) N=313	**22.4** (18.2, NE) N=219	**20.8** (11.3, NE) N=58
	HR 1.12 (95% CI: 0.86, 1.46)		
ICI alone	**16.4** (13.4, 19.7) N=240	**16.2** (11.1, NE) N=135	**11.8** (8.2, NE) N=45
	HR 1.01 (95% CI: 0.76, 1.34)		
Chemo alone	14.9 (12.2, 16.6) N=322	17.1 (12.3, 18.9) N=201	17.5 (10.7, 21.1) N=54
	HR 1.02 (95% CI: 0.81, 1.29)		

2022 ASCO 9001

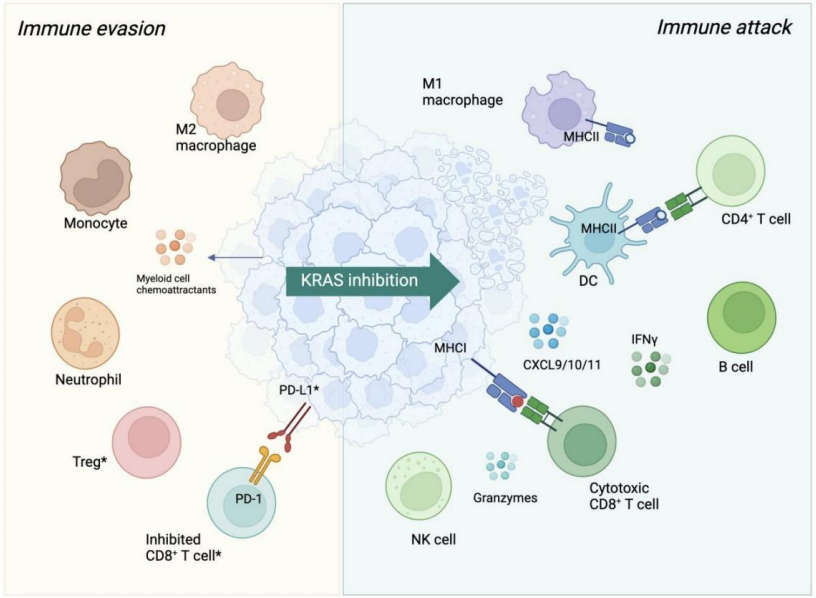
How To Differentiate KRAS From Other Oncogenic Drivers In NSCLC



KEAP1, kelch-like ECH-associated protein 1; *STK11*, serine/threonine kinase 11; TP53, tumour protein 53

Mhanna L, et al. Curr Treat Options Oncol 2019;20:60.

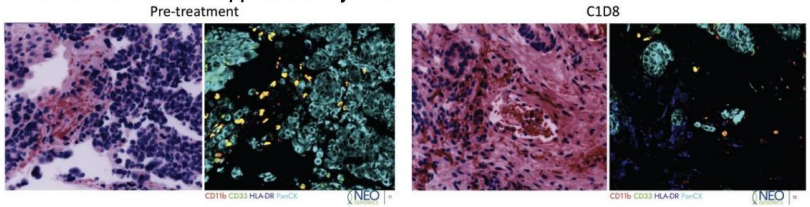
KRAS^{G12C} inhibitios reverse immune suppression and change the immune TME



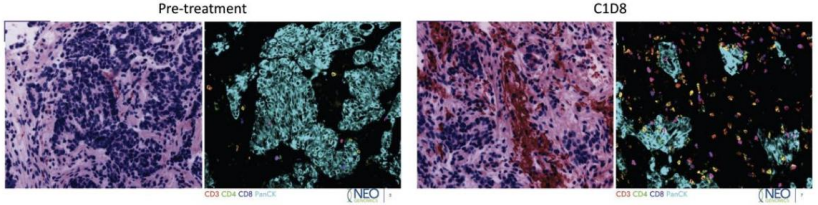
Molina-Arcas and Downward, Cancer Cell 2024

Pre-treatment vs adagrasib (cycle 1 day 8)

Reduction in immune suppressive myeloid cells



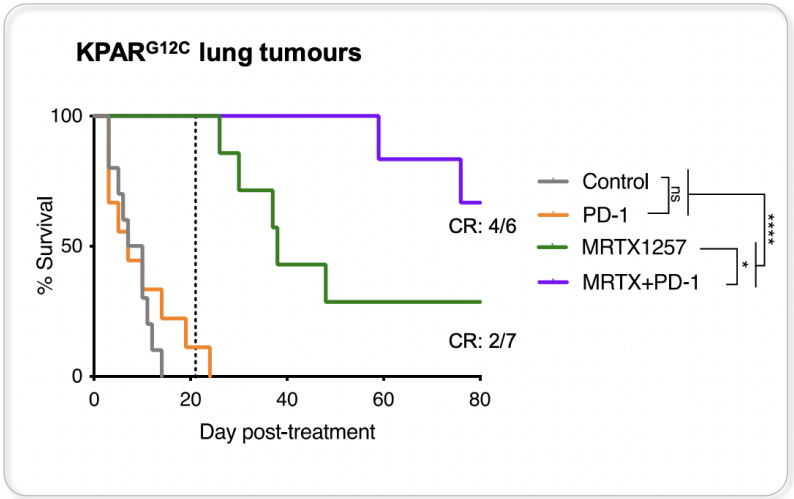
Increase in T cells



Hallin, NCI 4th RAS Initiative Symposium 2022

Molina-Arcas and Downward, Cancer Cell 2024

KRASG12C inhibitors combine with anti-PD1



Mugarza, Science Advances 2022

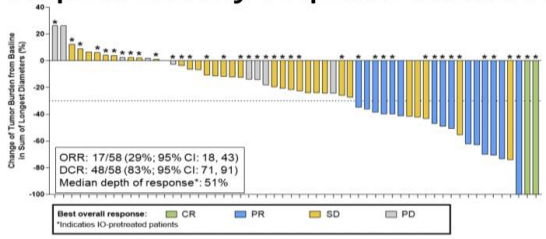
Clinical trials

Drug	Combination	Clinical trial	Phase
Sotorasib *Amgen*	Anti PD-1/PD-L1[a]	CodeBreak 100 (NCT03600883)	Phase 1
Sotorasib *Amgen*	Pembrolizumab (PD-1) Atezolizumab (PD-L1)	CodeBreak 101 (NCT04185883)	Phase 1/2
Adagrasib *Mirati Ther*	Pembrolizumab (PD-1)	KRYSTAL-1 (NCT03785249)	Phase 1b
Divarasib *Genentech*	Atezolizumab (PD-L1)	NCT04449874	Phase 1
Opnurasib Novartis	Tislelizumab (PD-1) -/+ TNO155 (SHP2i)	KontRASt-01 (NCT04699188)	Phase 1/2
Olomorasib *Eli Lilly*	Pembrolizumab (PD-1)	NCT04956640	Phase 1
MK-1084 *Merck*	Pembrolizumab (PD-1)	NCT05067283	Phase 1
IBI351 *Innovent Biol*	Sintilimab (PD-1) -/+ chemotherapy	NCT05504278	Phase 1/2
RMC-6291 (G12C) or **RMC-6236** (multi) *RevMed*	Pembrolizumab (PD-1) -/+ chemotherapy	NCT06162221	Phase 1/2
Adagrasib *Mirati Ther*	Pembrolizumab (PD-1)	KRYSTAL-7 (NCT04613596)	Phase 2-3 (PD-L1 TPS >=50%)
Adagrasib *Mirati Ther*	Nivolumab (PD-1)	Neo-Kan (NCT05472623)	Phase 2 (neoadjuvant)
Adagrasib *Mirati Ther*	Pembrolizumab (PD-1) +/- chemotherapy	NCT05609578	Phase 2 (PD-L1 TPS between ≥1% and <50%)

KRASG12C inhibitors and Immunotherapy

CodeBreaK 100/101: pembrolizumab+Sotorasib

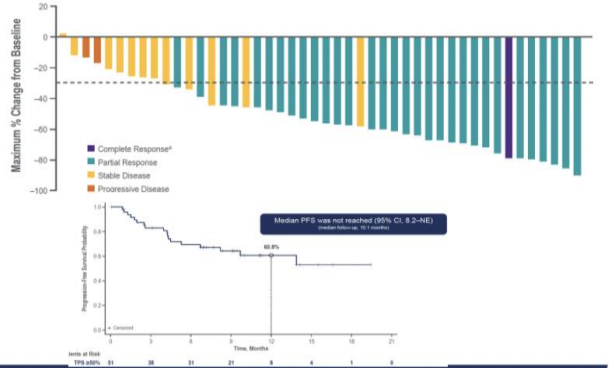
- ORR 29%, DCR 83%; mOS 15.7m
- Hepatotoxicity requires attention



TRAE*, n (%)	Sotorasib 120 mg (N = 3)		Sotorasib 240 mg (N = 5)		Sotorasib 360 mg (N = 11)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
All TRAEs	3 (100)	3 (100)	3 (60)	1 (20)	9 (82)	6 (55)
ALT increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	3 (27)
AST increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	2 (18)

KRYSTAL-7 pembrolizumab+Adagrasib

- PD-L1≥50% ORR 63% (Overall ORR 49%)
- Liver-related TRAEs were predominantly low grade and manageable
-



Most Frequent Liver TRAEs, %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Hepatitis	4	0	2	2	0
Hepatotoxicity[a]	1	0	1	1	0

1. Li B et al, WCLC 2022 OA03.06. 2. Garassino MC, et al. Presented at ESMO 2023

Data Summary of KRAS G12Ci + immunotherapy

Combination of divarasib with atezolizumab: phase I study

KEY ELIGIBILITY CRITERIA

- Locally advanced or metastatic NSCLC, harboring a *KRAS G12C* mutation
- At least one prior treatment or intolerability of standard therapy
- Measurable or evaluable disease per RECIST
- Previously treated brain metastases only
- Prior KRAS G12C inhibitor treatment allowed (no discontinuation due to toxicity)

DOSE ESCALATION

Divarasib oral QD, 21-day cycles
+ **atezolizumab** 1200 mg IV q3w
200mg → 400mg
N=3 N=6
Max Admin Dose MTD not reached

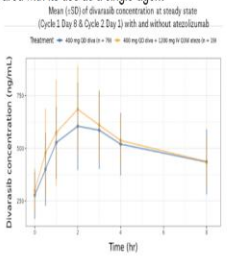
DOSE EXPANSION

Divarasib oral QD, 21-day cycles
+ **atezolizumab** 1200 mg IV q3w
200 mg / 400mg
N=15 N=15

KEY ENDPOINTS

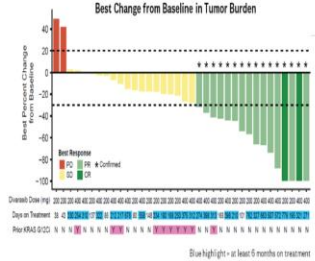
- Safety (NCI-CTCAE v5)
- Pharmacokinetics
- Preliminary antitumor activity (RECIST v1.1)

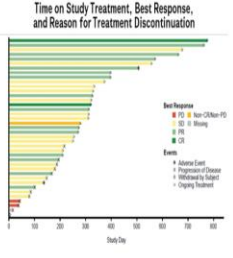
The steady-state PK profile of divarasib (400 mg QD) was similar in combination with atezolizumab in NSCLC when compared with its use as a single-agent

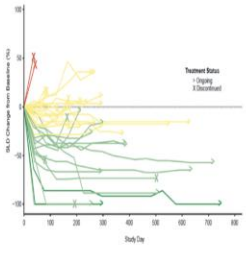


Confirmed ORR*	All Patients	No Prior KRAS G12Ci	Confirmed ORR (mono)
All Doses	42.1% (n=38)	55.6% (n=27)	55.6% (n=63)*
400 mg	45.0% (n=20)	61.5% (n=13)	59.1% (n=44)*

The ORR for patients without prior KRAS G12Ci treatment seemed similar to that of single-agent divarasib



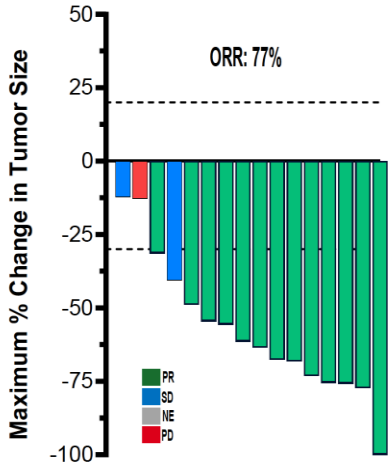




Blue highlight = at least 6 months on treatment

- Olomorasib, a potent 2nd generation KRAS G12C inhibitor, has previously demonstrated:
  - A favorable monotherapy safety profile and promising monotherapy efficacy, including in patients previously treated with KRAS G12C inhibitors[1]
    - Preliminary evidence of CNS activity in NSCLC with untreated measurable brain metastases[1]
  - Ability to combine with pembrolizumab with an acceptable safety profile

Olomorasib + pembrolizumab in 1L mNSCLC[2]



1Heist RS et al. Presented at ASCO Annual Meeting 2024. 2Burns TF et al. Presented at ASCO Annual Meeting 2024.

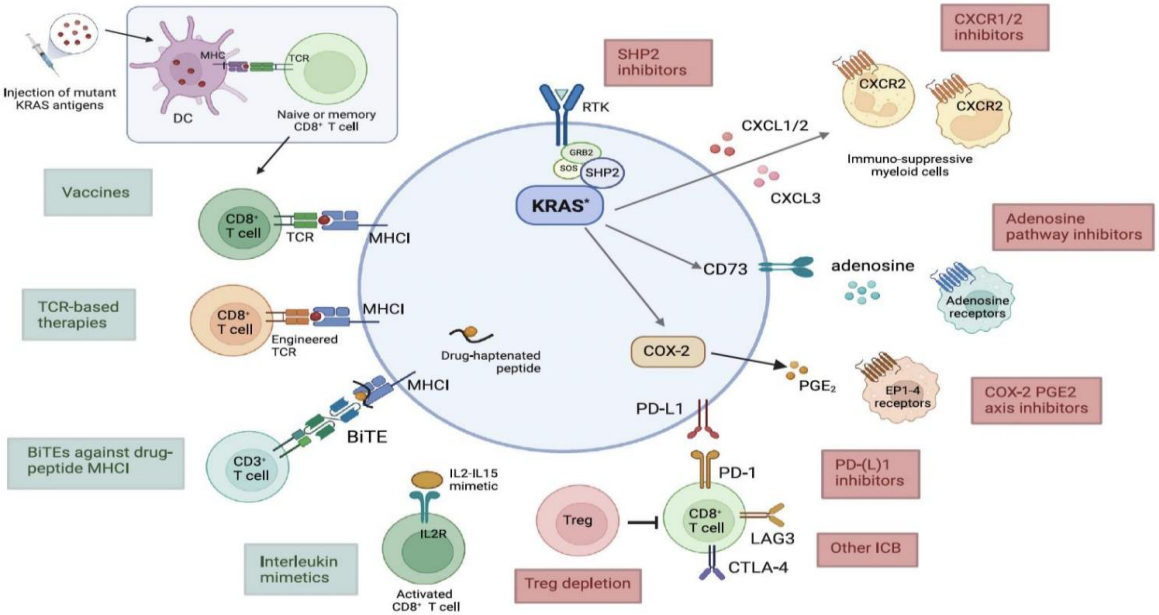
Fujiwara Y, WCLC 2024; OA14.04

Data Summary of KRAS G12Ci + immunotherapy

Combinations	Adagrasib + pembro	Sotorasib + atezo/pembro		Divarasib + atezo		Olomorasib + pembro		Olomorasib + Pembro + chemo
Trial (phase)	**KRYSTAL-7 (Ph2)**	**CodeBreaK 100/101 (Ph1/2)**		**Ph1**		**Ph1b**		**Ph 1b**
Efficacy	**PD-L1 ≥50%, 1L N=51**	**N=58 (21% as 1L)**		**N=38 2L**	**400mg N=20 2L**	**1L N=17**	**2L N=42**	**1L N=20**
ORR, %	**63**	29		**42.1**	**45.0**	**77**	**40**	**50**
DCR, %	84	83		-	-	88	81	85
Median DOR, months	NR	17.9		-	-	NE	NE	NR
12-month PFS rate, %	60.8	-		-	-	72.8	-	-
Median OS, months	-	15.7		-	-	-	-	-
Safety, %	**N=148**	**Con-Atezo =10**	**Con-Pembro =19**	**N=39**		**N=64**		**N=20**
Any grade TRAEs	94	90	89	95		70		90
Grade 3–4 TRAEs	**66**	60	79	**28**		**27**		**45**
ALT increased	**10**	-	Concurrent 720mg 100% 960mg 75%	**5**		**6**		**5**
AST increased	**14**	-		**5**		**8**		**-**
Dose reduction due to TRAE	46	-	-	**23**		**17**		-
Dose interruption due to TRAE	59	-	-	36*		25		-
Dose discontinuation due to TRAE	A+P:4, A:6, P:11	50	53	Diva: 3; Atezo: 15		Olo:3; Pembro:11; O+P: 5		All: 10; O:5; P:10; chemo:10
ongoing studies	**KRYSTAL-7 (Ph3)** Ada + pembro PD-L1 ≥50%	**CB 201 (Ph2)** PD-L1 <1% and/or STK11m		**KRASCENDO 170** Diva + pembro ± chemo		**SUNRAY-01** olomorasib + pembrolizumab ± chemo		

1. 2023ESMO LBA65; 2.2022WCLC OA03.06; 3. 2024WCLC OA14.06; 4. 2024ASCO #195; 5 2024WCLC OA14.04

Potential Immunotherapy approaches to target KRASm tumors



Miriam Molina-Arcas, et al. Cancer cell, 2024

Sotorasib + Chemotherapy

Phase 1b CodeBreaK 101 Study

Key eligibility criteria

- *KRAS* G12C–mutated advanced NSCLC, identified through molecular testing
- Patients were treatment-naive or previously treated*
- Measurable disease per RECIST v1.1
- ECOG ≤ 2
- No active brain metastases

→

Up to 4 cycles†

Sotorasib 960 mg PO daily
+
Carboplatin AUC 5 IV Q3W
+
Pemetrexed 500 mg/m² IV Q3W

→

Maintenance†

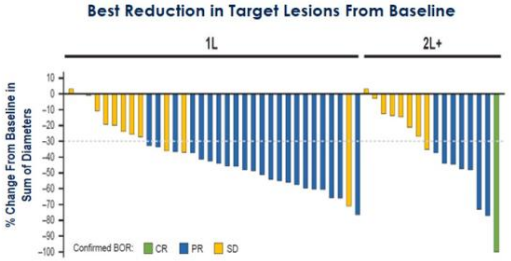
Sotorasib 960 mg PO daily
+
Pemetrexed 500 mg/m² IV Q3W

Data were pooled from dose exploration and expansion cohorts and analyzed by exposure to prior therapy in the locally advanced/metastatic setting: **1L (n = 37) and 2L+ (n = 21)‡**

Primary endpoints: Safety and tolerability (including DLT)
Secondary endpoints: ORR, DCR, DOR, TTR, OS, PFS, duration of SD, and PK

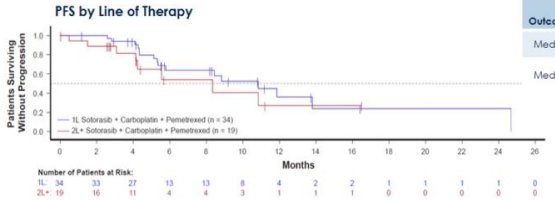
Efficacy

Confirmed response by investigator assessment*	Sotorasib + Carboplatin + Pemetrexed 1L (n = 34)	Sotorasib + Carboplatin + Pemetrexed 2L+ (n = 19)
ORR, n (%)	22 (65)	8 (42)
Best overall response, n (%)		
Complete response	0	1 (5)
Partial response	22 (65)	7 (37)
Stable disease	12 (35)†	8 (42)
Progressive disease	0	1 (5)
Not evaluable / not done	0	2 (11)
DCR, n (%)	34 (100)	16 (84)

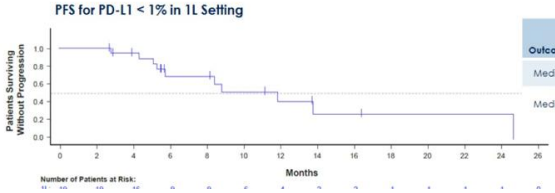


- Among patients treated in the 1L setting, ORR was 65% and DCR was 100%
- 94% of all patients had reduction in target lesions

Progression-Free Survival*



Outcome	Sotorasib + Carboplatin + Pemetrexed 1L (n = 34)	Sotorasib + Carboplatin + Pemetrexed 2L+ (n = 19)
Median PFS, months (95% CI)	10.8 (5.4–NE)	8.3 (4.1–NE)
Median follow-up, months (95% CI)	9.2 (5.6–13.7)	4.4 (2.7–NE)



Outcome	PD-L1 < 1% in 1L Setting (n = 19)
Median PFS, months (95% CI)	11.9 (5.3–NE)
Median follow-up, months (95% CI)	13.7 (5.6–NE)

Li BT, et al. ASCO 2024

Sotorasib + Chemotherapy

SCARLET study: Phase 2 Chemotherapy Combination
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^2 [q3W, 4 cycles] (n = 30)

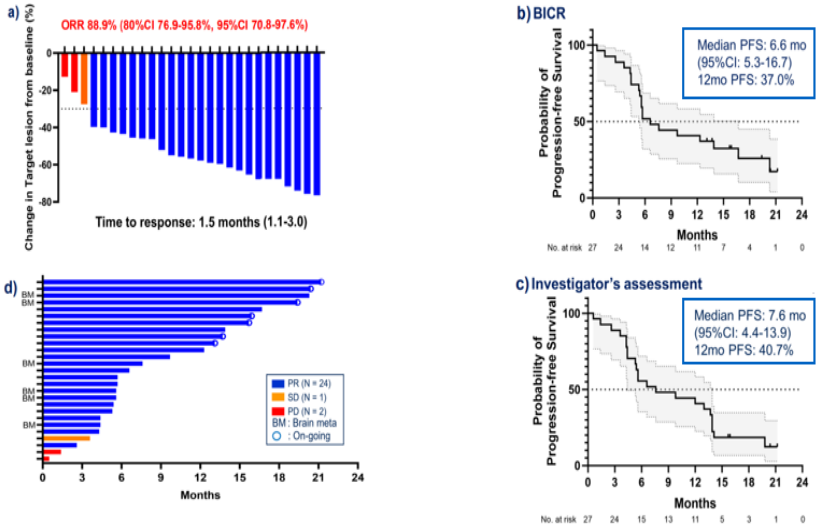
Maintenance phase: Sotorasib + PEM [q3W, until PD]

- 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])

Participants were treated with sotorasib 960mg, QD plus carboplatin (AUC5)/pemetrexed 500mg/m² for four cycles, followed by sotorasib plus pemetrexed until disease progression. This study was funded by AMGEN Inc. and Trial identification no. is jRCT2051210086.

AE, adverse event; AUC, area under the curve; CBDCA, carboplatin; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; KRAS, Kirsten rat sarcoma virus; Mets, metastasis; NGS, next-generation sequencing; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PEM, pemetrexed; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; Sq, squamous; TTR, time to response.
Yoshioka H, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31 – June 4, 2024; Chicago, IL. Abstract 8616.

SCARLET study: Phase 2 Chemotherapy Combination
Efficacy



Among patients treated in the 1L setting, ORR was 89%

CI, confidence overall; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Yoshioka H, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31 – June 4, 2024; Chicago, IL. Abstract 8616.

1. 2024 ASCO 8512; 2. Shinya Sakata, et al. ASCO Abstract#9006

CodeBreak 202
Sotorasib + Chemo vs Pembro + Chemo in PD-L1 <1%

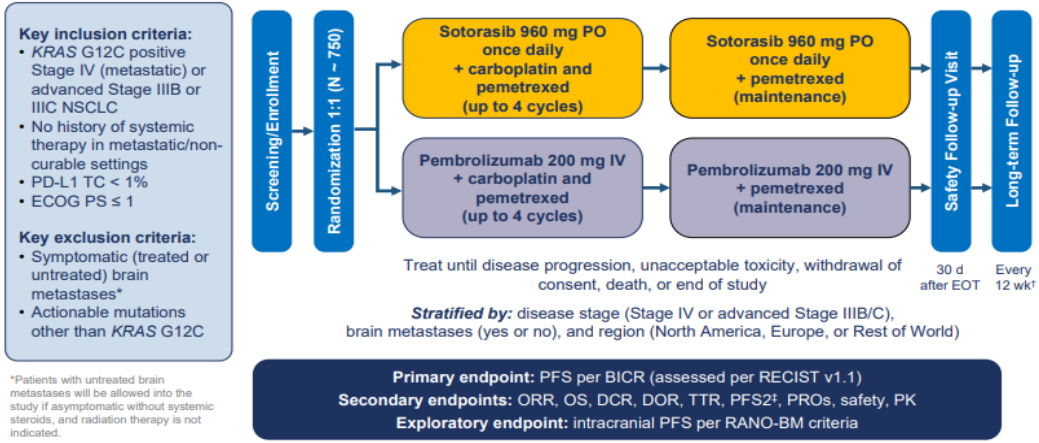
Background

- Currently, there are no targeted first-line (1L) treatment options for *KRAS* G12C-mutated, advanced non-small cell lung cancer (aNSCLC)
- Outcomes with standard immunotherapy-based regimens in metastatic, PD-L1 negative, NSCLC remain poor, with a 5-year progression free survival (PFS) ranging from approximately 2% to 10% in the 1L setting[1,2]
- In the CodeBreaK 101 phase 1b study, sotorasib plus platinum doublet chemotherapy showed encouraging preliminary efficacy with a manageable safety profile, including an objective response rate of 62% (8/13) in patients with treatment-naïve, PD-L1 negative, *KRAS* G12C-mutated aNSCLC[3]
- A phase 2 study of Japanese patients with *KRAS* G12C-mutated aNSCLC and any PD-L1 expression level (n = 29) treated with sotorasib plus carboplatin and pemetrexed in the 1L setting showed an objective response rate (ORR) of 89% with favorable tolerability[4]
- Based on these findings, we hypothesize that sotorasib plus platinum doublet chemotherapy will demonstrate a significant improvement in PFS and overall survival compared with standard chemo-immunotherapy in this patient population

CodeBreaK 202 (NCT05920356) is a global phase 3 randomized study evaluating the efficacy of sotorasib versus pembrolizumab in combination with platinum doublet chemotherapy as 1L treatment for PD-L1 negative, *KRAS* G12C-mutated aNSCLC

Study Design

CodeBreaK 202: Phase 3, International, Multicenter, Randomized, Open-label Study



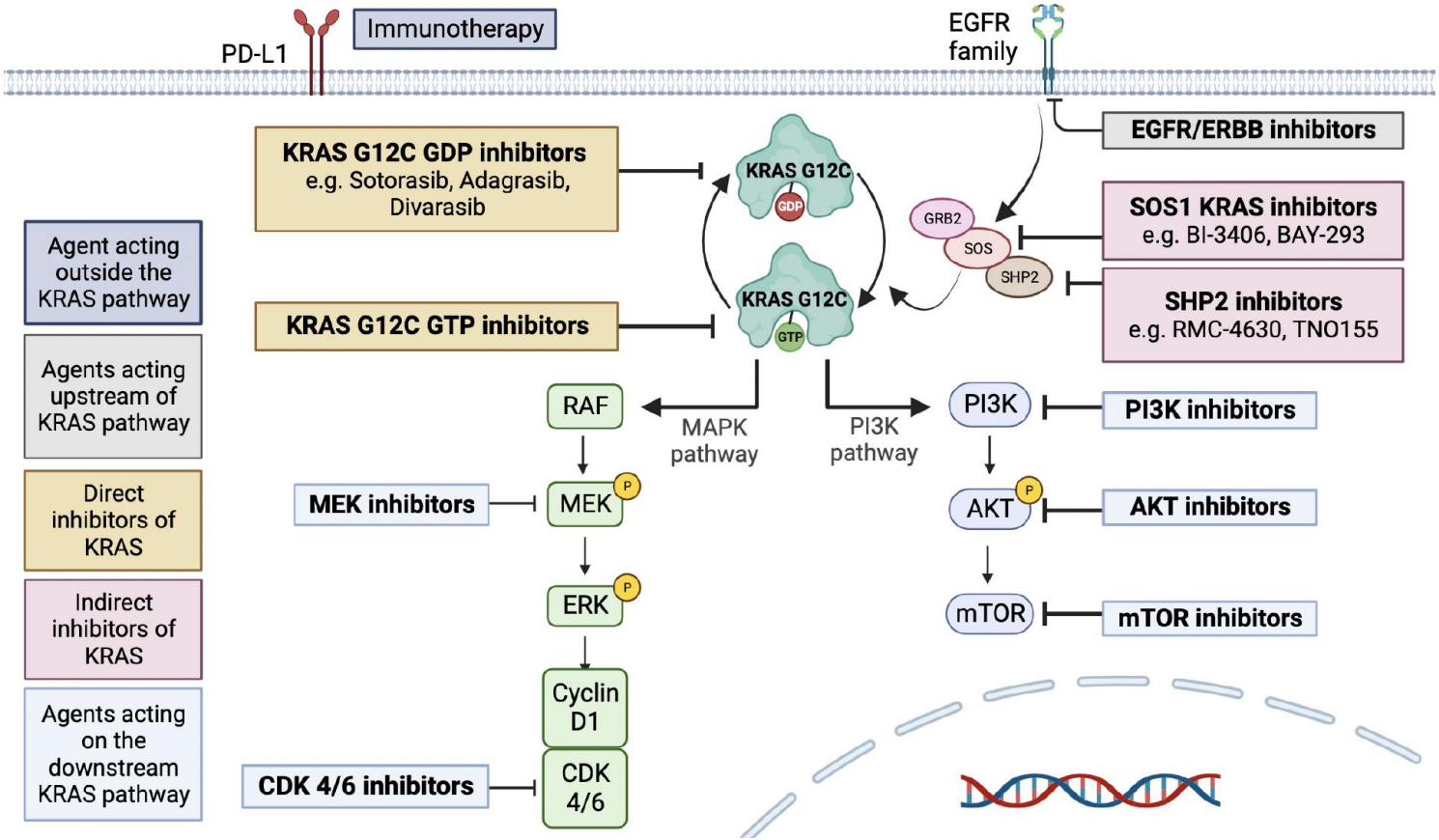
*Patients with untreated brain metastases will be allowed into the study if asymptomatic without systemic steroids, and radiation therapy is not indicated.

† Continues until patient is removed from study due to either decision by sponsor, end of study, withdrawal of consent, lost to follow-up, or death, whichever occurs first; patients who discontinue treatment for a reason other than disease progression will continue imaging and tumor assessment until BICR-confirmed progressive disease, unacceptable toxicity, death, withdrawal of consent, or end of study.

‡ Defined as time from randomization to progression per investigator after initiation of new anticancer therapy or treatment beyond progression (i.e., second progression) or death from any cause.

BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; IV, intravenous; *KRAS*, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, Programmed death-ligand 1; PFS, progression free survival; PK, pharmacokinetics; PO, orally; PRO, patient reported outcome; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors; TC, Tumor cells, TTR, time to response

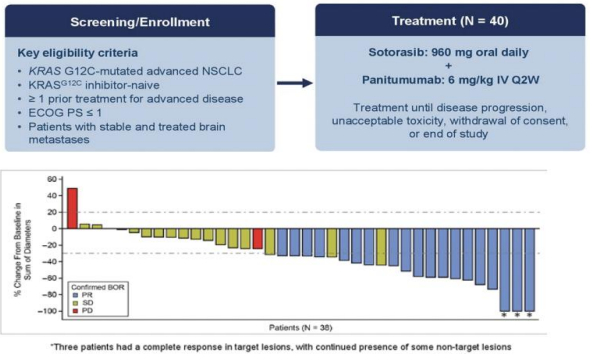
Barlesi F et al. ASCO 2024


PD-L1
Immunotherapy
EGFR family
EGFR/ERBB inhibitors
KRAS G12C GDP inhibitors
e.g. Sotorasib, Adagrasib, Divarasib
KRAS G12C
GDP
GRB2
SOS
SHP2
SOS1 KRAS inhibitors
e.g. BI-3406, BAY-293
SHP2 inhibitors
e.g. RMC-4630, TNO155
KRAS G12C GTP inhibitors
KRAS G12C
GTP
Agent acting outside the KRAS pathway
Agents acting upstream of KRAS pathway
Direct inhibitors of KRAS
Indirect inhibitors of KRAS
Agents acting on the downstream KRAS pathway
RAF
MAPK pathway
PI3K pathway
PI3K
PI3K inhibitors
MEK inhibitors
MEK
P
AKT
AKT inhibitors
ERK
mTOR
mTOR inhibitors
Cyclin D1
CDK 4/6 inhibitors
CDK 4/6

KRAS inhibitors and EGFR inhibitors

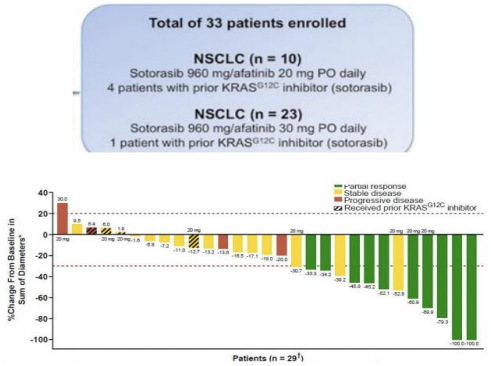
CodeBreak101 in previously treated KRAS G12C NSCLC:

Sotorasib + panitumumab



- Grade≥3 TRAE 52.5%
- Sotorasib+panitumumab demonstrated ORR 48% and DCR 90%
- mPFS 6.9m with median follow-up 16.8m

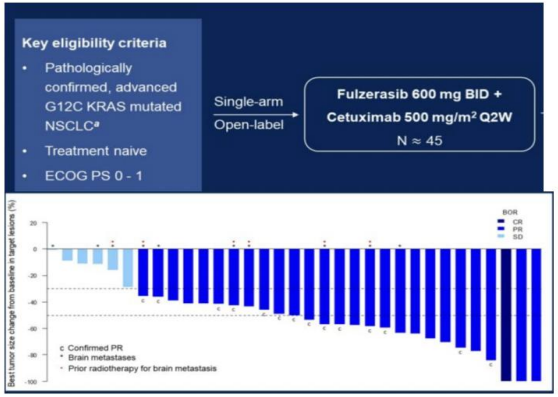
Sotorasib + afatinib



- Grade≥3 TRAE 30% (afatinib 20mg qd)/35%(afatinib 30mg qd)
- ORR 20% and 34.8%, respectively
- DCR 70% and 73.9%, respectively
- mPFS 4.1m

KROCUS in first-line:

Fulzerasib +Cetuximab

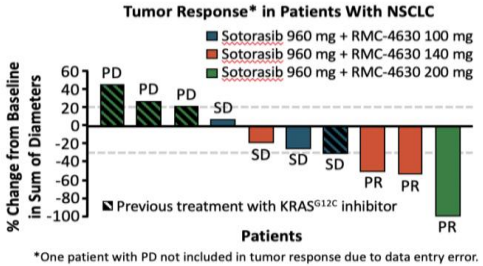


- N=33 ORR of 81.8%, DCR of 100%
- Grade≥3 TRAE 17.5% , most common are rash, asthenia, pruritus, nausea

1. Rona Yaeger,, 2024ASCO abs #128; 2. Mol Cancer Ther (2021) 20 (12_Supplement): P05-02. 3. Ryan MB, et al. Cell Rep 2022; 4. 2024 ASCO LBA8511

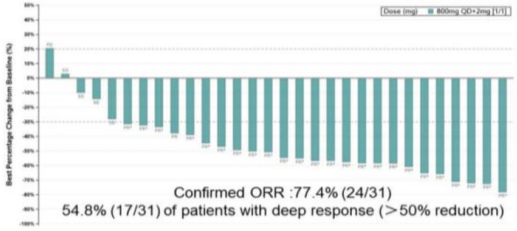
KRAS inhibitors and SHP2 inhibitors

Sotorasib (KRASG12C inhibitor)+ RMC4630 (SHP2 inhibitor)



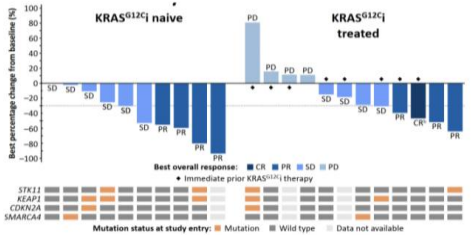
- ✓ In 11 NSCLC, ORR 27%, DCR 64%
- ✓ KRAS^{G12C} treatment naive (N=6), ORR 50%, DCR 100
- ✓ Stop further development

JAB-21822 (KRASG12C inhibitor)+ JAB-3312 (SHP2 inhibitor)



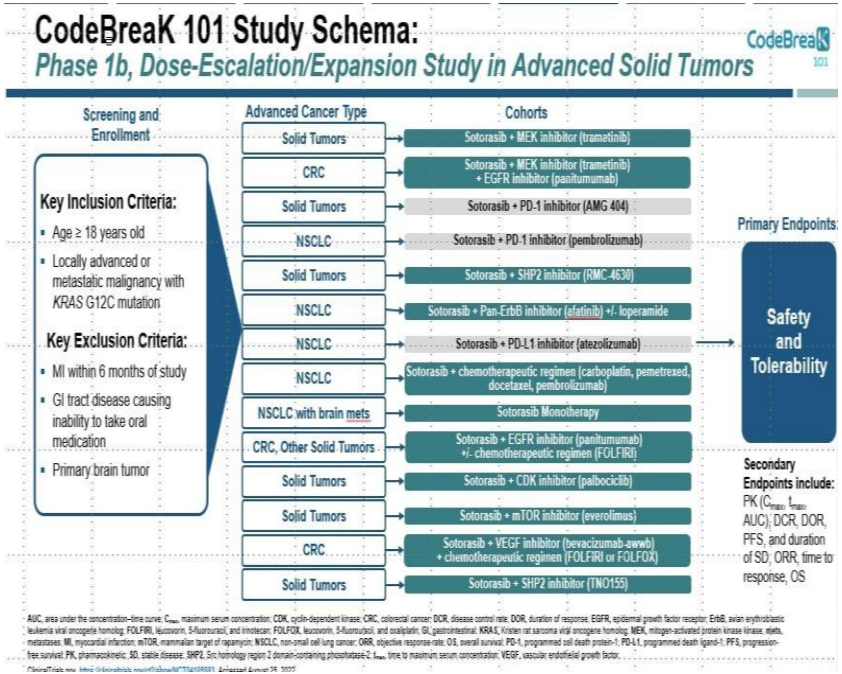
- ✓ In 102 frontline NSCLC*, ORR 77.4%, DCR 93.1%; mPFS 12.2m;
- ✓ Grade 3 or 4 TRAE 44.1%;
- ✓ ongoing phase III clinical trial

JQD443 (KRASG12C inhibitor)+ TNO155 (SHP2 inhibitor)

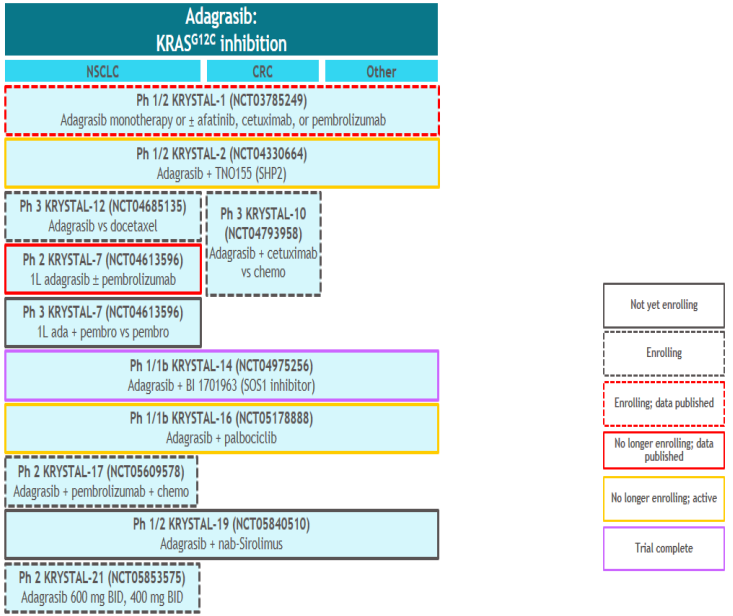


- ✓ In 24 NSCLC, ORR 33.3% in KRAS^{G12C} naive and ORR 25% in KRASi treated;
- ✓ Grade ≥3 TRAE 26.7%

*Frontline NSCLC, ≤2line of prior treatment, KRAS inhibitor naive; 1. G.Falchook, et al. 2022 WCLC, OA03.03; 2. Jun Zhao, et al. 2024 ASCO; 3. Marcelo V Negrao, et al. 2023 WCLC MA06.03

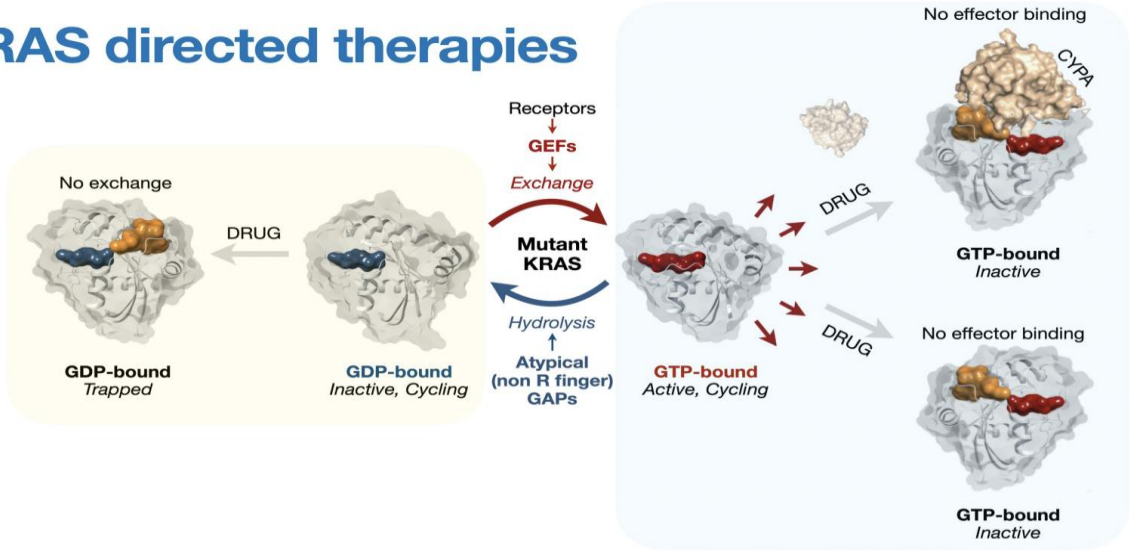


AUC, area under the concentration–time curve; C_{max}, maximum serum concentration; CDK, cyclin-dependent kinase; CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; ErbB, avian erythroblastic leukemia viral oncogene homolog; FOLFIRI, leucovorin, 5-fluorouracil, and irinotecan; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; GI, gastrointestinal; KRAS, Kirsten rat sarcoma viral oncogene homolog; MEK, mitogen-activated protein kinase kinase; mets, metastases; MI, myocardial infarction; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; PK, pharmacokinetic; SD, stable disease; SHP2, Src homology region 2 domain-containing phosphatase-2; t_{max}, time to maximum serum concentration; VEGF, vascular endothelial growth factor.

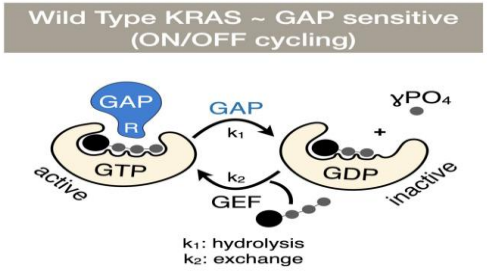


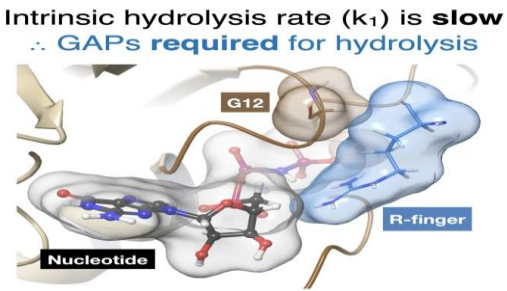
1L, first-line; BID, twice daily; CRC, colorectal cancer; FIH, first-in-human; IND, investigational new drug; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; Ph, phase.

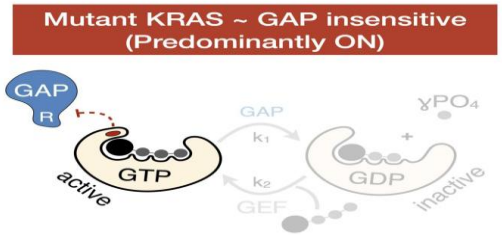
Emerging RAS directed therapies



Tri-Complex inhibitors (ON)







$KRAS^{G12C}$ treatment in 2024

- Unmet needs: bad prognosis, high tumor burden, brain mets
- Chemo + IO: similar Benefit tan KRASWT
- Druggable disease: sotorasib and adagrasib
  2L: OR: 40%, PFS 6 m, active in brains mets
- Fast resistance: tumor intrinsic mechanisms and microenviroment resistance
- Improving treatment option
  Combos: IO, Chemo, Chemo + IO
  New IO? Vaccines?
- Alternative targets: EGFR, SHP2, SOS, YAP
- New agents: 2nd gen, Tri-Complex

KRAS should be determined at diagnosis for all mNSCLC patients

SEAP-SEOM Guidelines On Testing Predictive Biomarkers In Non-small-cell Lung Cancer

Clinical and Translational Oncology
https://doi.org/10.1007/s12094-022-03046-9

SPECIAL ARTICLE

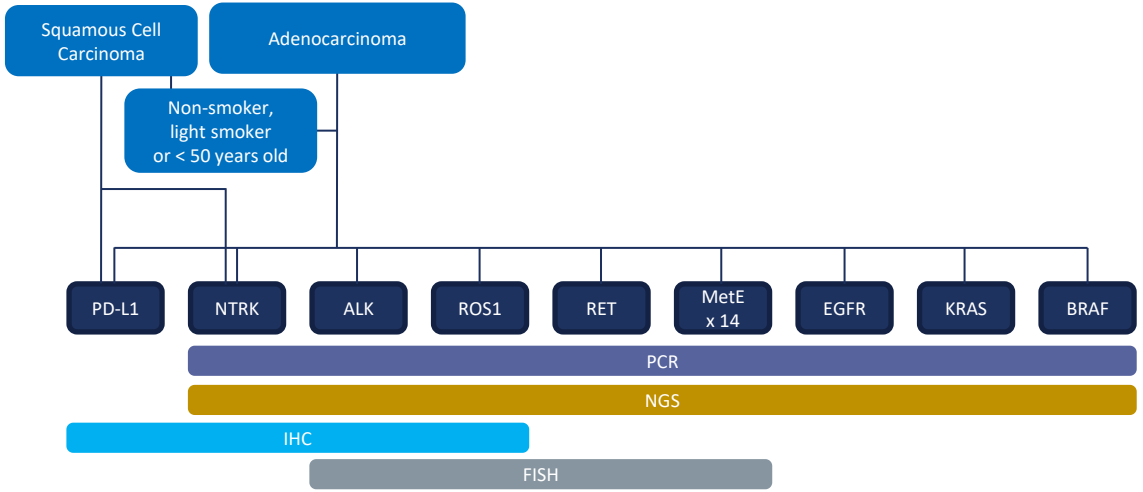
New update to the guidelines on testing predictive biomarkers in non-small-cell lung cancer: a National Consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology

Dolores Isla[1] · Maria D. Lozano[2] · Luis Paz-Ares[3] · Clara Salas[4] · Javier de Castro[5] · Esther Conde[6] · Enriqueta Felip[7] · Javier Gómez-Román[8] · Pilar Garrido[9] · Ana Belén Enguita[10]

Received: 2 November 2022 / Accepted: 7 December 2022

Abstract
Non-small cell lung cancer (NSCLC) presents the greatest number of identified therapeutic targets, some of which have therapeutic utility. Currently, detecting *EGFR*, *BRAF*, *KRAS* and *MET* mutations, *ALK*, *ROS1*, *NTRK* and *RET* translocations, and PD-L1 expression in these patients is considered essential. The use of next-generation sequencing facilitates precise molecular diagnosis and allows the detection of other emerging mutations, such as the *HER2* mutation and predictive biomarkers for immunotherapy responses. In this consensus, a group of experts in the diagnosis and treatment of NSCLC selected by the Spanish Society of Pathology and the Spanish Society of Medical Oncology have evaluated currently available information and propose a series of recommendations to optimize the detection and use of biomarkers in daily clinical practice.

Keywords *ALK* · Biomarkers · *BRAF* · *EGFR* · Non-small cell lung cancer · PD-L1 · *ROS1*



KRAS should be included in NGS panels

ALK anaplastic lymphoma kinase, BRAF B-Raf proto-oncogene, EGFR epidermal growth factor receptor, FISH fluorescence in situ hybridisation, IHC immunohistochemistry, KRAS kirsten rat sarcoma virus, MetEx 14 mesenchymal epithelial transition factor exón 14, NGS next-generation sequencing, NSCLC non-small cell lung cancer, NTRK neurotrophic tyrosine receptor kinase, PCR polymerase chain reaction, PD-L1 programmed death ligand-1, ROS1 c-ros oncogene 1, RET rearranged during transfection

Isla D, et al. Rev Esp Patol. 2023;56(2):97-112.

GRACIAS

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