Pan-(K)RAS inhibitors: where are we going?

Ferdinandos Skoulidis, M.D., Ph.D.

Associate Professor
Department of Thoracic/Head and Neck Medical Oncology

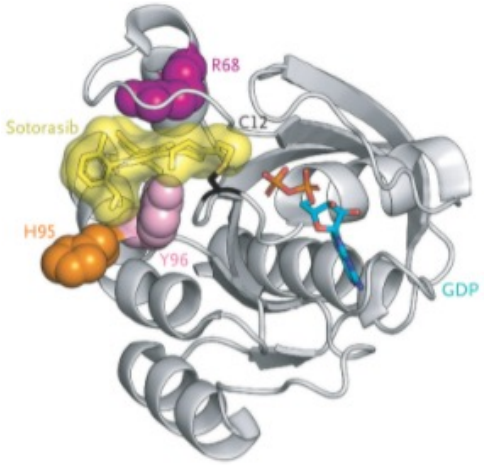
Masters in Thoracic Oncology Summit (MaTOS™), Albuquerque, New Mexico

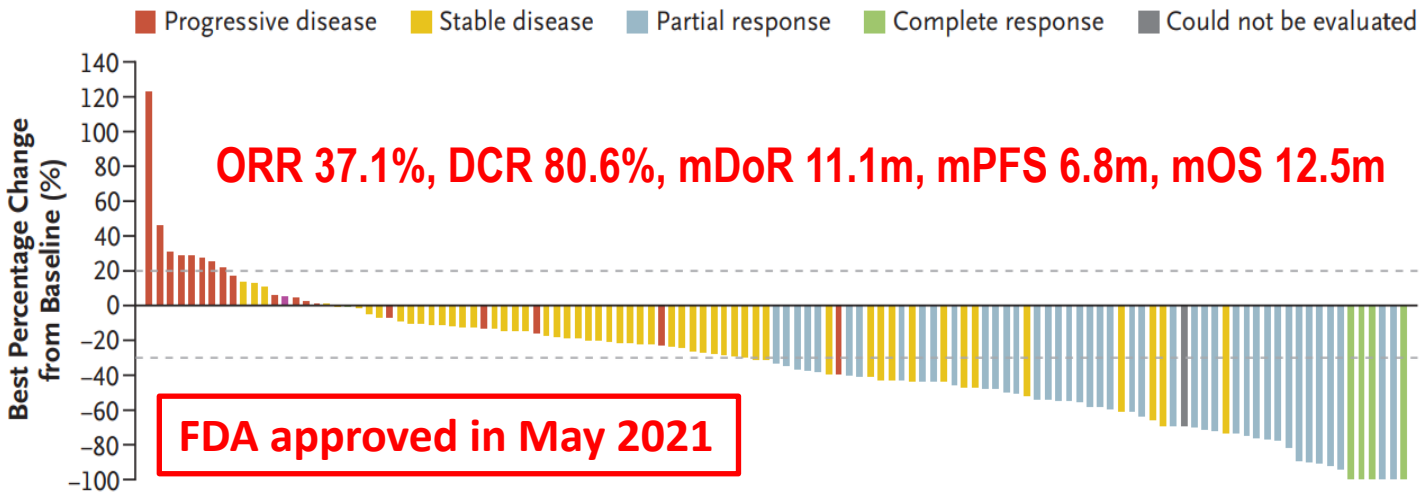
November 18, 2023

Covalent *KRAS*^{G12C} inhibitors: a breakthrough in targeted cancer therapy

A.

Sotorasib (AMG 510)



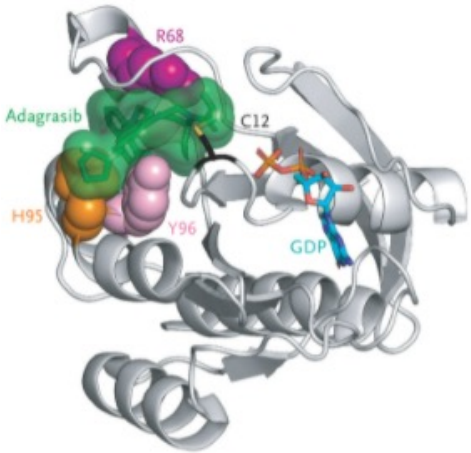


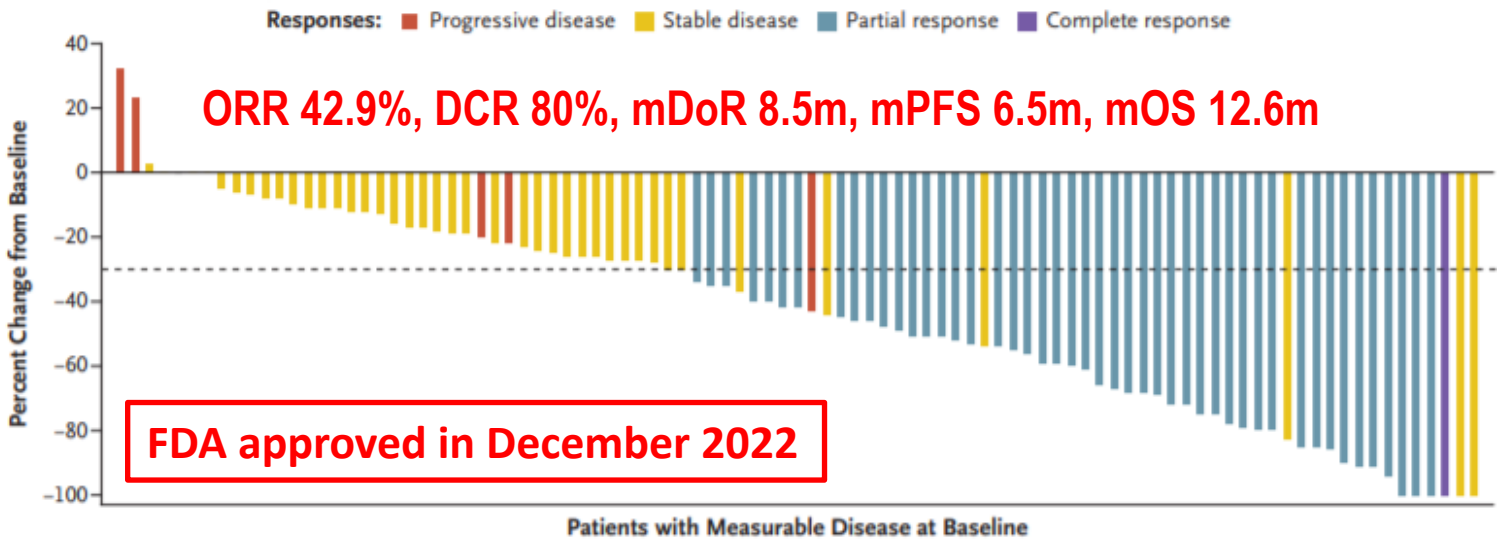
Awad MM et al. *N Engl J Med* 2021 Jun24;384(25):2382-2393

Skoulidis F et al. *N Engl J Med* 2021 Jun 24;384(25):2371-2381

B.

Adagrasib (MRTX849)



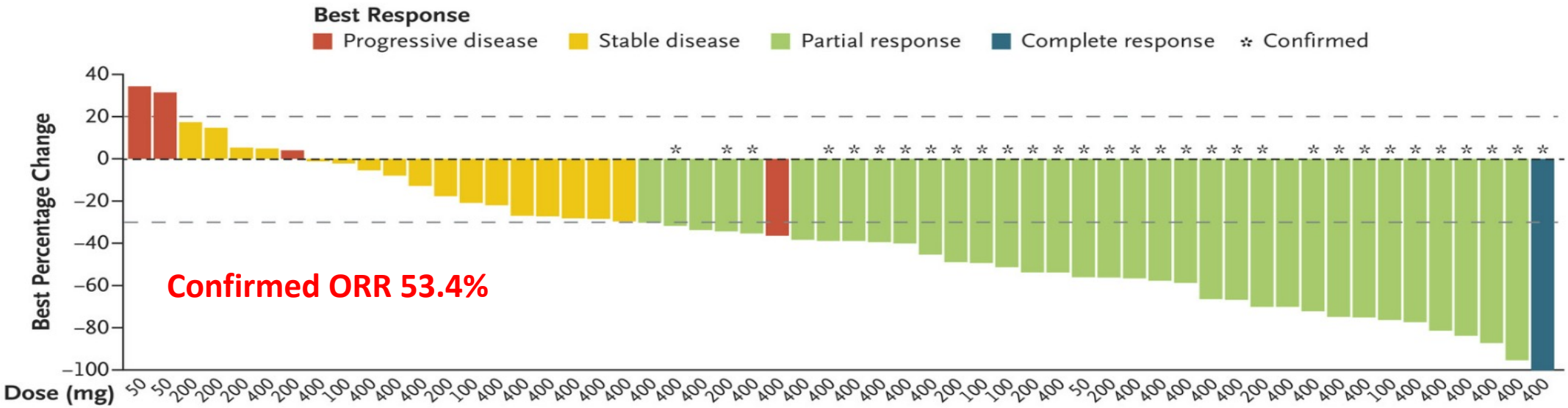


Awad MM et al. *N Engl J Med* 2021 Jun24;384(25):2382-2393

Jänne PA al. *N Engl J Med* 2022 Jul 14;387(2):120-131 (Epub 2022 June 3)

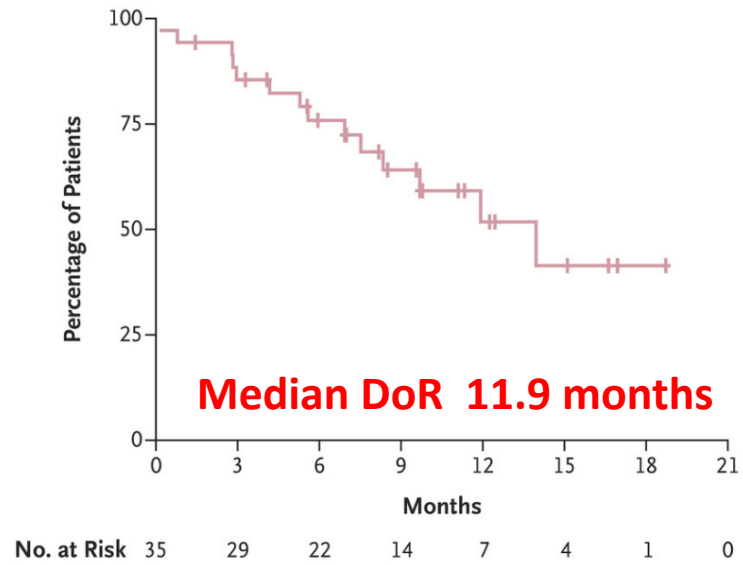
Divarasib efficacy in NSCLC

A.

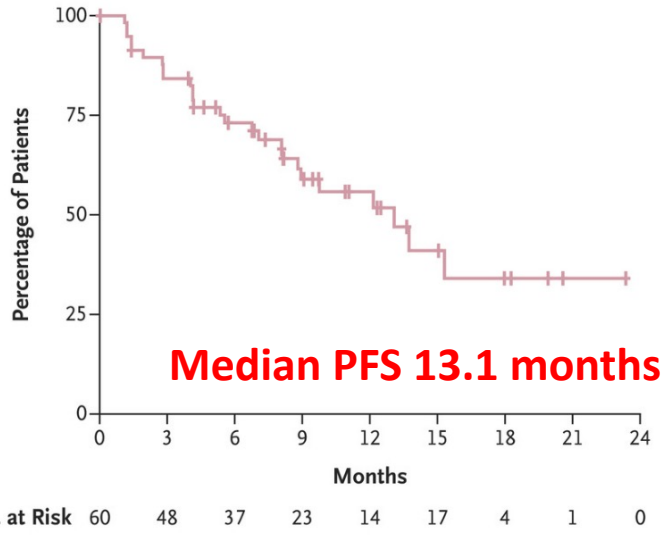


Confirmed ORR 53.4%

B.



Median DoR 11.9 months



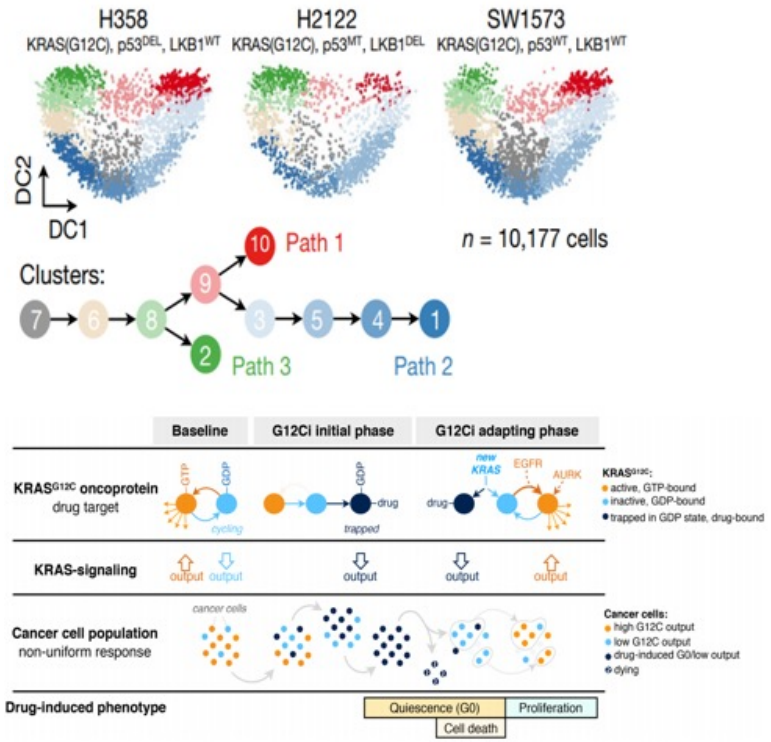
Median PFS 13.1 months (13.7 m at 400mg dose)

Sacher A et al., NEJM, 2023

Mechanisms of innate, adaptive and acquired resistance to OFF state-selective KRAS G12Ci frequently converge on accumulation of "active" KRAS^{G12C}-GTP

A.

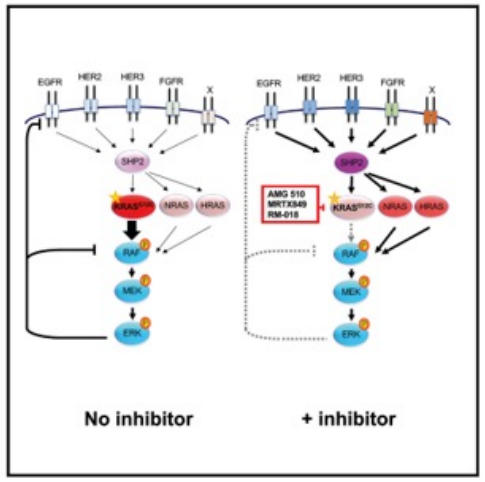
Synthesis of new KRAS^{G12C} protein



Xue JY et al., *Nature*, 2020

B.

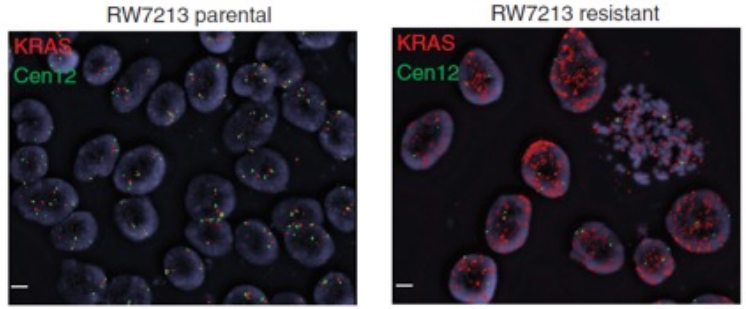
Increased RTK drive

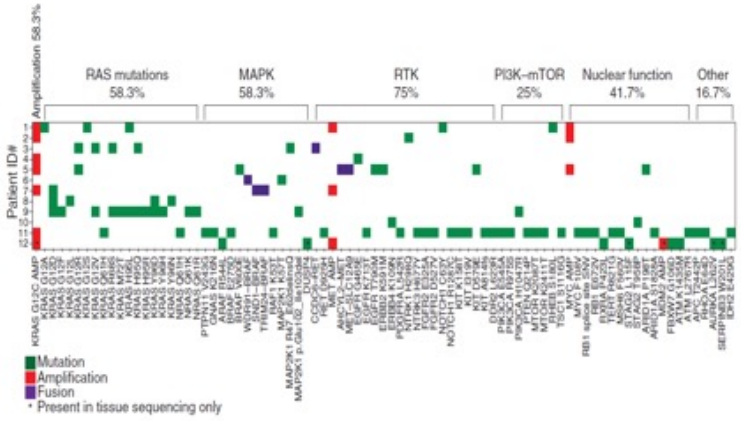


Ryan MB et al., *Cell Reports*, 2022

C.

KRAS^{G12C} amplification



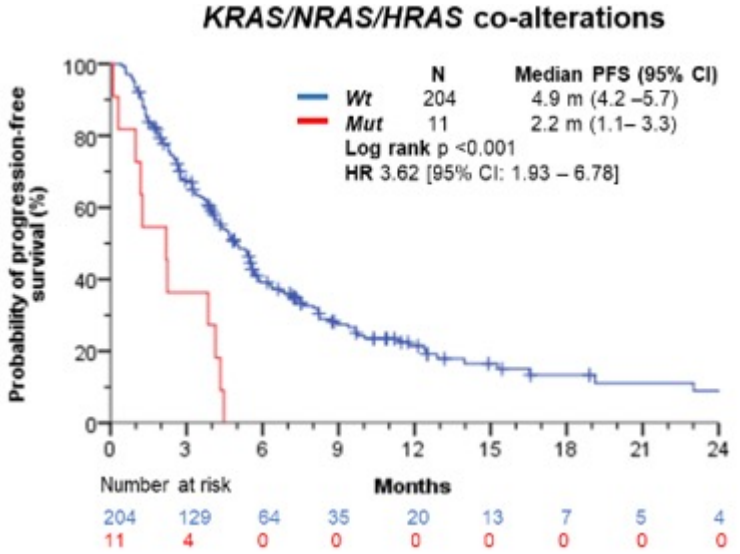


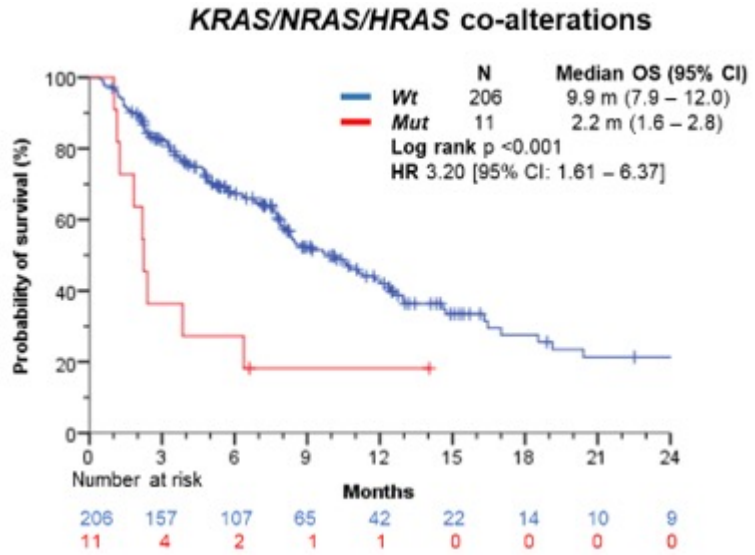
Yaeger R et al., *Cancer Discov*, 2023

KRAS^{G12C}-GTP → Incomplete target coverage

Alterations in *RAS* genes (frequently involving *KRAS* amplification) are associated with worse clinical outcomes with sotorasib or adagrasib

Baseline *RAS* gene co-alterations





Negrao MV et al., *Cancer Discov*, 2023

CodeBreaK 200 phase III trial

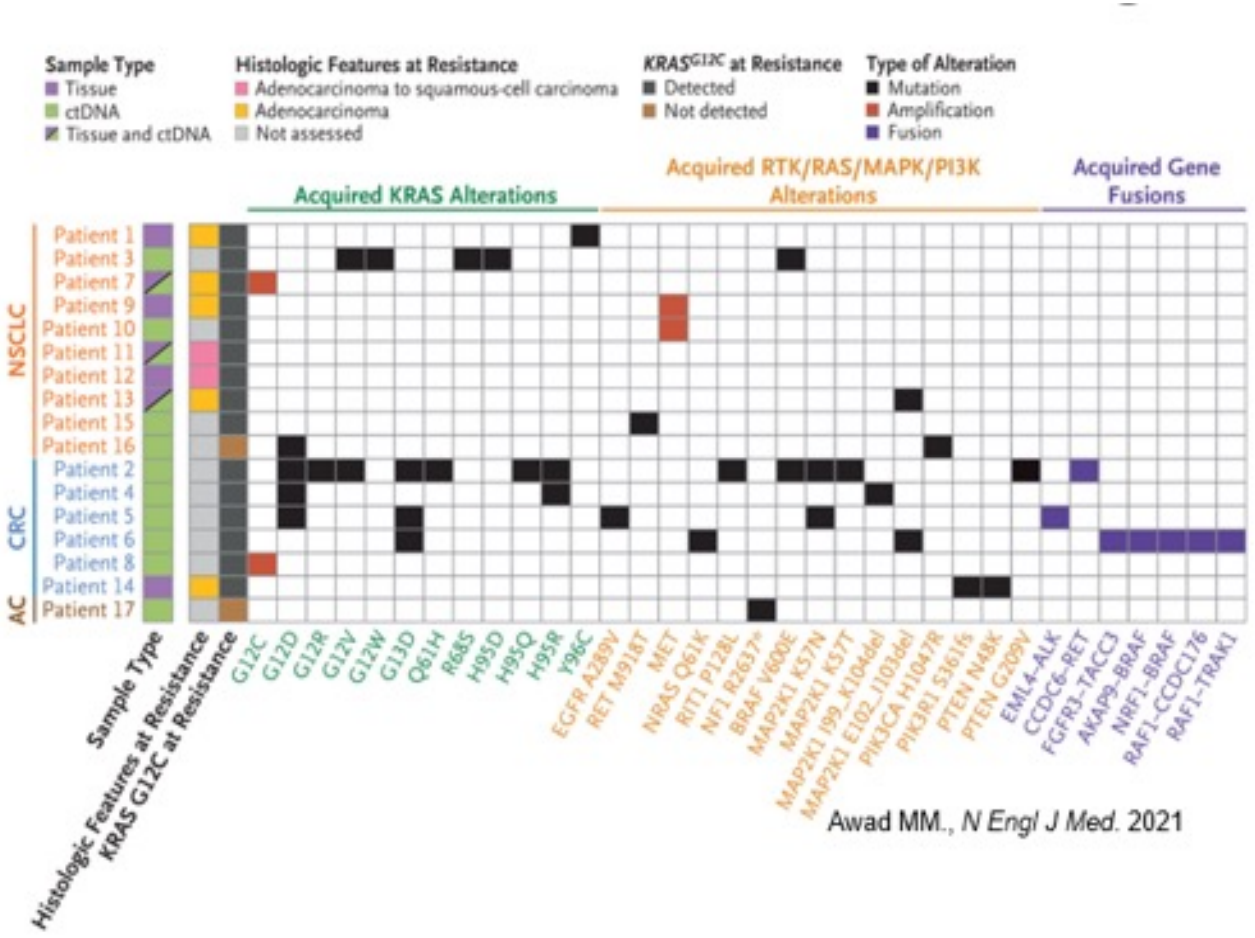
The picture can't be displayed.

	Sotorasib (n = 164)	Docetaxel (n = 154)	Treatment Difference (*P*-value)
[illegible]	[illegible]	KRAS co-alteration, n (%)	9 (5)
0	–	ORR, n (%)	0
2.5 (1.4, 3.1)	0.015	Median PFS (95% CI)	1.6 (0.8, 3.0)
[illegible]		HR (95% CI)	[illegible]

Skoulidis F et al., ASCO Annual Meeting, 2023

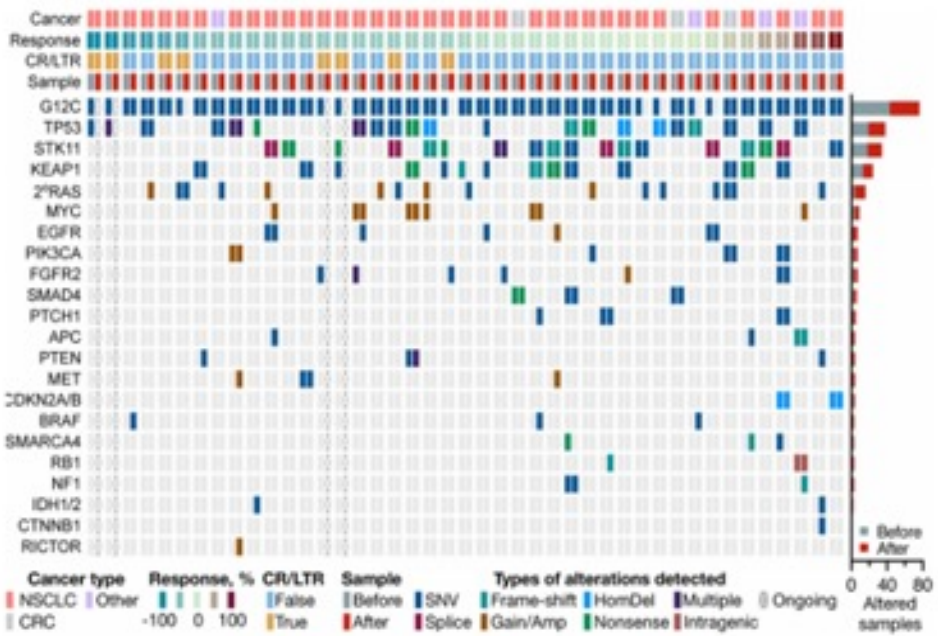
Acquired resistance to off-state selective KRAS^{G12C} inhibitors frequently involves secondary alterations in *RAS* alleles or upstream RTK-MAPK pathway genes

A.



Awad MM., *N Engl J Med.* 2021

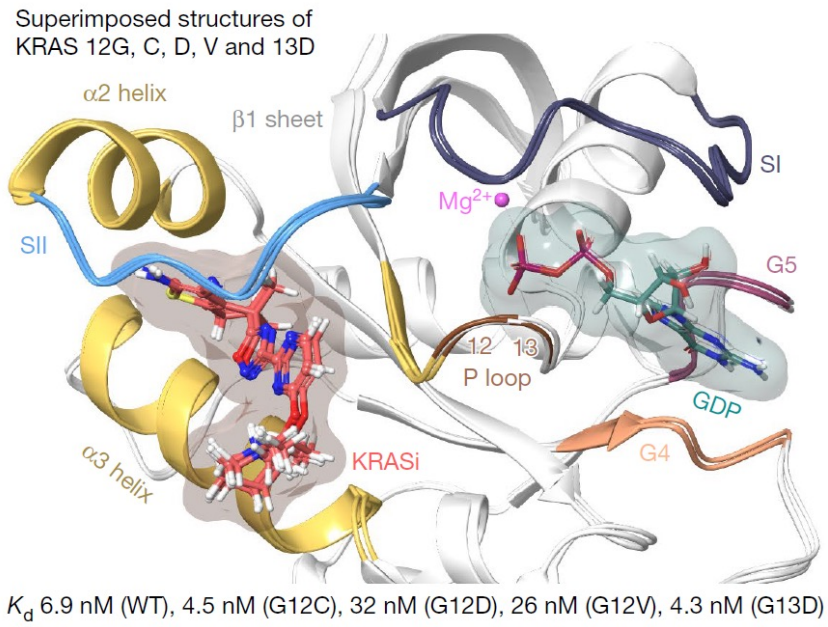
B.



Zhao Y et al., *Nature.* 2021

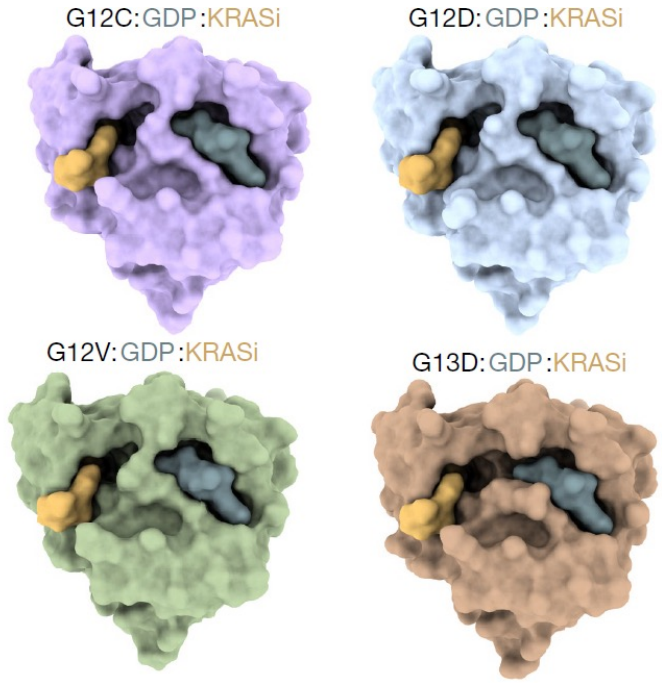
BI-2865 is a novel, non-covalent off state-selective pan KRAS inhibitor

A.

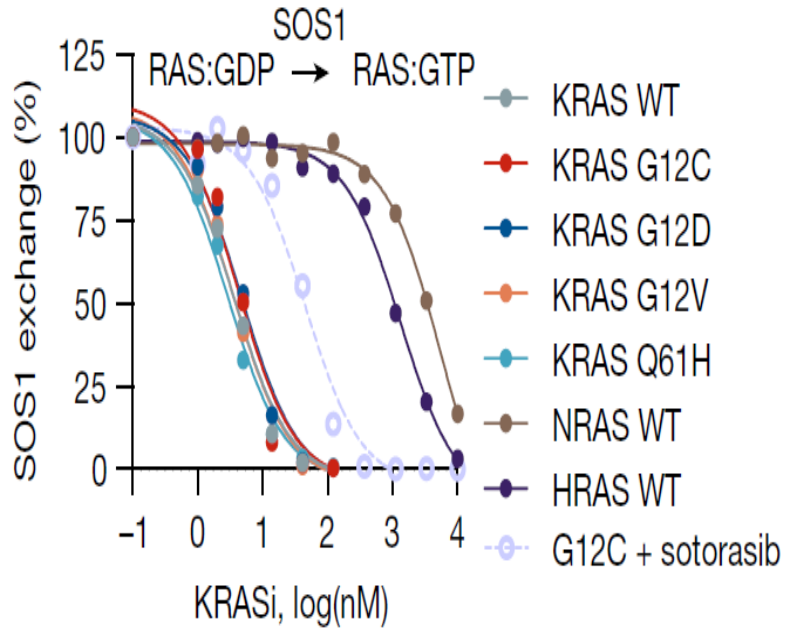


K_d 6.9 nM (WT), 4.5 nM (G12C), 32 nM (G12D), 26 nM (G12V), 4.3 nM (G13D)

B.



C.

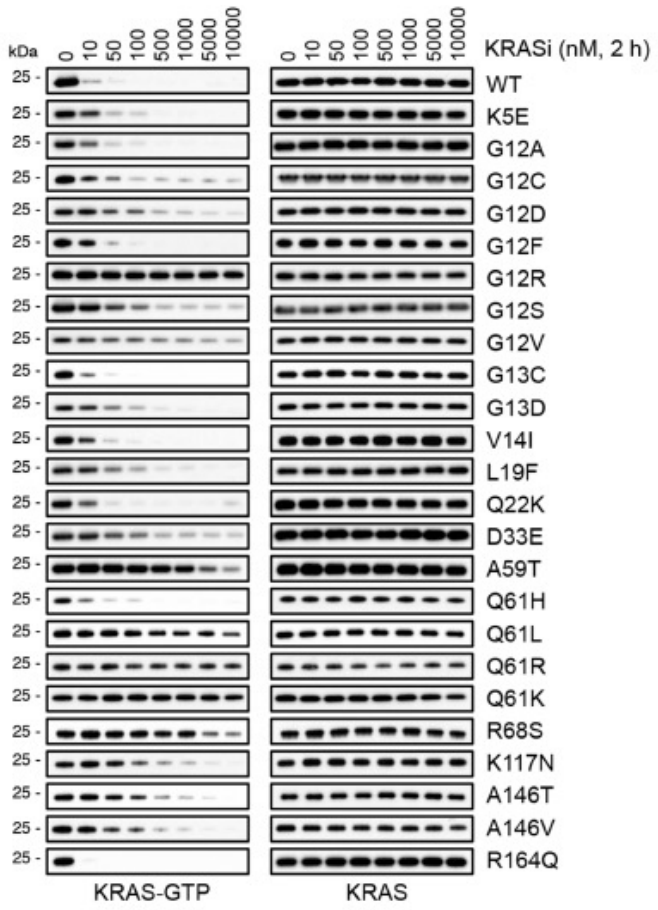


The interaction with His95 is critical for KRAS selectivity

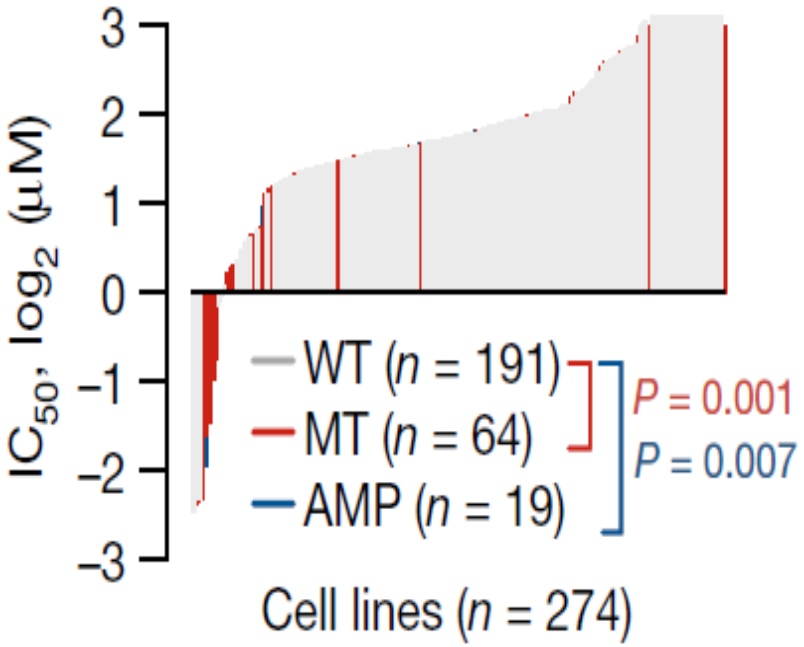
Kim D et al., *Nature*, 2023

BI-2865 inhibits KRAS signaling and *in vivo* tumor growth

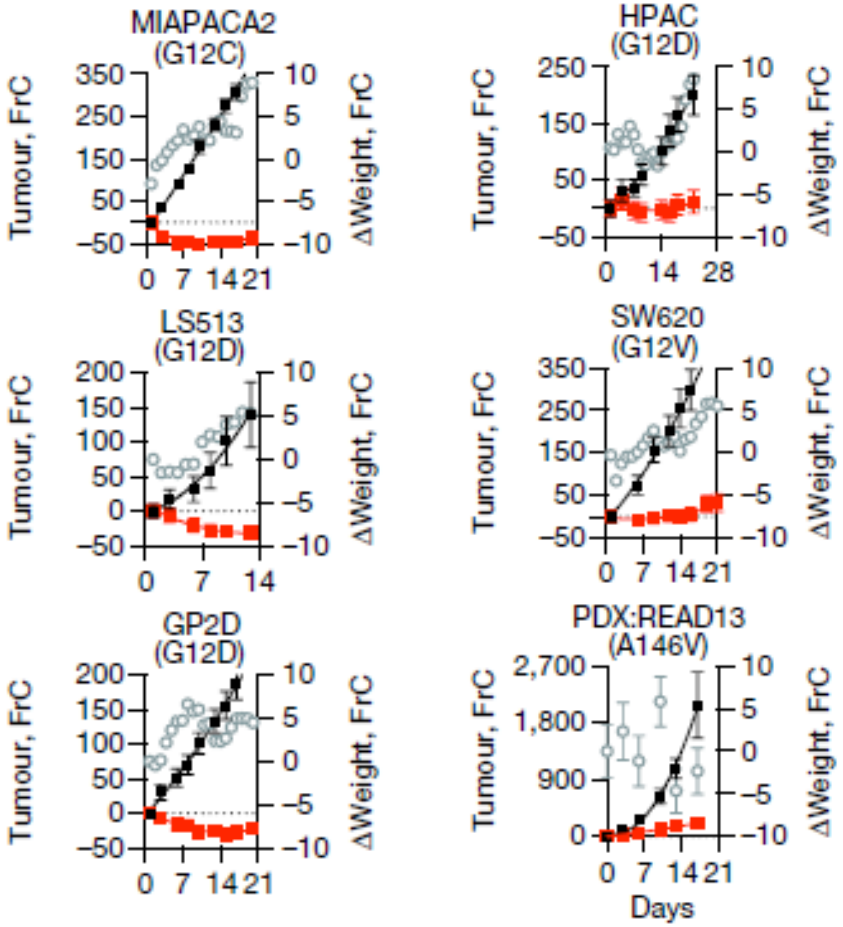
A.



B.



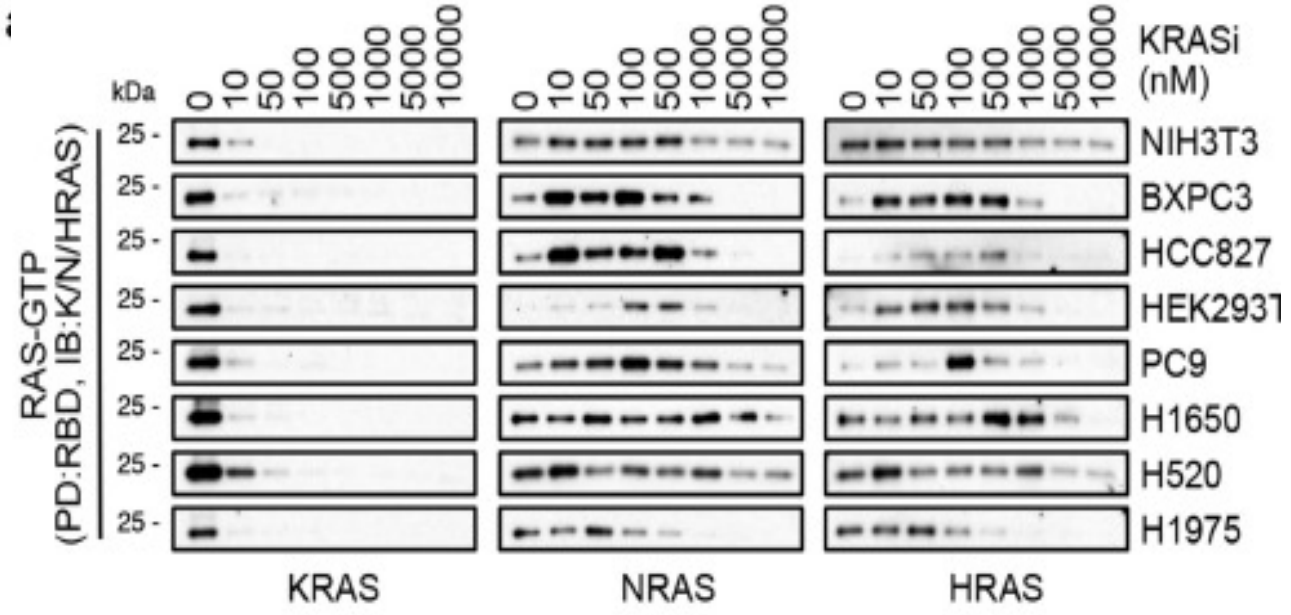
C.



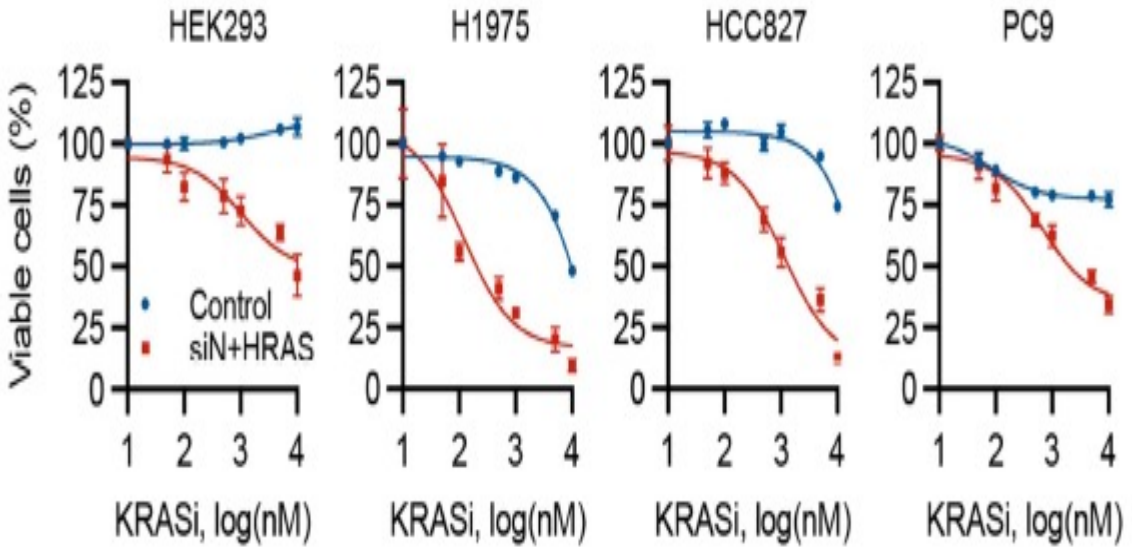
Kim D et al., *Nature*, 2023

Pan-KRASi induced HRAS and NRAS activation may curtail antitumor efficacy

A.

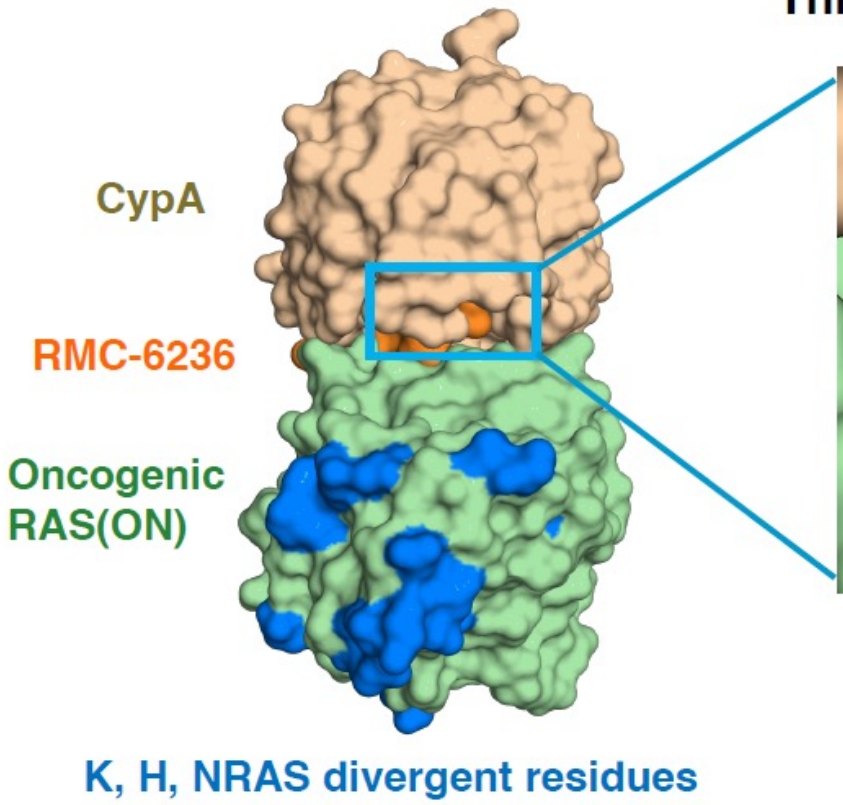


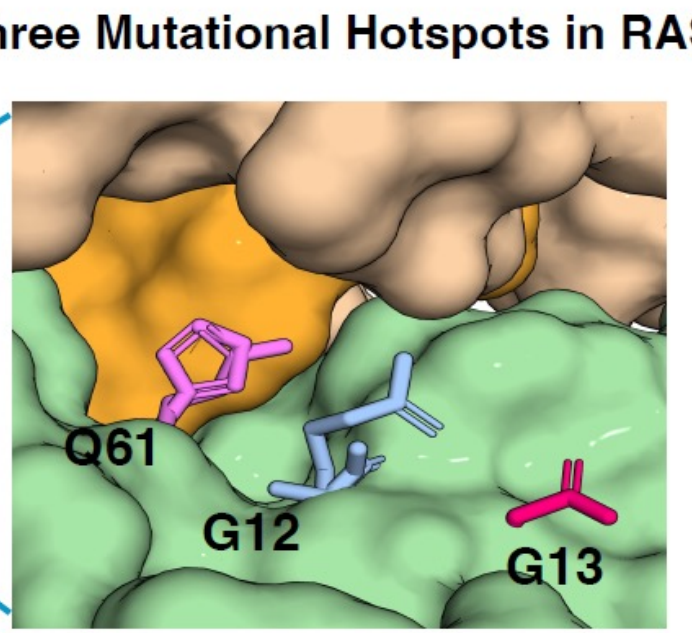
B.

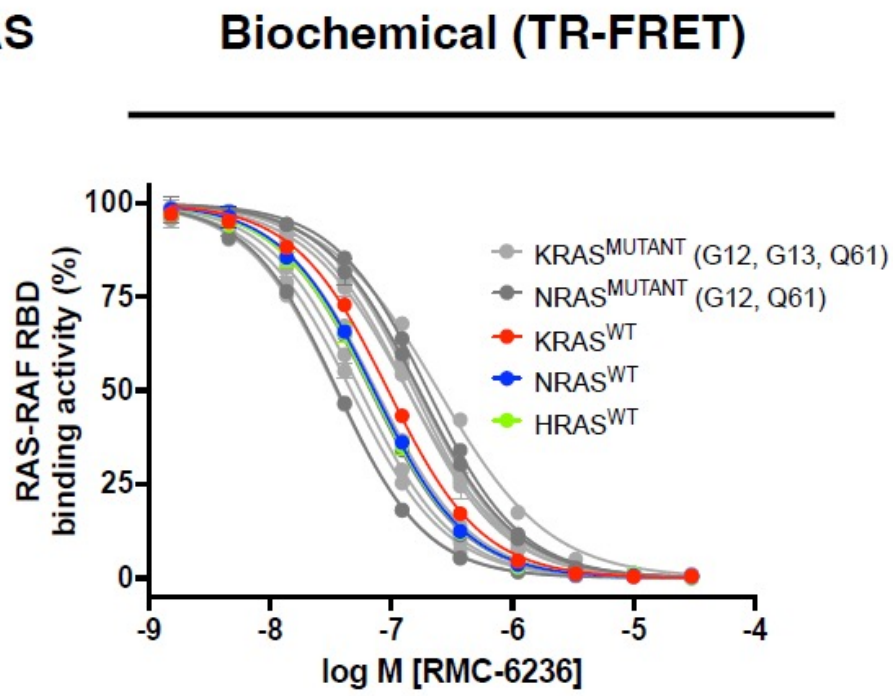


Kim D et al., *Nature*, 2023

RMC-6236 is a first-in-class potent non-covalent tricomplex RAS^{MULTI} (ON) inhibitor



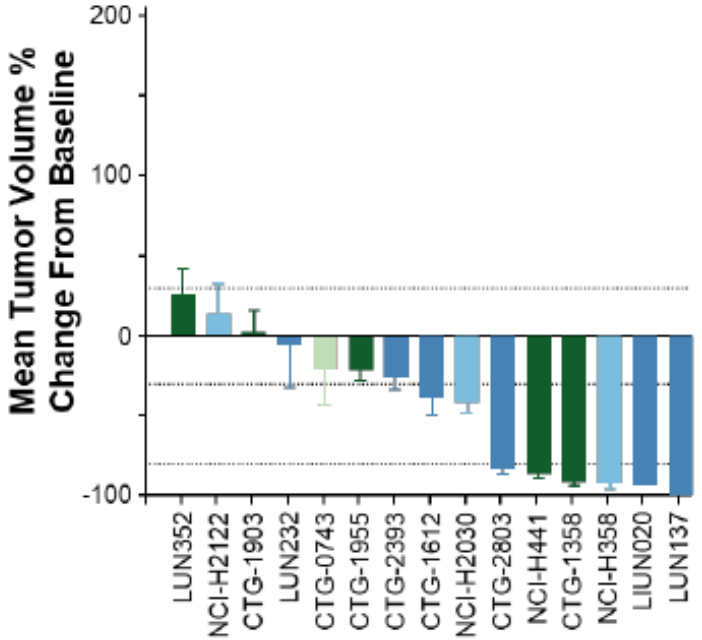




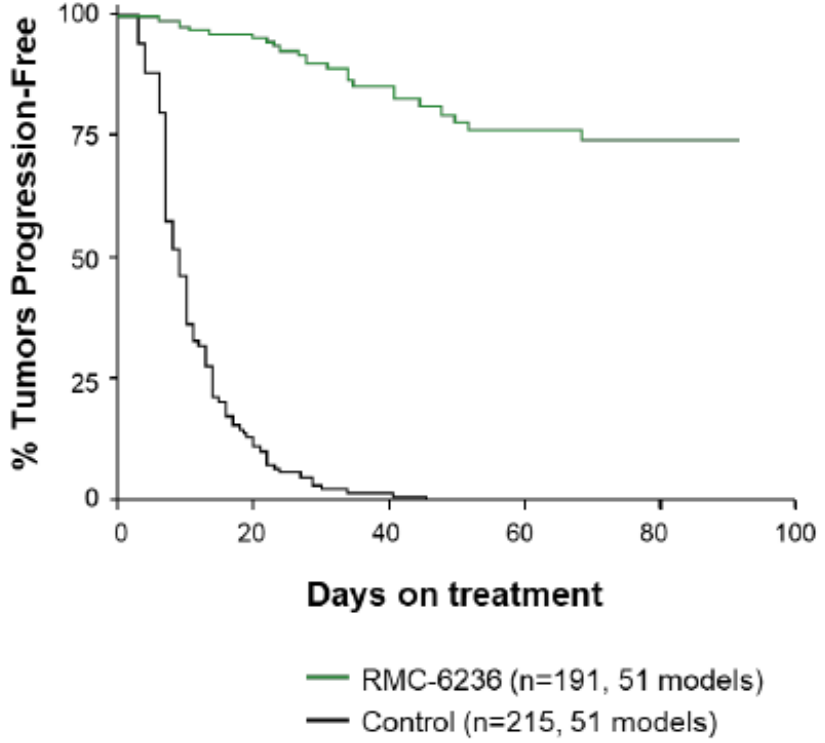
TR-FRET, time-resolved fluorescence with Förster's resonance energy transfer.

RMC-6236 exhibits robust and sustained activity against diverse models of RAS-mutant tumors that can be further enhanced with combinations with mutant-selective inhibitors

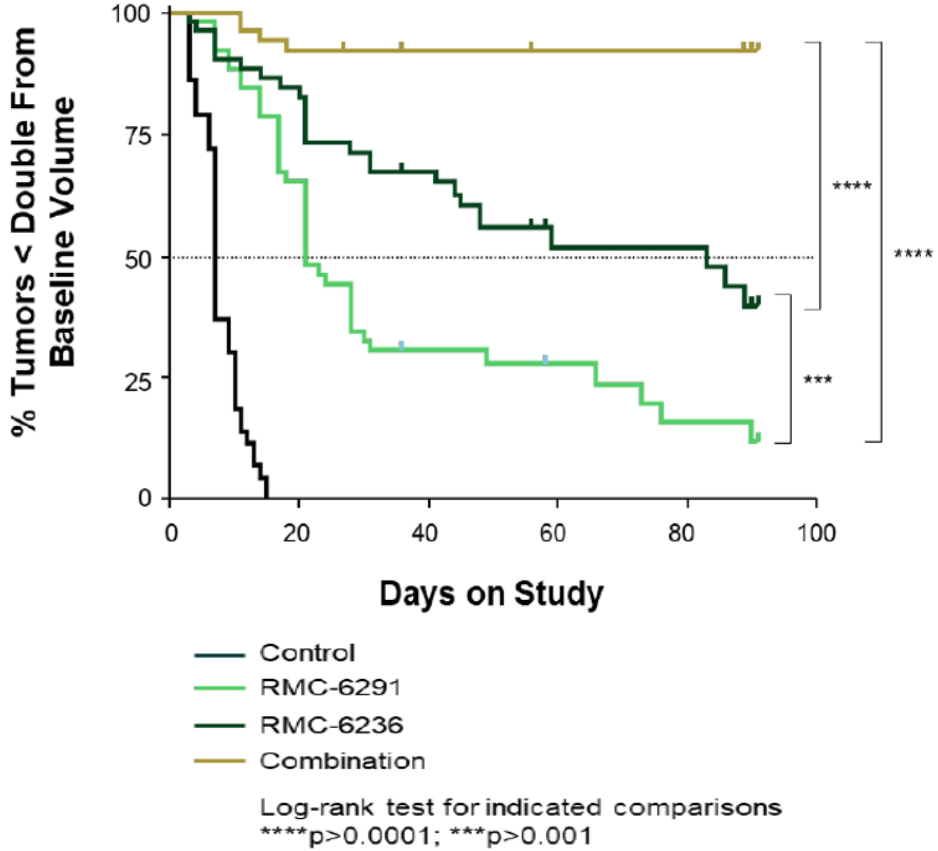
A.



B.



C.



Gustafson WC et al., 2023 AACR/EORTC/NCI Molecular Targets and Cancer Therapeutics meeting

RMC-6236-001 Phase 1 clinical trial design

Key Eligibility Criteria

- Advanced solid tumors with $KRAS^{G12X}$ mutations (currently excluding $KRAS^{G12C}$)
- Received prior standard therapy appropriate for tumor type and stage
- ECOG PS 0–1
- No active brain metastases

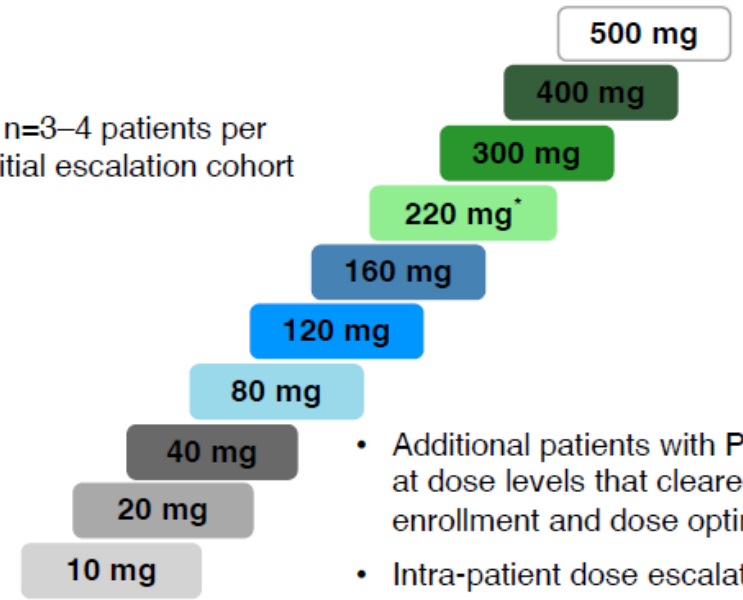
Key Endpoints

- Safety and tolerability
- Pharmacokinetics
- Anti-tumor activity

Dose Escalation

RMC-6236 administered orally QD, 21-day treatment cycle

n=3–4 patients per initial escalation cohort



- Additional patients with PDAC or NSCLC were enrolled at dose levels that cleared DLT evaluation (backfill enrollment and dose optimization)
- Intra-patient dose escalation to a dose level that has cleared DLT evaluation permitted

Dose Expansion / Optimization

Dose Level (mg)	# Patients Treated†
10	3
20	13‡
40	9
80	10
120	19
160	20
200/220	27
300	26
400	4
TOTAL	131

*220 mg cleared DLT evaluation and dose of 200 mg was selected for further expansion/optimization; †Additional patients enrolled for backfill and/or dose optimization; ‡Includes patients treated in preliminary food effect cohort (n=8). $KRAS^{G12X}$ defined as mutation at codon 12 which encodes glycine (G) to X where X= A, D, R, S, or V; PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status; QD, once daily.

Data Extracted 11 Sep 2023.

Spira A et al., 2023 AACR/EORTC/NCI Molecular Targets and Cancer Therapeutics meeting

Treatment-related adverse events

	Total (N=131)				
Maximum severity of TRAEs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**
TRAEs occurring in ≥10% of patients, n (%)					
Rash*	57 (44)	29 (22)	6 (5)	0	92 (70)
Nausea	41 (31)	14 (11)	0	0	55 (42)
Diarrhea	32 (24)	9 (7)	1 (1)	0	42 (32)
Vomiting	27 (21)	9 (7)	0	0	36 (28)
Stomatitis	10 (8)	9 (7)	2 (2)	0	21 (16)
Fatigue	12 (9)	4 (3)	0	0	16 (12)
Other select TRAEs, n (%)					
ALT elevation	6 (5)	1 (1)	1 (1)‡	0	8 (6)
AST elevation	6 (5)	0	1 (1)‡	0	7 (5)
Electrocardiogram QT prolonged	1 (1)	0	0	0	1 (1)
TRAEs leading to dose reduction†, n (%)	0	9 (7)	2 (2)	0	11 (8)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	1 (1)	1 (1)

- Median duration of treatment at the time of data extraction was 2.27 months (range: 0.2–14).
- One Grade 4 TRAE occurred in a patient with PDAC treated at 80 mg who had a large intestine perforation at the site of an invasive tumor that reduced in size while on treatment (TRAE leading to treatment discontinuation).
- No fatal TRAEs were observed. Two patients discontinued study treatment due to death: one patient with PDAC (120 mg) died due to PD; one patient with NSCLC (200 mg) died due to unknown cause reported as unrelated to RMC-6236.

‡ Post-data extraction, the Grade 3 ALT and AST elevations were associated with biliary obstruction and reported as unrelated to RMC-6236.

*Includes preferred terms of dermatitis acneiform, rash maculopapular, rash, rash pustular, dermatitis psoriasiform, erythema, rash erythematous; multiple types of rash may have occurred in the same patient; †The most common TRAE leading to dose reduction was rash (acneiform or maculopapular); there were no reductions at doses ≤80 mg. AE, adverse event; ALT, alanine transaminase; AST, aspartate transferase; PD, progressive disease; TRAEs, treatment-related adverse events.

Spira A et al., 2023 AACR/EORTC/NCI Molecular Targets and Cancer Therapeutics meeting

Treatment-related skin toxicity

Summary of Treatment-Related Rash by Dose Level

	20 mg* (n=13)	40 mg* (n=9)	80 mg (n=10)	120 mg (n=19)	160 mg (n=20)	200/220 mg (n=27)	300 mg (n=26)	400 mg (n=4)
Rash†, n (%)	4 (31)	6 (67)	7 (70)	15 (79)	20 (100)	21 (78)	15 (58)	4 (100)
Dermatitis acneiform	3 (23)	4 (44)	5 (50)	11 (58)	19 (95)	16 (59)	10 (39)	4 (100)
Rash maculopapular	1 (8)	1 (11)	3 (30)	4 (21)	1 (5)	5 (19)	5 (19)	0
Rash by maximum grade, n (%)								
1	3 (23)	4 (44)	5 (50)	12 (63)	11 (55)	11 (41)	10 (39)	1 (25)
2	1 (8)	2 (22)	2 (20)	2 (11)	8 (40)	7 (26)	5 (19)	2 (50)
3	0	0	0	1 (5)	1 (5)	3 (11)	0	1 (25)
Time to first event in days, median (range)	112 (42–225)	54 (17–136)	15 (8–22)	11 (1–57)	13 (3–22)	9 (2–22)	11 (6–16)	7 (5–11)
Required dose reduction, n (%)	0	0	0	2 (11)	1 (5)	3 (11)	0	1 (25)

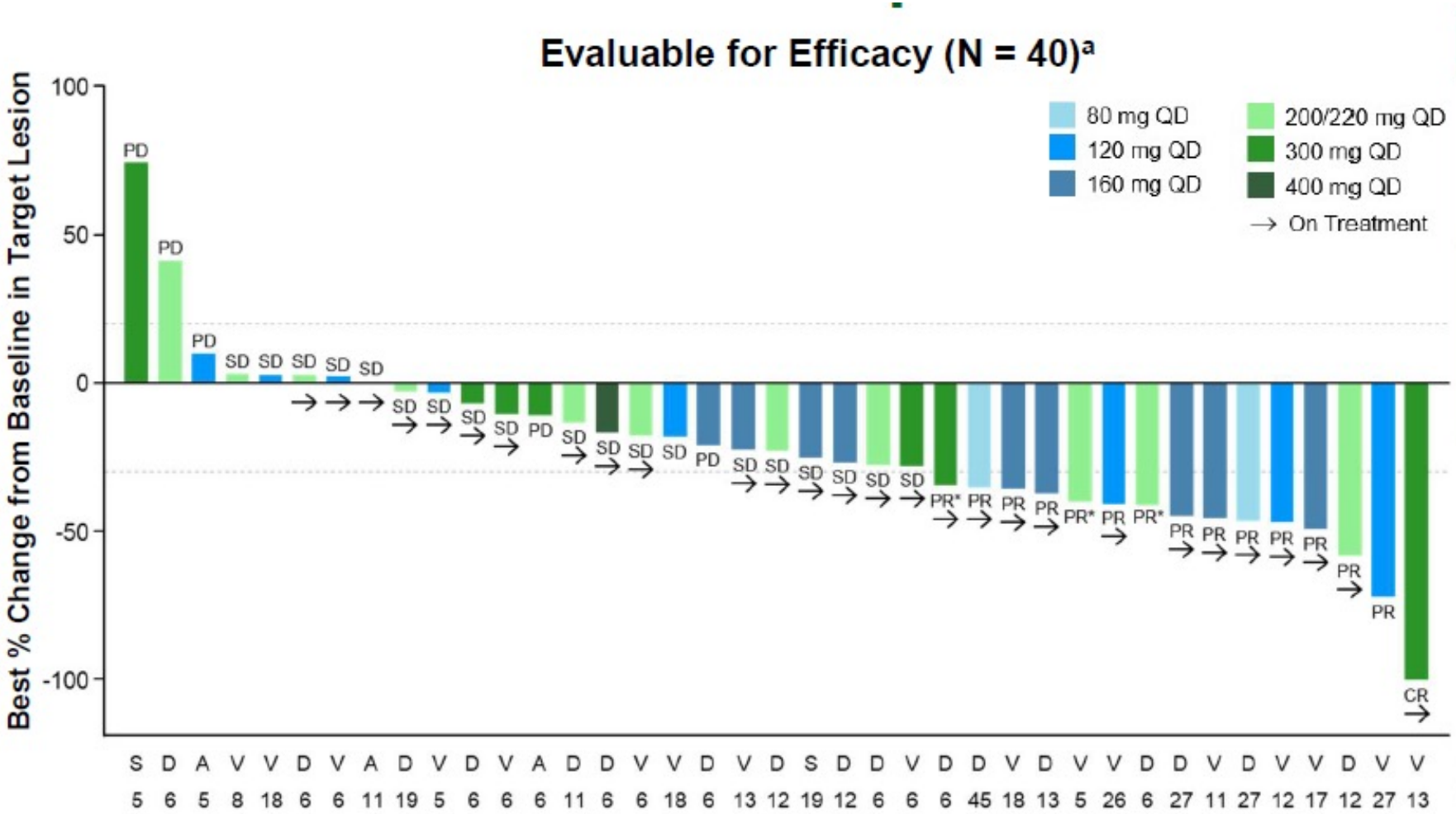
- The presentation of acneiform or maculopapular rash is consistent with on-target activity of RAS pathway inhibitors.
- Rash generally occurred in Cycle 1 or 2 and was primarily Grade 1 or 2 in severity.
- Supportive care interventions included topical antibiotics, topical steroids, and/or oral antibiotics.

No adverse events of rash were reported at 10 mg. *Includes onset after intra-patient dose escalation to 80 mg: 20 mg (n=3); onset 13–31 days at 80 mg; 40 mg (n=3), onset 5–31 days at 80 mg; †Includes preferred terms of dermatitis acneiform, rash maculopapular, rash, rash pustular, dermatitis psoriasiform, erythema, rash erythematous; multiple types of rash may have occurred in the same patient.

Data Extracted 11 Sep 2023.

Spira A et al., 2023 AACR/EORTC/NCI Molecular Targets and Cancer Therapeutics meeting

RMC-6236 efficacy in *KRAS*^{G12X} NSCLC : Best Response



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)

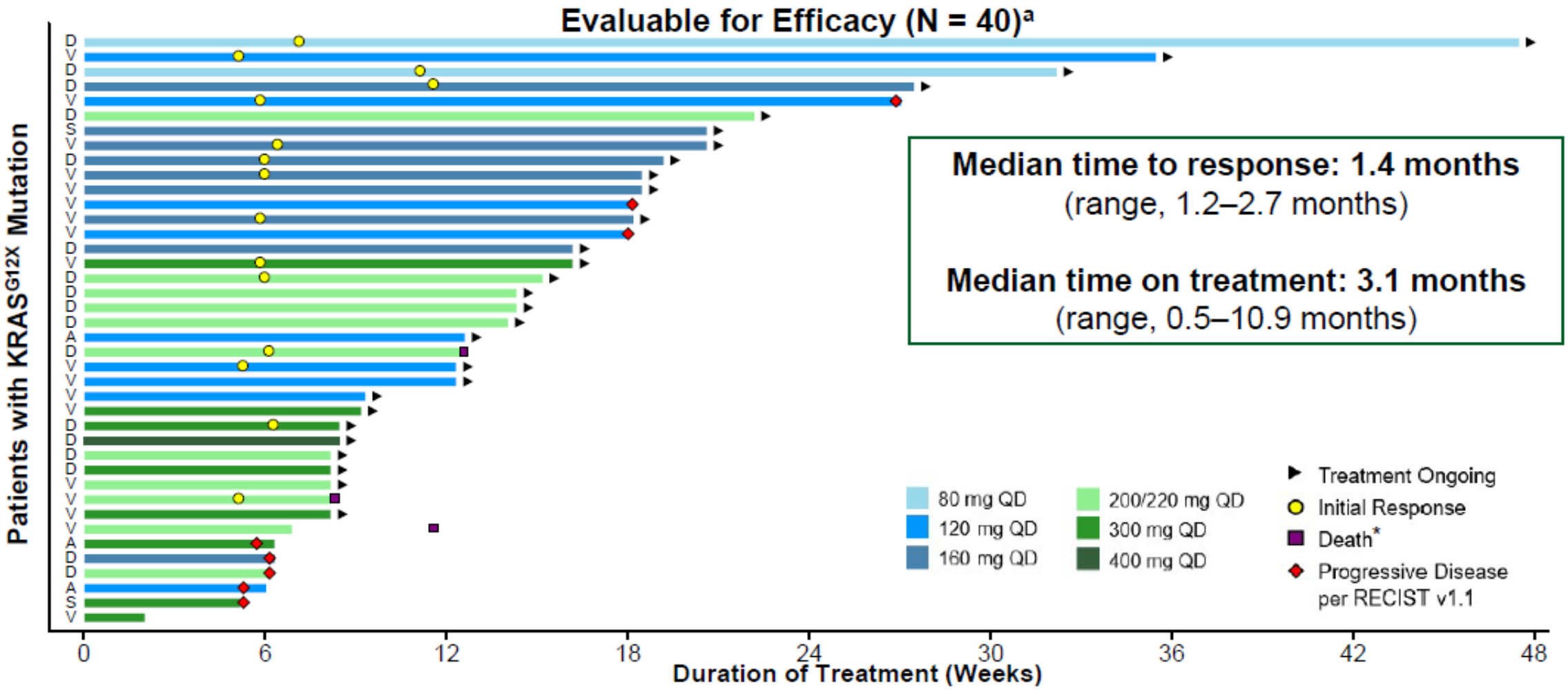
*Unconfirmed PR per RECIST 1.1.

[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.

Arbour KC et al., 2023 ESMO Annual Meeting

RMC-6236 efficacy in *KRAS*^{G12X} NSCLC : duration of treatment and response

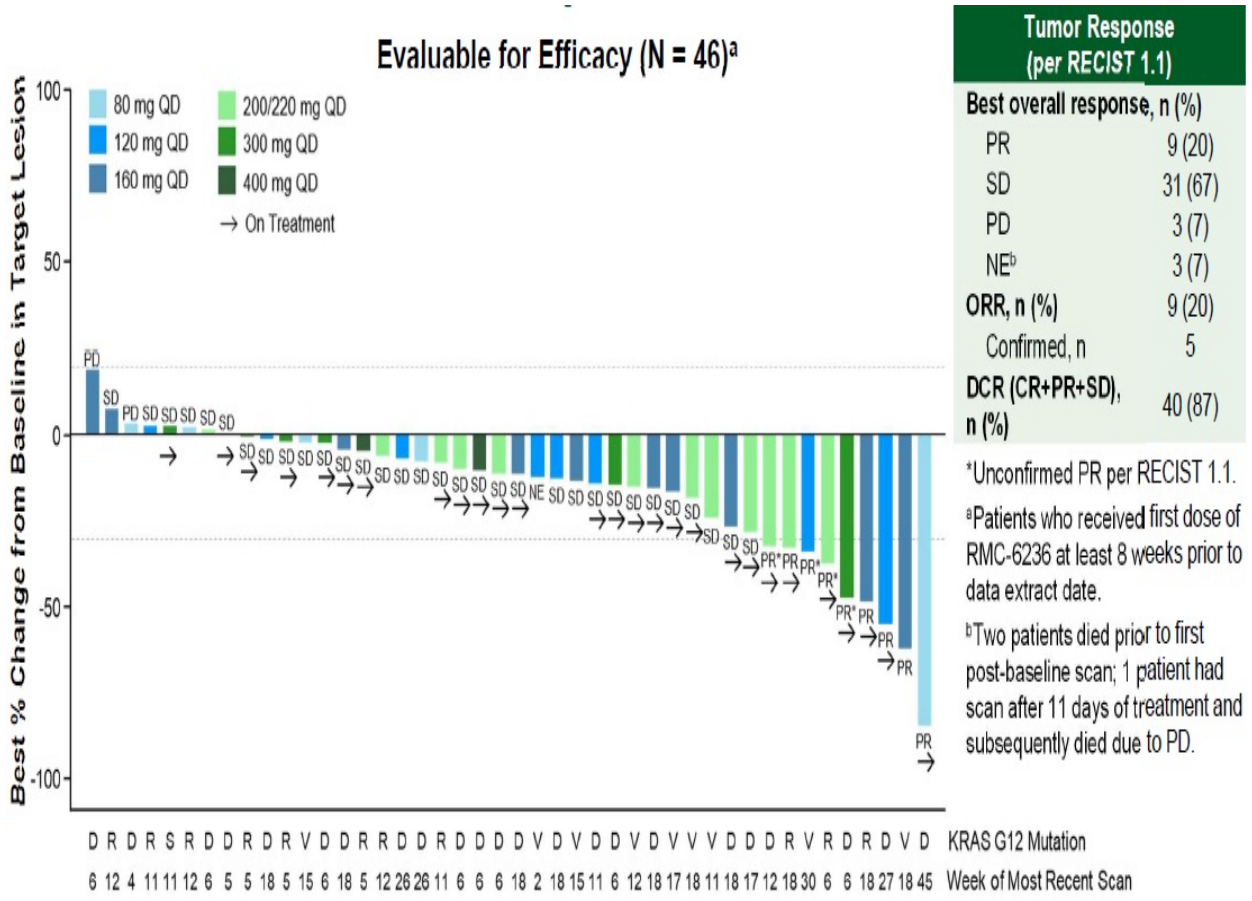


[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.
*Death due to PD (n=1), Death due to unrelated AE (n=1), Death due to unknown cause reported as unrelated to RMC-6236 (n=1).

Arbour KC et al., 2023 ESMO Annual Meeting

RMC-6236 efficacy in *KRAS*^{G12X} PDAC : best response and treatment duration

A.



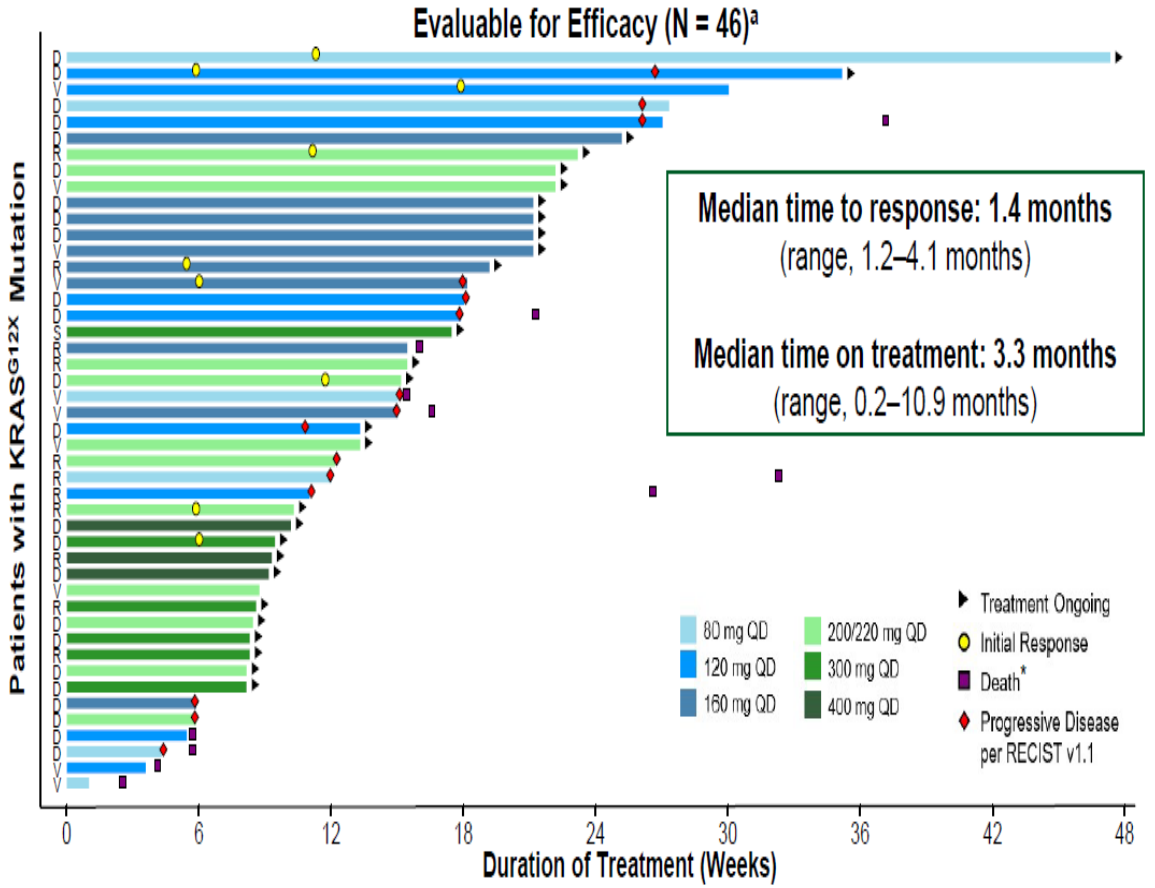
Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
PR	9 (20)
SD	31 (67)
PD	3 (7)
NE[b]	3 (7)
ORR, n (%)	9 (20)
Confirmed, n	5
DCR (CR+PR+SD), n (%)	40 (87)

*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]Two patients died prior to first post-baseline scan; 1 patient had scan after 11 days of treatment and subsequently died due to PD.

B.



[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date. *Death due to PD (n = 9), Death due to unrelated AE (n = 2).

Arbour KC et al., 2023 ESMO Annual Meeting

Pan-(K)RAS inhibitor clinical development strategies

Pan- (K) RAS (RAS^{MULTI}) inhibitors

- Monotherapy for (K)RAS – addicted tumors.
- In combination with mutant selective inhibitors (covalent or non covalent)
- In combination with SOC therapies (chemotherapy, immunotherapy)
- In combination with novel therapies that target adaptive/DTP states
- Potential as tumor agnostic therapy

Unanswered questions

- Efficacy of monotherapy vs SOC
- Pan-(K)RAS monotherapy or combos with mutant-selective inhibitors
- Safety/efficacy of combo with chemo/immunotherapy
- Mechanisms of primary, adaptive or acquired resistance, DTP programs

pan-RAS or pan-KRAS?

Conclusions

- Pan-(K)RAS inhibitors hold significant promise to improve outcomes for patients with (K)RAS-driven tumors by:

➢ Targeting a larger patient population with different oncogenic *KRAS* mutations (for pan-KRAS inhibitors) or *KRAS/NRAS/HRAS* mutations (for pan-RAS inhibitors) across diverse tumor types.

➢ Preventing/delaying the emergence of secondary alterations in *KRAS* (for pan-KRASi) or *KRAS/NRAS/HRAS* (for pan-RASi) that drive acquired resistance to mutant-selective inhibitors.

➢ Preventing/delaying adaptive pathway reactivation/resistance through WT KRAS (for pan-RASi) or WT KRAS/NRAS/HRAS (for pan-RASi)

- Sparing RAS signaling in normal cells may provide an improved therapeutic window but adaptive pathway reactivation via NRAS and HRAS may curtail clinical efficacy. The relative merits of KRAS-selective versus pan-RAS inhibitor-based therapeutic strategies remains to be determined.

- The activity of the off-state selective pan-KRASi BI-2865 to inhibit oncogenic signaling across a broad range of *KRAS* mutant isoforms suggests that most of them undergo nucleotide cycling.

- The relative merits of ON versus OFF state selective (K)RAS inhibitors in patients remain to be defined.

Conclusions

- RMC-6236 is a first-in-class oral, clinical-stage, non-covalent, tricomplex ON-state-selective inhibitor of multiple RAS isoforms (RAS^{MULTI}). RMC-6236 binds to cyclophilin A to create a neomorphic interface that binds to GTP-bound RAS isoforms and sterically inhibits interactions with downstream effectors.
- Recently reported data from the dose escalation component of the Phase 1 RMC-6236 trial supports the safety and feasibility of RMC-6236 in doses that induce tumor regressions. Rash is the most common TRAE and in most cases is G1/2 and manageable with standard supportive care measures. Absence of significant ALT/AST rise and QTc prolongation may support feasibility of combos with IO and/or chemo.
- Preliminary antitumor activity of RMC-6236 monotherapy is encouraging, with 38% ORR in $KRAS^{G12X}$ NSCLC (20% ORR in KRASG12X PDAC) and DCR 85%-87%.
- In preclinical models, combinations of RMC-6291 with RMC-6236 improved the durability of responses in $KRAS^{G12C}$ NSCLC models and exhibited activity in RMC-6291 resistant models.
- Several additional pan-KRAS inhibitors are undergoing early phase clinical development.
- Little is currently known regarding mechanisms of adaptation/resistance/persistence with pan-KRAS or pan-RAS inhibitors.