15th CONGRESS on Lung CANCER

MADRID

23&24 November 2023

#15CongressGECP

Fundación GECP lung cancer research

KRAS. Is it a real target?

Dr. Oscar Juan-Vidal

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KRAS for “Undruggable” to “real target”

- KRAS proteins have a structurally **smooth surface**
- Extremely **high GTP-binding affinity**
- **Continuously regenerate** every 24-48 hours
- **Complexity** and heterogeneity of the **signaling pathway**

1. Ghimessy A, et al. Cancer Metastasis Rev. 2020. 2. Liu P, et al. Acta Pharmaceutica Sinica B. 2019. 3. Punekar SR, et al. *Nat Rev Clin Oncol.* 2022. *4. Shukla S, et al. Neoplasia. 2014. 5. Hallin J, et al. Cancer Discov. 2020.*

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Discovery of the Switch II Binding Pocket

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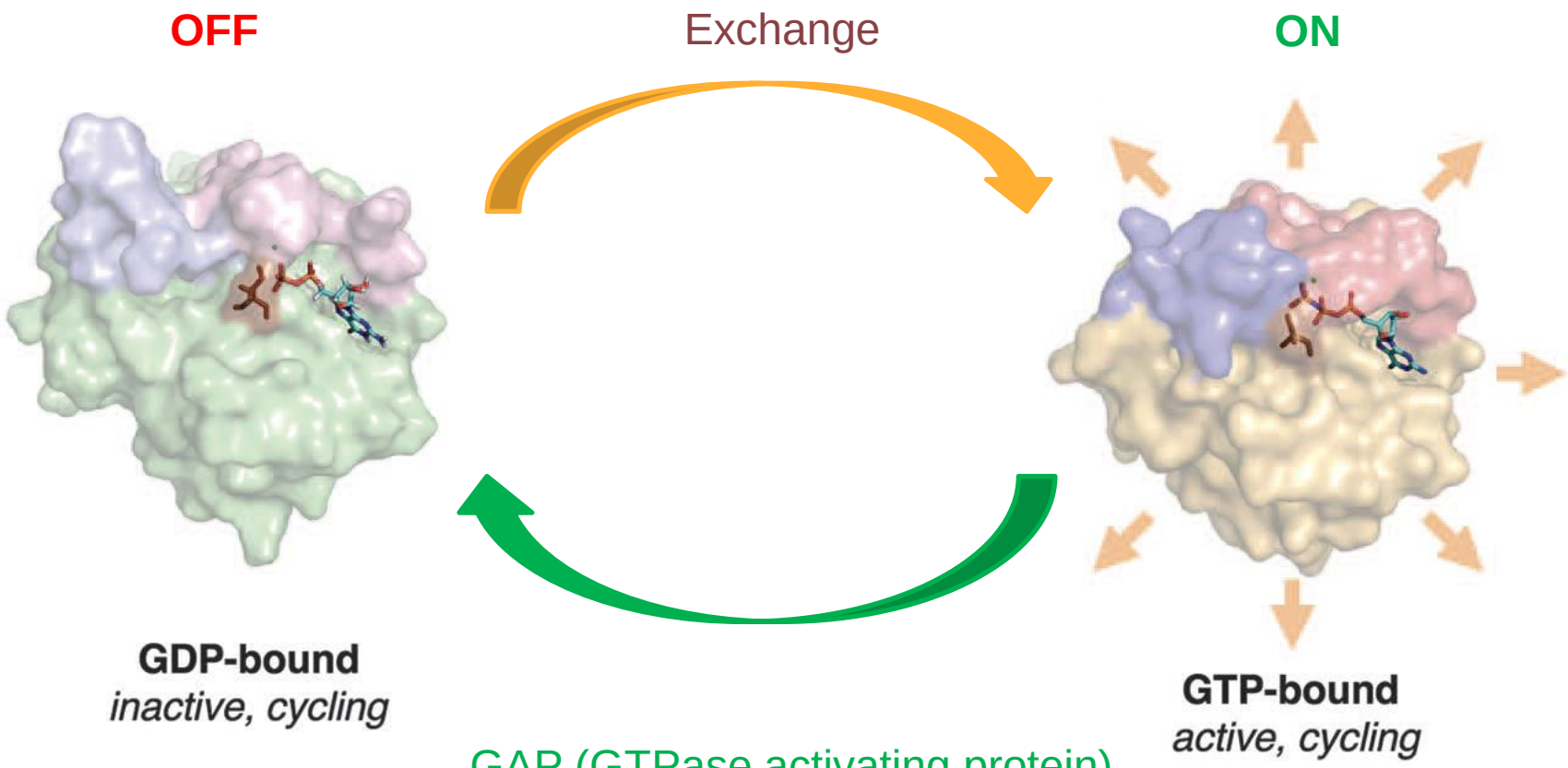
KRAS structure and function

GEF (Guanine nucleotide exchange factor)
(SOS1, SOS2, GBR2, SHC1-4, RasGRP1-4, RaspGEF1-2, RASGRF1-2)



GAP (GTPase activating protein)
(RASA1-3, RASAL1-3, DAB2IP, NF1, SPRED1-3, SYNGAP1)

Addapted from Lito P. Science 2016

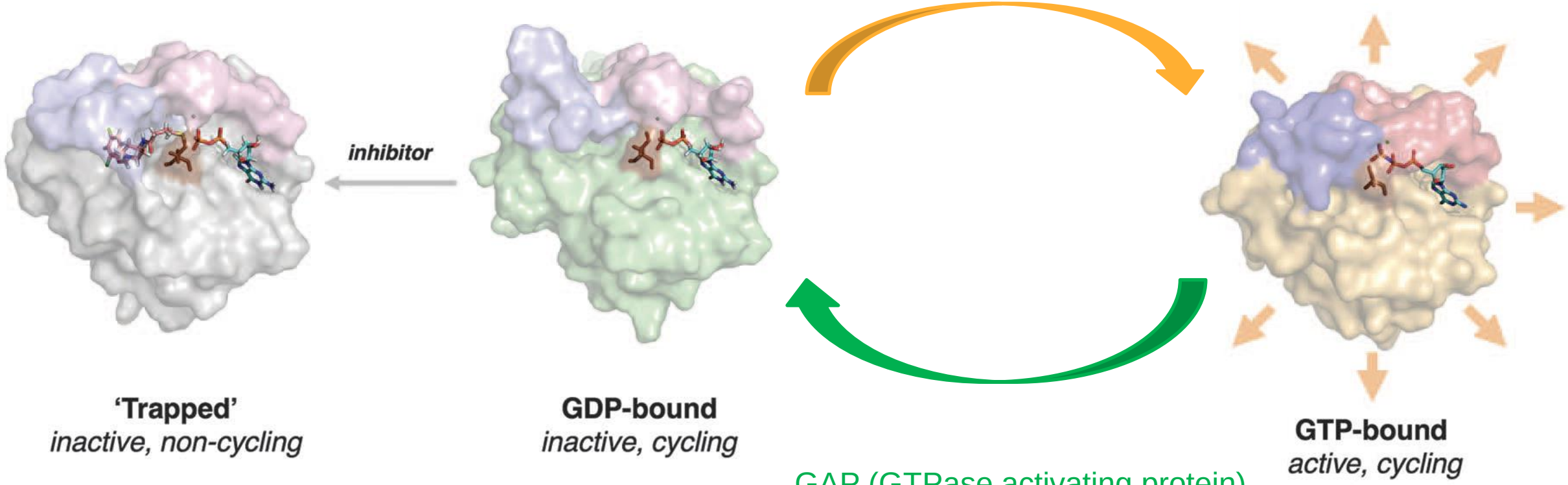
KRAS structure and function

GEF (Guanine nucleotide exchange factor)
(SOS1, SOS2, GBR2, SHC1-4, RasGRP1-4, RaspGEF1-2, RASGRF1-2)

OFF

Exchange

ON



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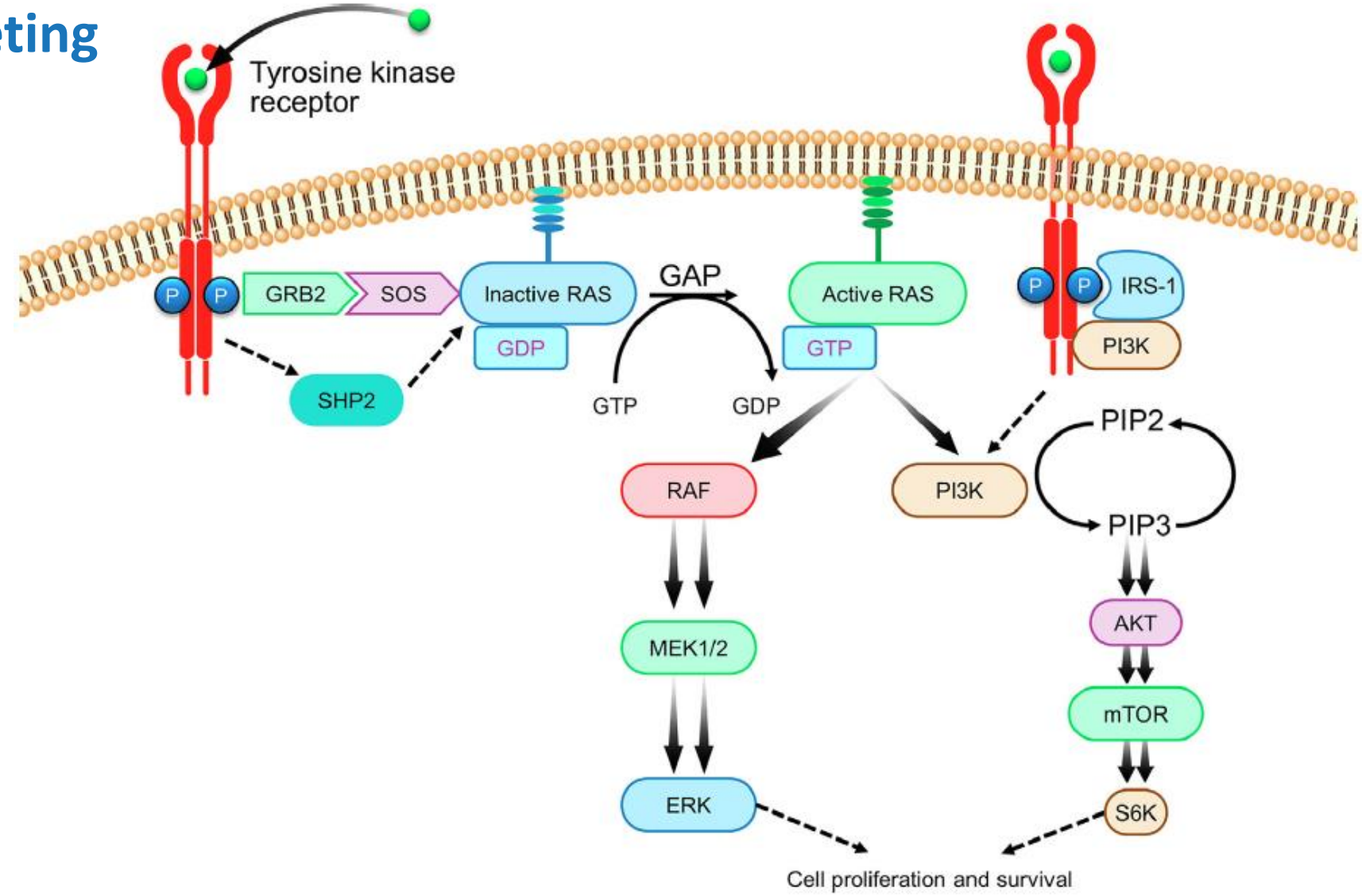
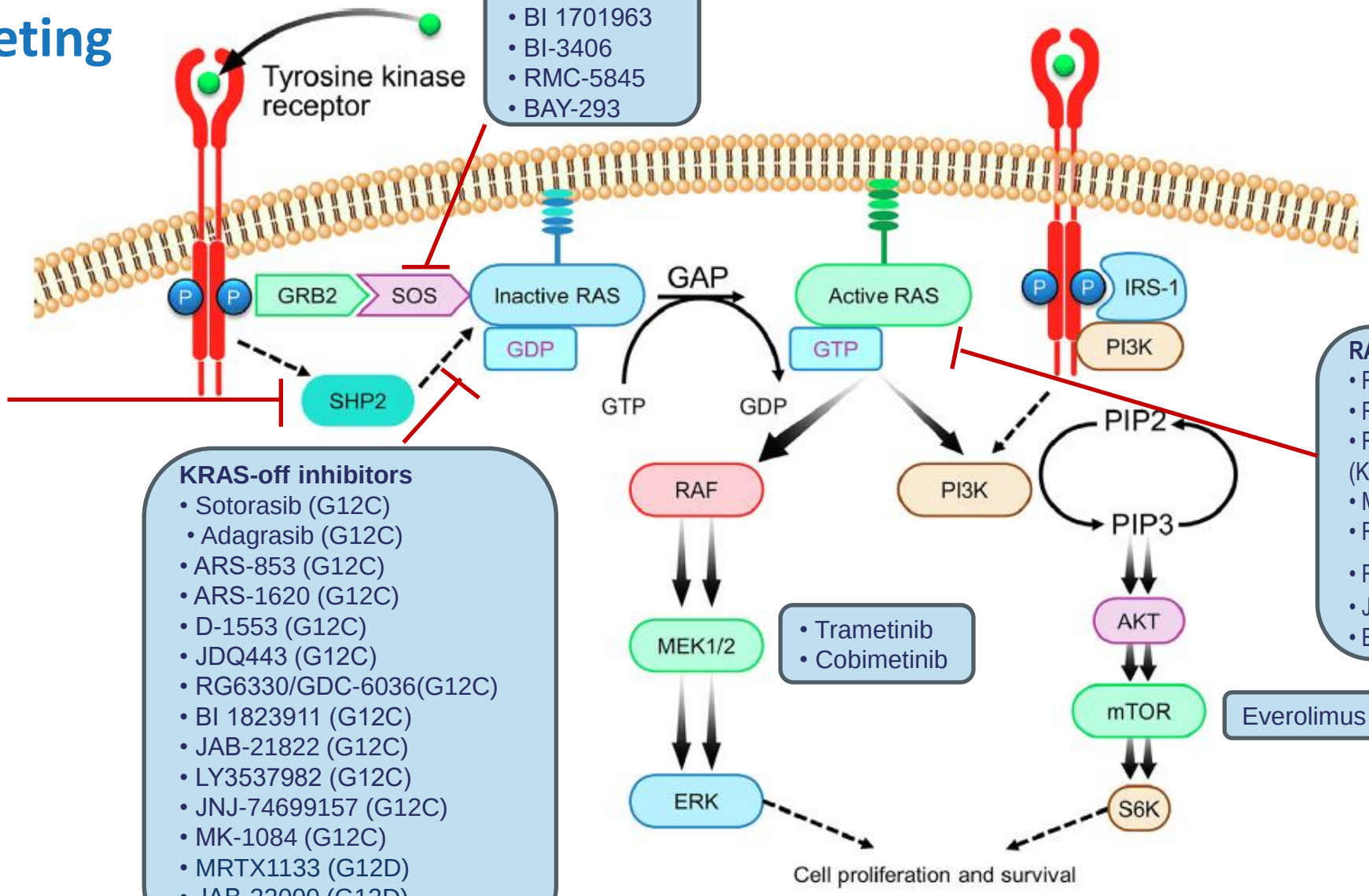
KRAS targeting



Uprety D. et al. Can Treat Rev 202; Punekar SR. Nat Rev Clin Oncol 2022

KRAS targeting



SOS1inhibits
- BI 1701963
- BI-3406
- RMC-5845
- BAY-293

SHP2 inhibitors
- SHP099
- TNO155
- RMC-4630
- RMC-4550
- GDC-1971
- JAB-3068
- JAB-3312
- ERAS-601

KRAS-off inhibitors
- Sotorasib (G12C)
- Adagrasib (G12C)
- ARS-853 (G12C)
- ARS-1620 (G12C)
- D-1553 (G12C)
- JDQ443 (G12C)
- RG6330/GDC-6036(G12C)
- BI 1823911 (G12C)
- JAB-21822 (G12C)
- LY3537982 (G12C)
- JNJ-74699157 (G12C)
- MK-1084 (G12C)
- MRTX1133 (G12D)
- JAB-22000 (G12D)
- JAB-23000 (G12V)

RAS-ON inhibitors
- RM-018 (KRASG12C)
- RMC-6291 (KRASG12C)
- RMC-9805/RM-036 (KRASG12D)
- MRTX1133 (KRASG12D)
- RMC-8839 (KRASG13C)
- RMC-6236 (RASMULTI)
- JAB-23400 (KRASMULTI)
- BBP-454 (KRASMULTI)

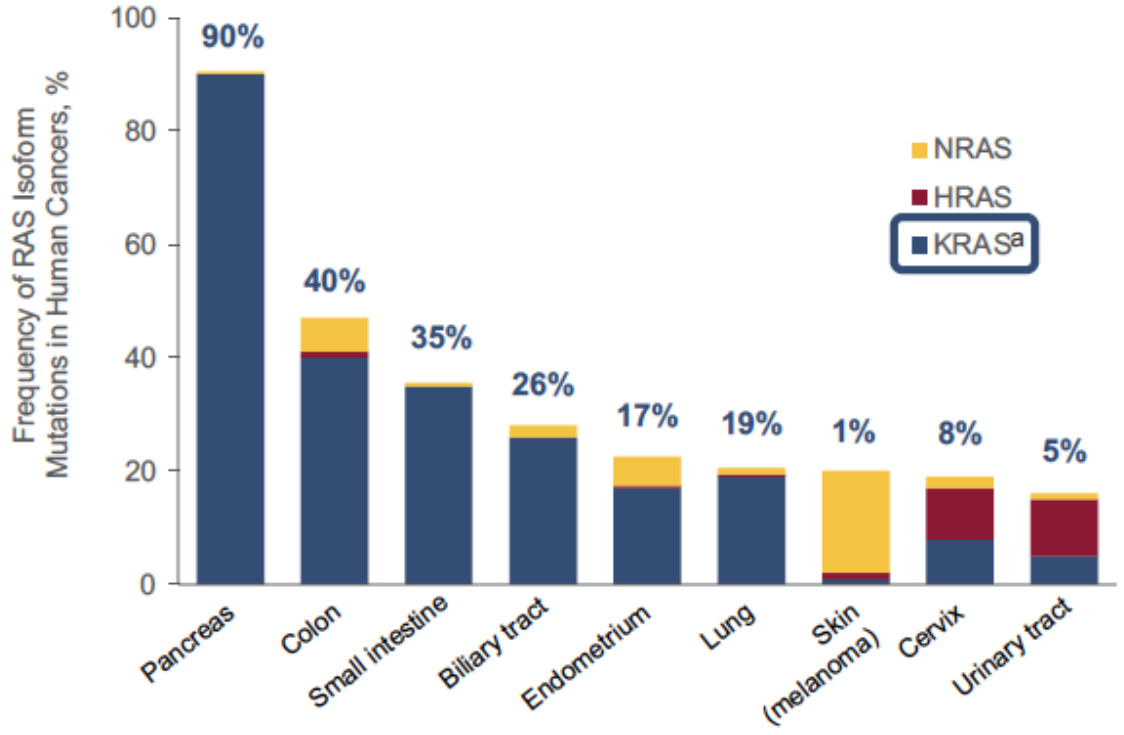
- Trametinib
- Cobimetinib

Everolimus

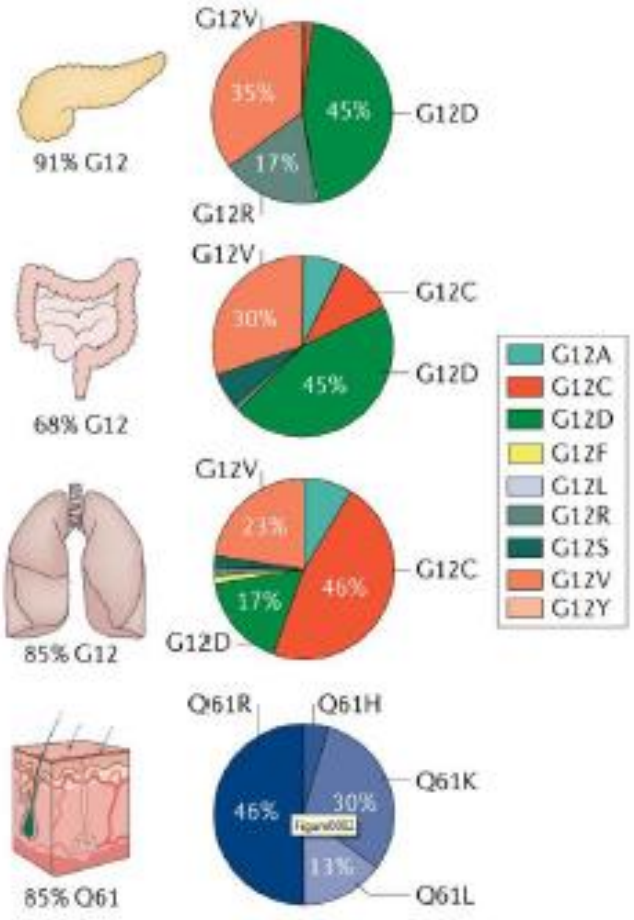
Uprety D. et al. Can Treat Rev 202; Punekar SR. Nat Rev Clin Oncol 2022

KRAS in Human Cancer

KRAS is the most frequently mutated RAS isoform, comprising 86% of RAS mutations across tumor types



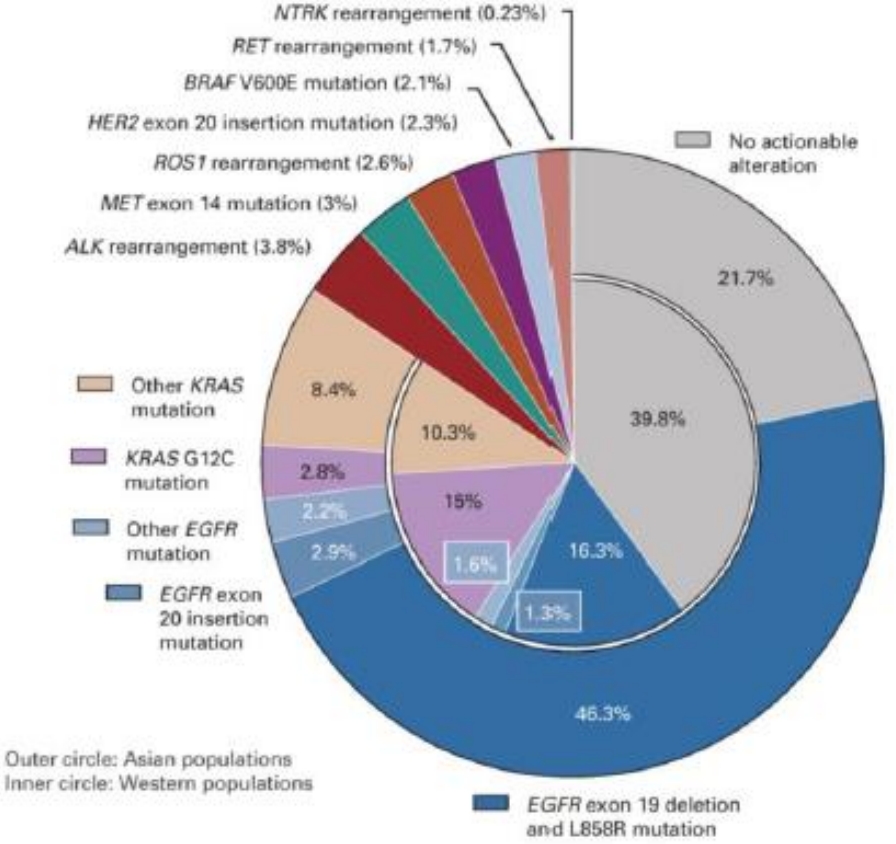
G12 Mutations

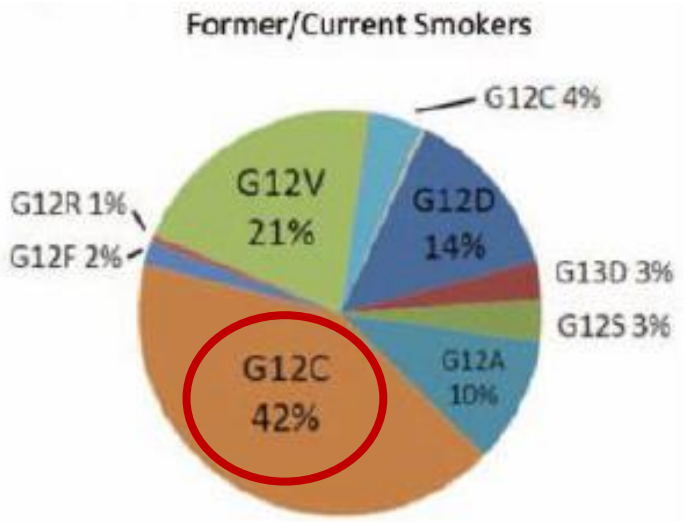


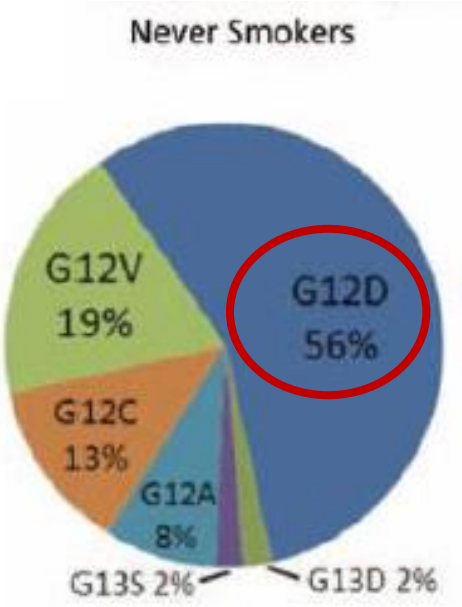
Liu P, et al. Acta Pharmaceutica Sinica B. 2019; Hobbs GA, et al. J Cell Sci. 2016; Yang H, et al. Front Oncol. 2019.; Moore et al. Nat Rev Drug Discover 2020

KRAS in lung cancer

- **KRASm** in **30%** of LC
- More common in western populations
- KRAS **G12C** the most common (**50-60%**)
- KRASm type depens on the smoking history:
  - KRAS G12C → smoking history
  - KRAS G12D → Never smokers



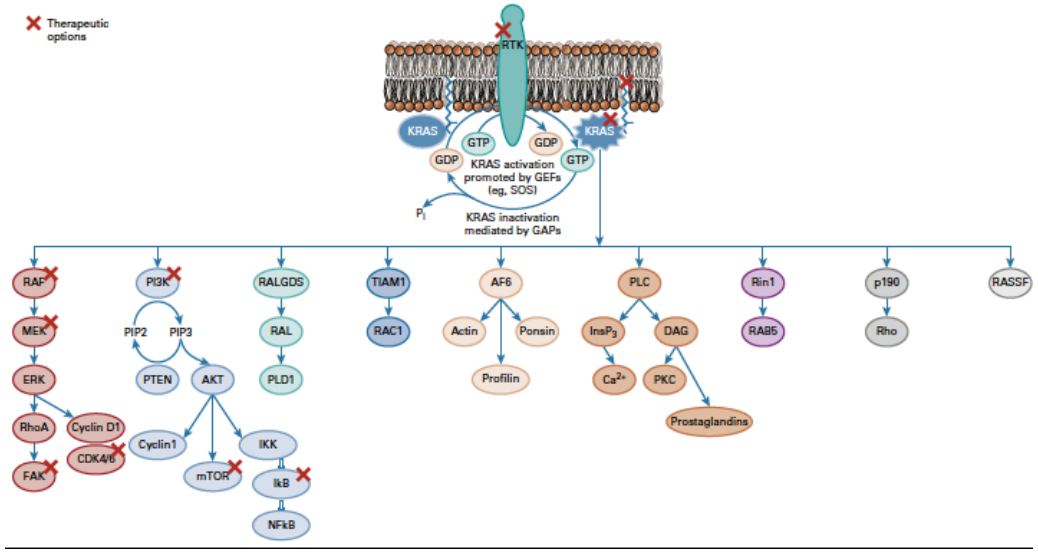




Tan et al. JCO 2022; Yu HA et al. JTO 2015

Unsuccesful attemps to inhibit KRAS

Mechanism of Action	Reason for Lack of Apparent Success
Inhibit KRAS protein binding	
Small molecule antagonist to KRAS-GTP protein[13]	High picomolar affinity of RAS for GTP and high cellular concentration of GTP; difficult for successful competition for the nucleotide-binding pocket
Disrupt binding of KRAS protein to a GEF catalyst of nucleotide exchange[63]	Not sufficiently potent
Disrupt membrane binding of KRAS	
Farnesyl transferase inhibitor[13]	Geranyl-geranylation provides an alternative mechanism to farnesylation for activation of KRAS proteins
Competitive inhibition of attachment of GTP-bound protein to plasma membrane[59]	Not sufficiently potent to warrant further investigation
Inhibit KRAS signaling of downstream effector pathways	
MEK inhibition as monotherapy[13,60] and in combination with chemotherapy[61,62]	Upregulation of compensatory effector pathways, dose-limiting toxicities, and development of resistance
BRAF inhibition as monotherapy[64]	Paradoxical ERK signal activation
Dual BRAF and ERK1/2 inhibitors[64]	Importance of BRAF and ERK targets in normal cells
Inhibition of FAKi[65]	Combination therapy may be required
Direct inhibitors of KRAS proteins	
Noncovalently bind to RAS proteins and inhibit RAS/RAF complex formation[66]	Not sufficiently potent; off-target activity could be problematic

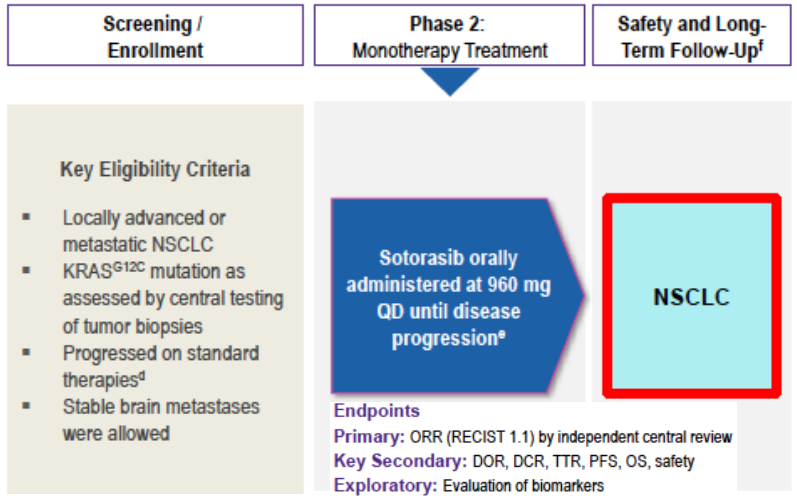


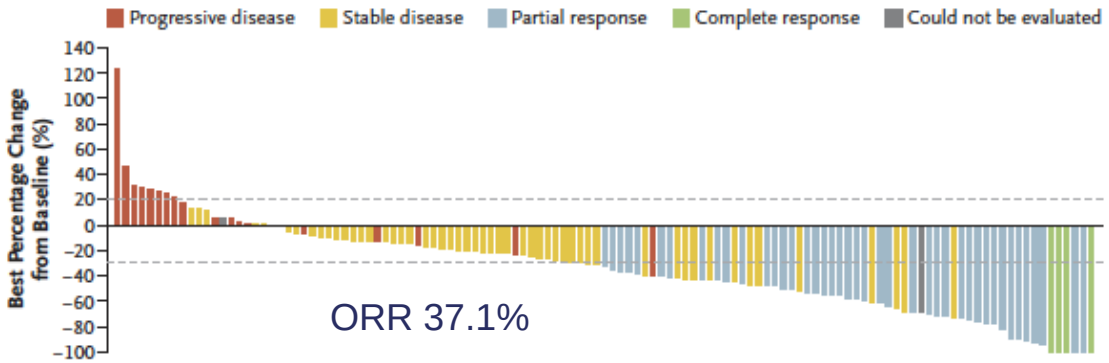
Burns TF, et al JCO 2022

KRAS G12C inhibitors: Sotorasib and Adagrasib

Sotorasib

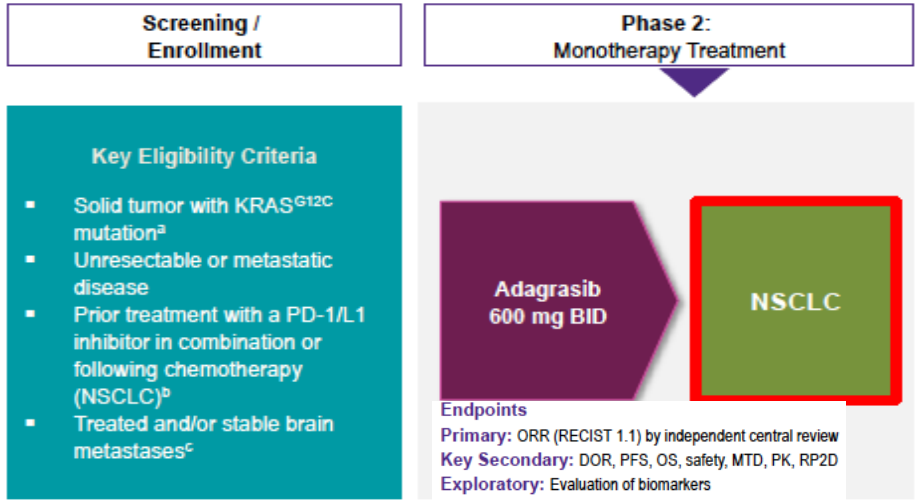
CodeBreaK 100 Study Design

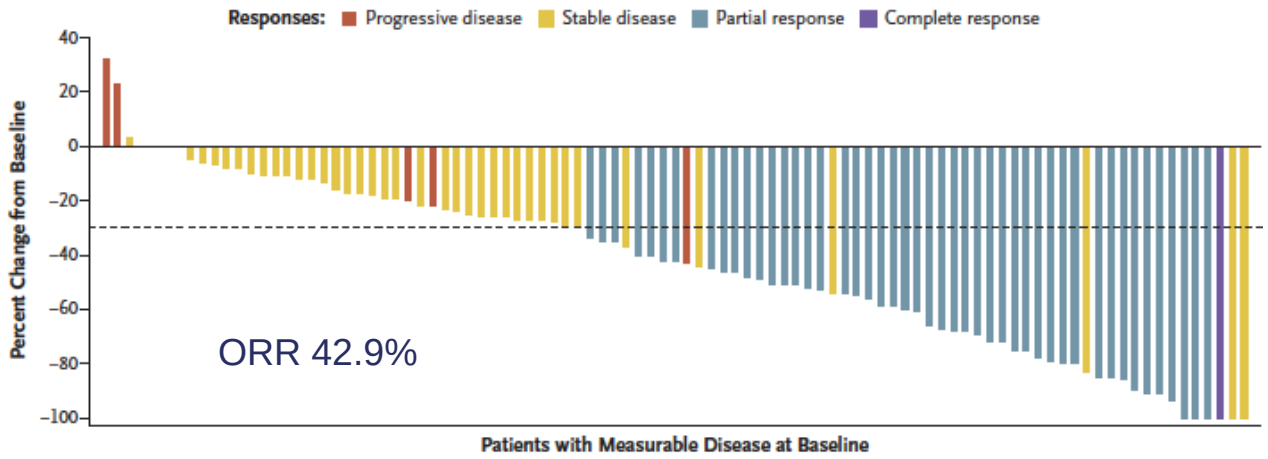




Adagrasib

KRYSTAL-1 Study Design

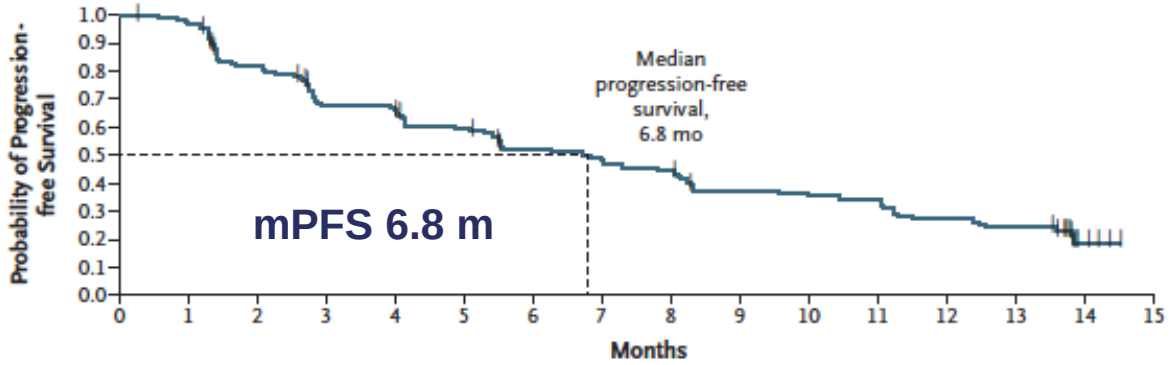


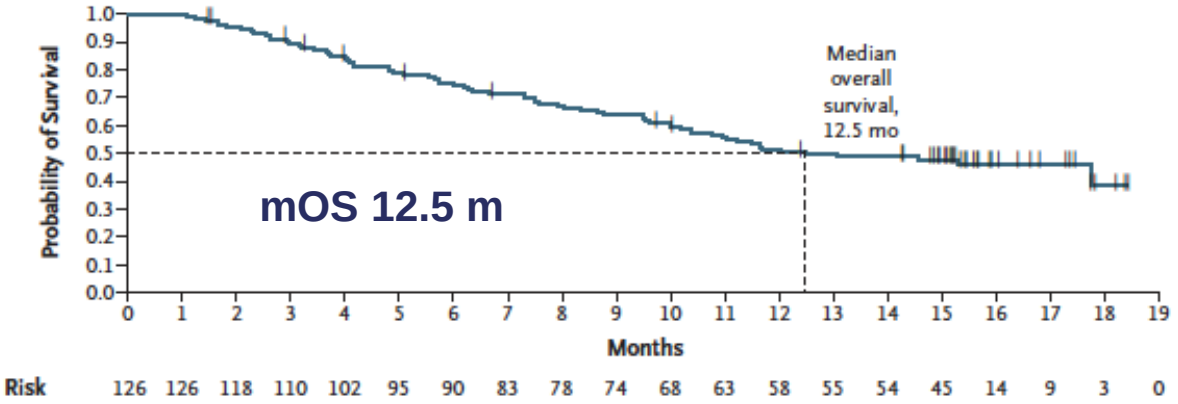


Skoulidis et al. NEJM 2021;; Janne et al. NEJM 2022;

KRAS G12C inhibitors: PFS & OS

Sotorasib





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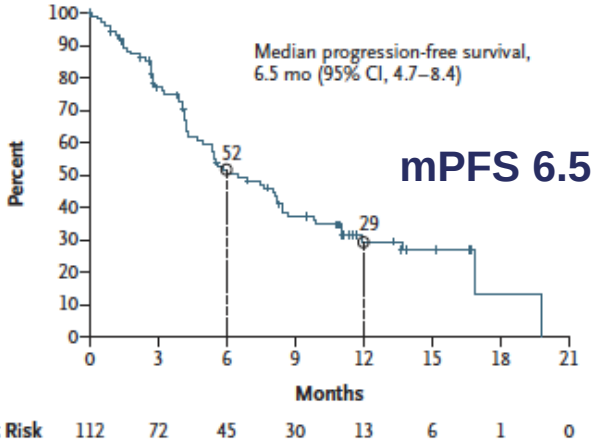
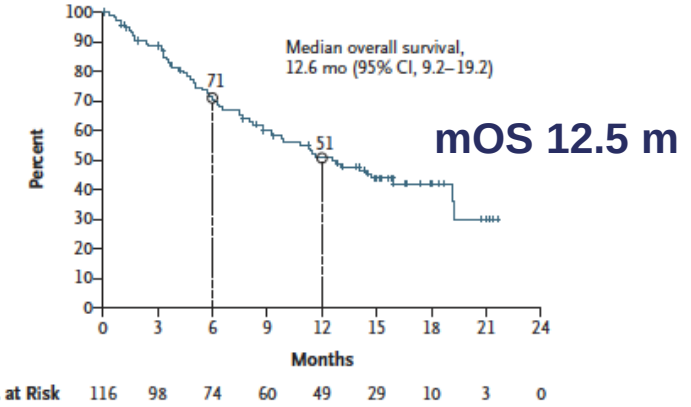




Skoulidis et al. NEJM 2021; Janne et al. NEJM 2022

KRAS G12C inhibitors: Safety

Sotorasib

Sotorasib[2]	Enrolled Patients (n=126)	
TRAEs, %	**Any Grade**	**Grade 3**
Any TRAEs	69.8%	19.8%
Most Frequent TRAEs[e], %		
Diarrhea	31.7%	4.0%
Nausea	19.0%	0%
Inc. ALT	15.1%	6.3%
Inc. AST	15.1%	5.6%
Fatigue	11.1%	0%
Vomiting	7.9%	0%
Inc. blood alkaline phosphatase	7.1%	0.8%
Maculopapular rash	5.6%	0%

- 1 patient (0.8%) reported grade 4 TRAEs (pneumonitis and dyspnea)
- No grade 5 TRAEs occurred
- 7.1% of TRAEs led to discontinuation of treatment

Adagrasib

Adagrasib[1]	All Cohorts Pooled, 600 mg BID[a] (n=110)	
TRAEs[b,c], %	**Any Grade**	**Grades 3-4**
Any TRAEs	85%	30%
Most Frequent TRAEs[a,d], %		
Nausea	54%	2%
Diarrhea	51%	0%
Vomiting	35%	2%
Fatigue	32%	6%
Inc. ALT	20%	5%
Inc. AST	17%	5%
Inc. blood creatinine	15%	0%
Dec. appetite	15%	0%
QT prolongation	14%	3%
Anemia	13%	2%

- Grade 5 TRAEs included pneumonitis in a patient with recurrent pneumonitis (n=1) and cardiac failure (n=1)
- 4.5% of TRAEs led to discontinuation of treatment

Skoulidis et al. NEJM 2021; Janne et al. AACR 2020; Janne et al. NEJM 2022

Phase III Codebreak 200: Sotorasib vs. docetaxel

Key eligibility criteria
- Locally advanced/unresectable or metastatic *KRAS* G12C-mutated NSCLC
- ≥ 1 prior treatment including platinum-based chemotherapy and checkpoint inhibitor*
- No active brain metastases
- ECOG performance status ≤ 1

Stratification factors
- Prior lines of therapy (1 vs 2 vs > 2)
- Race (Asian vs non-Asian)
- History of CNS involvement (yes vs no)

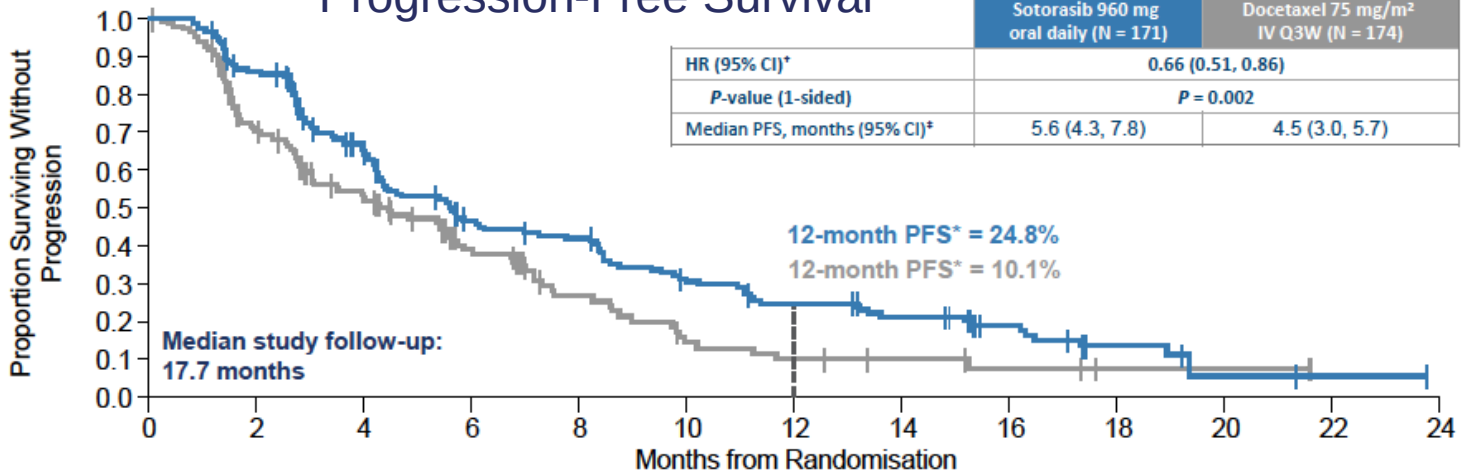
Randomisation 1:1 (N = 345)

- Sotorasib 960 mg oral daily N = 171
- Docetaxel 75 mg/m² IV Q3W N = 174

primary end point PFS by BIRC
crossover permitted with amendment

Progression-Free Survival

	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* = 0.002	
Median PFS, months (95% CI)‡	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)



Number of Patients at Risk:

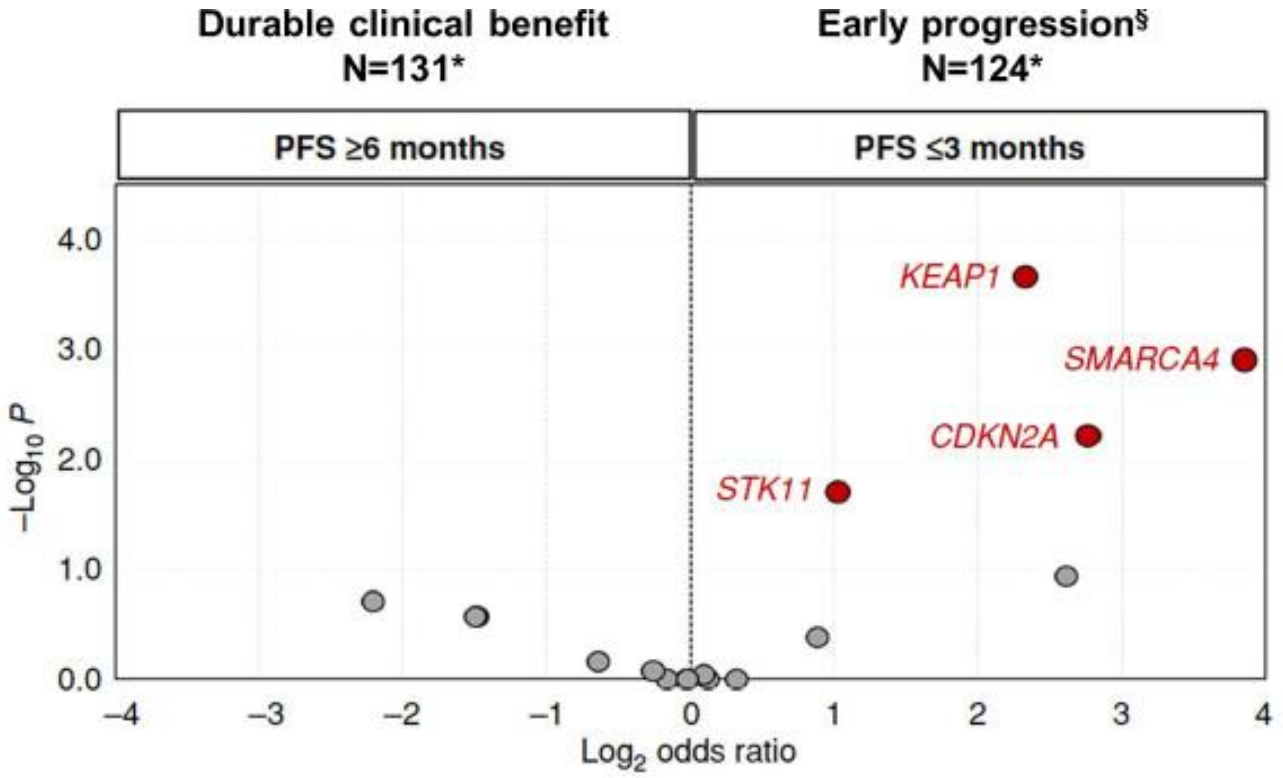
Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

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

Johnson et al. ESMO 2022; de Langen et al. Lancet 2023

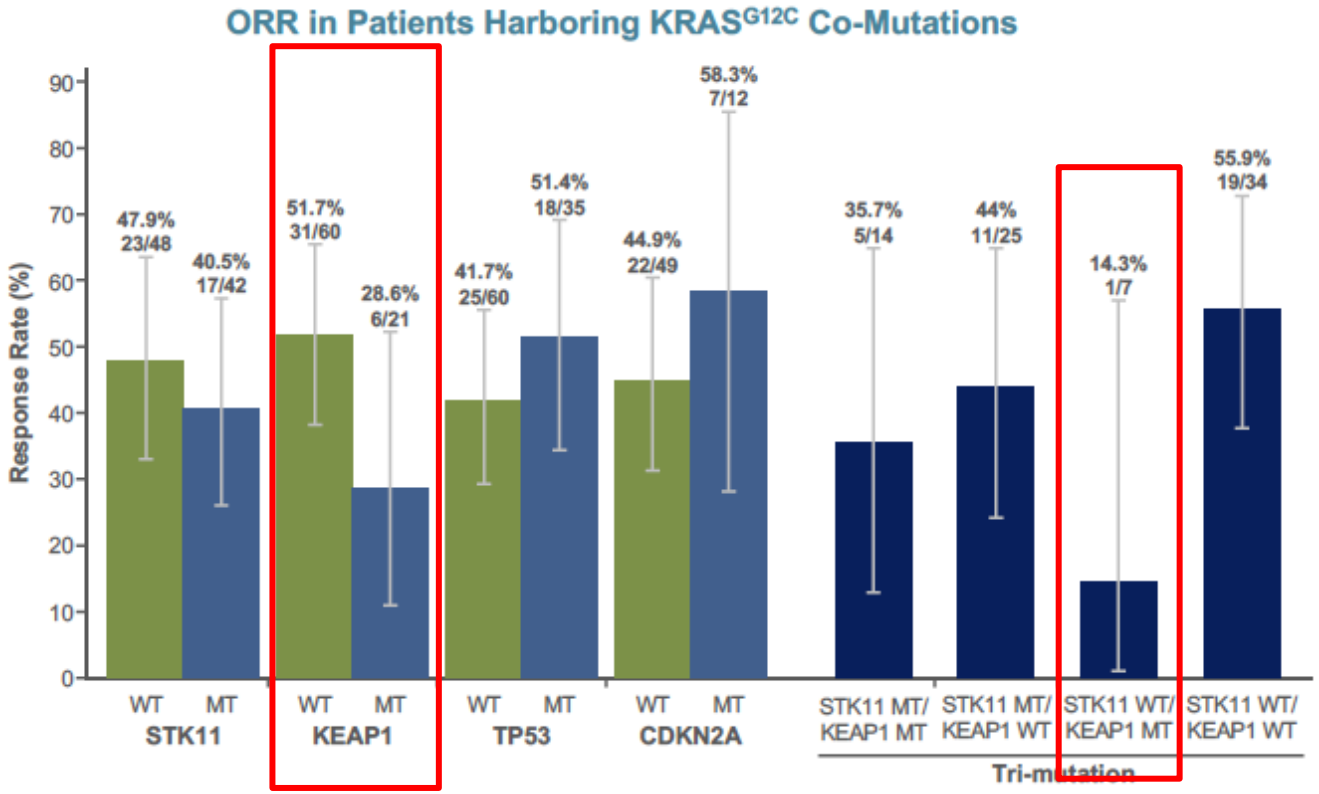
Primary resistance to KRAS G12C inhibitors

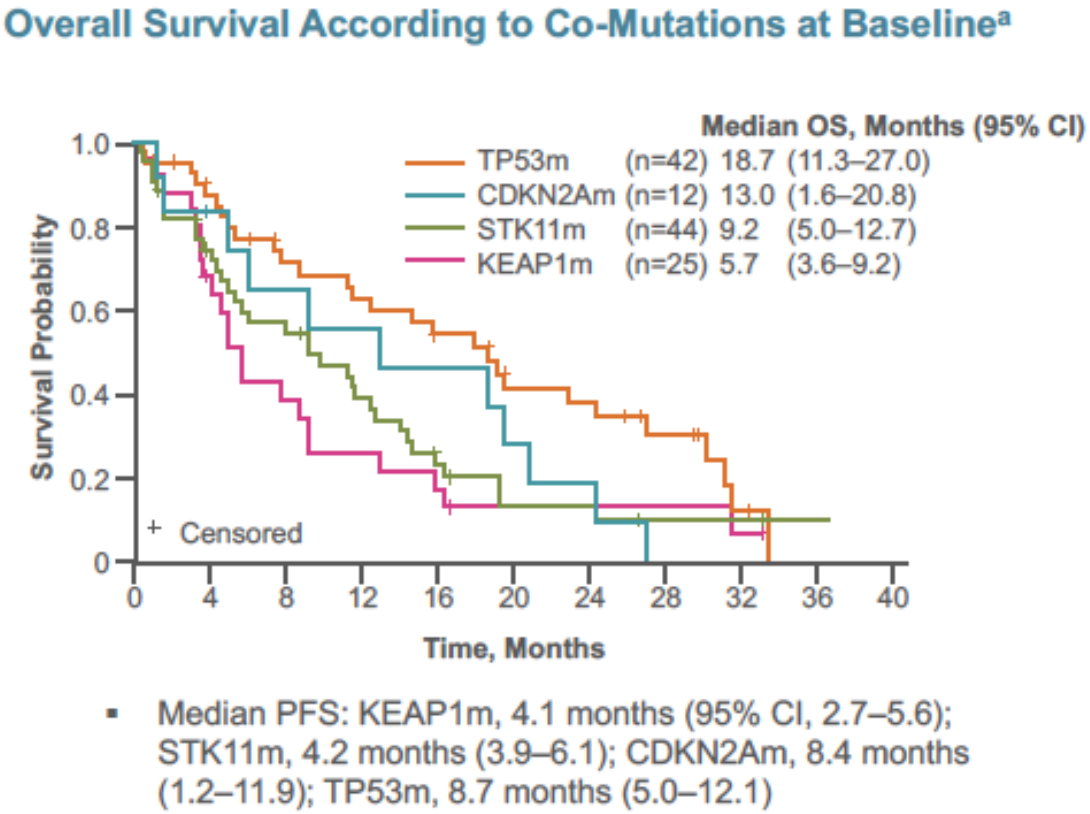
- 424 NSCLC treated with sotorasib (83%) or adagrasib
- **TP53** was the most common co-mutated gen. No association with clincial outcome
- **KEAP1**, **SMARCA4** and **CDKN2A** **associated with early progression**
- **STK11** (without KEAP1, SMARCA4 and CDKN2A) not associated with ORR, PFS or OS



Negrao et al. Cancer Discovery 2023

KRYSTAL 1: Impact of co-mutations in patientes treated with Adagrasib



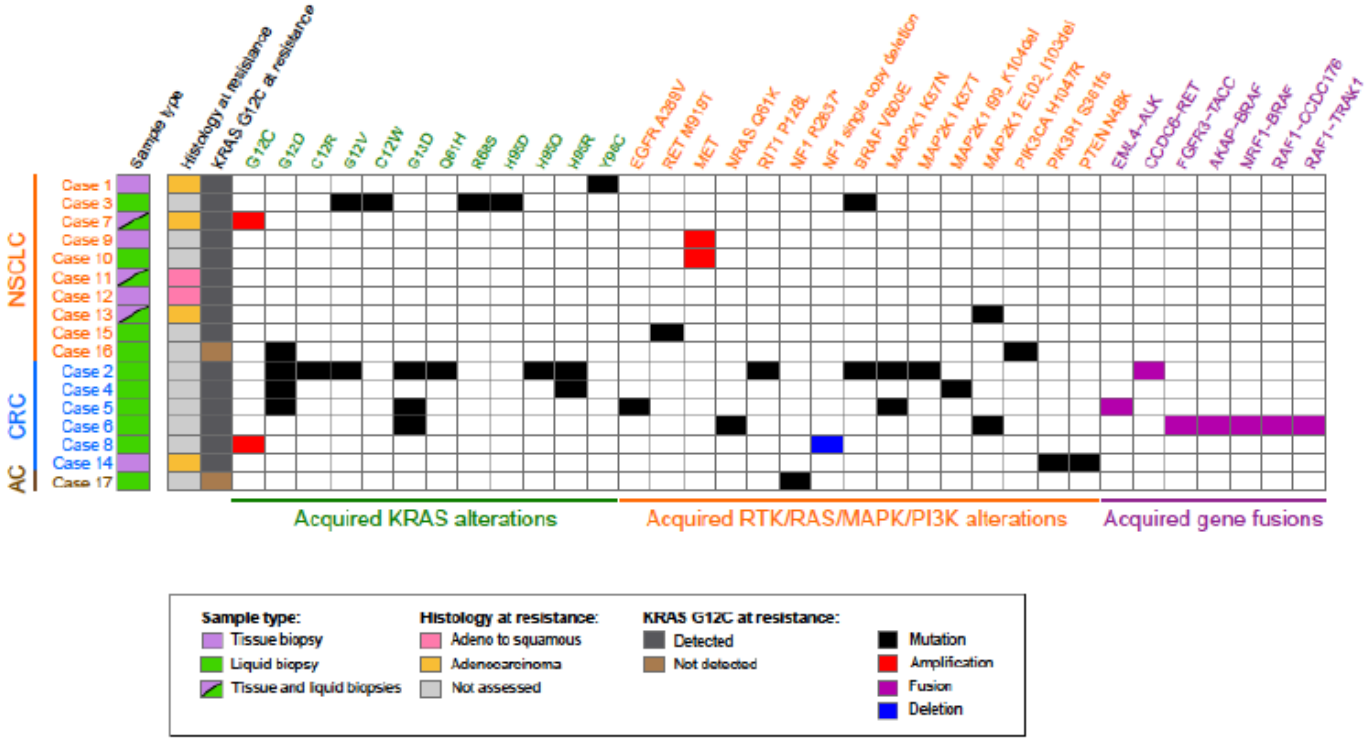


- Median PFS: KEAP1m, 4.1 months (95% CI, 2.7–5.6); STK11m, 4.2 months (3.9–6.1); CDKN2Am, 8.4 months (1.2–11.9); TP53m, 8.7 months (5.0–12.1)

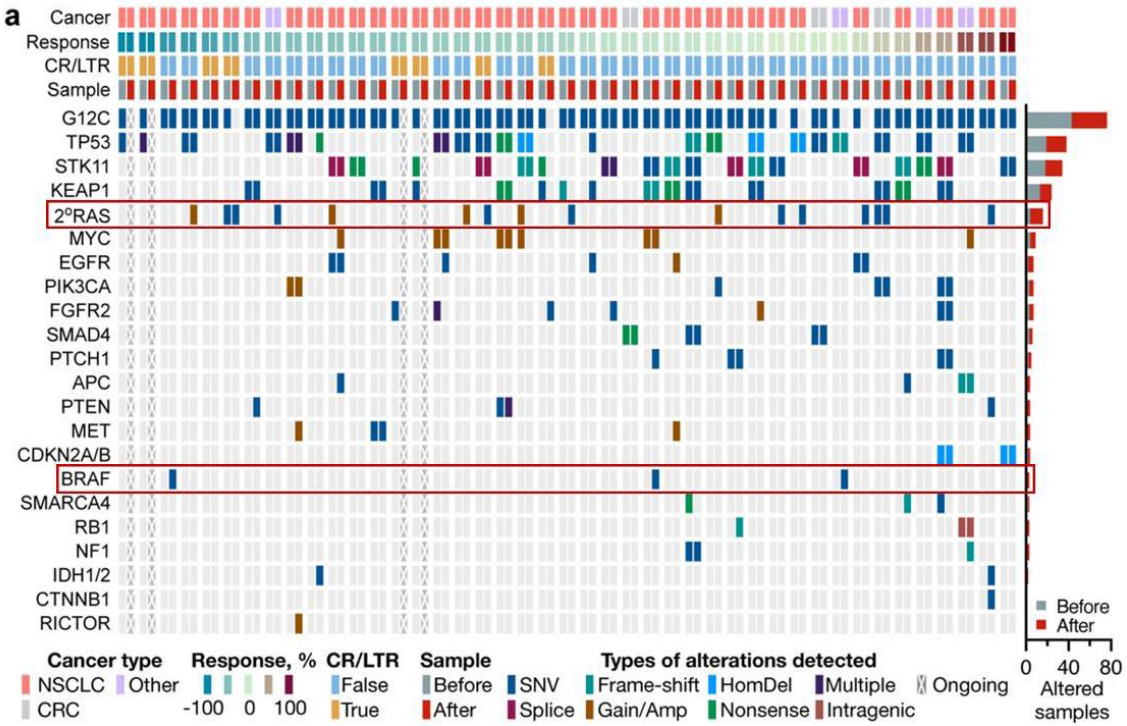
Janne et al. NEJM 2022;Gadgeel et al. WCLC 2023

Adquired resistance to KRAS G12C inhibitors

Adagrasib



Sotoraxib



Award et al. NEJM 2021; Zhao et al. Nature 2021

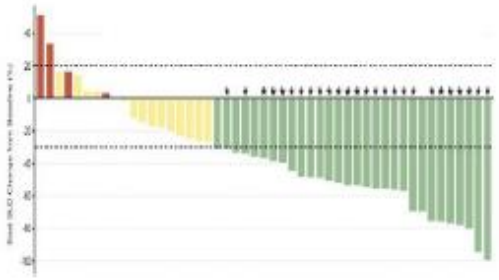
How to improve the treatment efficacy in KRAS G12C patients?

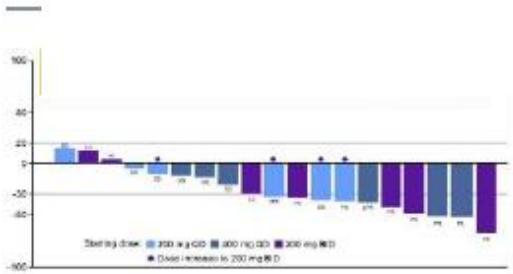
- More potent agents
- Combination therapies
- Agents with different mechanism of action

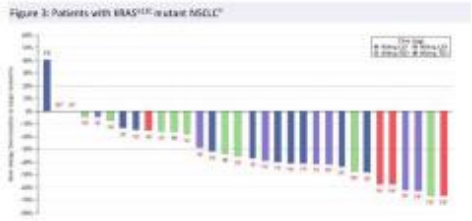
Other KRAS G12C inhibitors. Preliminary efficacy

	GDC-6036	JDQ443	JAB-21822	IBI351 (GFH925)
	Sacher et al WCLC 2022	Tan et al, AACR 2022	Li et al, ASCO 2022	Zhou et al ASCO 2022
	400mg QD	200mg BID	ranging	
N	57	20	32	12
ORR	*46% (27/57)	*35% (7/20) 56% (4/7) at RP2D	56% (18/32) 67% (8/12) QD dosing	50% (6/12)
Differentiating factor		novel interactions within SWII those with G12C/H95	Improved bioavailability	

* confirmed







Combining KRAS G12C inhibitos with ICIs

CodeBreaK 100/101 Study Design

- Phase 1b multicenter, open-label studies

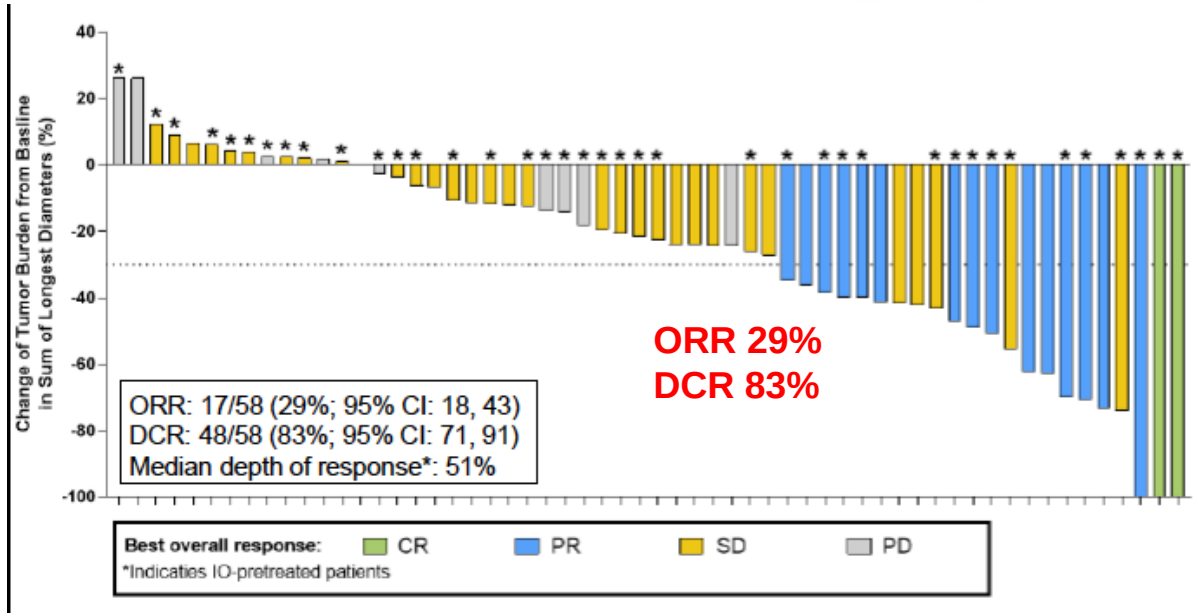
Key Eligibility
- Advanced *KRAS* p.G12C-mutated NSCLC
- Received (or refused) prior standard therapies
- No prior KRAS^{G12C} inhibitor
- No active brain mets

Screening/Enrollment

Sotorasib* (oral daily) at:	Sotorasib lead-in 21d or 42d then combination (N = 29)	Concurrent treatment (N = 29)
960 mg	Atezolizumab 1200 mg Q3W (N = 10)	Atezolizumab 1200 mg Q3W (N = 10)
720 mg	OR	OR
360 mg	Pembrolizumab 200 mg Q3W (N = 19)	Pembrolizumab 200 mg Q3W (N = 19)
240 mg		
120 mg		

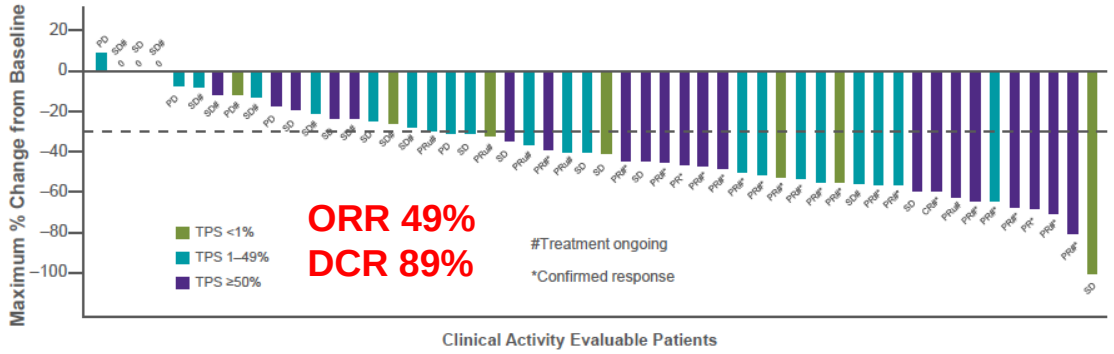
Primary endpoints: safety
Key secondary endpoints: ORR, DOR, DCR, PK

*Not all doses were tested for each cohort



KRYSTAL-1 (849-001) Phase 1b and KRYSTAL-7 (849-007) Phase 2 Cohorts

Key Eligibility Criteria	KRYSTAL-1 Phase 1b	KRYSTAL-7 Phase 2
• Advanced, unresectable or metastatic NSCLC with KRAS^{G12C} mutation[a] • No prior systemic therapy for locally advanced/ metastatic disease • Stable brain metastases allowed	Adagrasib 400 mg[b] BID + Pembrolizumab N=7	Cohort 1a, PD-L1 TPS <1%[a,c] Adagrasib 400 mg BID + Pembrolizumab N=11 Cohort 2, PD-L1 TPS ≥1%[a] Adagrasib 400 mg BID + Pembrolizumab N=64
	Key Study Objectives • Primary endpoint: safety • Secondary endpoints: ORR (RECIST v1.1), DOR, PFS, OS	**Key Study Objectives** • Primary endpoint: ORR (RECIST v1.1) • Secondary endpoints: DOR, PFS, OS, safety, PK



- Objective responses were observed in 49% (26/53)[a] of patients across all PD-L1 levels, with a disease control rate of 89% (47/53)
- Responses were observed in 59% (13/22)[a] of patients with PD-L1 TPS ≥50%, 48% (10/21)[a] with PD-L1 TPS 1–49%, and 30% (3/10)[a] with PD-L1 TPS <1%

Li et al. WCLC 2022; Janne et al ESMO IO 2022

Combining KRAS G12C inhibitos with ICIs Toxicity

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)
ALP increased	2 (67)	0	0	0	3 (27)	2 (18)
Diarrhea	1 (33)	0	1 (20)	0	6 (55)	1 (9)
Arthralgia	1 (33)	0	0	0	2 (18)	0
Nausea	0	0	0	0	4 (36)	0
Fatigue	0	0	0	0	4 (36)	0
Hypokalemia	0	0	0	0	3 (27)	2 (18)
Decreased appetite	0	0	0	0	3 (27)	0
Headache	0	0	0	0	2 (18)	0
Hepatotoxicity	**2 (67)**	**2 (67)**	**2 (40)**	**1 (20)**	**6 (55)**	**5 (45)**

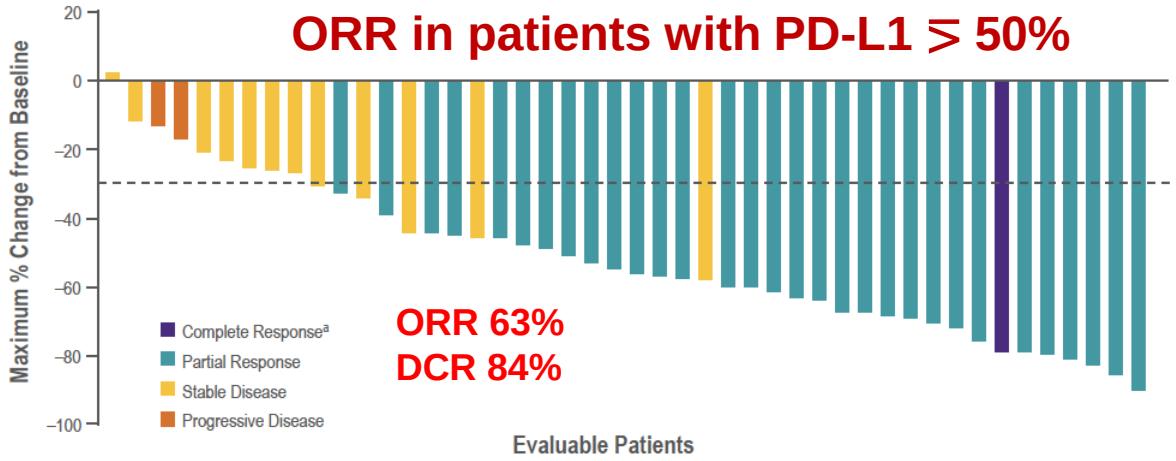
Most Frequent TRAEs	Concurrent 400 mg BID Adagrasib + Pembrolizumab (n=75)				
TRAEs, %	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any TRAEs	83%	15%	24%	40%	4%[a]
Most frequent TRAEs[b], %					
Nausea	48%	24%	19%	5%	0%
Diarrhea	43%	33%	5%	4%	0%
Vomiting	24%	13%	9%	1%	0%
ALT increased	21%	7%	7%	8%	0%
AST increased	21%	7%	5%	9%	0%
Fatigue	21%	9%	8%	4%	0%
Decreased appetite	20%	11%	9%	0%	0%
Amylase increased	16%	5%	11%	0%	0%

Combination of KRAS G12C inhibitors and ICIs increases the risk of hepatotoxicity

Li et al. WCLC 2022; Janne et al ESMO IO 2022

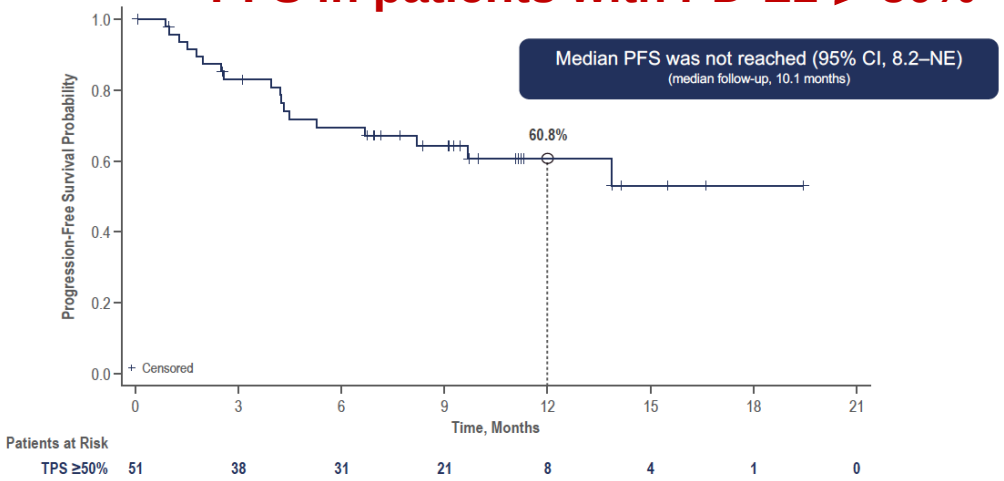
Combining KRAS G12C inhibitors with ICIs. KRYSTAL 07

ORR in patients with PD-L1 ⩾ 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[b], ORR was 70% (14/20; 95% CI, 46–88)

PFS in patients with PD-L1 ⩾ 50%



Liver treatment-related AEs

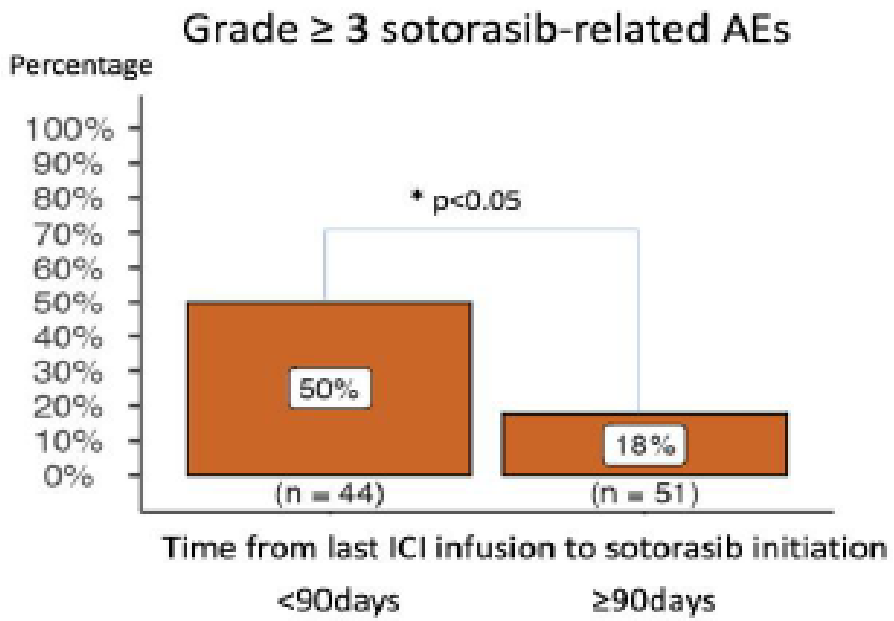
Most Frequent Liver TRAEs, %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Hepatitis	4	0	2	2	0
Hepatotoxicity[a]	1	0	1	1	0
Liver injury	1	0	1	0	0
Drug-induced liver injury	1	1	0	0	0
Hepatic failure	1	0	0	1	0
Acute hepatitis	1	0	1	0	0
Immune-mediated hepatitis	1	0	0	1	0

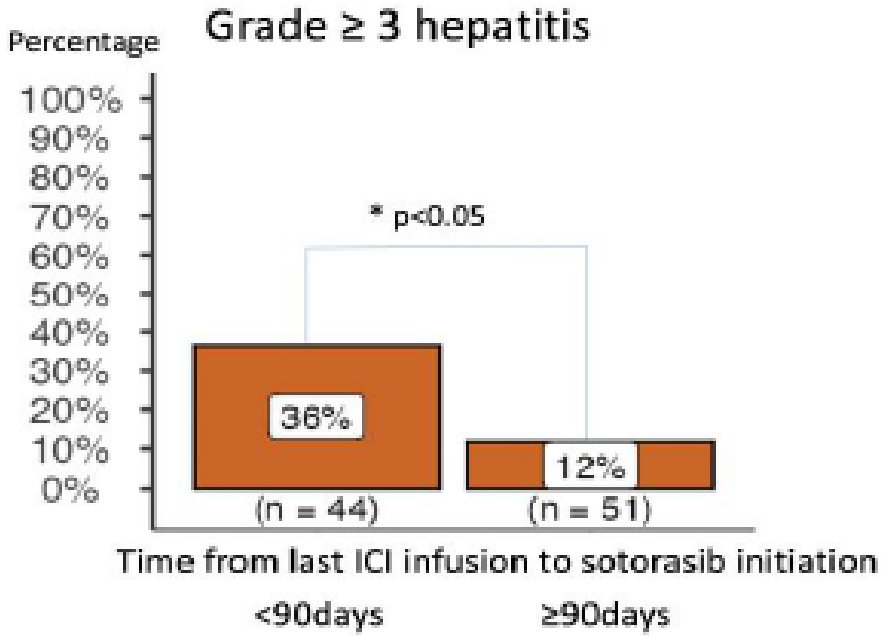
<10%
No cause of discontinuation
Time to resolution 22 days
24 (16%) increasing AST/ALT ⩾3

Garasino et al ESMO 2023

Sequencing KRAS G12C inhibitos with ICIs. Toxicity

ICI within prior 90 days

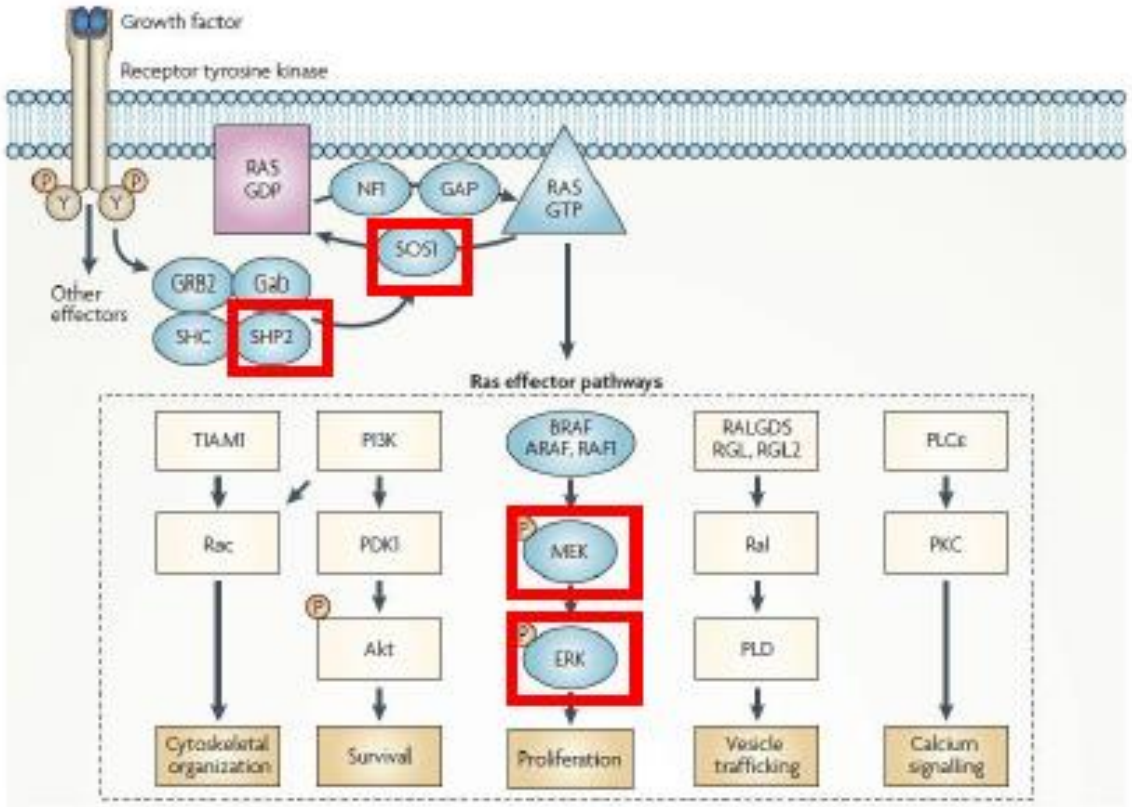




102 patients enrolled in the French EAP. 48 pts treated with sotorasib after ICI

Chour et al. Ann Oncol 2022; 33 (suppp 2): S49-50

Other combinations



- **SOS1** plays a role in the activation of KRAS through the exchange from GDP-bound to GTP-bound.
- **SHP2** acts synergistically with SOS1 and promotes KRAS activation
- **MEK**, **ERK1** and **ERK2** are downstream of KRAS and inhibiting them can eliminate residual signaling
- **EGFR**: KRAS G12C inhibition can lead to activation of upstream EGFR and HER2 signaling

Uprety et al. Cancer treat Rev 2020

Sororasib + trametininb

Response assessed by investigator	NSCLC: Sotorasib 960 mg + Trametinib 2 mg (N = 18)*	
	Prior KRAS^{G12C} inhibitor (n = 3)	KRAS^{G12C} inhibitor naïve (n = 15)
ORR, % (95% CI)	**0**	**20.0 (4.3, 48.1)**
Best overall response, n (%)		
Partial response, confirmed	0	3 (20.0)
Stable disease	2 (66.7)	10 (66.7)
Progressive disease	1 (33.3)	1 (6.7)
Not evaluable†	0	1 (6.7)
Disease control rate, n (%)	**2 (66.7)**	**13 (86.7)**
Duration of Response (min, max), mo.	**-**	**6.1, 15.3**

In previously NSCLC patients treated with KRAS G12C inhibitor 2 of 3 (67%) achieved disease control

Diarrhea 43%
Rash 34%
Nausea 29%

Ramlingam et al. AACR 2021

Sotorasib + afatinib

Response assessed by investigator	Sotorasib 960 mg PO QD + Afatinib 20 mg or 30 mg QD Combined Cohorts (N = 33)
ORR,‡ % (95% CI)	**30.3 (15.6, 48.7)**
Best overall response, n (%)	
Partial response, confirmed	10 (30.3)
Stable disease	15 (45.5)
Progressive disease	5 (15.2)
Not done	3 (9.1)
Disease control rate, n (%)	**25 (75.8)**

Patients receiving previous KRAS inhibitor: 3 SD, 1 PD

Diarrhea 70%
Rash 27%
Nausea 21%

Gandara et al. AACR 2021

KRAS G12C ihnibitor + SHP2 inhibitor

Sotorasib + RMC-4630

Response assessed by investigator	NSCLC	
	All enrolled (N = 11)	KRAS^{G12C} inhibitor-naïve (N = 6)
ORR, % (95% CI)	27 (6, 61)	50 (12, 88)
Best overall response, n (%)		
Partial response	3 (27)	3 (50)
Stable disease	4 (36)	3 (50)
Progressive disease	4 (36)	0
Disease control rate, n (%)	**7 (64)**	**6 (100)**

Other tumor types: 8 CRC (5 SD; 3 PD); 1 ovarian cancer (PR with an 81% reduction in tumor burden); 1 pancreatic adenocarcinoma (SD), and 2 other solid tumors (1 SD, 1 NE).

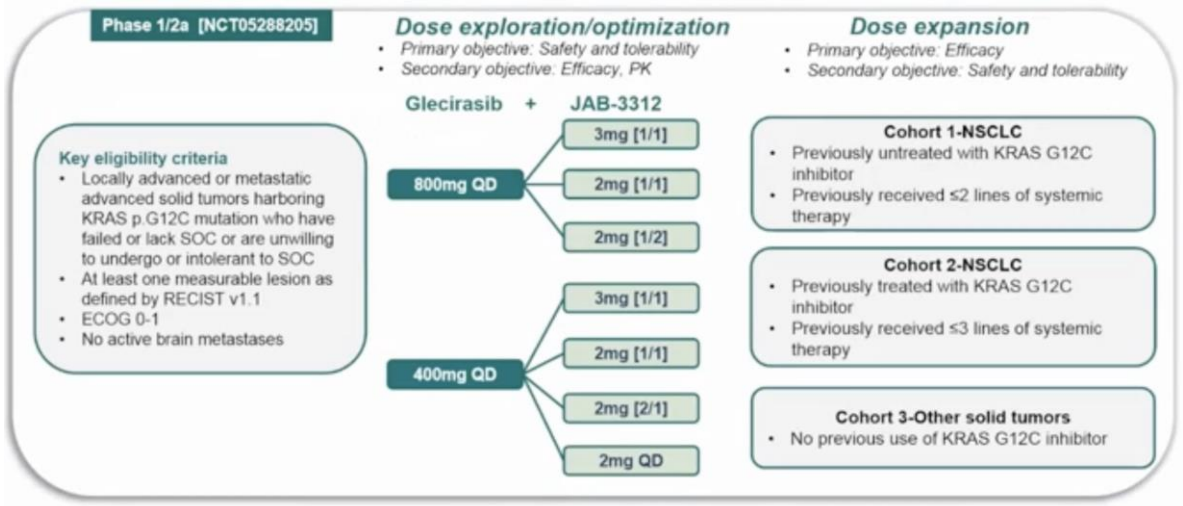
- **Disease control in 7 of 11 patients with NSCLC and in all patients who were KRAS^{G12C} i-naïve**
- **Promising early efficacy observed in patients with NSCLC who were KRAS^{G12C} i-naïve**

At the 2 higher doses, responders included 3 of 4 patients who were KRASi naïve

Edema 30%
Diarrhea 26%

Falchook et al. WCLC 2022

Glecirasib + JAB-3312



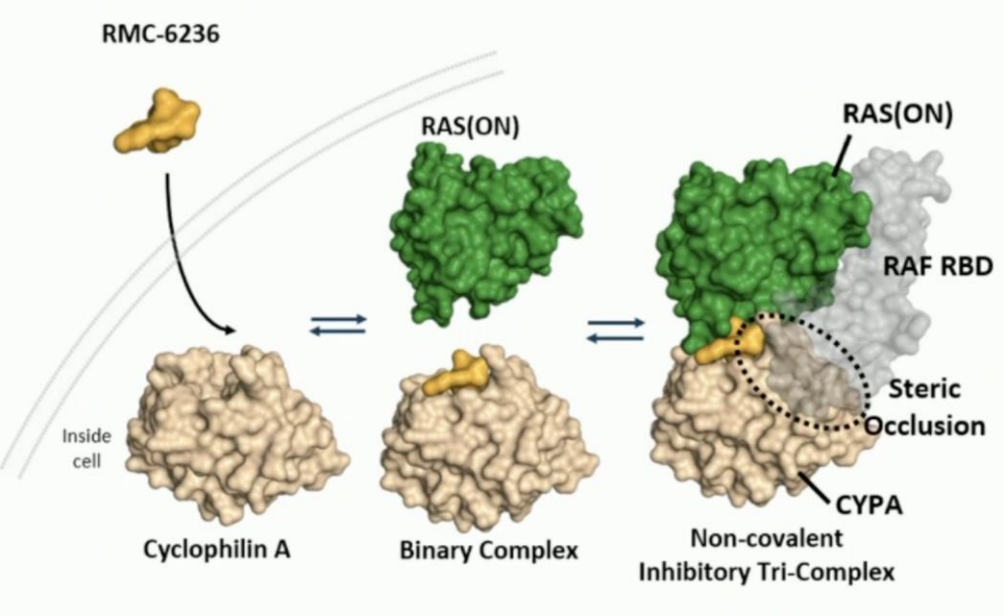
ORR NSCLC KAS G12C

ORR 62.1%
1L 65.5% ; >1 L 55.2%
DCR 100%

Dosis 800 mg + 2 mg ORR 86.7%

Wang et al. ESMO 2023

RAS on inhibitors

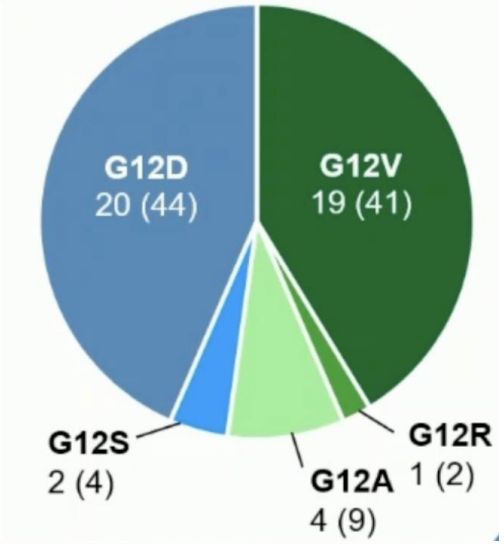


Estudio fase 1

RMC-6236 10-600 mg QD

	NSCLC[a] N = 46	PDAC[a] N = 65
Age, median (range), years	65 (31–83)	64 (30–86)
Female, n (%)	25 (54)	31 (48)
ECOG PS, n (%)		
0	11 (24)	20 (31)
1	35 (76)	45 (69)
Smoking status, n (%)		
Current	2 (4)	2 (3)
Past	28 (61)	14 (22)
Never	16 (35)	49 (75)
Number of prior anti-cancer therapies, median (range)	2 (1–6)	3 (1–7)
Select type of prior anti-cancer therapy/regimens, n (%)		
Checkpoint inhibitor[b]	44 (96)	–
Platinum-based chemotherapy	46 (100)	–
FOLFIRINOX	–	45 (69)
Gemcitabine + nab-paclitaxel	–	49 (75)

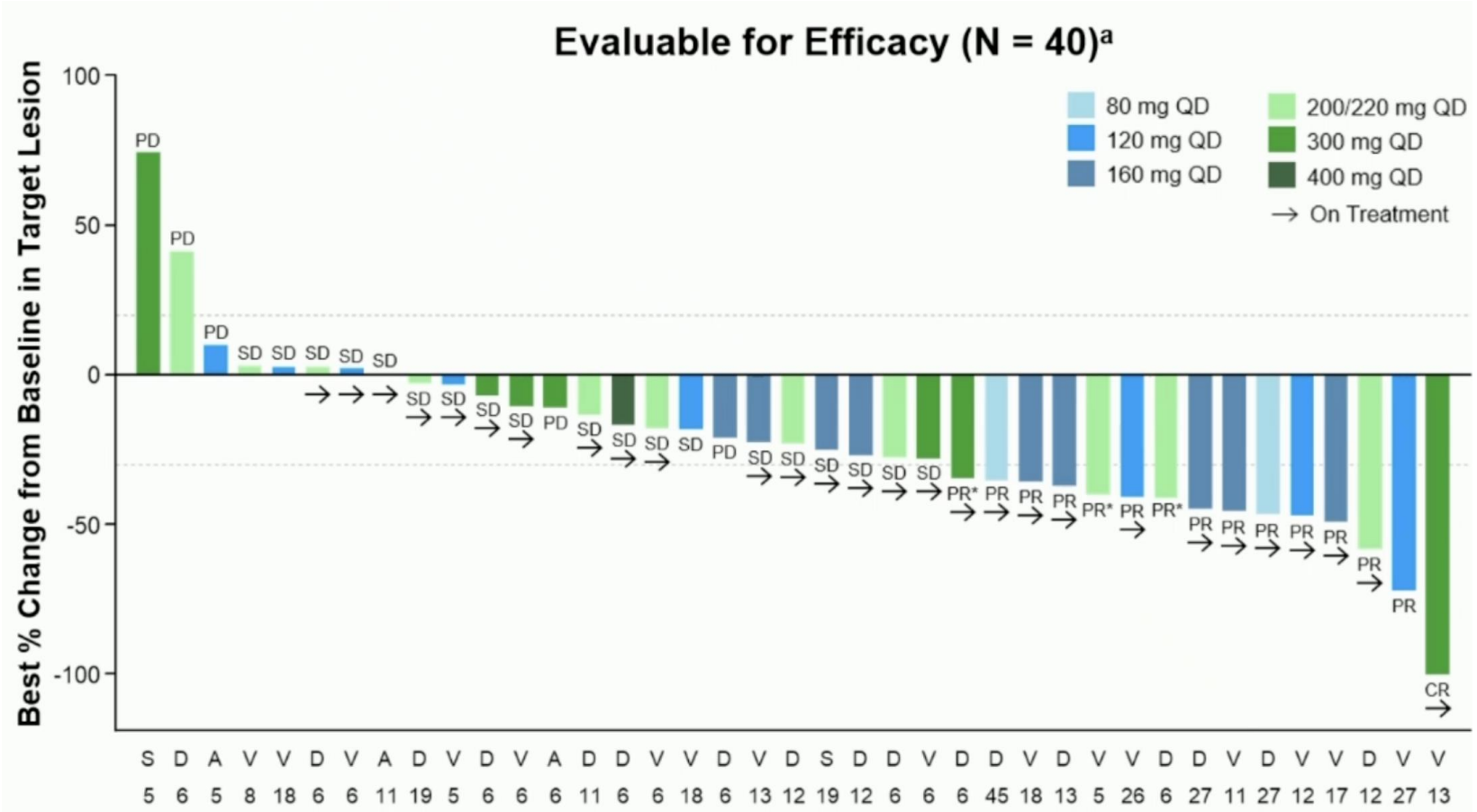
NSCLC



Arbour et al. ESMO 2023

RMC-6236

KRAS G12X NSCLC patients



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
CR	1 (3)
PR	14 (35)
SD	19 (48)
PD	5 (13)
NE[b]	1 (3)
ORR, n (%)	15 (38)
Confirmed, n	12
DCR (CR+PR+SD), n (%)	34 (85)

Median time to response 1.4 m
Median time on treatment 3.1 m

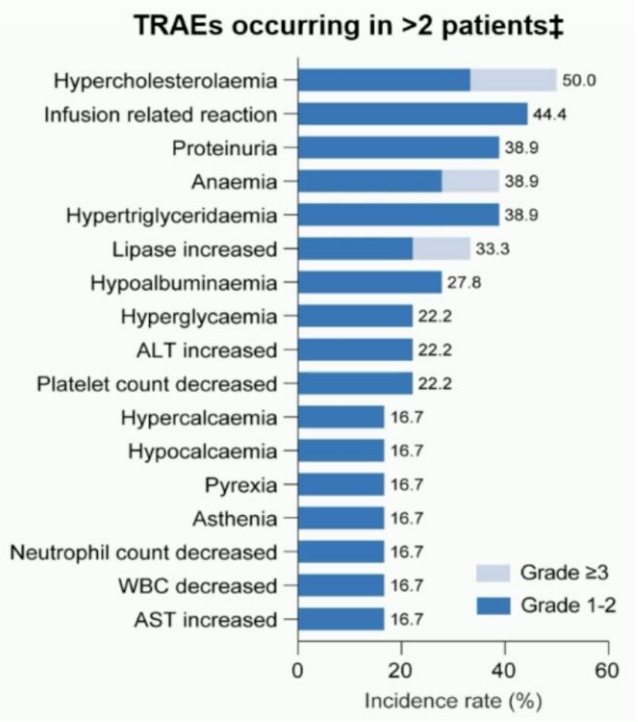
Arbour et al. ESMO 2023

HRA-4642 KRAS G12D inhibitor

Phase 1 study N =18

Safety

	All patients (n=18)
Any AE, n (%)	18 (100%)
Grade ≥3	9 (50.0%)
Any TRAE, n (%)	18 (100%)
Grade ≥3	6 (33.3%)*
Leading to dose reduction	0
Leading to dose interruption	8 (44.4%)
Leading to treatment discontinuation	0
Leading to death	0
Serious	1 (5.6%)†



Eficacy

	All tumors (n=18)	NSCLC (n=10)
BoR	1 PR, 11 SD, 2 non-CR/non-PD	1 PR, 7 SD, 1 non-CR/non-PD
DCR	77.8% (14/18)	90.0% (9/10)
Patient with target lesion shrinkage*	53.8% (7/13)	62.5% (5/8)

Zhou et al. ESMO 2023

Conclusions

- Long way for “undruggagle” to “real target”
- Current KRAS G12C inhibitors are clinically effective in KRAS G12C patients
- KRAS NSCLC is a molecular diverse and clinically heterogeneous
- Multiple new agents in development
- KRAS ”ON” inhibitors with efficacy in G12X
- Understanding resistance mechinism to improve the efficacy
- Developing combinations
- New inhibitors for non G12C mutations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Muchas Gracias