KRAS Therapies in NSCLC

New Orleans Summer Cancer Meeting, July 2024

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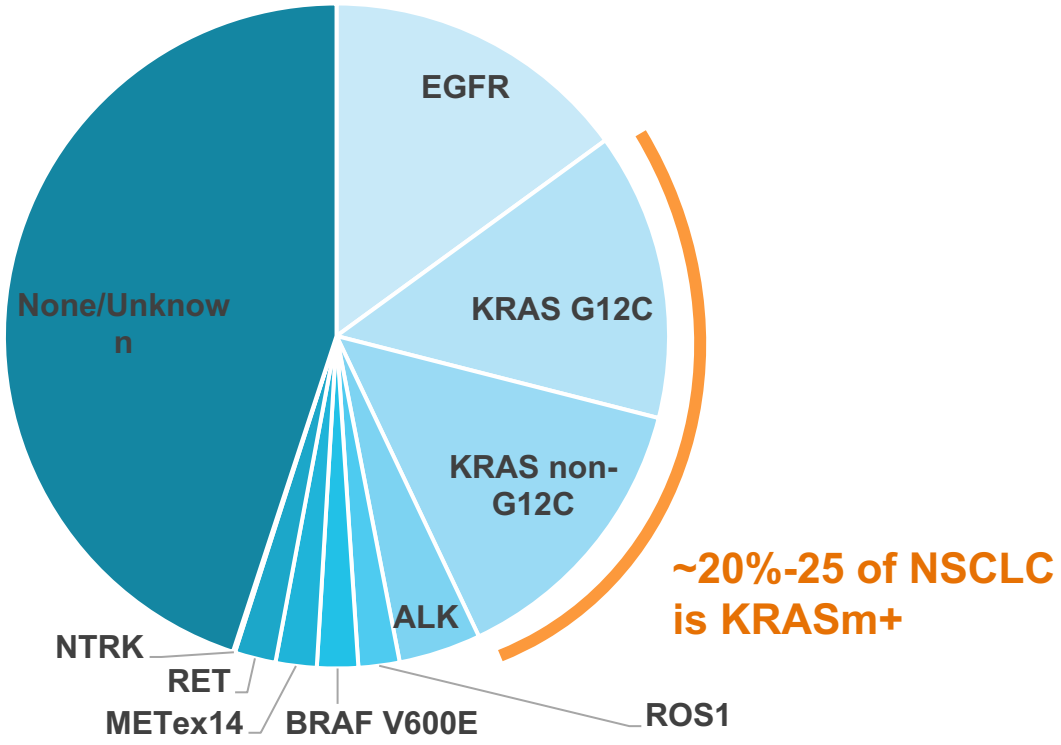
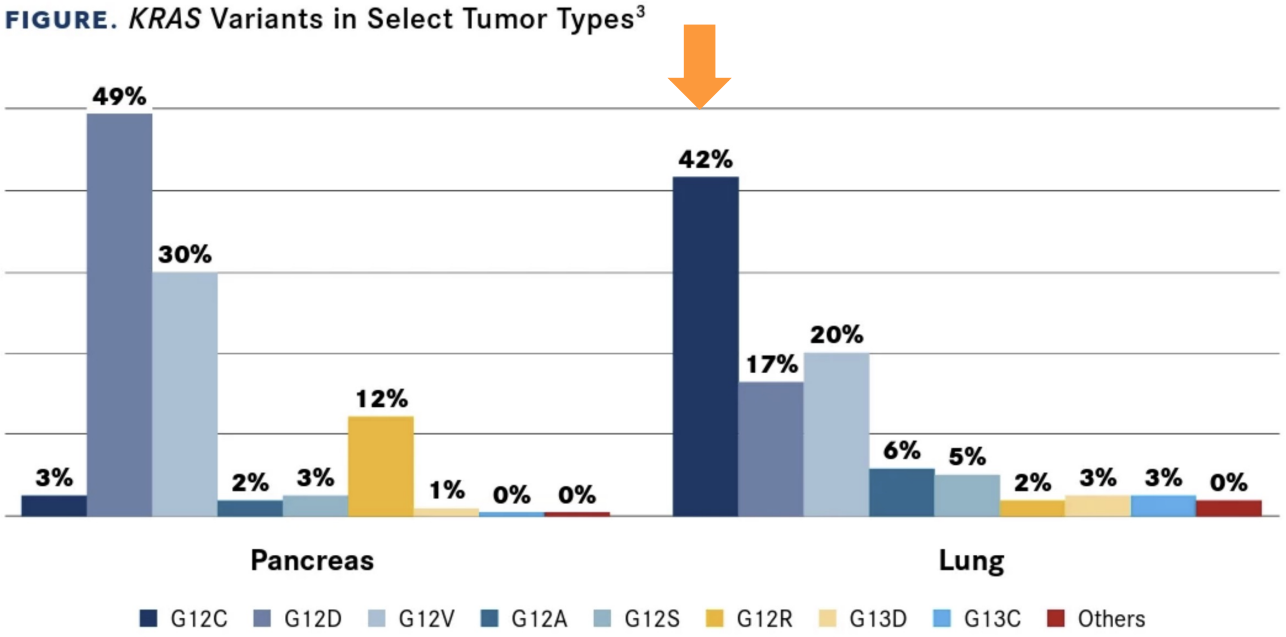
Spectrum of KRAS mutations in NSCLC



~20%-25 of NSCLC is KRASm+

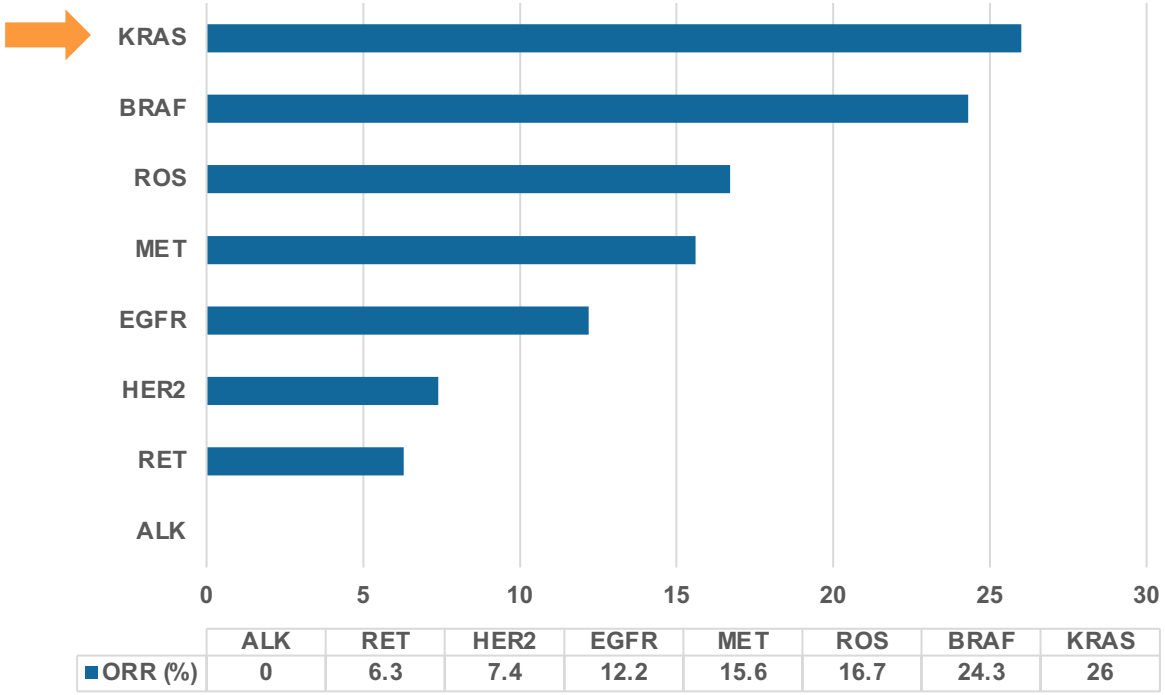
KRAS G12C comprises nearly 50% of KRAS mutations in NSCLC



Uprety et al. Cancer Treat Rev. 2020;89:102070

KRASm NSCLC is ICI responsive

ORR (%) in the IMMUNOTARGET Registry



KRASm Subgroup Analysis of KEYNOTE-189

	With Any KRAS Mutation		Without Any KRAS Mutation	
	Pembro + Chemo (N = 59)	Placebo + Chemo (N = 30)	Pembro + Chemo (N = 145)	Placebo + Chemo (N = 55)
ORR, % (95% CI)	40.7%	26.7%	47.6%	10.9%
	(28.1-54.3)	(12.3-45.9)	(39.2-56.0)	(4.1-22.3)
PFS, median, mo (95% CI)	9 (7-14)	5 (5-9)	9 (7-14)	5 (4-5)
PFS, HR (95% CI)	0.47 (0.29-0.77)		0.40 (0.29-0.57)	
OS, median, mo (95% CI)	21 (16-NR)	14 (8-NR)	23 (19-NR)	9 (7-17)
OS, HR (95% CI)	0.79 (0.45-1.38)		0.55 (0.37-0.81)	

Current first-line standard of care in KRASm NSCLC is immunotherapy +/- chemotherapy

Mazieres et al. Ann Oncol. 2019;30(8):1321-1328; Gadgeel et al. Annals of Oncology. 2019. 30(11);X164-165. LBA5.

Why has KRAS been difficult to target?

1984
KRAS Found in NSCLC

>30 years of negative studies

2021
1st KRAS inhibitor approval in NSCLC

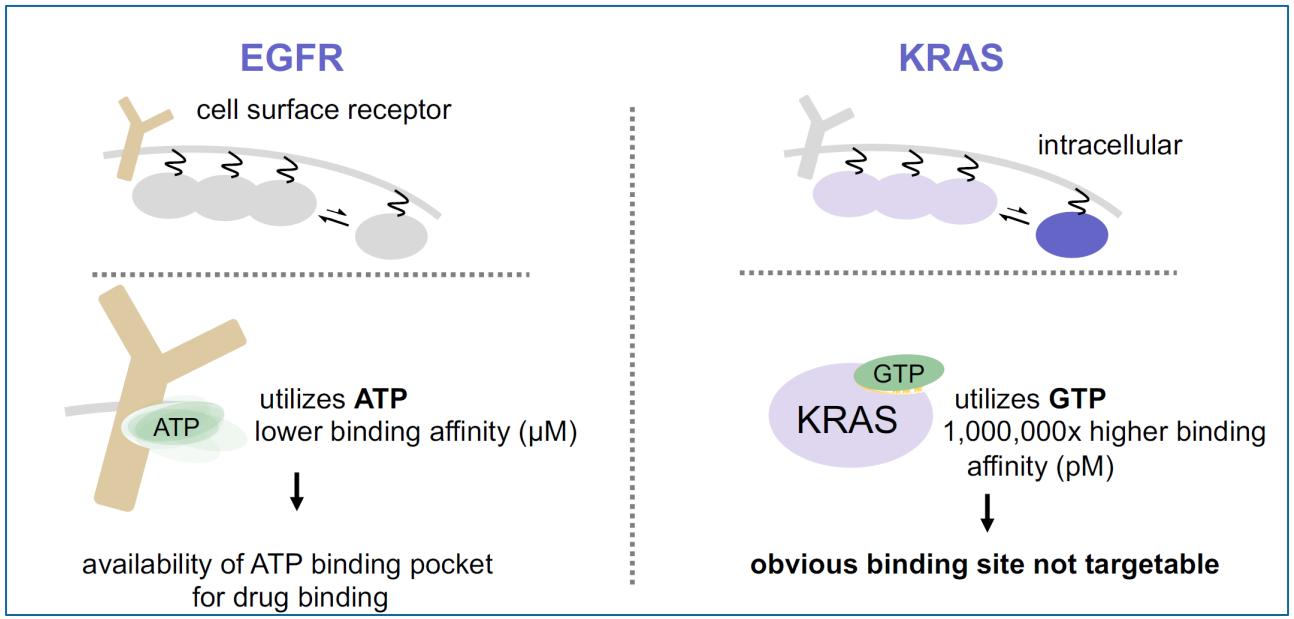


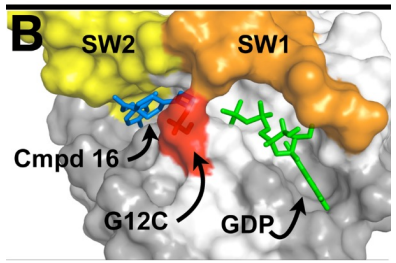
Figure courtesy of Dr Jia Luo

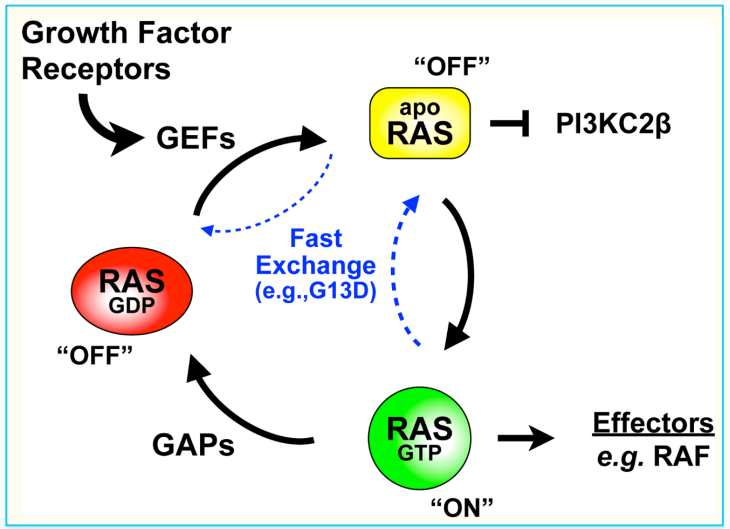
Small molecule without obvious binding pockets

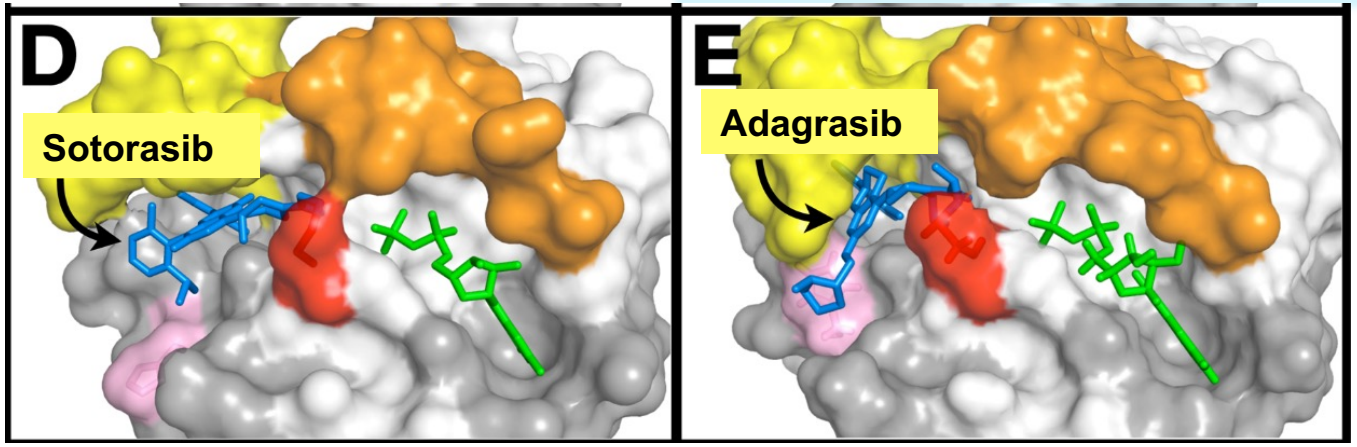
Dramatically higher binding affinity for GTP than tyrosine kinases hold for ATP = More difficult to out-compete

Bar-Sagi et al. *Nat Cancer*. 2020;1(1):25-27

Targeting KRAS G12C with current covalent RAS(OFF) Inhibitors





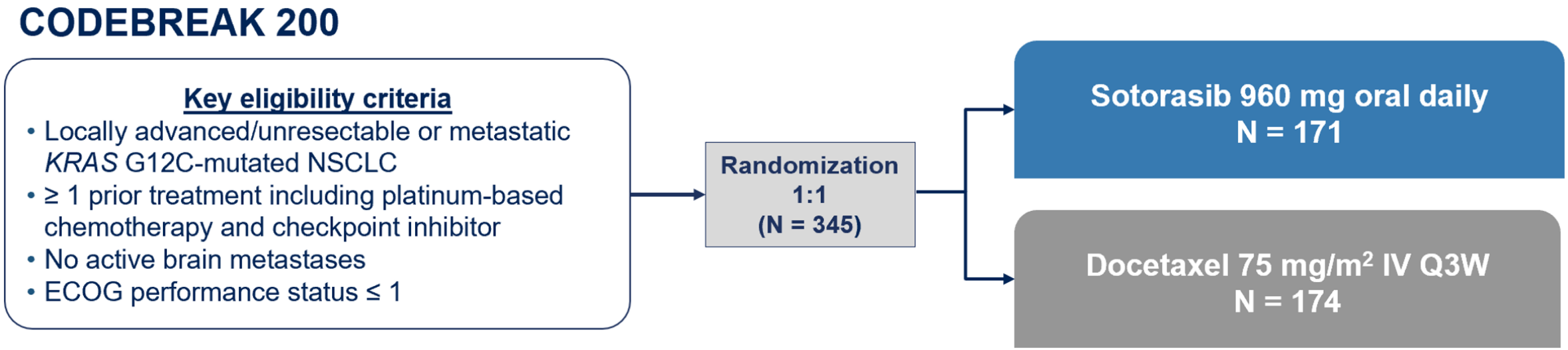


Adapted from Zuberi et al.Biochem Soc Trans. 2020; 48(5):1831-41

Current approved G12C inhibitors (adagrasib/sotorasib) capitalize on:

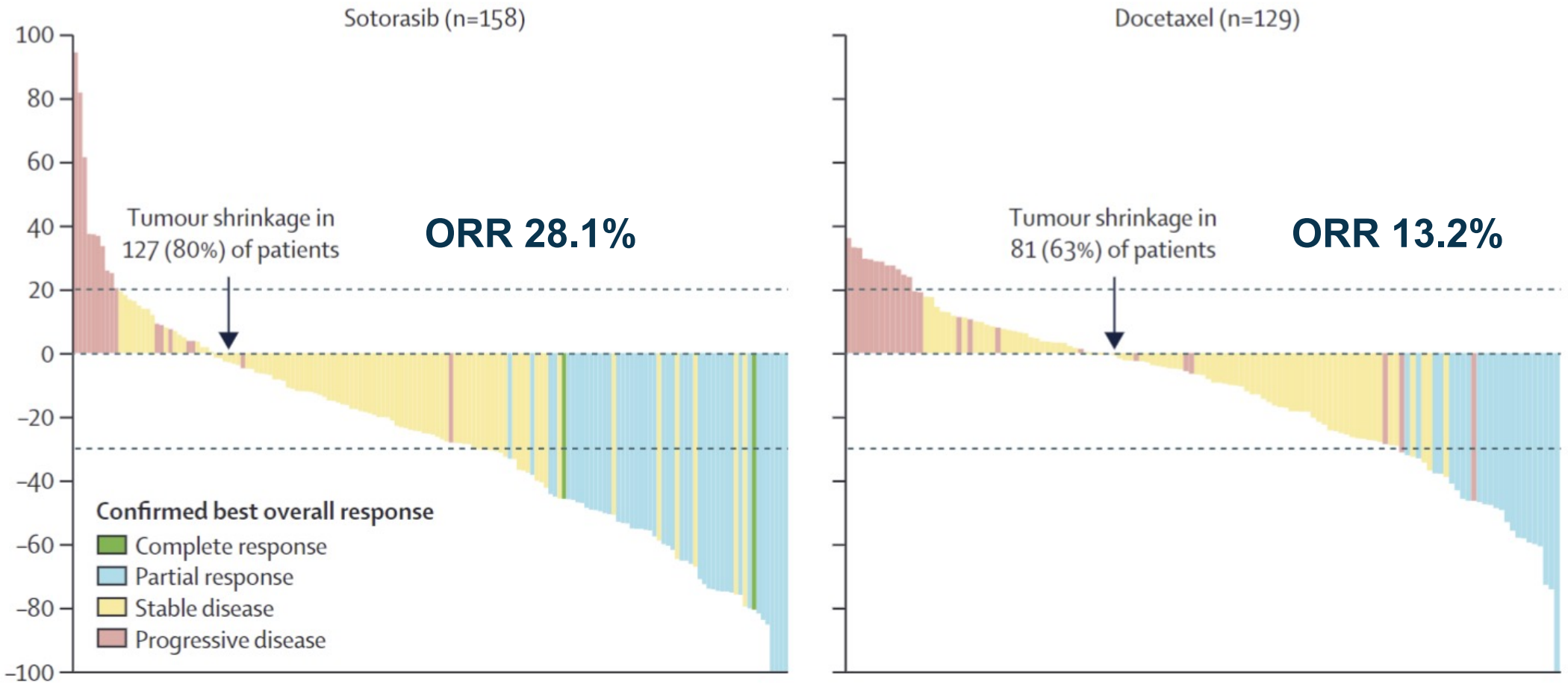
- Cysteine as a covalent binding site
- Preserved GTPase activity despite mutation, facilitates binding and trapping in the "OFF" GDP state

CodeBreaK 200: Sotorasib vs Docetaxel in Previously Treated KRAS G12C+ NSCLC



M Johnson. ESMO 2022. LBA10

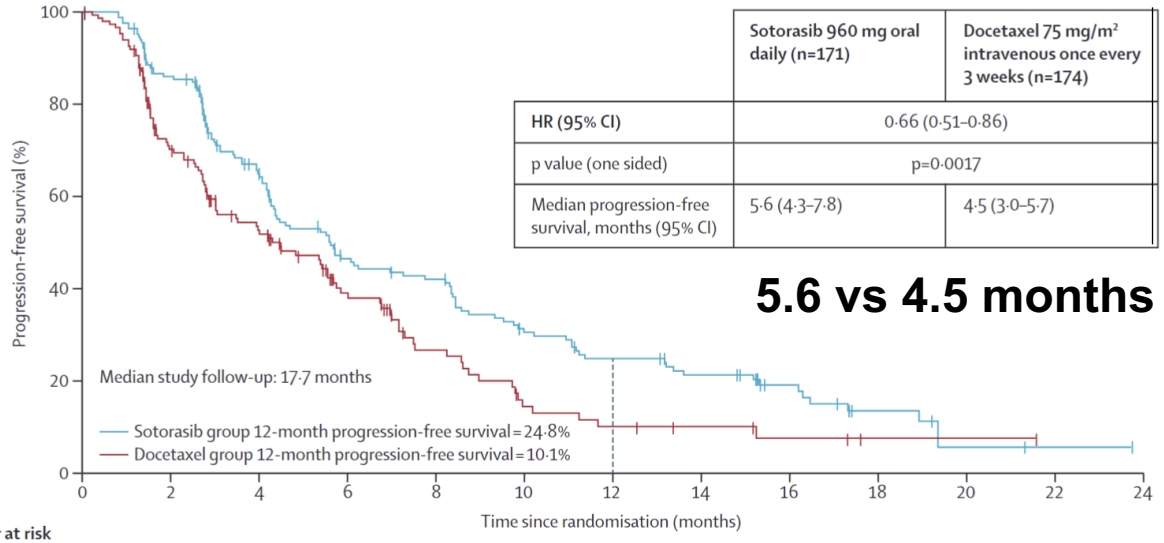
CodeBreaK 200: Sotorasib vs Docetaxel, Previously Treated KRAS G12C+ NSCLC



De Langen et al. Lancet. 2023;401(10378)

Survival Outcomes
CodeBreaK 200

PFS

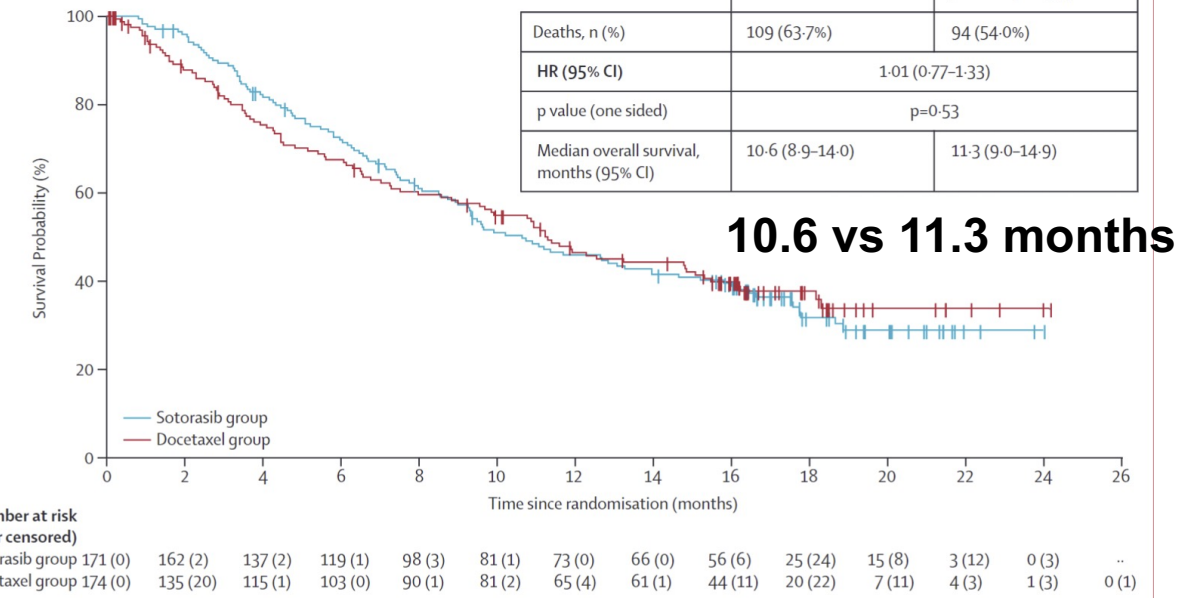


	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
HR (95% CI)	0·66 (0·51–0·86)	
p value (one sided)	p=0·0017	
Median progression-free survival, months (95% CI)	5·6 (4·3–7·8)	4·5 (3·0–5·7)

5.6 vs 4.5 months

Number at risk (number censored)													
Sotorasib group	171 (0)	139 (9)	93 (14)	63 (4)	56 (1)	38 (3)	30 (1)	24 (2)	14 (8)	6 (4)	2 (1)	1 (1)	0 (1)
Docetaxel group	174 (0)	93 (39)	62 (9)	36 (12)	20 (6)	10 (1)	7 (0)	5 (2)	3 (1)	1 (2)	1 (0)	0 (1)	..

OS



	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
Deaths, n (%)	109 (63·7%)	94 (54·0%)
HR (95% CI)	1·01 (0·77–1·33)	
p value (one sided)	p=0·53	
Median overall survival, months (95% CI)	10·6 (8·9–14·0)	11·3 (9·0–14·9)

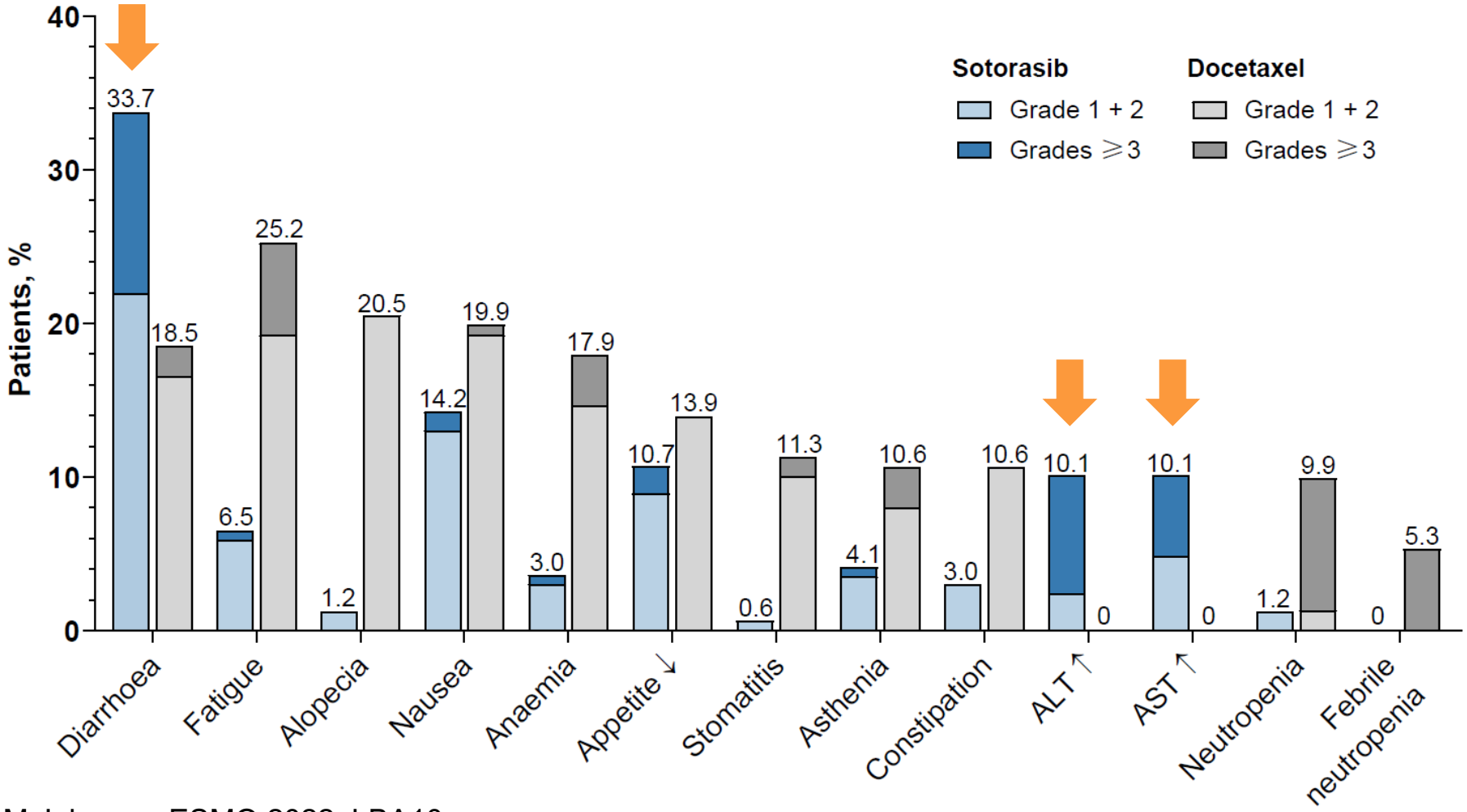
10.6 vs 11.3 months

Number at risk (number censored)													
Sotorasib group	171 (0)	162 (2)	137 (2)	119 (1)	98 (3)	81 (1)	73 (0)	66 (0)	56 (6)	25 (24)	15 (8)	3 (12)	0 (3)	..
Docetaxel group	174 (0)	135 (20)	115 (1)	103 (0)	90 (1)	81 (2)	65 (4)	61 (1)	44 (11)	20 (22)	7 (11)	4 (3)	1 (3)	0 (1)

de Langen AJ, et al. *Lancet*. 2023;401(10378):733-746

Sotorasib Adverse Effects

Most Common TRAEs (Any grade ≥10% or grade 3+ ≥ 5%)

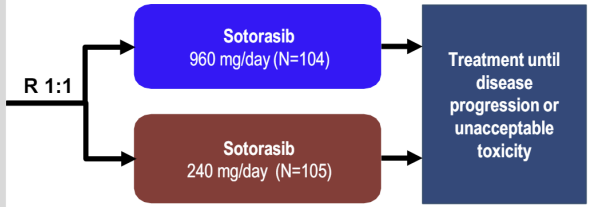


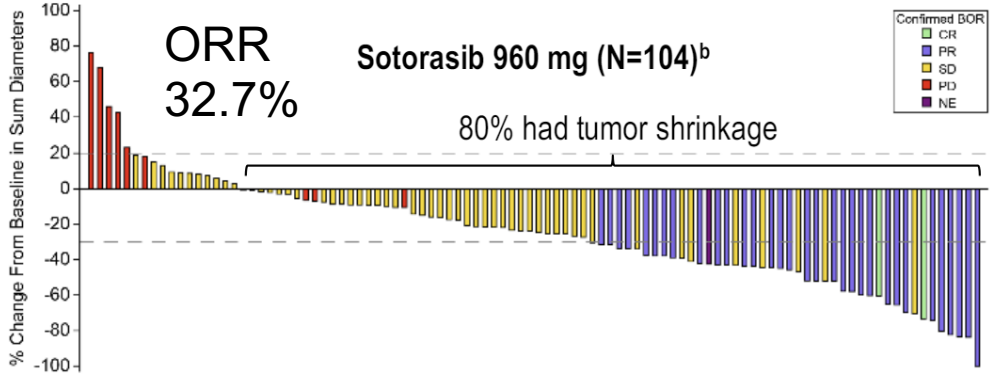
Presented by M Johnson. ESMO 2022. LBA10

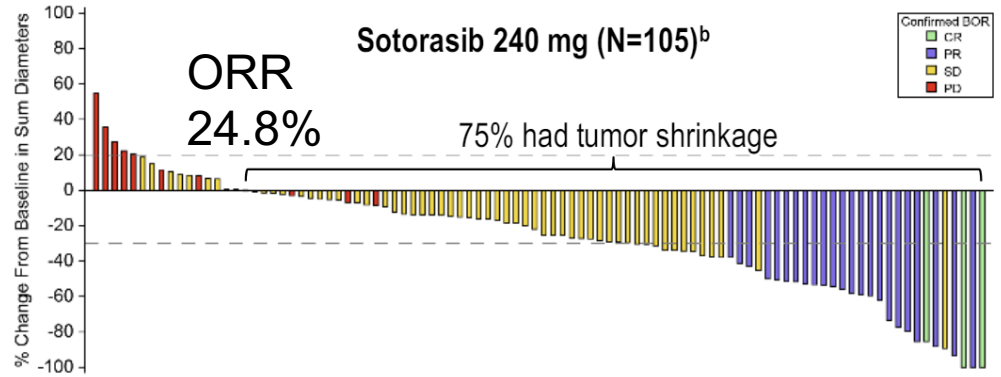
Sotorasib 960 mg vs 240 mg

Key eligibility criteria
- Adults with previously treated, advanced *KRAS* G12C+ NSCLC
- Prior PD-(L)1 inhibitor and/or platinum-based chemotherapy
- ECOG PS ≤ 2
- Absence of active brain metastases

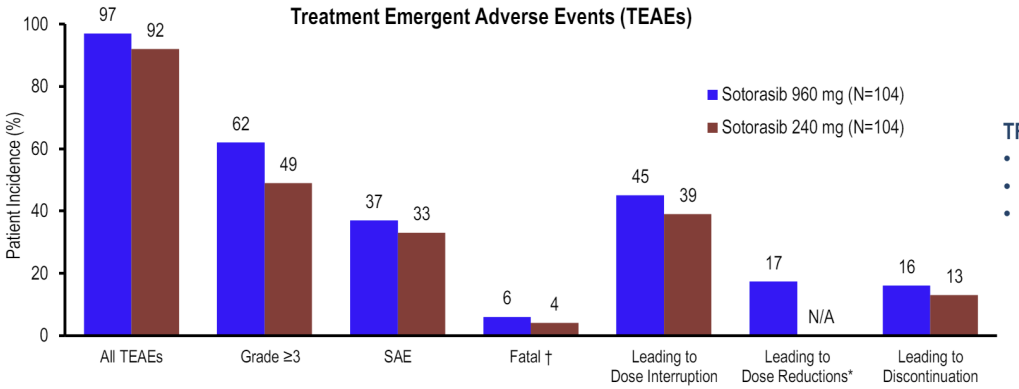
Randomization stratification
- Number of prior lines of therapy: 1–2 vs > 2
- History of CNS metastasis: Yes vs No
- Race: Asian vs non-Asian
- ECOG PS: < 2 vs 2







Safety Profile

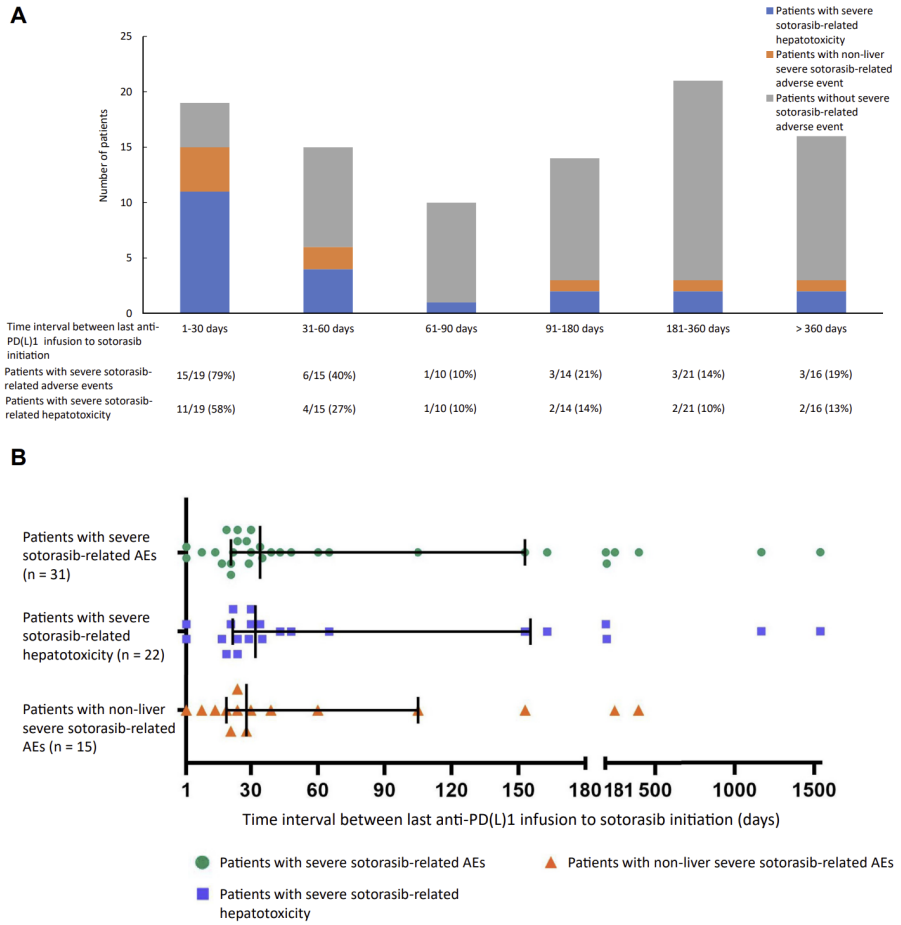


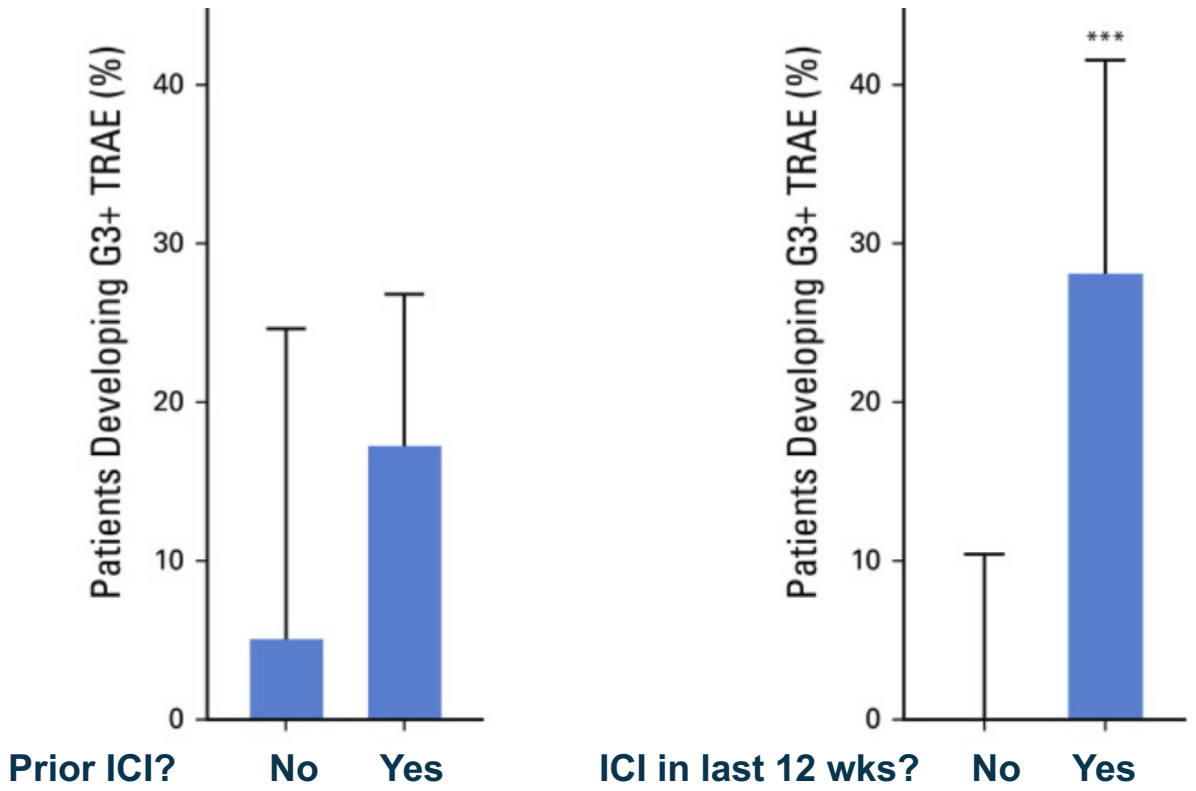
TRAEs (960 mg vs 240 mg):
- Overall (83% vs 62%)
- Grade ≥3 (36% vs 19%)
- SAEs (14% vs 8%)

960 mg vs 240 mg Dosing
PFS 5.4 vs 5.6 months
OS 13.0 vs 11.7 months
ORR 32.7% vs 24.8%

Hochmair et al. ESMO Virtual Plenary 2023

Increased hepatotoxicity with sotorasib immediately following ICI exposure



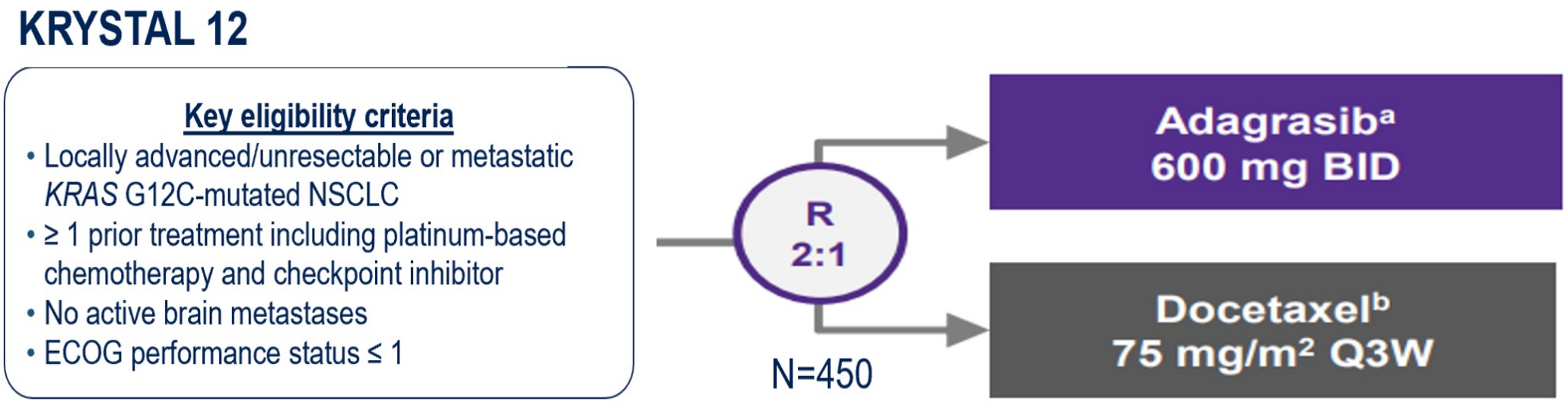


Chour et al. J Thorac Oncol. 2023

Adapted from Thummalapalli et al JCO Precis Oncol 2023

KRYSTAL-12:

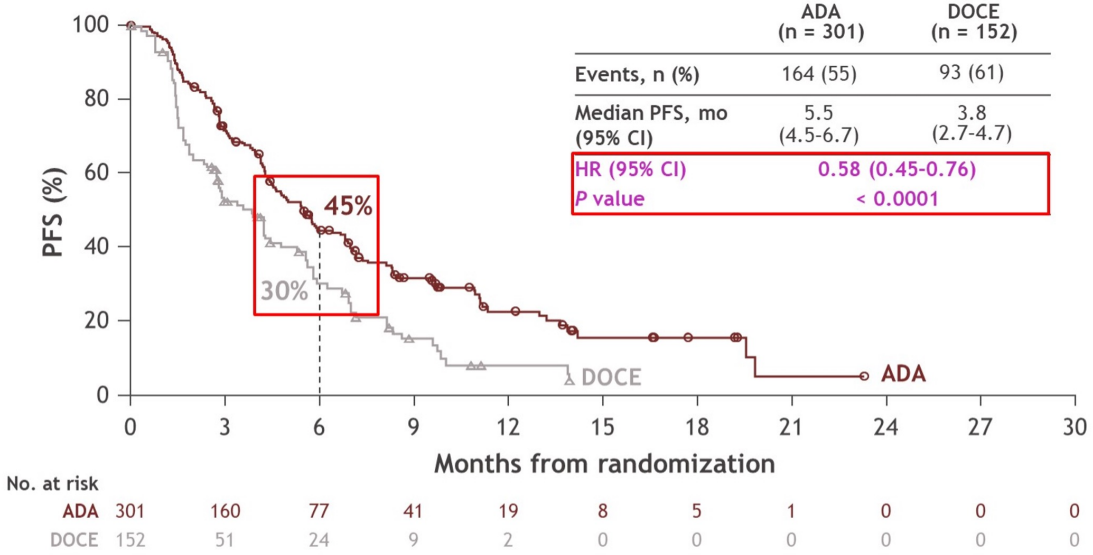
Sotorasib vs Docetaxel in Previously Treated KRAS G12C+ NSCLC



Mok et al. ASCO 2021.

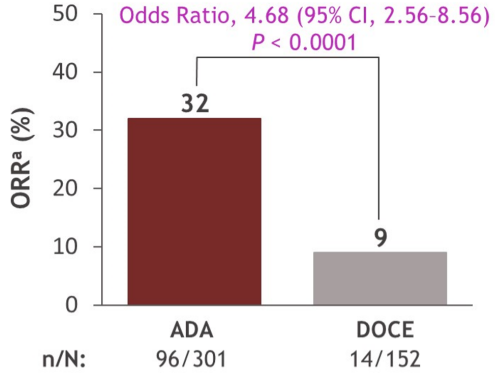
KRYSTAL-12: Adagrasib vs Docetaxel in Previously Treated KRAS G12C+ NSCLC

Primary endpoint: PFS[a] per BICR

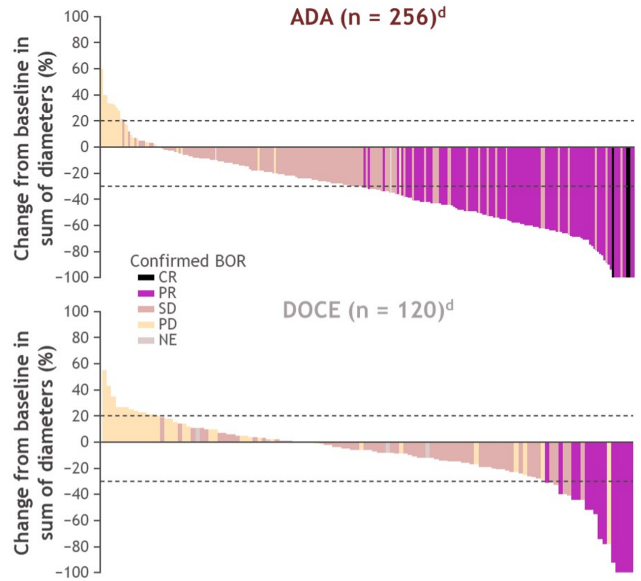


	ADA (n = 301)	DOCE (n = 152)
Events, n (%)	164 (55)	93 (61)
Median PFS, mo (95% CI)	5.5 (4.5-6.7)	3.8 (2.7-4.7)
HR (95% CI)	0.58 (0.45-0.76)	
P value	< 0.0001	

Tumor response per BICR

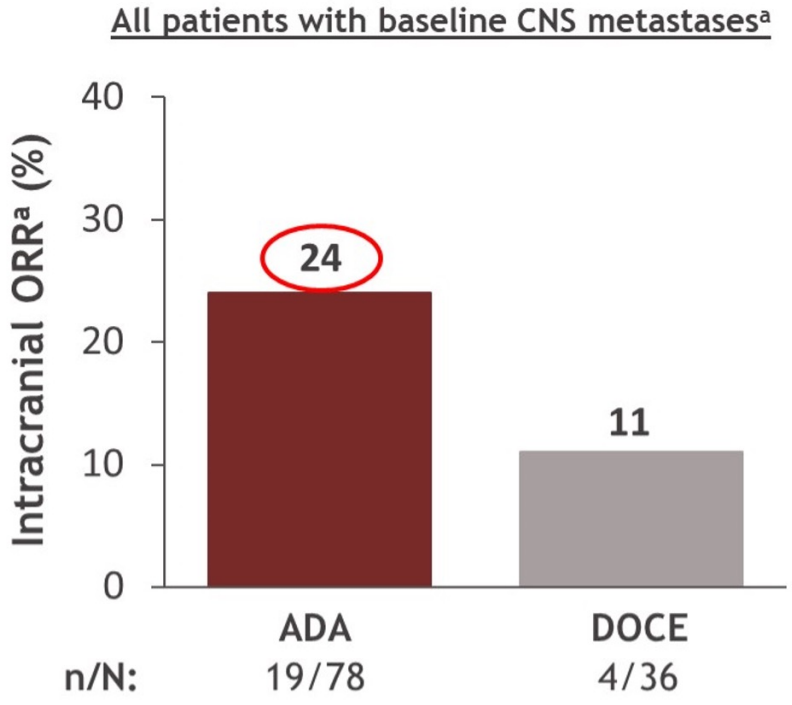


Tumor response	ADA (n = 301)	DOCE (n = 152)
DCR,[b] n (%)	236 (78)	89 (59)
Median DOR,[c] mo (95% CI)	8.3 (6.1-10.4)	5.4 (2.9-8.5)
Remaining in response at 6 mo, %	64	39

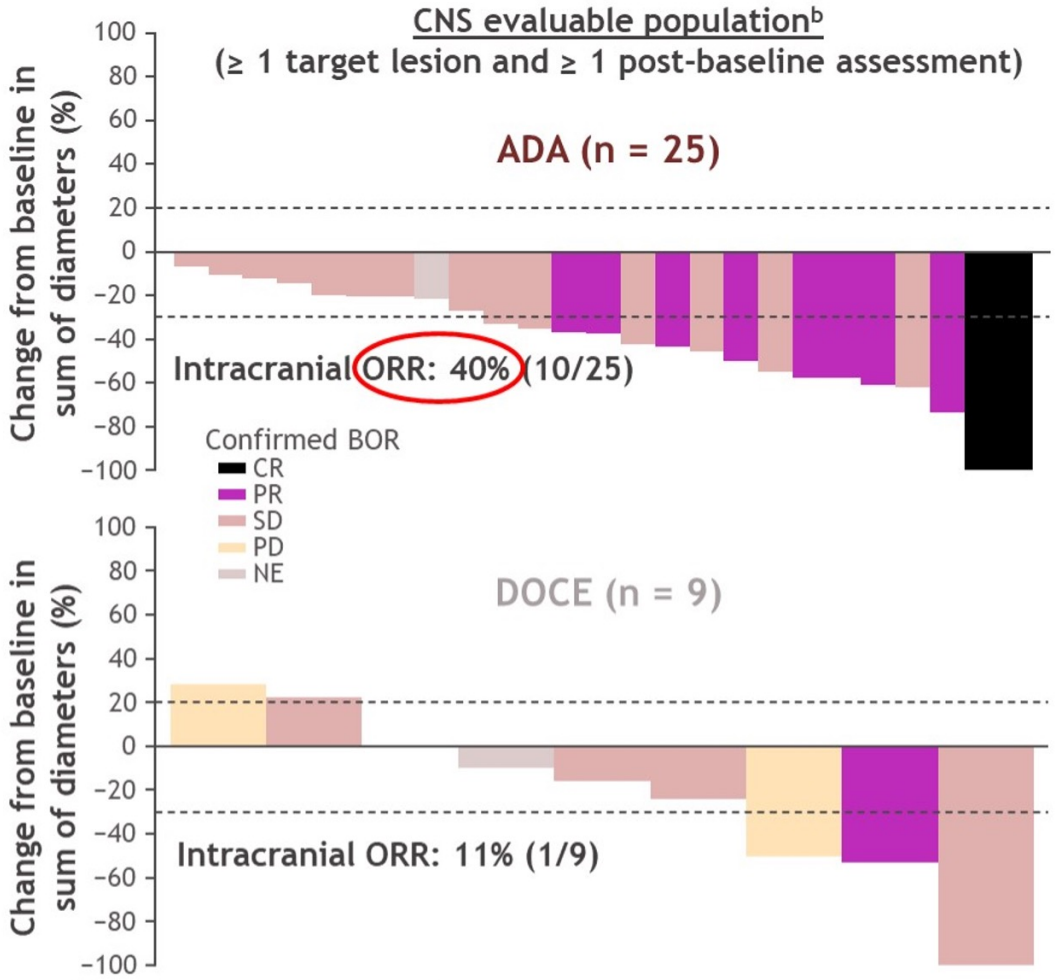


Presented by T Mok. ASCO 2024. LBA8509

KRYSTAL-12 Adagrasib Intracranial Response per BICR

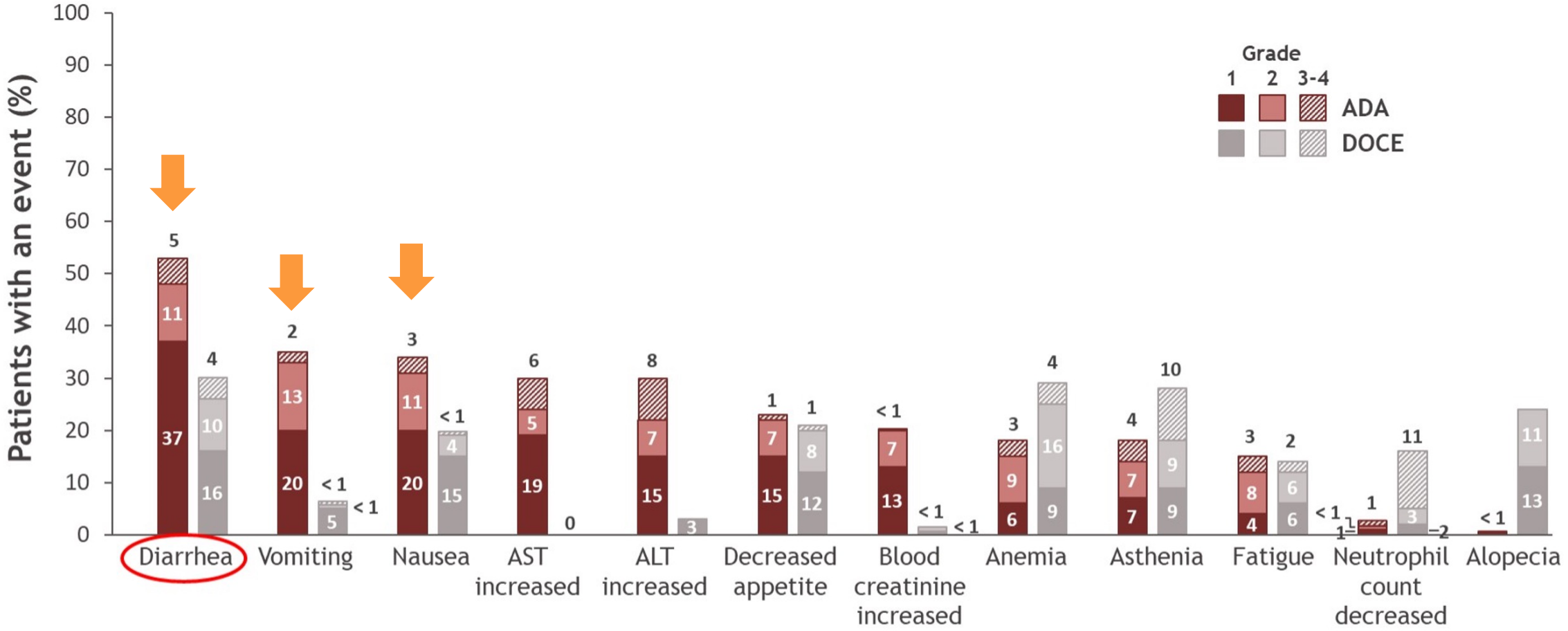


Intracranial response[a]	ADA (n = 78)	DOCE (n = 36)
Intracranial DCR, n (%)	64 (82)	20 (56)



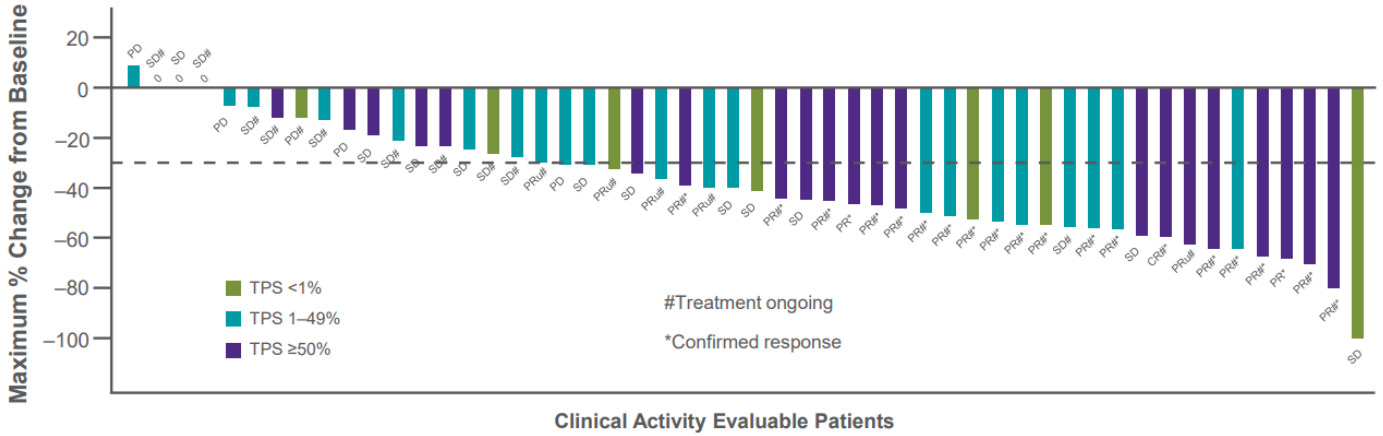
Presented by T Mok. ASCO 2024. LBA8509

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



Presented by T Mok. ASCO 2024. LBA8509

KRYSTAL-7: First-line Adagrasib + Pembrolizumab in KRAS G12C+ NSCLC



Unconfirmed ORR (all PD-L1 scores) 49%

- ***Combination with acceptable side effect profile***
- ***10-14% rate of G3+ AST, ALT increase***

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

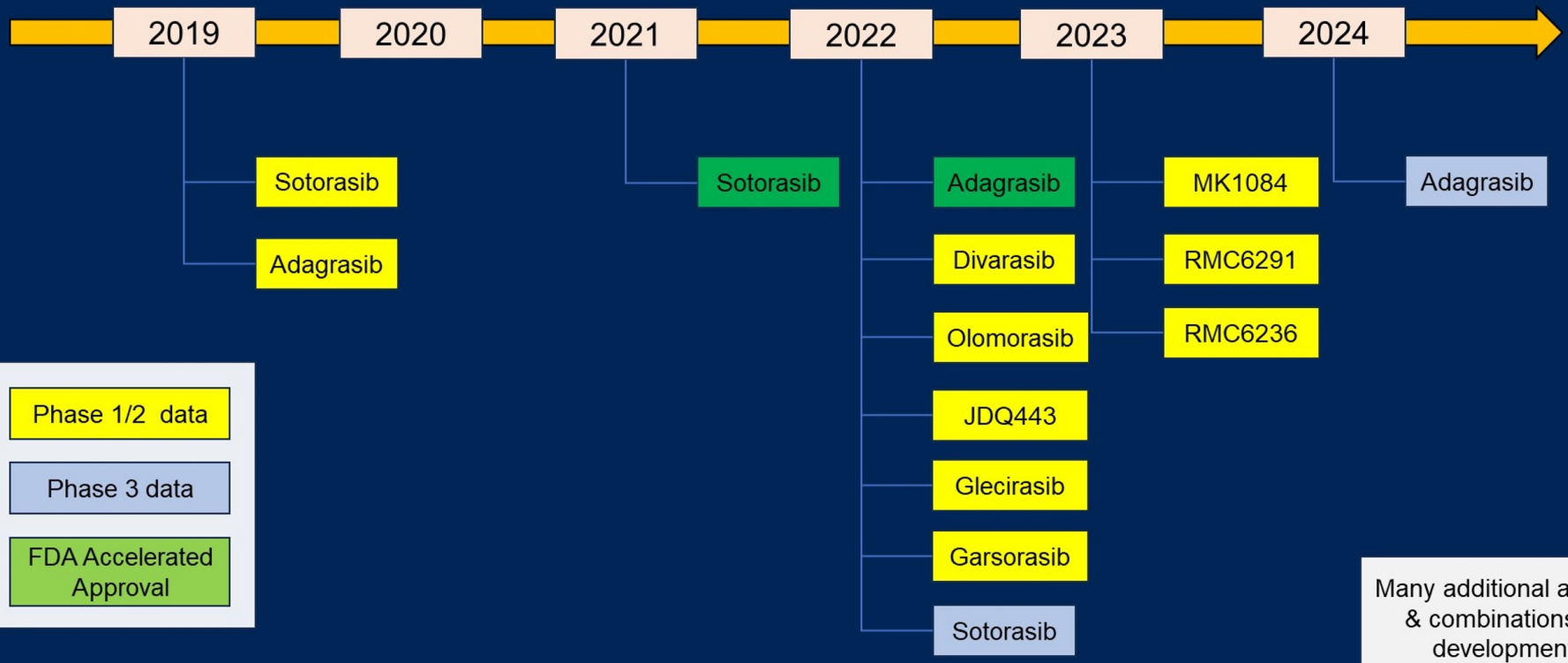
Jänne et al, ESMO IO 2022

Comparing across studies…

	KRYSTAL-12		CodeBreaK 200	
	Adagrasib	Docetaxel	Sotorasib	Docetaxel
ORR	**32%**	**9%**	**28.1%**	**13.2%**
DCR	78%	59%	82.5%	60.3%
PFS	**5.5 months**	**3.8 months**	**5.6 months**	**4.5 months**
OS	-	-	10.6 months	11.3 months
Discontinuation Rate	8%	14%	10%	11%
Dose Reduction Rate	**48%**	**24%**	**15%**	**27%**

Mok et al. ASCO 2024. LBA8509; de Langen AJ, et al. *Lancet*. 2023;401(10378):733-746

KRAS G12C Inhibitors – State of the Field

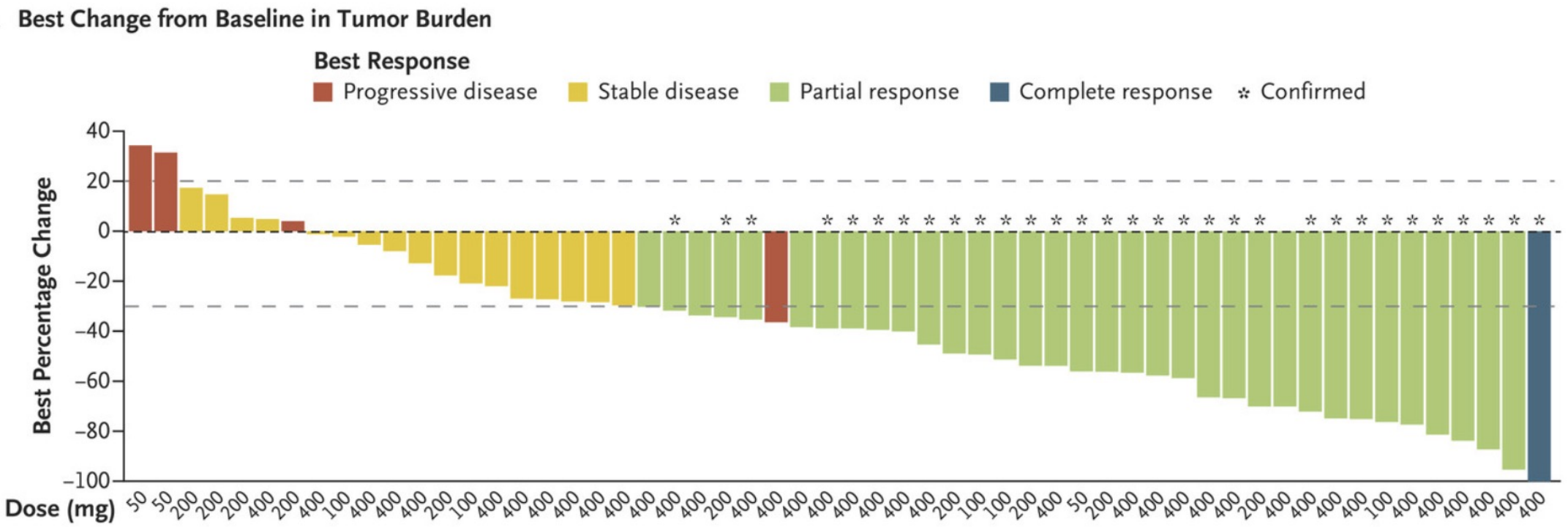


2024 ASCO ANNUAL MEETING
#ASCO24

PRESENTED BY: Adrian G. Sacher, M.D.

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Divarasib

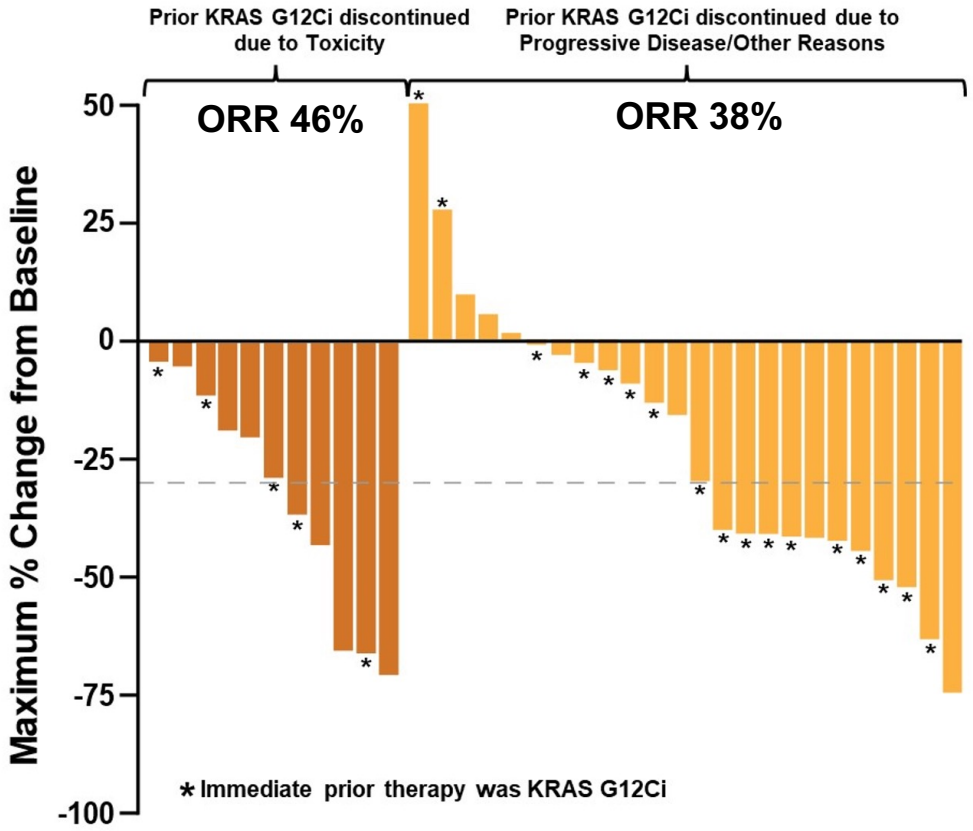


Confirmed response rate 53.4%
PFS 13.1 months

Sacher et al. NEJM. 2023;389(8): 710-721

Olomorasib

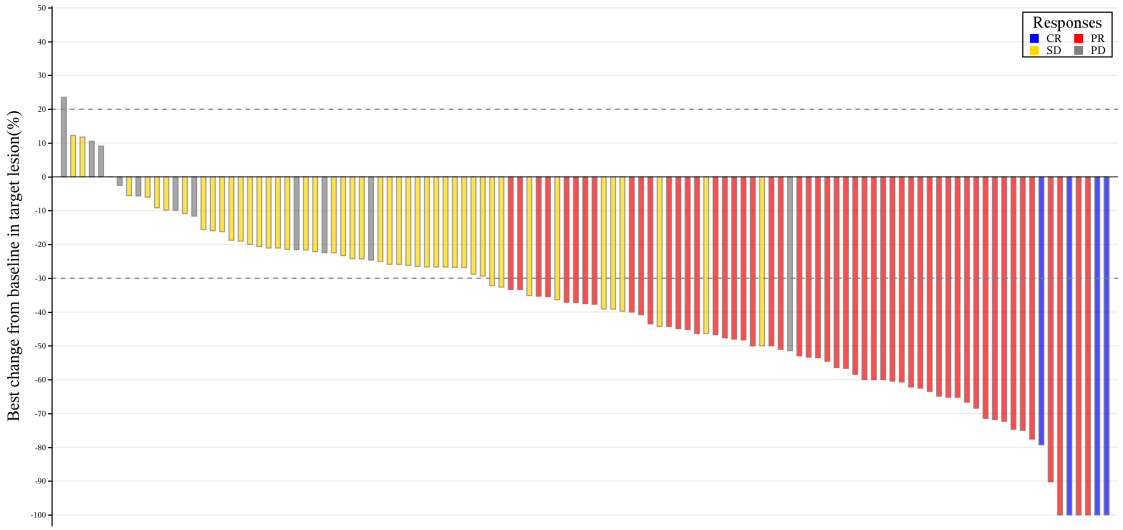
ORR 41% in KRASi Pretreated NSCLC



Heist et al, ASCO 2024

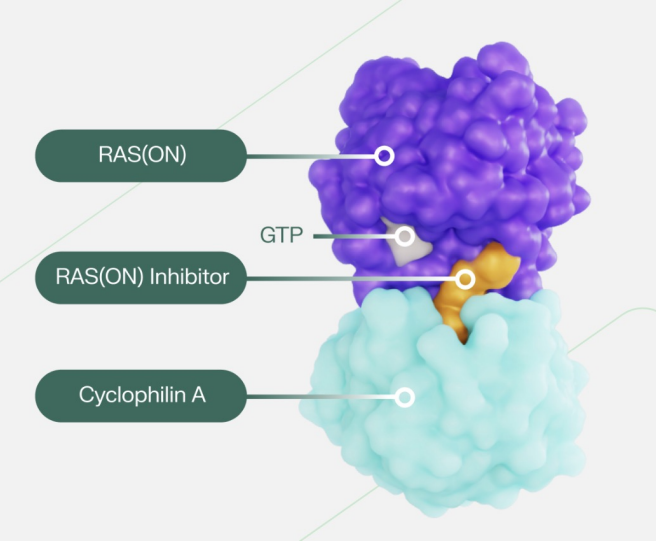
Glecirasib

ORR 47.9%, prior chemotherapy and ICI

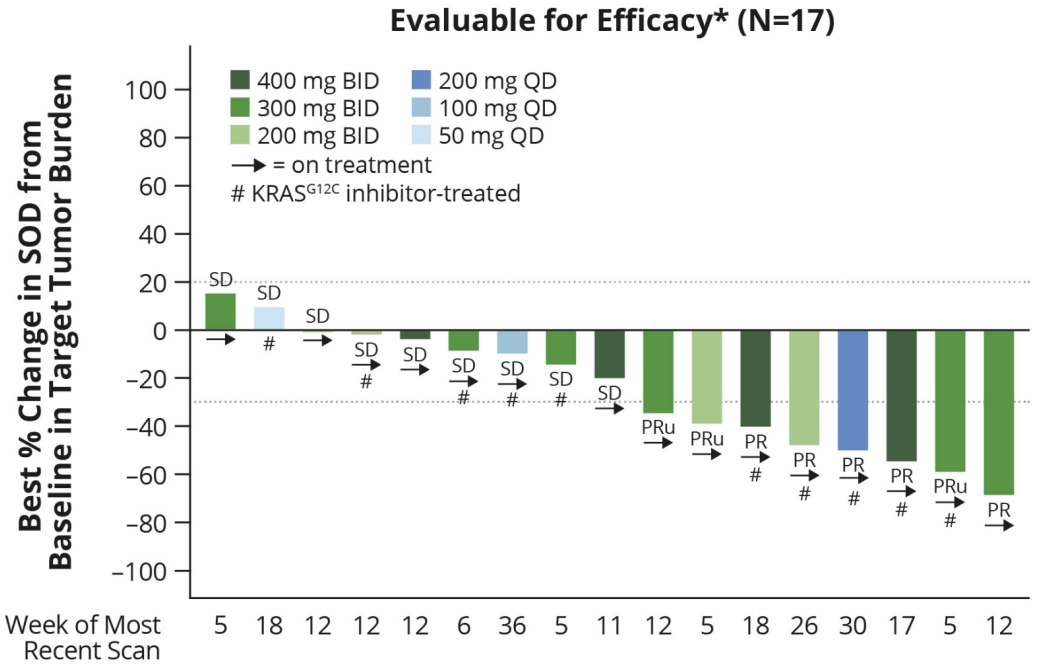


Shi et al. ASCO Plenary Series: April 2024 Session (Abstract 468214).

RAS(ON) Inhibitors



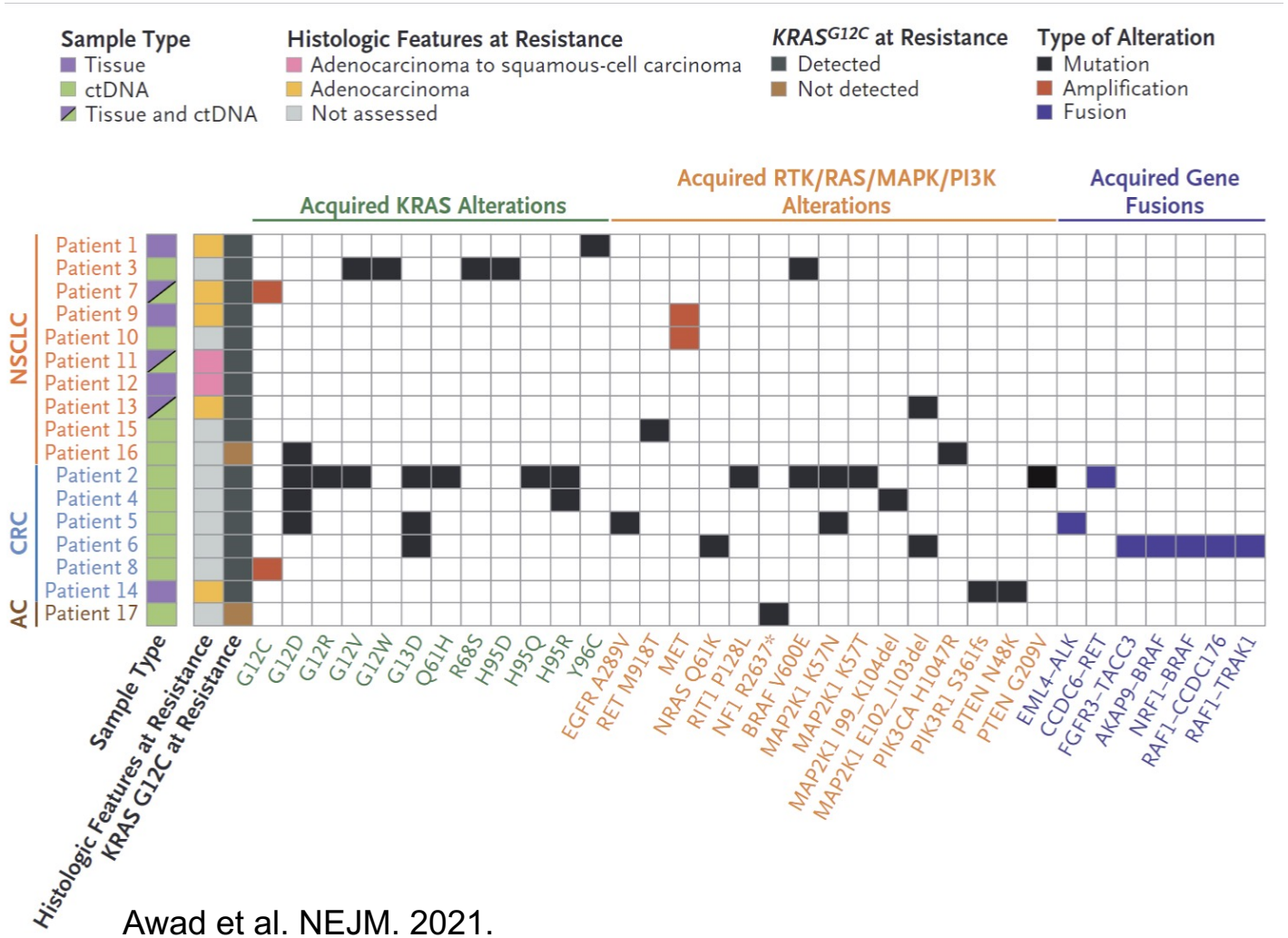
RMC-6291 for KRAS G12C+ NSCLC



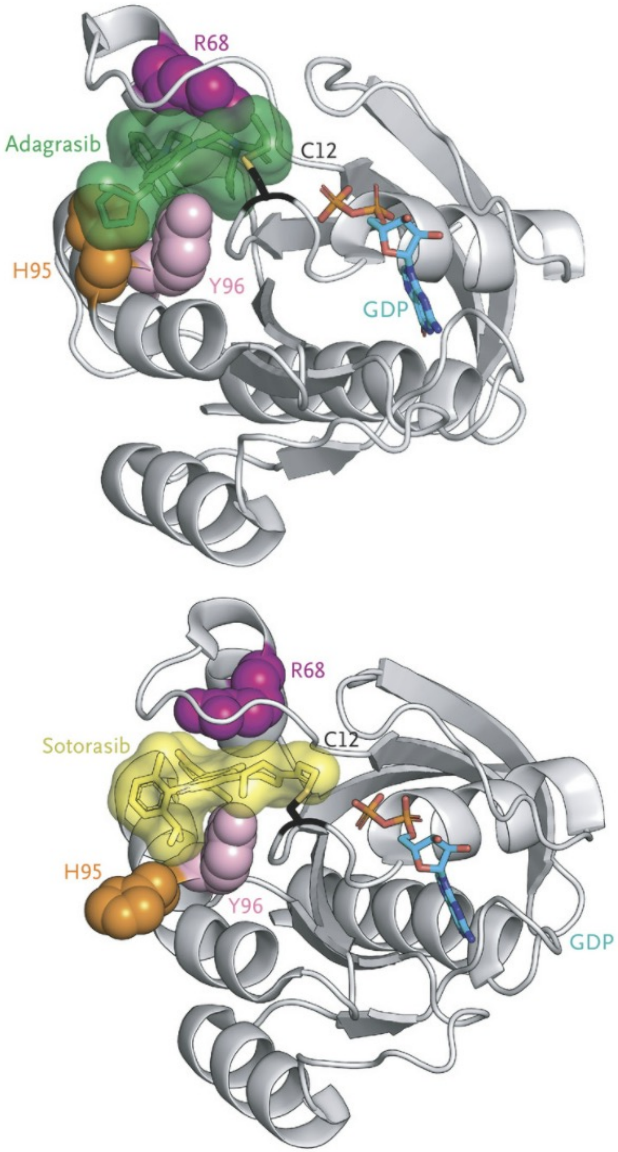
Tumor Response (per RECIST 1.1)		
Best overall response, n (%)	**Prior G12Ci (n=10)**	**Naïve to G12Ci (n=7)**
Partial response†	5 (50)	3 (43)
Stable disease	5 (50)	4 (57)
Progressive disease	0	0
ORR, n (%)	5 (50)	3 (43)
DCR (CR+PR+SD), n (%)	10 (100)	7 (100)

Janne et al. ENA 2023. Abstract PR014

KRAS G12C Inhibitor Resistance

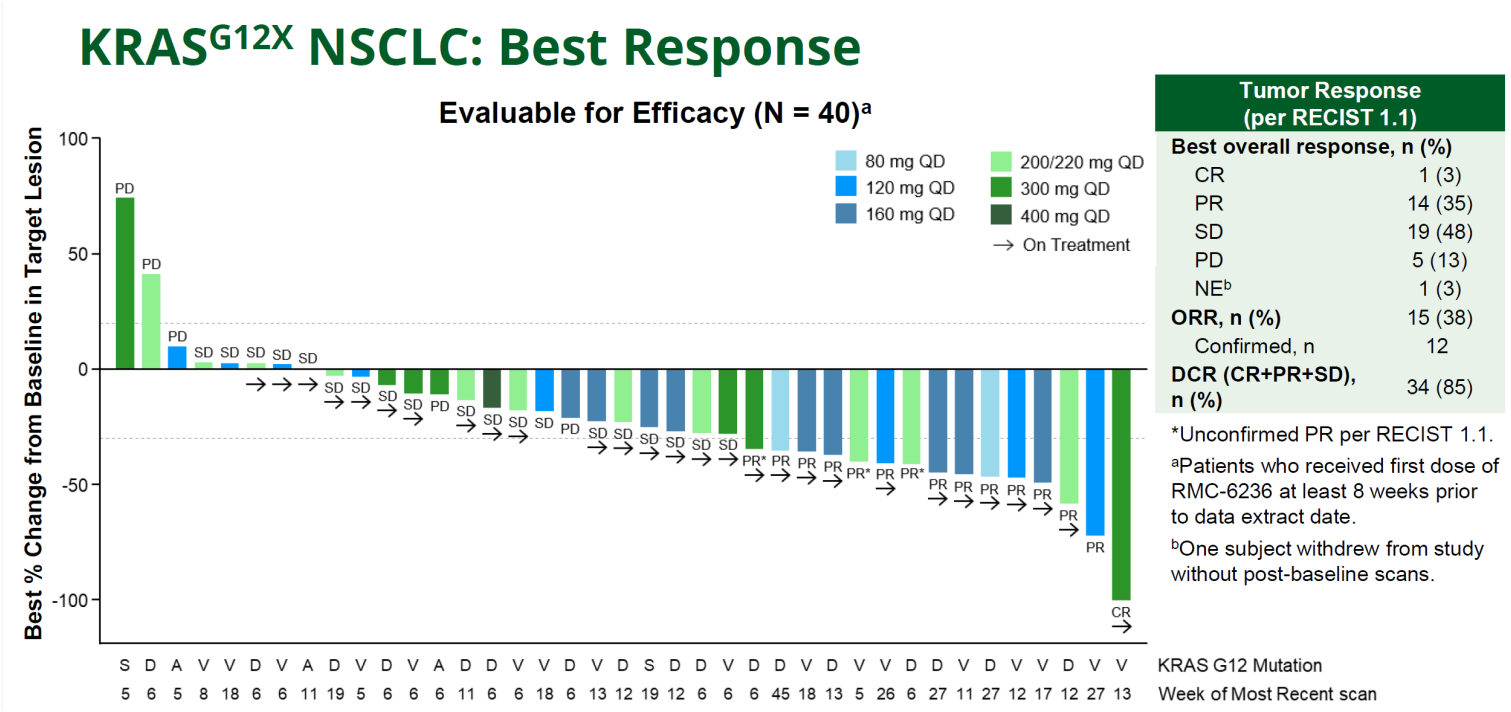


Awad et al. NEJM. 2021.



Targeting non-G12C KRAS Mutations

- **Pan-RAS Inhibitors: RMC-6236 KRAS G12X NSCLC, excluding G12C**



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)

*Unconfirmed PR per RECIST 1.1.

[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.

[b]One subject withdrew from study without post-baseline scans.

- **KRAS G12D Inhibitors**

Arbour et al. ESMO 2023.

$KRAS^{G12C}$ inhibitor combinations: ongoing trials

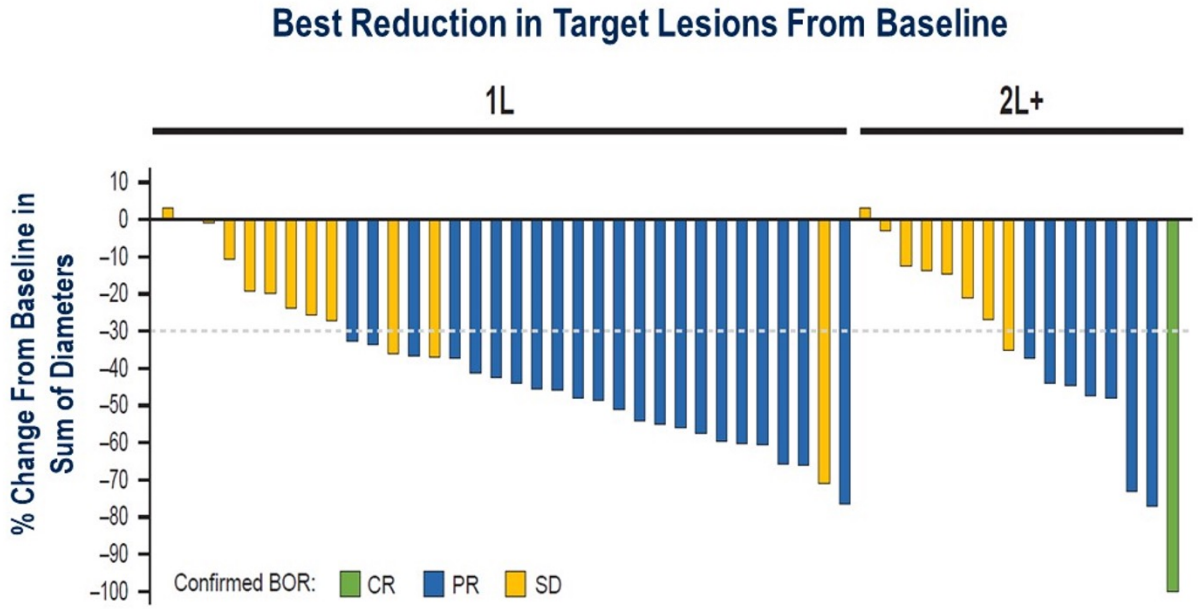
Addition of		KRAS G12Ci	Population	Clinical trial
Chemotherapy	carboplatin and pemetrexed	sotorasib	advanced	CodeBreaK 101, WCLC 2023 CodeBreaK 202
	carboplatin and pemetrexed	sotorasib	advanced	SCARLET/WJOG14821L, ASCO 2023; CodeBreaK 101, WCLC 2023
	platinum and pemetrexed	adagrasib	advanced	KRYSTAL-17
PD1 IO	pembro/ atezo	sotorasib	advanced	CodeBreaK 100/101
	pembrolizumab	adagrasib	advanced	KRYSTAL-7, ESMO 2023
	pembro/ atezo	divarasib	advanced	GO42144, BO44426
	nivolumab	adagrasib	stage IB-IIIA	Neo-KAN
SHP2i	RMC-4630	sotorasib	advanced	WCLC 2022
	TNO-155	adagrasib	advanced	KRYSTAL-2, ASCO 2021
	GDC-1971	divarasib	advanced	GO42144

Select other combinations: VS-6766 (MEKi) [sotorasib], inavolisib (PI3Ki) [divarasib], BI 1701963 (SOS1i) [adagrasib], VIC-1911 (AURKAi) [sotorasib], KO-2806 (FTi) [adagrasib], ribociclib (CDK4/6i) [JDQ 443], RMC-6236 (RAS-ON-multi) [RMC-6291], AMG 193 (MTAP) [sotorasib]

Slide courtesy of Dr Jia Luo

CodeBreak 101
Sotorasib + carboplatin/pemetrexed

Confirmed response by investigator assessment*	Sotorasib + Carboplatin + Pemetrexed	
	1L (n = 34)	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)

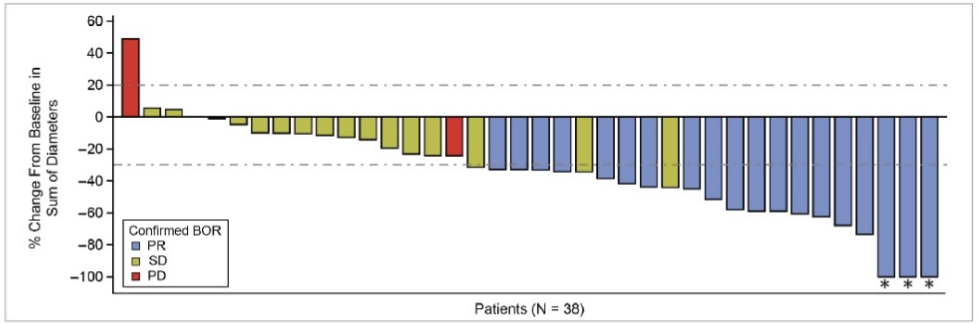


- **Among patients treated in the 1L setting, ORR was 65% and DCR was 100%**
- **94% of all patients had reduction in target lesions**

Presented by B Li et al. ASCO 2024. #8512.

Sotorasib + Panitumumab
KRAS inhibitors + anti-EGFR antibodies

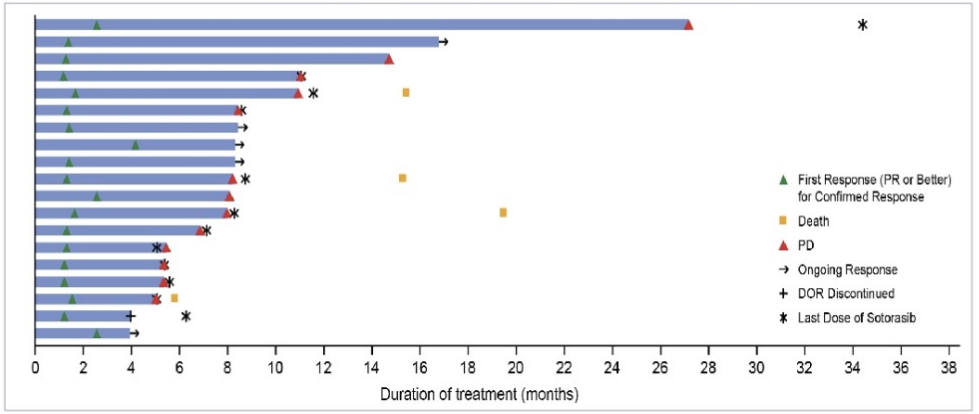
Responses by investigator assessment	N = 40
ORR, n (%)	19 (47.5)
CR	0
PR, n (%)	19 (47.5)
SD, n (%)	17 (42.5)
PD, n (%)	2 (5.0)
DCR, n (%)	36 (90.0)



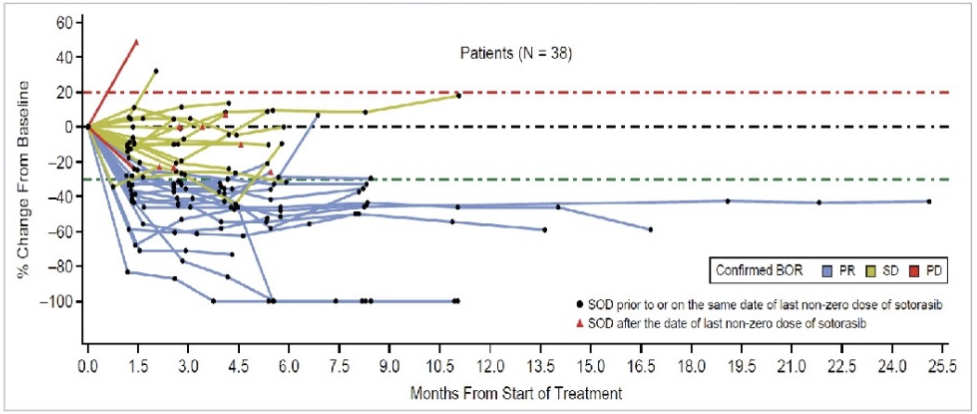
*Three patients had a complete response in target lesions, with continued presence of some non-target lesions

- **Median TTR was 1.4 (range, 1.2, 4.2) months and median DOR was 7.2 (95% CI: 4.2, 13.5) months**
- **Majority of patients had rapid reduction in target lesion dimensions, which remained steady or continued to decrease over time**

Duration of Response in Responders

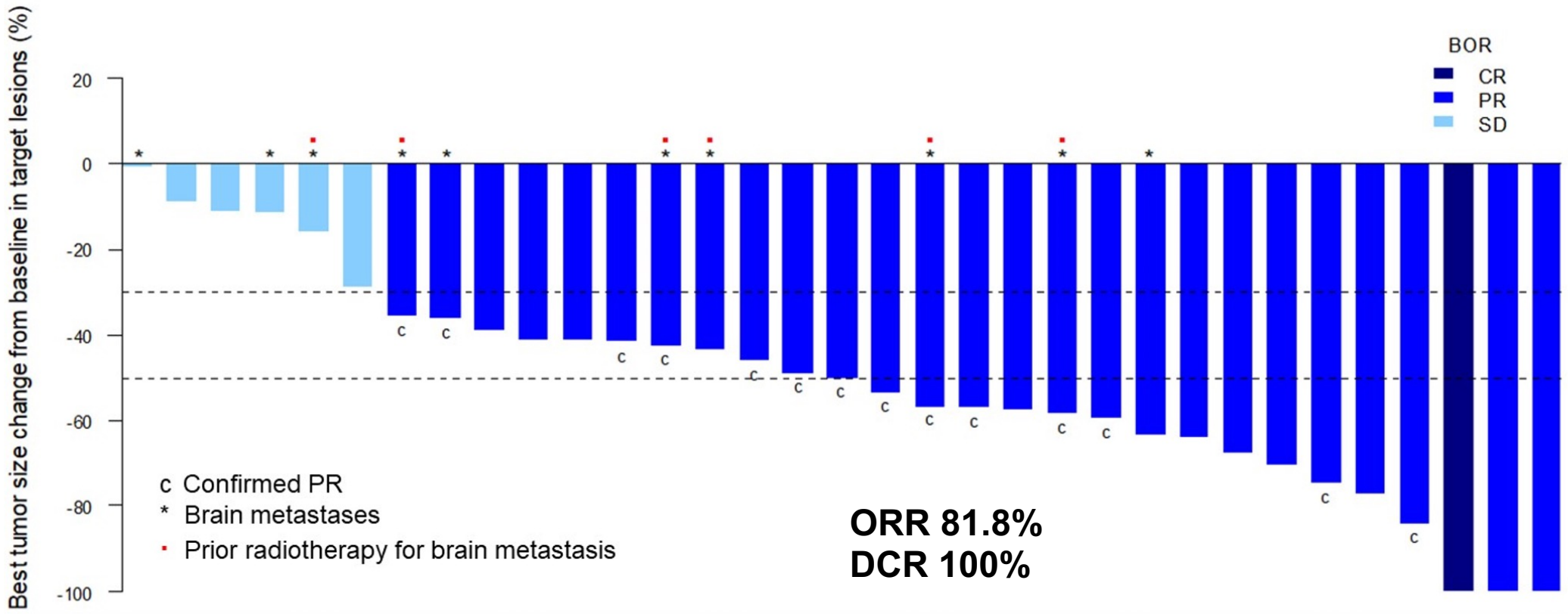


Change in Target Lesions Over Time



Langer et al ASCO 2024. Poster #8559

Fulzerasib + cetuximab first-line: KROCUS



Gregor et al. ASCO 2024.

Take Away Points and Unanswered Questions

KRAS G12C inhibitors are active in KRAS G12C mutated NSCLC

Optimal understanding of when and how to integrate KRAS-targeted therapies into the front-line setting remains to be established as does the role of KRAS-inhibitor based combination therapies at KRAS inhibitor resistance

More potent emerging KRAS inhibitors may improve clinical outcomes as may mechanistically novel RAS inhibitor strategies. Availability of non-G12C agents may expand the number of patients who can benefit from RAS-directed therapies