NCCN 2025
Lung Cancer Congress

KRAS Mutations in Non-Small Cell Lung Cancer:
Current Landscape and Evolving Therapies

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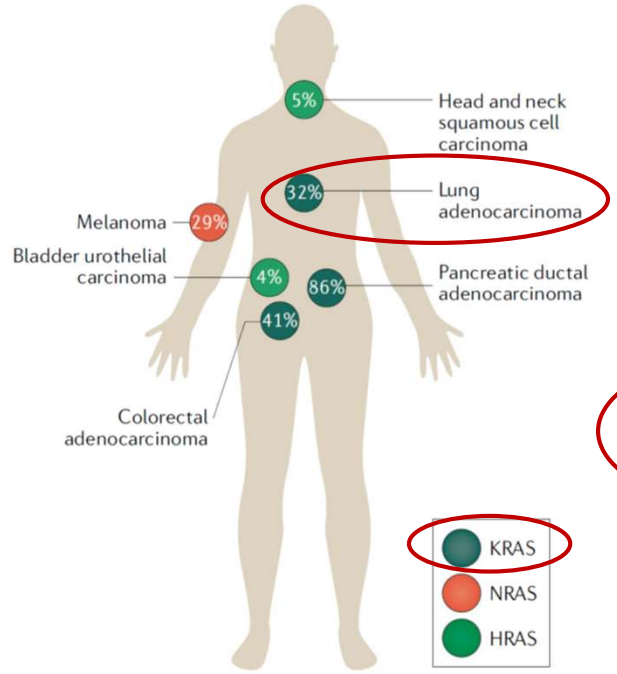
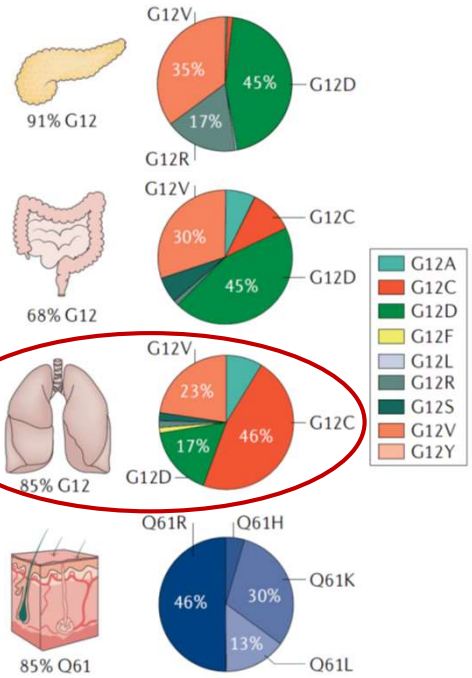
NCCN National Comprehensive Cancer Network®

Defining *KRAS* Mutations

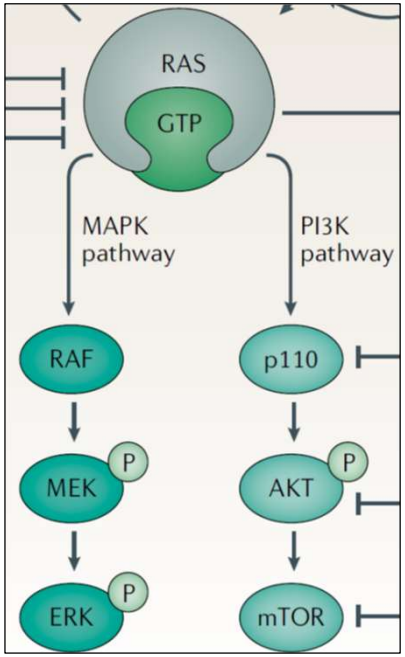
RAS Isoforms



RAS Mutation Subtypes

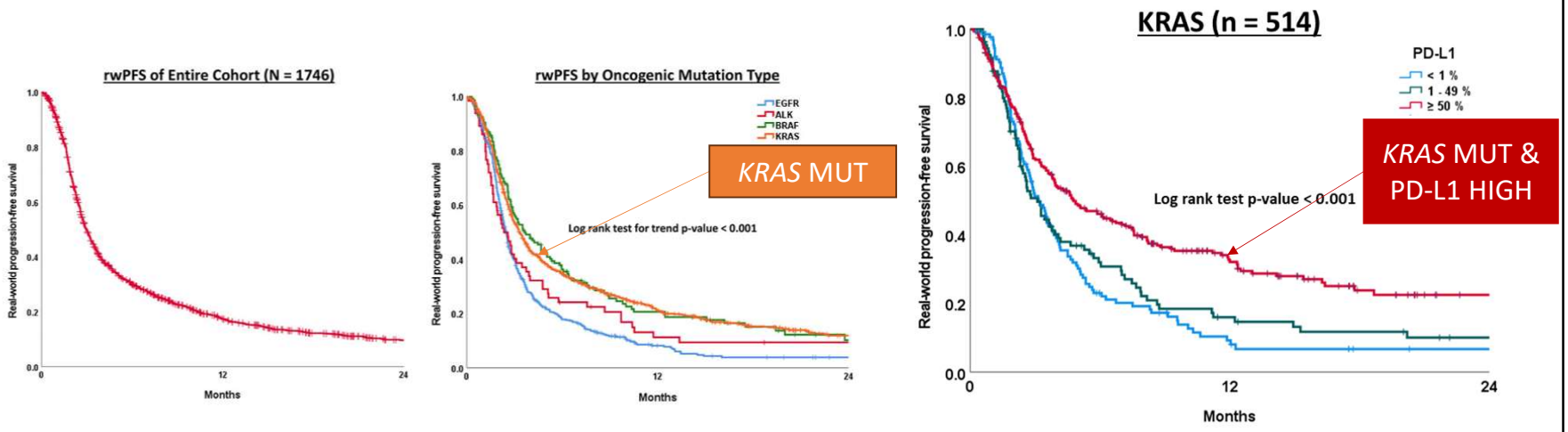


RAS signaling



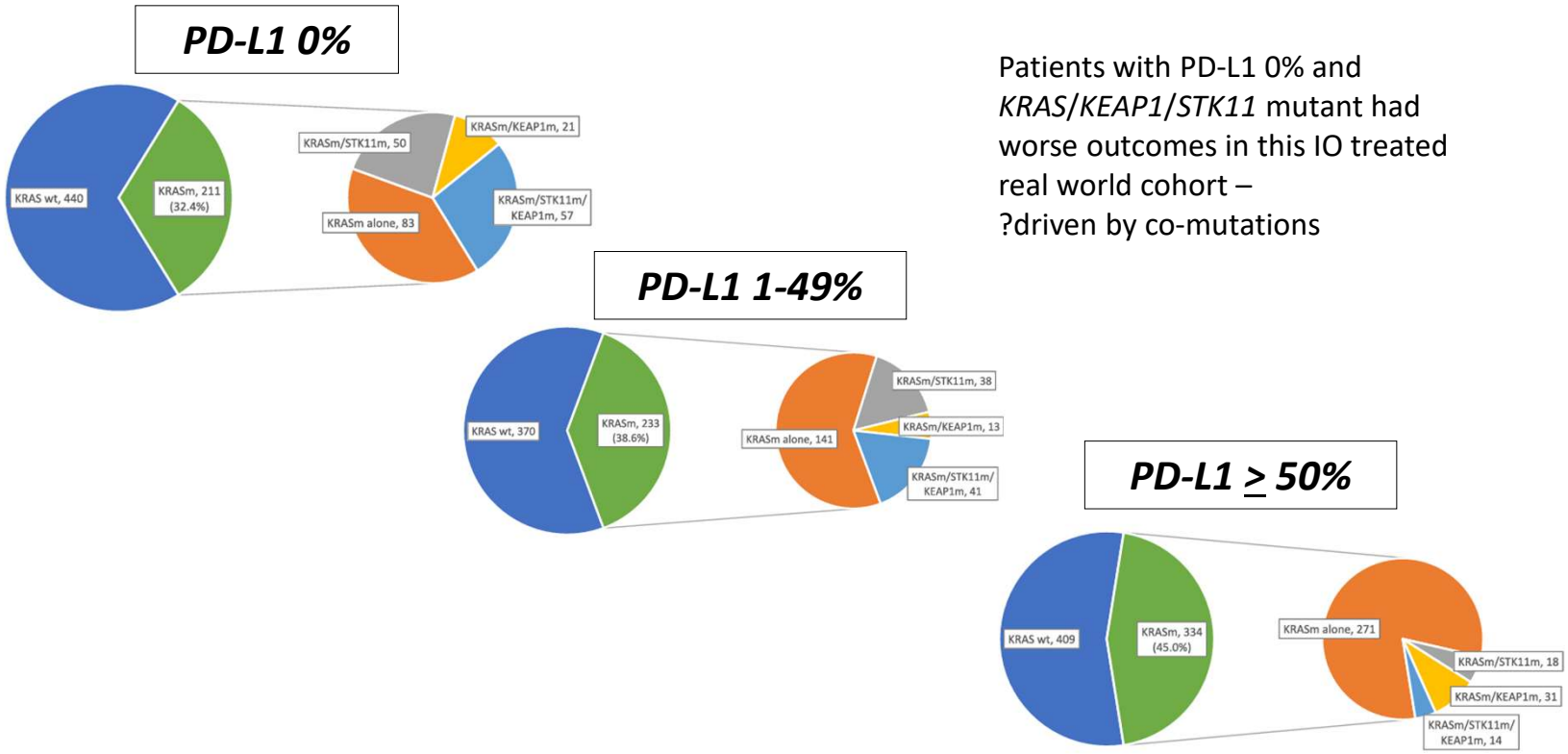
Figures from Moore, A.R., et al. Nat Rev Drug Discov 19, 533–552 (2020).

Impact of genomic alterations and PD-L1 expression on IO outcomes



Bodor JN, Bauman JR, Handorf EA, Ross EA, Clapper ML, Treat J. J Cancer Res Clin Oncol. 2023 May;149(5):1755-1763.

KRAS mutations alone more common in PD-L1 high while half of pts with PD-L1 negative had co-mutation in *KEAP1*, *STK11*, or both



Patients with PD-L1 0% and *KRAS*/*KEAP1*/*STK11* mutant had worse outcomes in this IO treated real world cohort –
?driven by co-mutations

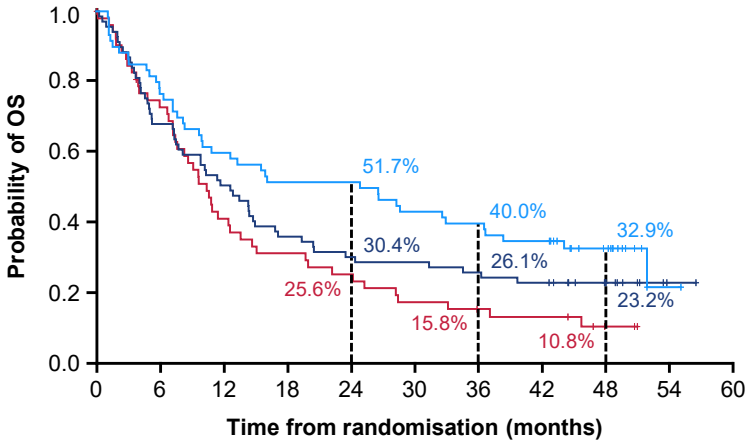
Sun L, Handorf EA, Zhou Y, Borghaei H, Aggarwal C, Bauman J. Lung Cancer. 2024 Apr;190:107510.

POSEIDON: Updated OS by *KRAS* Mutation Status

OS benefit observed for Tremelimumab (T)+Durvalumab(D)+Chemotherapy(CT) vs CT in *KRAS*m with HR 0.55 and estimated 40.0% alive at 3 yrs vs 15.8%

*KRAS*m

	T+D+CT	D+CT	CT
Events/patients, n/N	41/60	53/69	45/53
mOS, months (95% CI)	**25.7** (9.9–36.7)	**12.6** (7.5–16.9)	**10.4** (7.5–13.6)
HR* (95% CI)	**0.55** (0.36–0.85)	**0.78** (0.52–1.16)	–

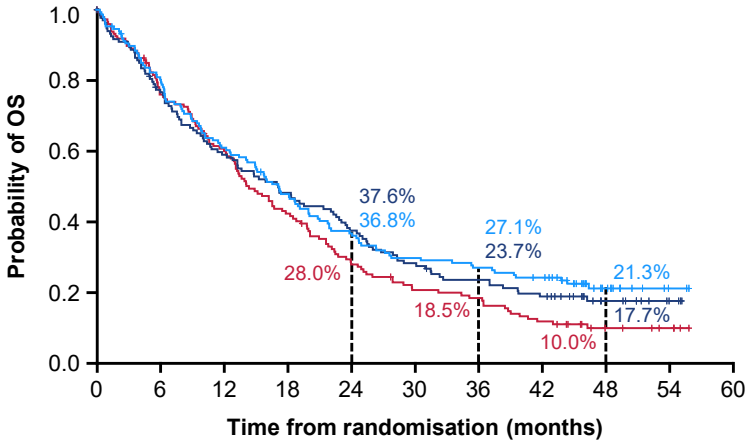


No. at risk

T+D+CT	60	46	36	31	31	26	24	21	12	1	0
D+CT	69	47	35	25	21	20	18	16	9	1	0
CT	53	37	21	16	13	9	7	6	2	0	0

*KRAS*wt

	T+D+CT	D+CT	CT
Events/patients, n/N	113/148	107/134	127/148
mOS, months (95% CI)	**17.1** (13.4–20.1)	**17.1** (12.3–22.6)	**14.4** (12.6–18.3)
HR* (95% CI)	**0.78** (0.60–1.00)	**0.83** (0.64–1.08)	–



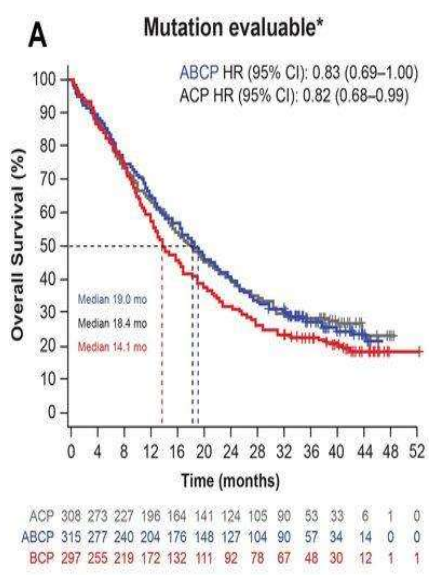
No. at risk

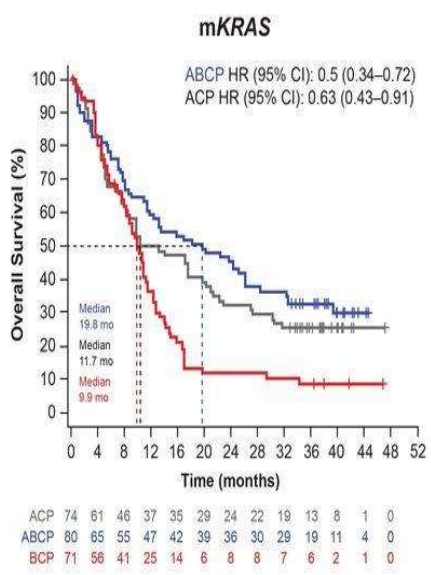
T+D+CT	148	118	89	69	53	43	39	34	12	2	0
D+CT	134	101	77	63	49	37	30	24	11	3	0
CT	148	110	86	60	39	28	25	16	7	4	0

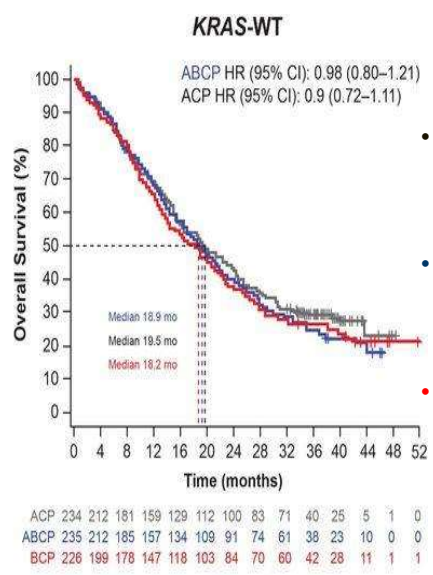
*HR <1 favours D(±T)+CT vs CT (unstratified analysis); Assessed among mutation-evaluable patients with NSQ tumour histology; DCO, 11 Mar 2022

Peters, ESMO, 2023

IMpower150: Survival heightened in *KRAS* mutant vs WT patients







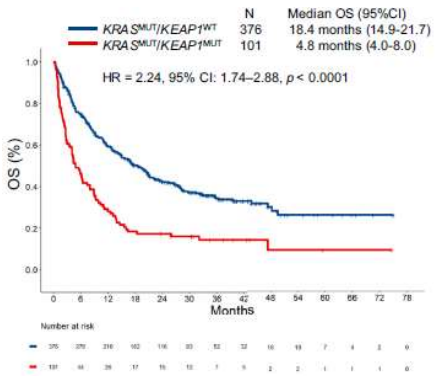
- **ACP: Atezo/chemo mOS**
  - **11.7 mo for mKRAS**
  - **19.5 mo for wt KRAS**
- **ABCP: Atezo/bev/chemo mOS**
  - **19.8 mo for mKRAS**
  - **18.9 mo for wt KRAS**
- **BCP: Bev/chemo mOS**
  - **18.2 mo for mKRAS**
  - **9.9 mo for wt KRAS**

West et al. J Immunother Cancer 2022;10:e003027

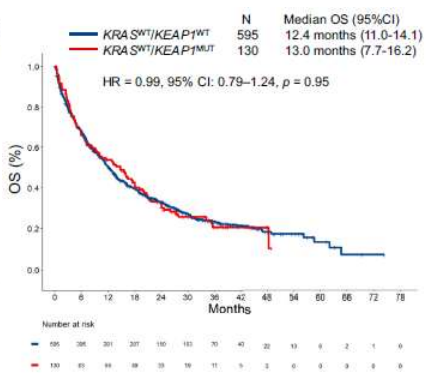
Co-mutation impact on IO may depend on *KRAS* context – mutated vs. wild type

KEAP1 mutation status / IO

KRAS MUT



KRAS WT



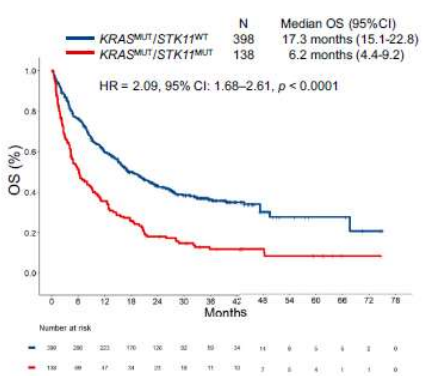
Multivariate of KRAS^{MUT}: **KEAP1^{MUT} HR 2.44** (95% CI 1.65-3.61; P<0.0001)

- KRAS WT: KEAP1^{MUT} HR 0.93 (95% CI 0.65-1.33; P=0.68)

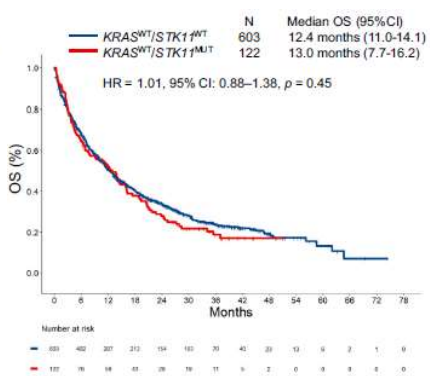
Worse OS KRAS^{MUT} across different PD-L1 expression (<1%, 1-49%)

STK11 mutation status / IO

KRAS MUT



KRAS WT



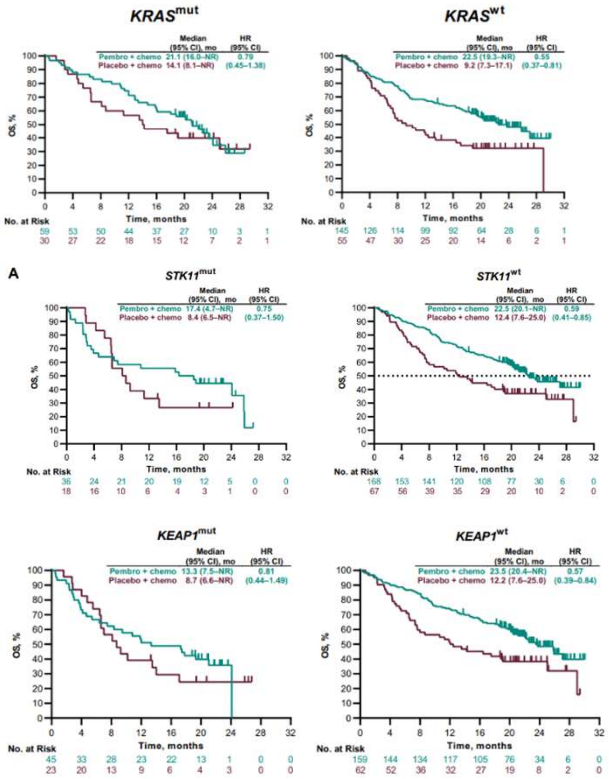
Multivariate of KRAS^{MUT}: **STK11^{MUT} HR 1.73** (95% CI 1.23-2.45 P=0.02)

- KRAS WT: STK11^{MUT} HR 1.14 (95% CI 0.81-1.61; P=0.45)

Worse OS KRAS^{MUT} across different PD-L1 expression (<1%, 1-49%, >=50%)

Ricciuti B et al. J Thorac Oncol. 2022 Mar;17(3):399-410

ChemoIO (KN-189) OS across *KRAS*, *STK11*, *KEAP1* mutations



	*KRAS*m	*KRAS* WT
n	89	200
OS HR (95% CI)	**0.79** (0.45-1.38)	**0.55** (0.37-0.81)
OS median, mo	21.1 vs 14.1	22.5 vs 9.2

	*STK11*m	*STK11* WT
n	54	235
OS HR (95% CI)	**0.75 (0.37-1.50)**	**0.59 (0.41-0.85)**
OS median, mo	17.4 vs 8.4	22.5 vs 12.4

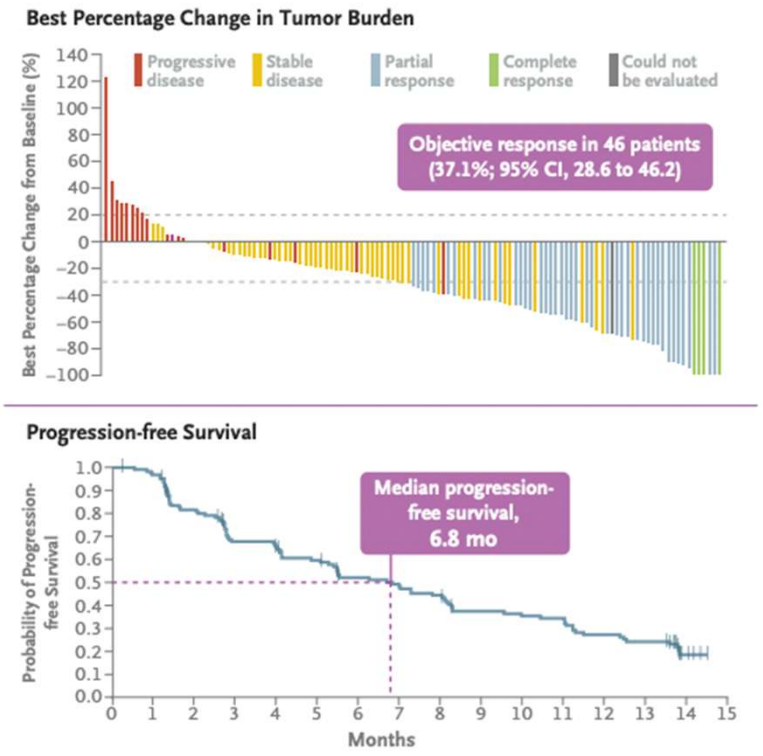
	*KEAP1*m	*KEAP1* WT
n	68	221
OS HR (95% CI)	**0.81 (0.44-1.49)**	**0.57 (0.39-0.84)**
OS median, mo	13.3 vs 8.7	23.5 vs 12.2

Garassino MC et al. JTO Clin Res Rep. 2022 Nov 8;4(1):100431.

KRAS G12C

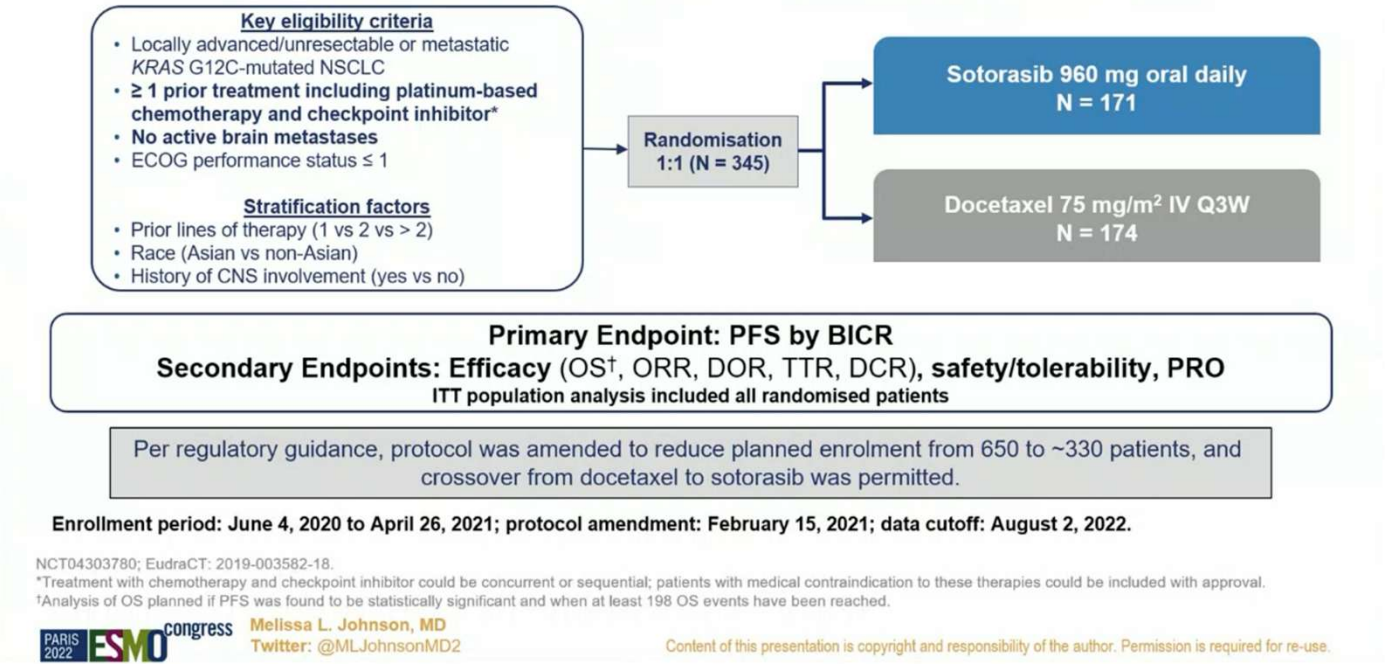
Single Agent Inhibitor

CodeBreaK100 Phase II - Sotorasib Efficacy



Skoulidis, NEJM 2021

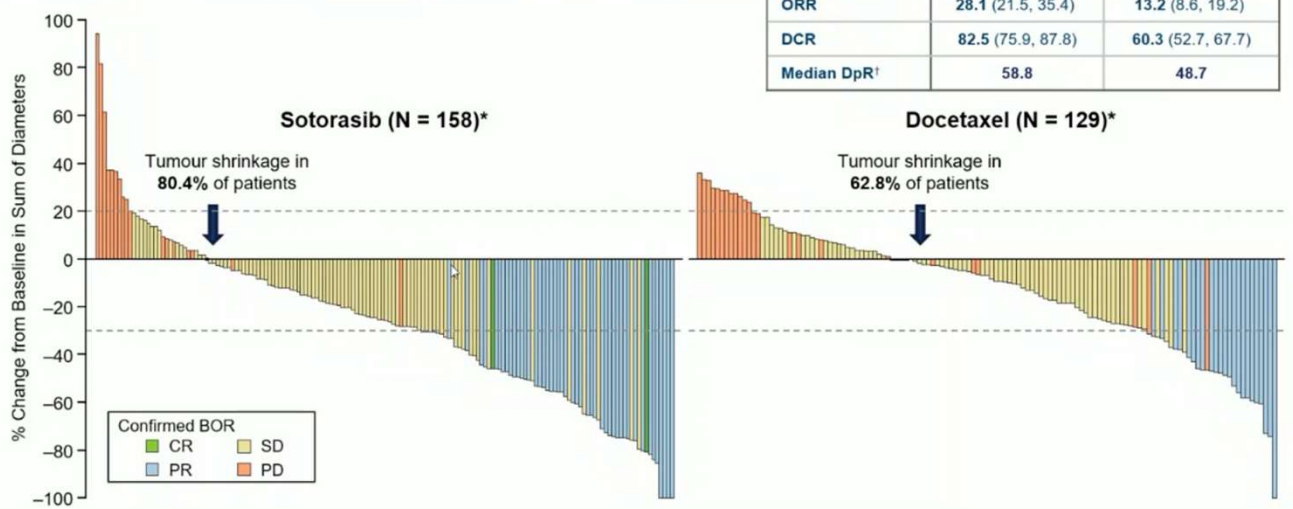
CodeBreaK 200 Phase 3 Study Design



Johnson ML, et al. ESMO 2022. Abstract LBA10

Tumour Response by BICR

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



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

*Patients without baseline target lesions or post-baseline percent changes, or with BOR of NE are not shown.
†Median of best percent change from baseline in sum of diameters for confirmed responders.

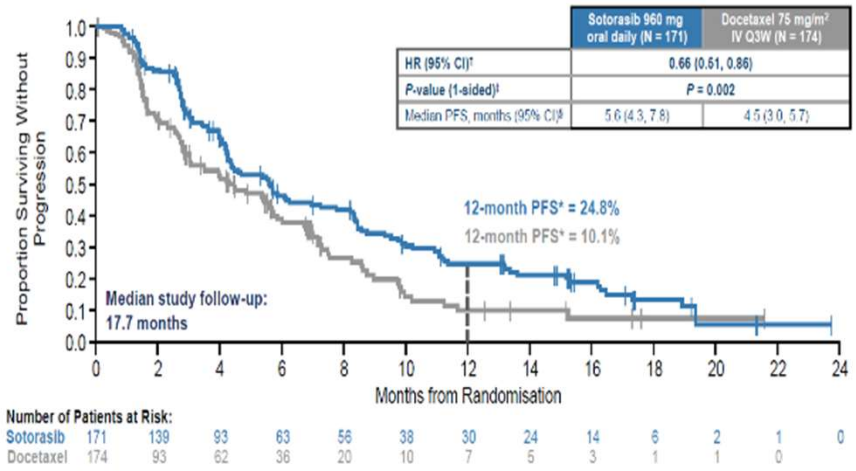
PARIS 2022 ESMO congress

Melissa L. Johnson, MD
Twitter: @MLJohnsonMD2

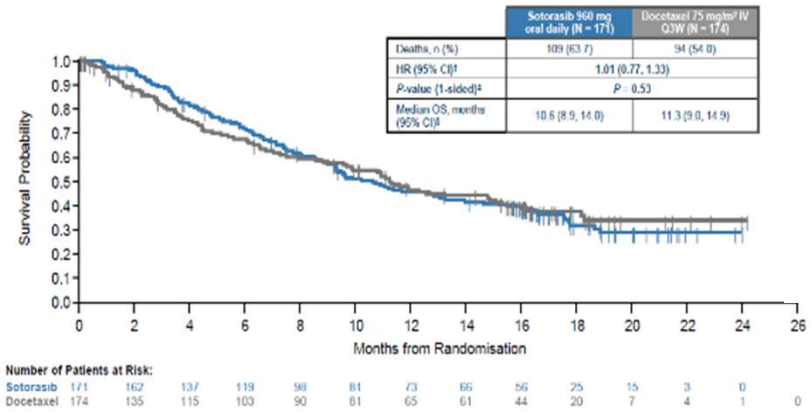
Johnson ML, et al. ESMO 2022. Abstract LBA10

CodeBreaK 200: Sotorasib vs Docetaxel

Primary Endpoint: PFS by BICR



OS: Sotorasib vs Docetaxel



CodeBreaK 100[2]

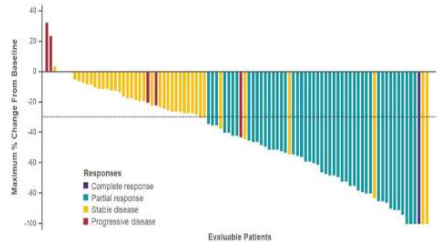
	Sotorasib (N = 158)	Docetaxel (N = 129)	Sotorasib N America (N=127)†
ORR, % (95% CI)	28.1 (21.5, 35.4)	13.2 (8.6, 19.2)	45.7 (36.8, 54.7)
DCR, % (95% CI)	82.5	60.3	85.9%

Johnson ML, et al. ESMO 2022. Abstract LBA10

Adagrasib

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

Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Best Tumor Change From Baseline



- Objective responses were observed in 43% (95% CI, 33.5–52.6); DCR was 80% (95% CI, 70.8–86.5)
- Responses were deep with 75% of responders achieving >50% tumor reduction

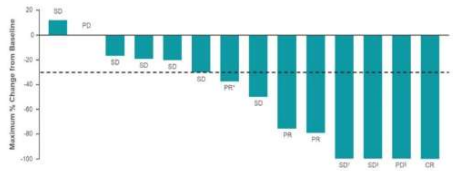
Jänne, NEJM 2022

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

KRAS-inhibitors in CNS-metastasis?

KRYSTAL-1: Adagrasib (MRTX849) KRAS^{G12C} Inhibitor in Active, Untreated CNS Metastases

Adagrasib in Patients with Active, Untreated CNS Metastases: Intracranial Best Tumor Change From Baseline



- Objective IC responses were observed in 32% (95% CI, 12.6–56.6)[a]
- IC DCR was 84% (95% CI, 60.4–96.6)

Sabari, ASCO 2022

KRAS G12C Inhibitors – Intracranial Activity

Table 1 Differences between sotorasib and adagrasib

Characteristics	Codebreak 200 (16)		KRYSTAL-1 (NSCLC cohort) (11)	KRYSTAL-1 (NSCLC CNS metastases cohort) (10)	KRYSTAL-12 (19)	
	Sotorasib	Docetaxel	Adagrasib	Adagrasib	Adagrasib	Docetaxel
Design	Phase III	Phase III	Registrational phase II study	Phase II	Phase III	Phase III
CNS metastases status/number of evaluable patients	Previously treated/n=40 (sotorasib)	Previously treated/n=29 (docetaxel)	Previously treated/n=42	Untreated asymptomatic/ n=20	Previously treated/ n=78	Previously treated/ n=36
Dose & schedule	960 mg daily	75 mg/m^2 q 21 days	600 mg BID	600 mg BID	600 mg BID	75 mg/m^2 q 21 days
IC ORR (RANO-BM criteria)	33.3%	15.4%	33%*	35%	40%	11%
IC DCR	83.3%	84.6%	90%	85%	82%	56%
IC PFS	9.6 months HR 0.53 (95% CI: 0.28–1.03, P=0.03)	4.5 months	5.4 months	5.4 months	NR	NR
IC DOR	NR	NR	11.2 months*	12.7 months	NR	NR

*, 33 of 42 patients evaluable for RANO-BM response criteria. NSCLC, non-small cell lung cancer; CNS, central nervous system; IC, intracranial; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; DOR, duration of response; HR, hazard ratio; q, every; BID, two times a day; CI, confidence interval; NR, not reported.

Olomorasib

Untreated brain mets

150mg BID

IC ORR – 43%
CR = 5 pt - 24%
All pts DOR > 6 months

IC DCR – 83.3%

IC PFS NR

Olomorasib – KRAS G12Ci of GDP bound KRAS G12C

Abhyanka A et al ACTR 2024, Cassier P et al ESMO 2025

KRAS G12C

Combination With A Checkpoint Inhibitor

KRYSTAL-7 (849-007) Phase 2 Cohorts

Key Eligibility Criteria

- Advanced, unresectable or metastatic NSCLC with *KRAS*^{G12C} mutation[a]
- No prior systemic therapy for locally advanced/ metastatic disease[b]
- Stable brain metastases allowed
- Known PD-L1 TPS score[c]

Cohorts 1a and 2[c]
Adagrasib 400 mg BID + Pembrolizumab
N=148

Key Study Objectives

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

- We report safety in all treated patients (N=148) and efficacy in patients with PD-L1 TPS ≥50% (n=51[d]) from the KRYSTAL-7 study evaluating adagrasib[e] + pembrolizumab (200 mg IV Q3W) in treatment-naïve patients with NSCLC harboring a *KRAS*^{G12C} mutation
- Median follow-up for all treated patients, 8.7 months; PD-L1 TPS ≥50%, 10.1 months

Garassino, ESMO, 2023

Treatment-Related Adverse Events (n=148)

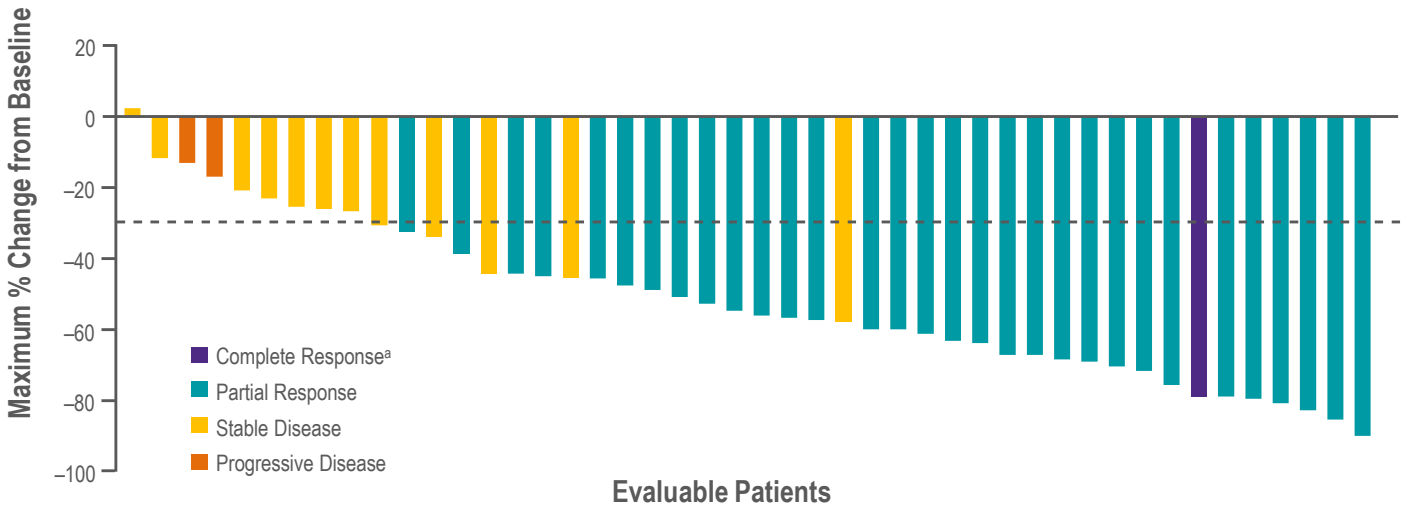
Most Frequent TRAEs[a], %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	51	28	20	3	0
Diarrhea	44	33	7	3	0
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Vomiting	29	17	11	1	0
Fatigue	26	12	10	4	0
Decreased appetite	24	14	9	1	0
Lipase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

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

- [a]Any grade TRAEs occurring in ≥20% of patients. [b]Includes all TRAEs of colitis, hepatitis, adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, type 1 diabetes mellitus, nephritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and pneumonitis
- Data as of 19 June 2023. Median follow-up 8.7 months

Garassino M et al ESMO 2023

ORR and Best Tumor Change from Baseline in Patients With PD-L1 TPS ≥50% (n=51)

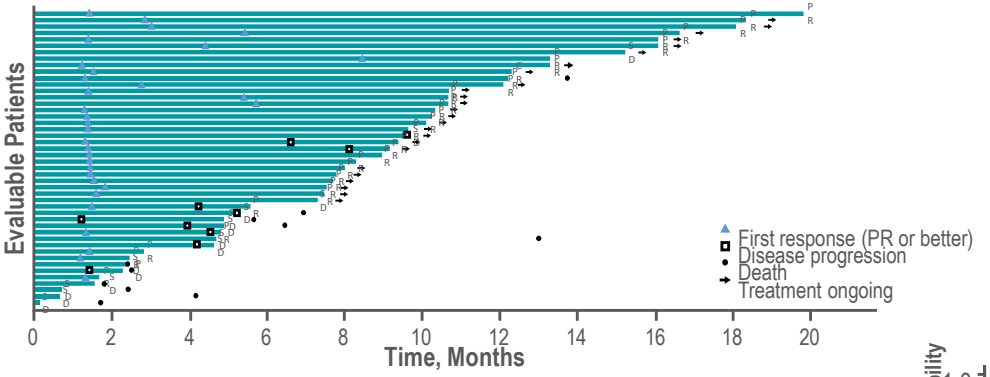


- **Confirmed ORR was 63% (32/51; 95% CI, 48–76) and DCR was 84% (43/51; 95% CI, 71–93)**
- **Of those patients who experienced any grade hepatotoxicity[b], ORR was 70% (14/20; 95% CI, 46–88)**

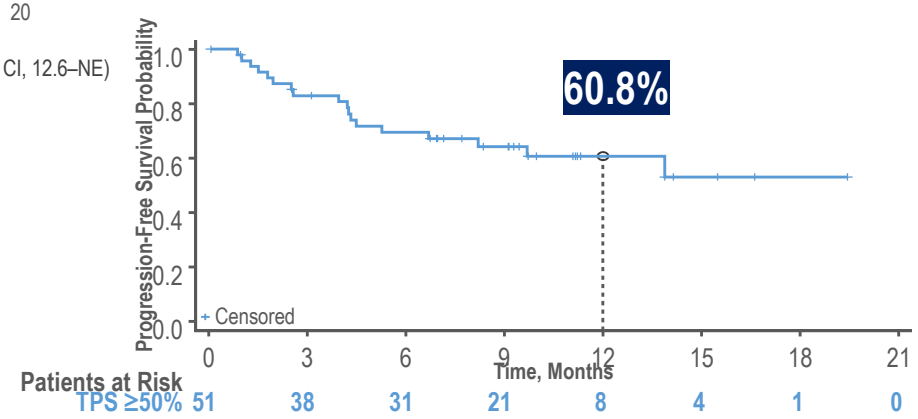
- Response per investigator assessment (n=51; modified full analysis set). Waterfall plot excludes three patients without post-baseline measurement and one patient without confirmatory scan (only one assessment of PR on day 28, but minimum duration requirement for SD is 42 days). [a]One patient had CR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

Garassino M et al ESMO 2023

Duration of Treatment in Patients With PD-L1 TPS ≥50%

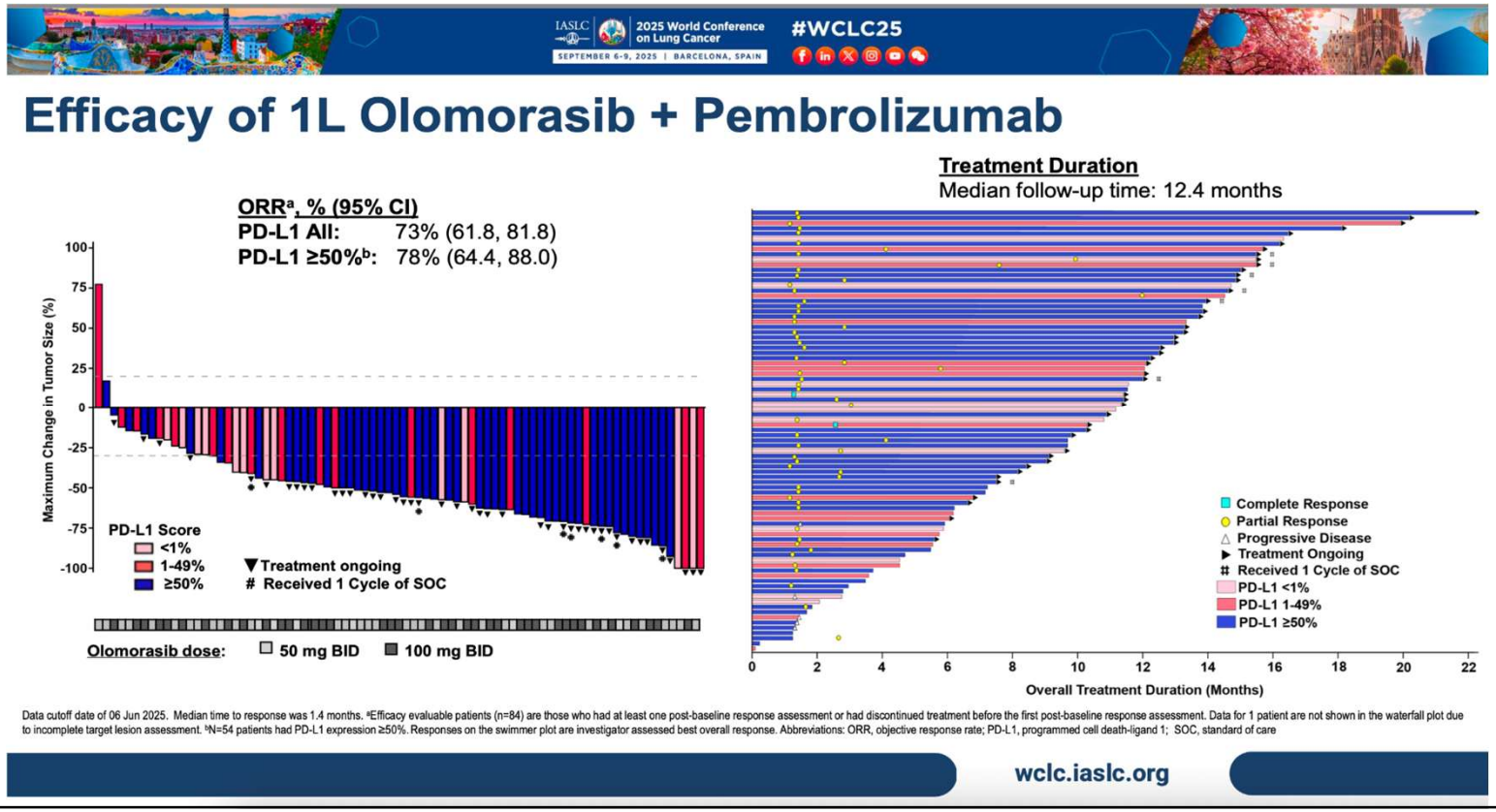


Median time to response was 1.4 months; median duration of response was not reached (95% CI, 12.6–NE)



Garassino M et al ESMO 2023

MA02.06 – Efficacy and Safety of 1L Olomorasib Plus Pembrolizumab in *KRAS* G12C-Mutant NSCLC: Results From LOXO-RAS-20001 and SUNRAY-01. Johnson ML, et al



Divarasib + Atezolizumab

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

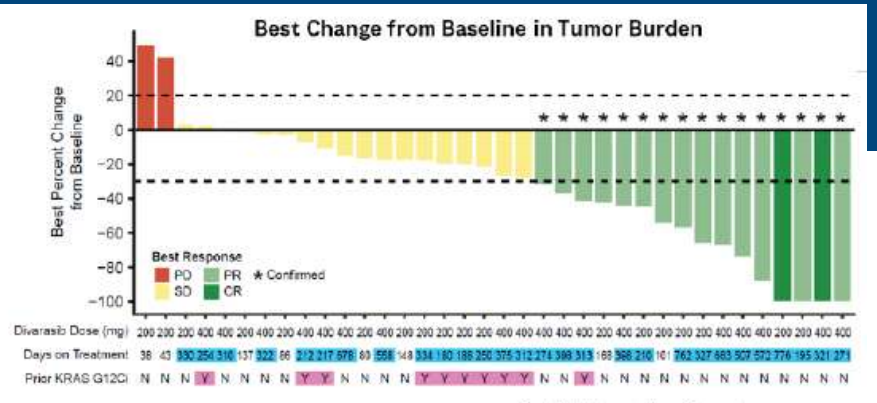
Divarasib oral QD, 21-day cycles
+ **atezolizumab** 1200 mg IV q3w
200mg → 400mg
N=3 **N=6** *Max Admin Dose MTD not reached*

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)



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)*

Safety summary: Divarasib + atezolizumab

STUDY TREATMENT ACTION DUE TO TRAEs	NSCLC N=39
Patients with TRAEs resulting in divarasib modification (interruption/reduction/withdrawal)	14 (36%)
Patients with TRAEs resulting in divarasib reduction	**9 (23%)**
Patients with TRAEs resulting in divarasib withdrawal	**1 (3%)**
Patients with TRAEs resulting in atezolizumab withdrawal	**6 (15%)**

TRAEs OVERALL & CORRESPONDING GRADE 3-5 AEs	N=39	
	All TRAEs	Grade 3-5 TRAEs
Patients with at least one TRAE	37 (95%)	**11 (28%)**
Diarrhea	24 (62%)	3 (8%)
AST increased	**10 (26%)**	**2 (5%)**
ALT increased	**10 (26%)**	**2 (5%)**
Lipase increased	5 (13%)	3 (8%)

Safety summary: single-agent divarasib

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 in divarasib reduction	**15 (23%)**
Patients with AEs resulting in divarasib withdrawal	**3 (5%)**

TRAEs OVERALL & 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%)
Diarrhea	**40 (62%)**	**2 (3%)**
Fatigue	16 (25%)	1 (2%)
ALT increased	**10 (15%)**	**4 (6%)**
Lipase increased	10 (15%)	2 (3%)
AST increased	**9 (14%)**	**3 (5%)**

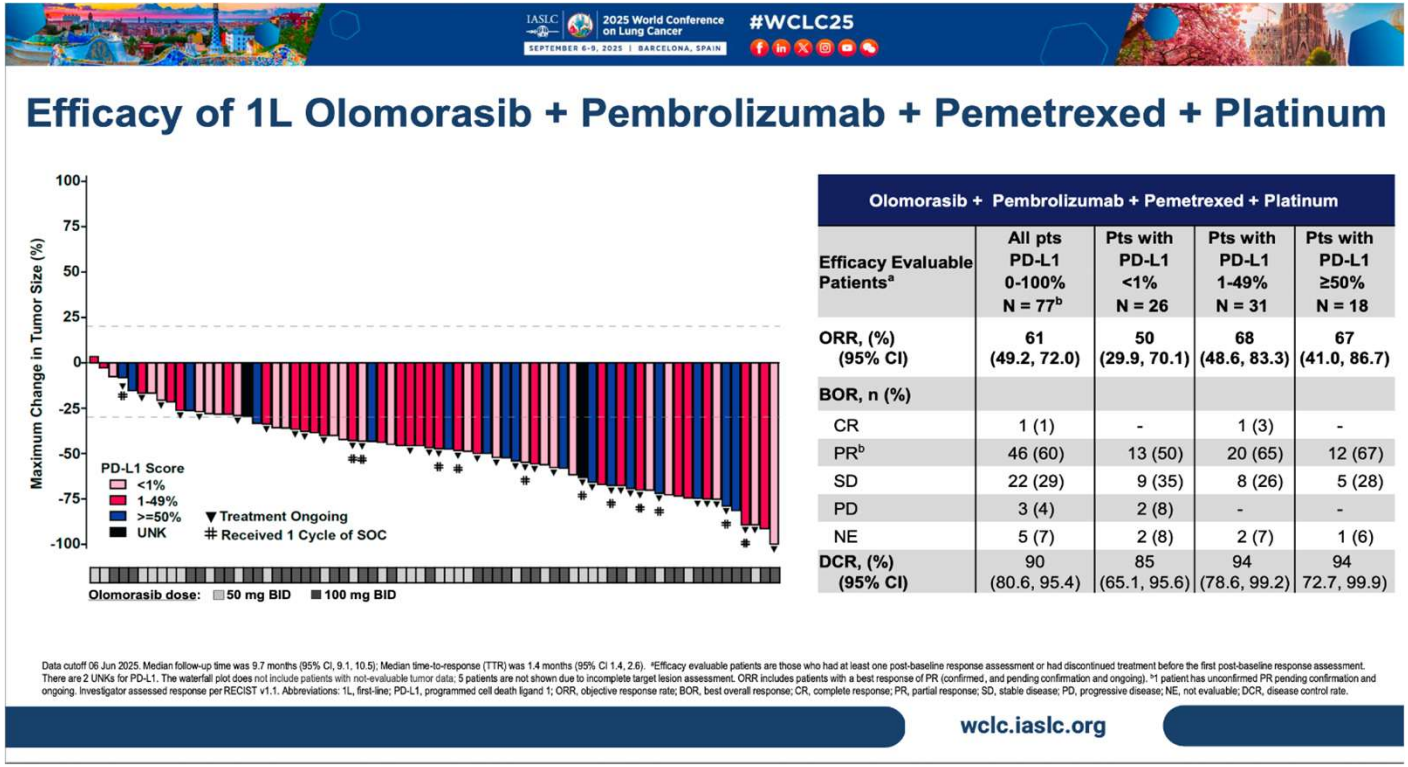
The overall safety profile was similar to that of single-agent divarasib, with slightly higher Grade 3-5 TRAEs. Hepatic toxicity was also similar.

Sacher et al. WCLC 2024

KRAS G12C

Combination With Chemo-Immunotherapy

OA08.02 – Efficacy and Safety of 1L Olomorasib + Chemoimmunotherapy in *KRAS* G12C-Mutant NSCLC: Results From LOXO-RAS-20001 and SUNRAY-01. Negrao MV, et al



Safety Profile: 1L Olomorasib + Pembrolizumab + Pemetrexed + Platinum

Olomorasib + Pembrolizumab +Pemetrexed +Platinum (n=77)[a]					
Parameter n (%)	TRAEs (≥10%)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any TRAE[a]	74 (96.1)	7 (9.1)	29 (37.7)	26 (33.8)	12 (15.6)
Nausea	34 (44.2)	18 (23.4)	13 (16.9)	3 (3.9)	-
Anaemia	31 (40.3)	6 (7.8)	14 (18.2)	10 (13.0)	1 (1.3)
Fatigue	29 (37.7)	15 (19.5)	13 (16.9)	1 (1.3)	-
AST increased	24 (31.2)	10 (13.0)	6 (7.8)	7 (9.1)	1 (1.3)
Diarrhea	24 (31.2)	12 (15.6)	8 (10.4)	4 (5.2)	-
Neutropenia	22 (28.6)	2 (2.6)	4 (5.2)	6 (7.8)	10 (13.0)
ALT increased	21 (27.3)	7 (9.1)	5 (6.5)	9 (11.7)	-
Platelet count decreased	13 (16.9)	3 (3.9)	2 (2.6)	3 (3.9)	5 (6.5)
Blood creatinine increased	11 (14.3)	7 (9.1)	4 (5.2)	-	-
Constipation	11 (14.3)	7 (9.1)	4 (5.2)	-	-
Vomiting	11 (14.3)	5 (6.5)	5 (6.5)	1 (1.3)	-
White blood cell count decreased	11 (14.3)	3 (3.9)	1 (1.3)	4 (5.2)	3 (3.9)
Decreased appetite	9 (11.7)	5 (6.5)	3 (3.9)	1 (1.3)	-
Pneumonitis/ILD	8 (10.4)	-	6 (7.8)	2 (2.6)	-
Pruritus	8 (10.4)	4 (5.2)	4 (5.2)	-	-
Rash	8 (10.4)	4 (5.2)	3 (3.9)	1 (1.3)	-
Other TRAEs of interest					
Pancytopenia	2 (2.6)	-	-	1 (1.3)	1 (1.3)

Dose modifications due to TRAEs

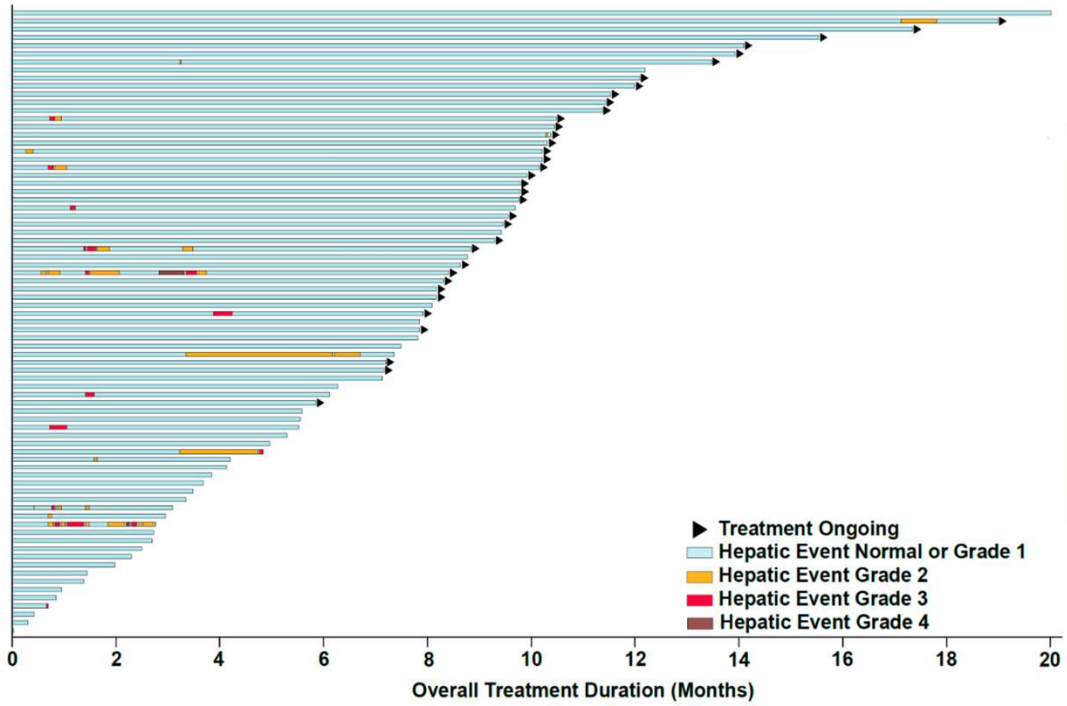
- TRAEs led to dose reductions of olomorasib[b] in 14 patients (18.2%)
- TRAEs led to permanent discontinuation[c] of the treatment regimen in 6 patients (7.8%)

Negrao, WCLC 2025

Data cutoff date of 06 Jun 2025. Median duration of treatment (IQR) was 10.5 months (6.5, 14.5). [a]Olomorasib 50 or 100 mg BID. No patients had grade 5 TRAEs. [b]Reasons for dose reductions of olomorasib: ALT/AST increased (n=8), neutrophil count decreased (n=2), diarrhea (n=1), fatigue (n=1), anemia (n=1) and biliary sepsis (n=1). [c]Reasons for discontinuation of the treatment regimen (olomorasib + pembrolizumab + pemetrexed + platinum): pancytopenia (n=2), pneumonitis (n=1), interstitial pneumonia (n=1), neutropenia followed by diarrhea (n=1) and anemia followed by declining kidney function (n=1). Total % may be different from the individual components due to rounding. Abbreviations: TRAEs, treatment-related adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD: Interstitial lung disease.

IASLC 2025 World Conference on Lung Cancer
SEPTEMBER 6-9, 2025 | BARCELONA, SPAIN
#WCLC25

Treatment-related hepatic events over time in 1L NSCLC



- Median time to onset of grade ≥3 hepatic event is 43 days, (range 13, 145); median duration of grade ≥3 hepatic event is 4 days.
- No total bilirubin elevation >1.5 x ULN or concurrent clinical symptoms.
- No patient discontinued the full regimen due to hepatic events.
- All grade ≥3 hepatic events resolved to grade 1 or baseline after dose modifications and/or corticosteroids.

Negrao, WCLC 2025

Note: Treatment-related hepatic events include alanine aminotransferase increase, aspartate aminotransferase increase, hepatitis, immune hepatitis, autoimmune hepatitis, hepatotoxicity.

wclc.iaslc.org

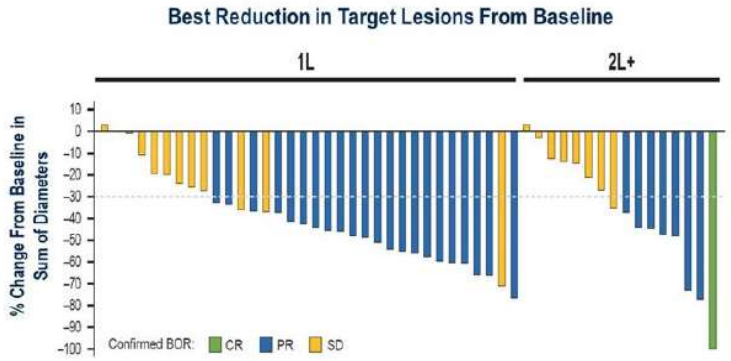
KRAS G12C

Combination Without IO

KRAS Inhibitors with Chemotherapy

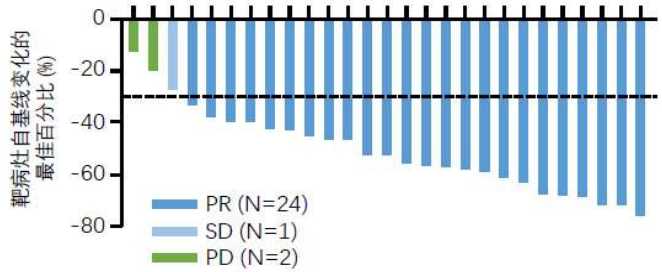
CodeBreaK 101, Phase1b
Sotorasib+Pemetrexed+Carboplatin

- 1L ORR 65%, DCR 100%, mPFS 10.8m
- 2L ORR 42%, DCR 84%, mPFS 8.3m
- Grade≥3 TRAE 49% (1L); 62% (2L)
- PD-L1 < 1% mPFS 11.9m



SCARLET, Phase II
Sotorasib+Pemetrexed+Carboplatin

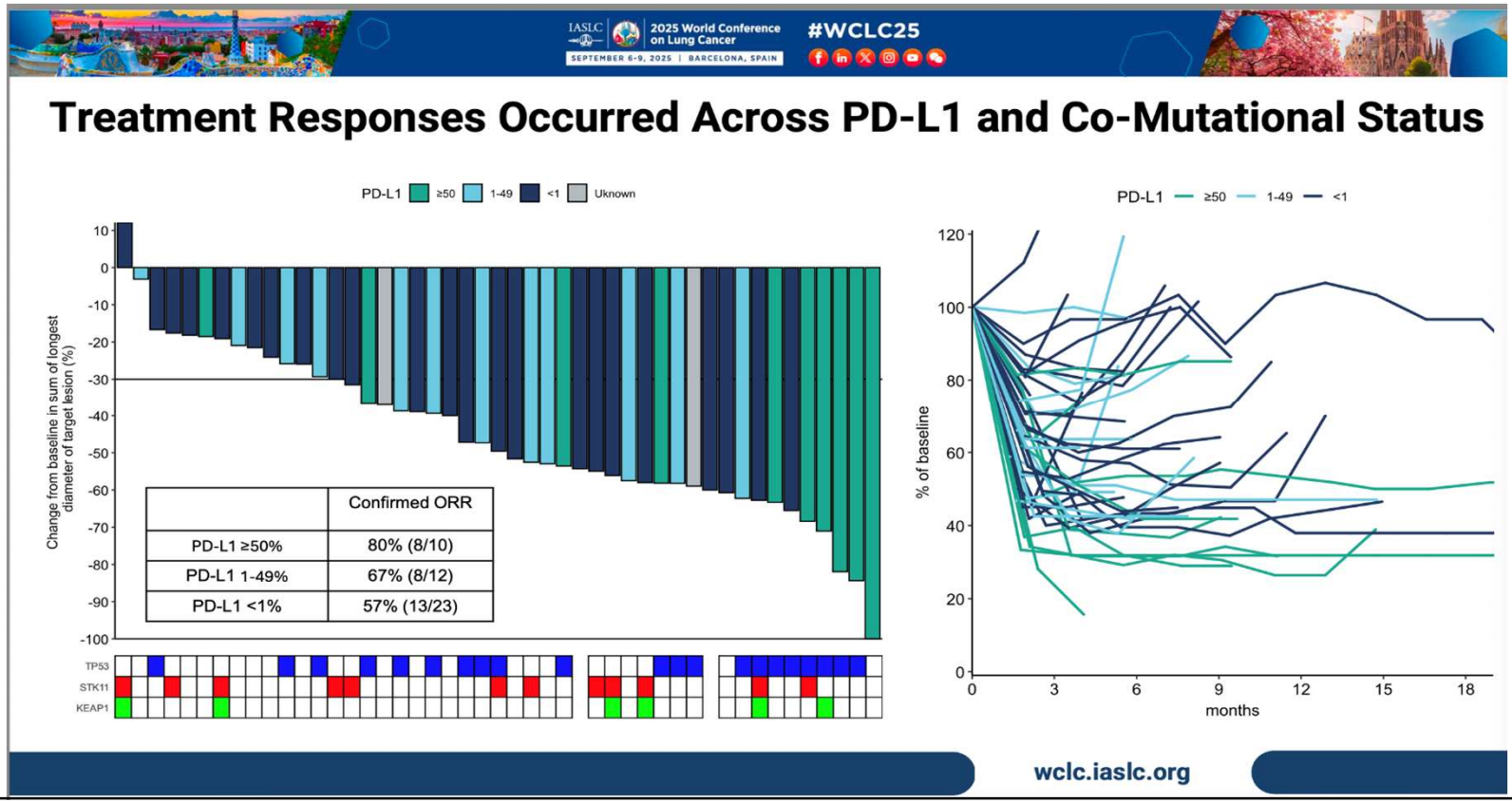
- 1L ORR 88.9%, mPFS 5.7m
- Grade≥3 TRAE 72.4% (1L), most are hematotoxicity



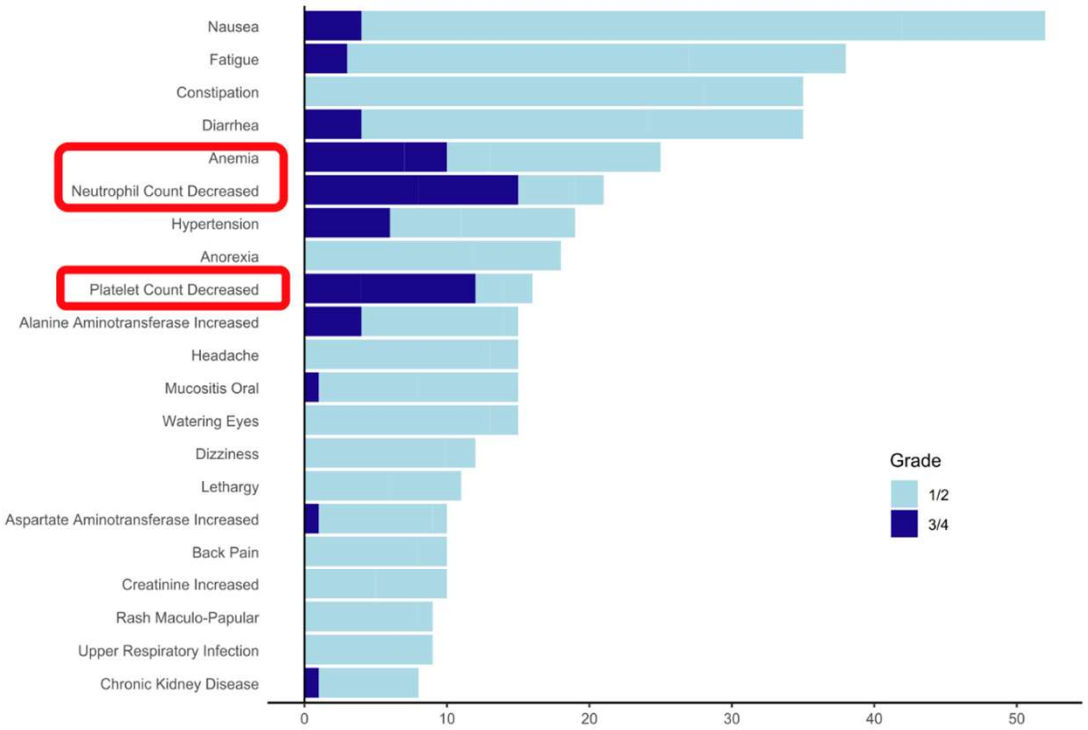
CodeBreaK 202-Phase 3 study for KRAS G12C+ and PD-L1 < 1% NSCLC is ongoing

1. 2024 ASCO 8512; 2. Shinya Sakata, et al. ASCO Abstract#900

OA08.04 – Primary Endpoint Results from SHERLOCK: a Phase 2 trial of Sotorasib, Bevacizumab and Chemotherapy in Advanced *KRAS* G12C NSCLC. Lee CK, et al



Common treatment related adverse events



Treatment discontinuation*:

- Sotorasib - 12 (23%)
- Carboplatin - 2 (4%)
- Pemetrexed - 4 (8%)
- Bevacizumab - 7 (13%)

*Some patients discontinued more than one agent.

Sotorasib dose reduction:

- 480mg - 8 (15%)
- 240mg - 2 (4%)

Grade 5 events of any cause: 5 (10%)

- Bronchopulmonary hemorrhage (n=1), stroke (n=1), sepsis (n=1), febrile neutropenia (n=1), cardiac arrest (n=1)

wclc.iaslc.org

Lee, IASLC 2025

KRAS INHIBITORS

Newer Agents

Multi-selective

GDP/OFF

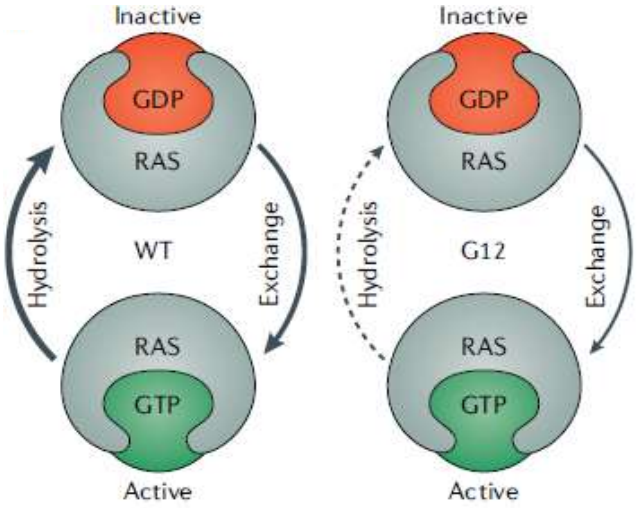
BI 3706674

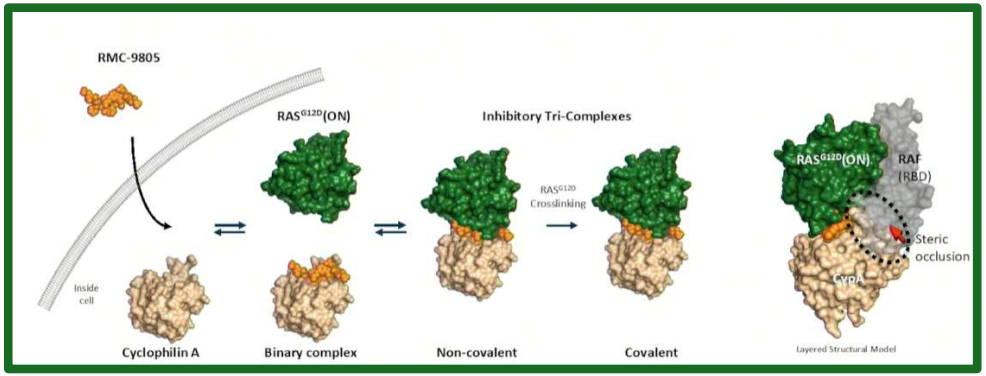
GTP/ON

Tri-complex

RMC-6236

Daraxonrasib





Mutant Selective

G12C

GDP/OFF

SIIPi

Adagrasib

Sotorasib

Divarasib

Opnurasib

Olomorasib

GTP/ON

SIIPi

BB0-8520

FMC-376

Tri-complex

RMC-6291

Elironrasib

G12D

GDP/OFF

MRTX1133

GTP/ON

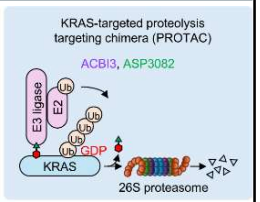
VS7375

Tri-complex

RMC-9805

Zoldonrasib

PROTACS



Cox et al. Genes & Dev 2025

HRS-7058: KRAS G12C Inhibitor
Phase 1 Trial Results

HRS-7058 – KRAS G12Ci – irreversibly binds to the cysteine residue of KRAS G12C mutation, locking the protein in an inactive state

- During dose escalation, no DLT was observed. MTD was not reached.
- Dose/Indication expansions at 200 mg BID and 400 mg BID dose levels are currently ongoing.
- The median follow-up duration was 3.0 months (IQR, 1.3–6.1).

- Grade ≥3 TRAEs occurred in 14.1% of patients, with a low incidence of TRAEs leading to treatment discontinuation (1.6%). No treatment-related deaths were observed.
- The most common TRAEs were gastrointestinal and hematologic toxicities, with diarrhea (mostly grade 1–2) as the predominant event.

Summary

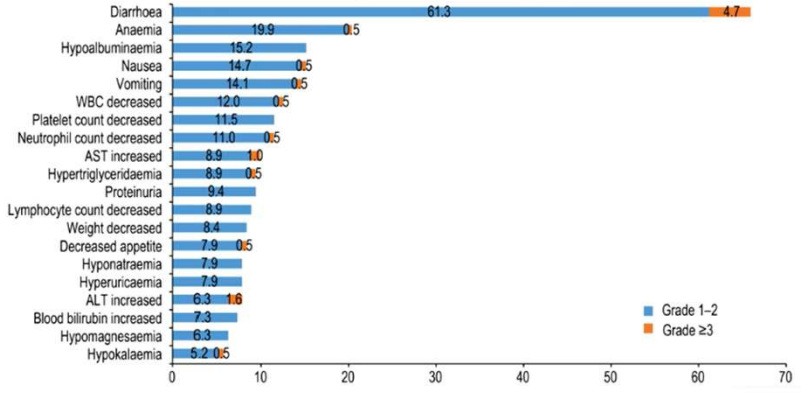
	Total (N=191)
TEAEs	167 (87.4%)
Grade ≥3 TEAEs	40 (20.9%)
TRAEs	164 (85.9%)
Grade ≥3 TRAEs	27 (14.1%)
Serious TRAEs	15 (7.9%)
TRAEs leading to death	0
TRAEs leading to treatment discontinuation	3 (1.6%)
TRAEs leading to dose reduction	11 (5.8%)
TRAEs leading to dose interruption	34 (17.8%)

Data are n (%).

TEAE, treatment-emergent adverse event ; TRAE, treatment-related adverse event.

Prof. Dingzhi Huang, MD

TRAEs occurring in ≥5% of total patients

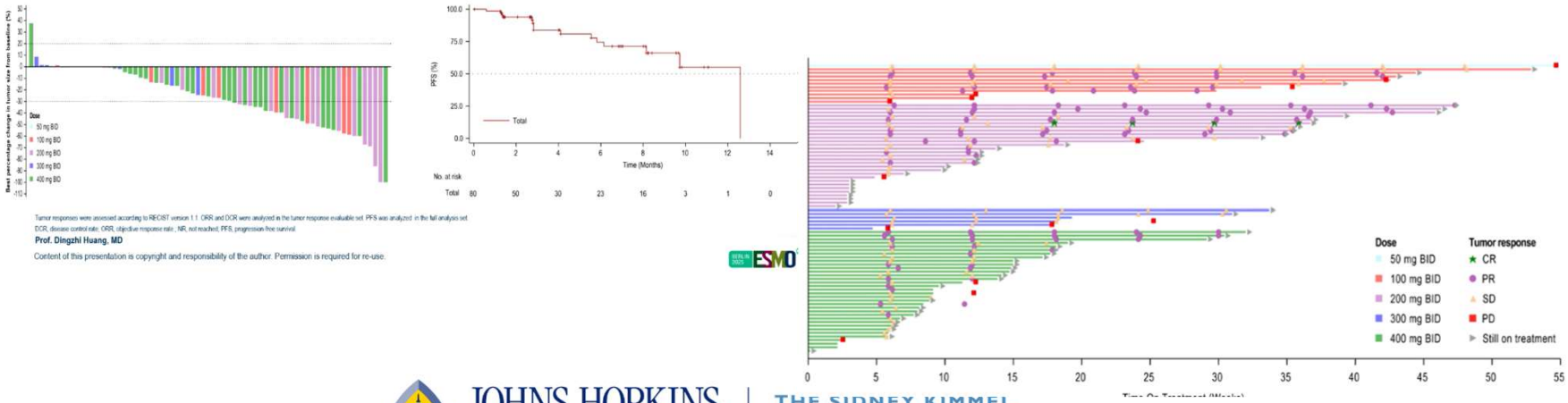


Huang D et al ESMO 2025

HRS-7058: KRAS G12C Inhibitor Phase 1 Trial Results

Tumor response and PFS in KRAS G12Ci naïve NSCLC

- Overall, ORR was 43.5% (30/69), DCR was 94.2% (65/69), and median PFS was 12.6 months (95% CI, 8.15–12.58) in KRAS G12Ci naïve NSCLC .
- 200 mg BID and 400 mg BID were selected for dose optimization.
  - 200 mg BID: ORR was 61.9% (13/21), DCR was 95.2% (20/21), and median PFS was NR.
  - 400 mg BID: ORR was 41.9% (13/31), DCR was 96.8% (30/31), and median PFS was NR.



Tumor responses were assessed according to RECIST version 1.1. ORR and DCR were analyzed in the tumor response evaluable set. PFS was analyzed in the full analysis set.
DCR, disease control rate; ORR, objective response rate; NR, not reached; PFS, progression free survival.

Prof. Dingzhi Huang, MD

JOHNS HOPKINS MEDICINE | THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

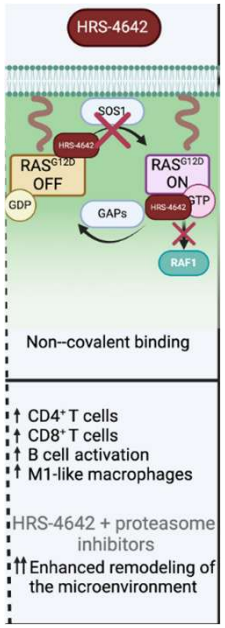
Huang D et al ESMO 2025

KRAS G12D Inhibitors

~ 4% of NSCLC, G12D 14-18% of *KRAS* mutant NSCLC, 46% of *KRAS* mutations in never smokers, ~16% *STK11*, *KEAP1* 9%

HRS-4642

- Extraordinarily high affinity (0.083 nM) to $KRAS^{G12D}$ while binding to $KRAS^{G12C}$ or wild-type KRAS was at least 17-fold lower,
- HRS-4642 had an IC_{50} of 2.329–822.2 nM and a K_D of 0.083 nM
- Targets on and off states of KRAS G12D
- Originally presented ESMO 2023 - 2/9 NSCLC responders, this trial is now with a new formulation.



INCB161734

Binds to both the GDP and GTP forms of the G12D mutant (ON/OFF) at the switch II pocket with picomolar affinity (K_D), and exhibits >80-fold selectivity over wildtype (WT) KRAS

Wahl SGF et al Cancers. 2021;13:4294, Tang Y et al Cancer Gene Therapy. 2024. 31, 961-969, Florez-Gomez A et al Cancer Cell. 2024 42. 1157-1159,

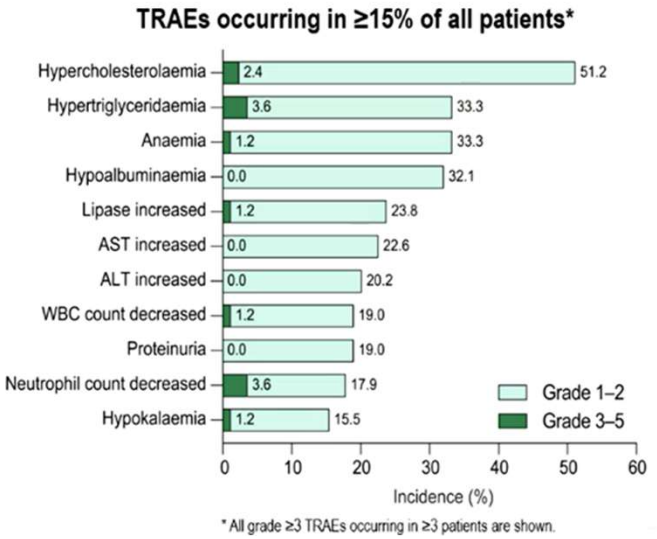
KRAS G12D Inhibitors

HRS-4642 - Safety

- No DLT was reported
- Most common TRAEs: hypercholesterolaemia, hypertriglyceridaemia, anaemia & hypoalbuminaemia

	All patients (N=84)
Any TRAE	81 (96.4)
Grade ≥3	20 (23.8)
Leading to dose discontinuation	1 (1.2)*
Leading to dose reduction	1 (1.2)
Leading to dose interruption	23 (27.4)
Serious	15 (17.9)
Leading to death	1 (1.2)†

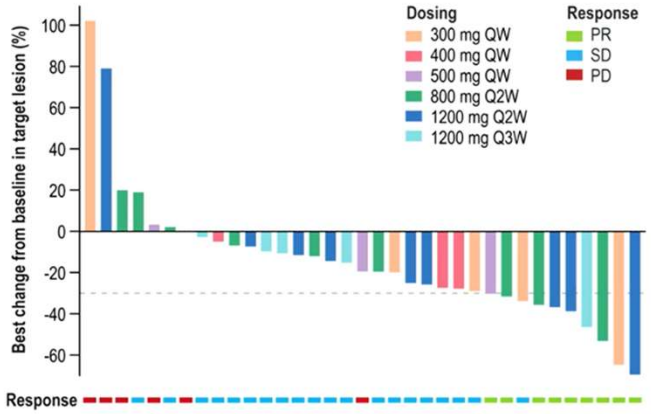
Data are n (%). * Gastrointestinal haemorrhage (PDAC). † Brain stem infarction (causality with study treatment could not be determined by investigator).



Xiong A et al ESMO 2025

KRAS G12D Inhibitors

HRS-4642 – NSCLC Efficacy



	NSCLC		
	800 mg Q2W (N=10)	1200 mg Q2W (N=9)	All (N=38)
Best overall response, n (%)			
PR	3 (30.0)	3 (33.3)	9 (23.7)
SD	5 (50.0)	5 (55.6)	20 (52.6)
PD	2 (50.0)	2 (20.0)	6 (15.8)
No post-baseline data	0	0	3 (7.9)
Confirmed ORR (95% CI), %	30.0 (6.7–65.2)	33.3 (7.5–70.1)	23.7 (11.4–40.2)
Confirmed DCR (95% CI), %	80.0 (44.4–97.5)	88.9 (51.8–99.7)	76.3 (59.8–88.6)

PFS

	Event, n/N (%)	Median (95% CI), mo
800 mg Q2W	9/10 (90.0)	6.3 (1.1–11.0)
1200 mg Q2W	7/9 (77.8)	8.4 (1.4–NR)
All patients	32/38 (84.2)	5.6 (2.8–6.9)

OS

	Event, n/N (%)	Median (95% CI), mo
800 mg Q2W	6/10 (60.0)	7.5 (4.1–NR)
1200 mg Q2W	1/9 (11.1)	NR (8.4–NR)
All patients	18/38 (47.4)	13.7 (7.6–NR)

Xiong A et al ESMO 2025

KRAS G12D Inhibitors

INCB161734

- TRAEs: Nausea 67%, Diarrhea 51%, fatigue 18%, Lipase increased 11%
- No TRAE leading to discontinuation
- Part 1 monotherapy – dosed 200-1600mg q day,
- Part 2 combinations – for NSCLC combination with retifanlimab

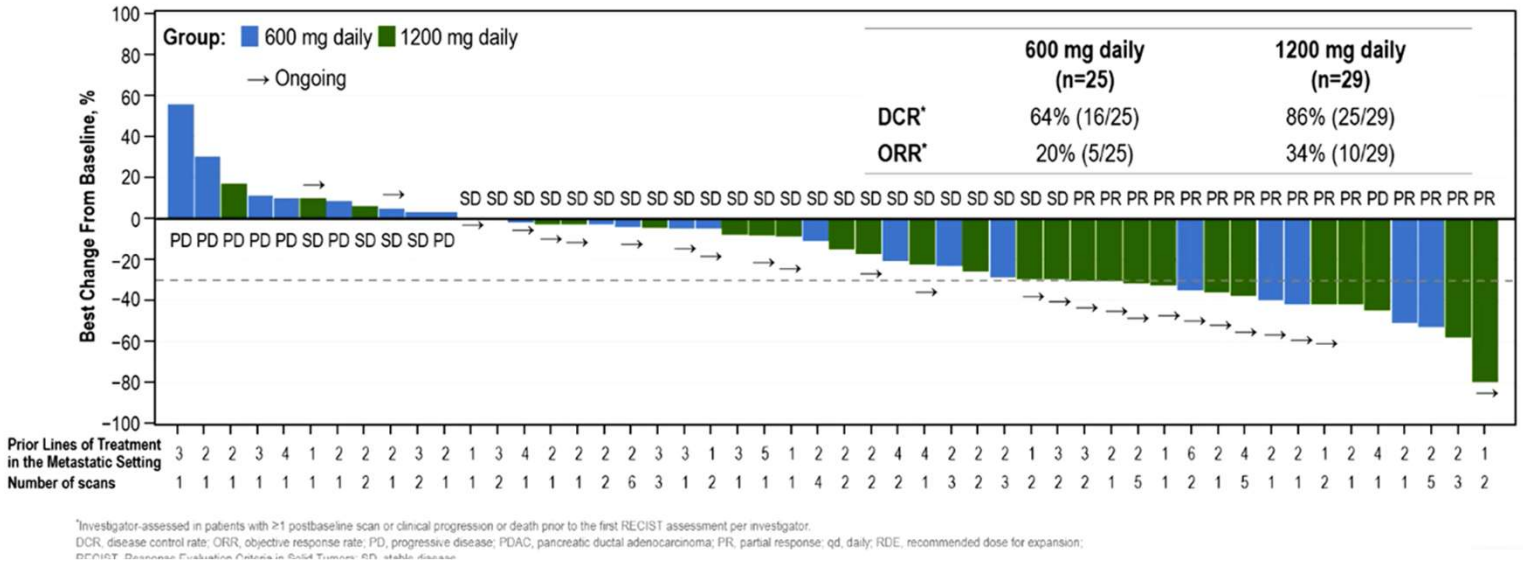
	TRAEs*					
	All Doses (n=136)		600 mg qd (n=43)		1200 mg qd (n=67)	
TRAE, n (%)	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any TRAE	120 (88.2)	15 (11.0)	36 (83.7)	6 (14.0)	59 (88.1)	6 (9.0)
Serious TRAE	4 (2.9)	3 (2.2)	2 (4.7)	2 (4.7)	2 (3.0)	1 (1.5)
TRAEs leading to						
Interruption	21 (15.4)	8 (5.9)	5 (11.6)	3 (7.0)	9 (13.4)	3 (4.5)
Reduction	9 (6.6)	1 (0.7)	0	0	5 (7.5)	1 (1.5)
Discontinuation	0	0	0	0	0	0

Desai J et al ESMO 2025

KRAS G12D Inhibitors

INCB161734

- NSCLC – N= 3
- 1200 mg daily dose moving forward



*Investigator-assessed in patients with ≥1 postbaseline scan or clinical progression or death prior to the first RECIST assessment per investigator.
DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; qd, daily; RDE, recommended dose for expansion;

Desai J et al ESMO 2025

Zoldonrasib G12D (ON) in NSCLC

Key Eligibility Criteria

- Advanced solid tumors with KRAS G12D mutations
- Received prior standard therapy appropriate for tumor type and stage
- ECOG PS 0–1
- No active brain metastases

Key Endpoints

- Safety and tolerability
- Pharmacokinetics
- Antitumor activity

Part 1: Dose Escalation

Zoldonrasib administered orally QD or BID, 21-day treatment cycle

1200 mg QD | 600 mg BID
900 mg QD | 450 mg BID
600 mg QD | 300 mg BID
300 mg QD
150 mg QD

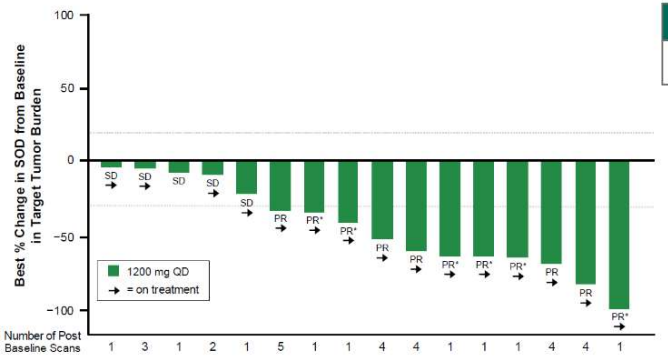
Part 2: Expansion and Dose Optimization (NSCLC and PDAC)

- Max administered dose was 1200 mg daily
- No dose limiting toxicities observed in Part 1
- Maximum tolerated dose not reached

	Patients with NSCLC Treated with 1200 mg QD Zoldonrasib (N = 28)
Age, years, median (range)	64 (36-86)
Male, n (%)	14 (50%)
ECOG PS 1, n (%)	18 (64%)
Smoking Status	
Current	1 (4%)
Past	12 (43%)
Never	15 (54%)
Number of prior anti-cancer therapies, median (range)	2 (0-6)[1]
Prior treatment with platinum chemotherapy	24 (86%)
Prior treatment with immune checkpoint inhibitor	24 (86%)
Brain metastases at baseline, n (%)	6 (21%)
Metastatic at diagnosis [stage IV], n (%)	21 (75%)

Patients Treated with 1200 mg QD Zoldonrasib (N = 90)[1]				
Maximum Severity of Treatment-Related AEs	**Grade 1**	**Grade 2**	**Grade 3**	**Any Grade**
Any TRAE	49 (54%)	16 (18%)	2 (2%)	67 (74%)
TRAEs occurring in ≥10% of patients, n (%)				
Nausea	30 (33%)	5 (6%)	0	35 (39%)
Diarrhea	18 (20%)	3 (3%)	1 (1%)	22 (24%)
Vomiting	12 (13%)	4 (4%)	0	16 (18%)
Rash[2]	11 (12%)	0	0	11 (12%)
Other select TRAEs, n(%)				
AST increased	5 (6%)	2 (2%)	0	7 (8%)
ALT increased	4 (4%)	1 (1%)	1 (1%)	6 (7%)
Stomatitis/mucositis[3]	1 (1%)	0	0	1 (1%)
TRAEs leading to dose reduction, n (%)	2 (2%)	2 (2%)	0	4 (4%)
TRAEs leading to dose interruption, n (%)	3 (3%)	3 (3%)	2 (2%)	8 (9%)
TRAEs leading to treatment discontinuation, n (%)	1 (1%)	0	0	1 (1%)
Mean dose intensity		98%		

No treatment-related Grade 4 or 5 AEs or SAEs have been reported



Tumor Response for Patients with NSCLC Treated with 1200 mg QD (N = 18)[1]	
ORR[2], % (n)	61% (11)
DCR (CR+PR+SD), % (n)	89% (16)

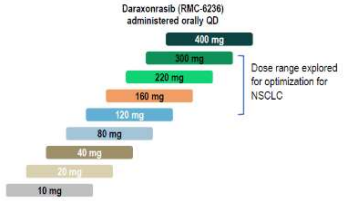
[1] per RECIST v1.1
[2] Includes confirmed PRs and unconfirmed PRs who were still on treatment and may yet be confirmed

mTTR=1.4 months
mDOR- 2.6 months

Arbour K et al. AACR 2025 (slides courtesy of Dr Arbour)

Daraxonrasib (multi-selective ON)(RMC-6236) in *KRAS* mutant NSCLC

Dose Escalation



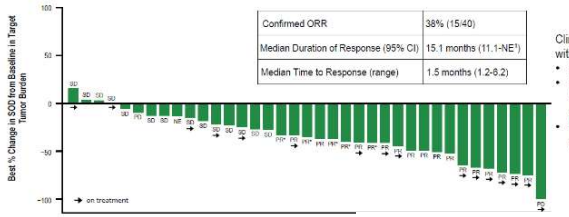
Study enrolled patients with tumors harboring RAS mutations in KRAS, HRAS, and NRAS at codon 12 (RAS G12X), codon 13 (G13) or codon 61

Baseline Characteristics of Patients with RAS Mutant NSCLC

Baseline Characteristics	120–300 mg N = 124*	120–220 mg N = 73
Age, years, median (range)	67 (31, 89)	68 (36, 89)
Male, n (%)	49 (40%)	28 (38%)
ECOG PS 1, n (%)	100 (81%)	59 (81%)
Number of prior anti-cancer therapies, median (range)	2 (1, 6)	2 (1, 6)
Smoking current/past, n (%)	94 (76%)	53 (73%)
Brain metastases at baseline, n (%)	36 (29%)	19 (26%)
Metastatic at diagnosis [stage IV], n (%)	70 (57%)	37 (51%)

All data included in this presentation is from the data cutoff of 30 Sep 2024

in 2L/3L Patients with RAS G12X NSCLC Treated with Daraxonrasib (RMC-6236) at 120-220 mg Daily



Confirmed ORR	38% (15/40)
Median Duration of Response (95% CI)	15.1 months (11.1-NE[1])
Median Time to Response (range)	1.5 months (1.2-8.2)

Clinical activity assessed in patients with NSCLC (n=40) that
- Harbor RAS G12X mutations
- Have received 1 or 2 prior lines of therapy (prior immunotherapy and platinum chemotherapy)
- Have not received docetaxel previously

	120–300 mg (N = 124)		120–220 mg (N = 73)		300 mg (N = 51)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any TRAE	121 (98%)	33 (27%)	71 (97%)	12 (16%)	50 (98%)	21 (41%)
TRAEs in ≥ 10% of patients, n (%)						
Rash*	110 (89%)	9 (7%)	66 (90%)	5 (7%)	44 (86%)	4 (8%)
Diarrhea	87 (70%)	10 (8%)	46 (63%)	1 (1%)	41 (80%)	9 (18%)
Nausea	68 (55%)	0	36 (49%)	0	32 (63%)	0
Vomiting	55 (44%)	3 (2%)	29 (40%)	2 (3%)	26 (51%)	1 (2%)
Stomatitis	47 (38%)	3 (2%)	25 (34%)	0	22 (43%)	3 (6%)
Paronychia	26 (21%)	0	14 (19%)	0	12 (24%)	0
Fatigue	20 (16%)	0	8 (11%)	0	12 (24%)	0
Dry skin	19 (15%)	0	9 (12%)	0	10 (20%)	0
AST increased	17 (14%)	2 (1.6%)	11 (15%)	0	6 (12%)	2 (4%)
ALT increased	15 (12%)	3 (2.4%)	10 (14%)	0	5 (10%)	3 (6%)
Decreased appetite	14 (11%)	0	4 (6%)	0	10 (20%)	0
Dysgeusia	12 (10%)	0	3 (4%)	0	9 (18%)	0
Other select TRAEs, n (%)						
Anemia	9 (7%)	3 (2%)	4 (6%)	2 (3%)	5 (10%)	1 (2%)

At 120–220 mg: Rash (7%) was the only G3 TRAE in ≥ 5% patients; no G4 or 5 TRAEs were observed
At 300 mg: One Grade 4 TRAE observed (pneumonitis) with patient recovering; no Grade 5 TRAEs

*Includes preferred terms of Rash pustular, Rash papular, Rash maculo-papular, Rash macular, Rash, Erythema, Dermatitis acneiform. Multiple types of rash may have occurred in the same patient.

TRAEs Leading to Dose Modifications

	120–300 mg (N = 124)	120–220 mg (N = 73)	300 mg (N = 51)
TRAEs leading to dose modification, n (%)	64 (52%)	30 (41%)	34 (67%)
Dose interruption	59 (48%)	25 (34%)	34 (67%)
Dose reduction	34 (27%)	15 (21%)	19 (37%)
TRAEs leading to dose discontinuation, n (%)	7 (6%)	3 (4%)	4 (8%)
Mean dose intensity	86%	91%	78%

For the 120–220 mg cohort,
- Median treatment duration was 5.5 months
- Median cumulative duration of dose interruption was 8.5 days

Rash Prophylaxis at 120-220 mg

	Without Prophylaxis for Rash (N = 58)	With Prophylaxis for Rash (N = 15)
Treatment related rash		
Grade ≥ 3	5 (9%)	0 (0%)
Dose modification due to treatment related rash		
Grade ≥ 3	4 (7%)	0 (0%)

Based on the overall benefit-risk, 200 mg was selected for evaluation in the Phase 3 study

Punekar S. ELCC (slides courtesy of Dr Arbour)

KRAS codon 13 mutations

- Associated with worse outcomes compared to other *KRAS* mutations, particularly G13D.
- *KRAS* G13X ~3-6% of adenocarcinomas
- Close interaction between *KRAS*-G13D and HER2-dependent pathway
- RMC-8839 - selective covalent tri-complex inhibitor of RAS G13C(ON)
- RAS-PM database – 100K Genomes Programme
- *KRAS* G13C co-mutates with *STK11, BRAF, KEAP1*
- *KRAS* G13D co-mutates with *NF1* and *KEAP1* (more with advanced disease)
- *KRAS* G13C cell lines selectively vulnerable to taxanes – combined with RMC-8839 synergistic anti-tumor activity

Hwang et al, 2025, Muthiah A et al JCO 40, 2022.

Conclusions

- This is an active area of investigation
- Multiple phase 3 trials are ongoing to evaluate the activity of KRAS G12C inhibitors in the first line setting with chemo-IO
- Newer agents targeting various *KRAS* subtypes are under investigation
- Newer drugs seem to have better toxicity profiles
- CNS activity is essential if these drugs are to have a major impact

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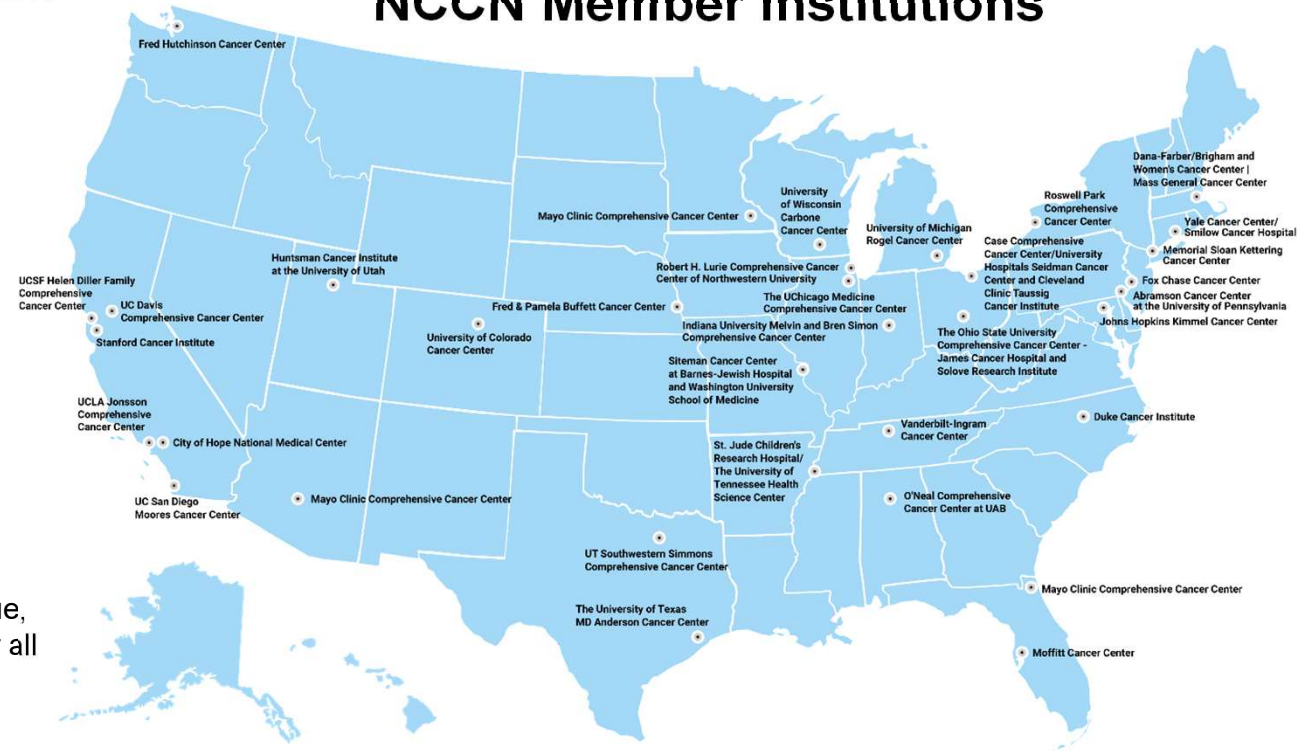

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