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KRAS Inhibition in Advanced NSCLC

John V. Heymach, M.D., Ph.D.
Chair, Dept. of Thoracic/Head and Neck Medical Oncology
David Bruton, Jr. Chair in Cancer Research

Atlanta Lung Cancer Symposium 2021
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DISCLOSURES

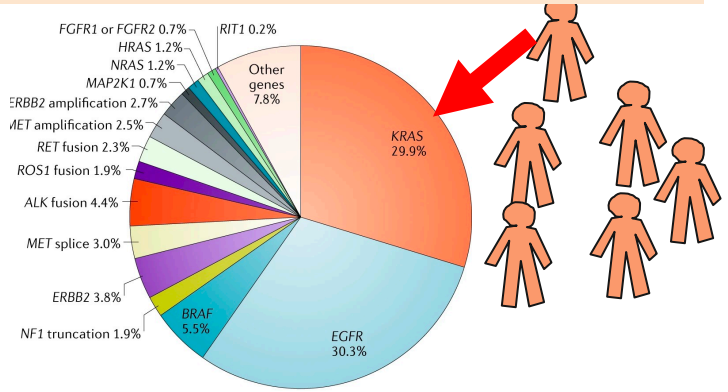
Advisory Committees – AbbVie, Amgen, AnHeart Therapeutics, Arrivent, AstraZeneca, BioNTech AG, BI, BMS, DAVA Oncology, Eli Lily & Co, EMD Serono, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Mirati Therapeutics, Moffitt Cancer Center, ModeX, Novartis Pharmaceuticals, OncoCyte, Pfizer, Sanofi, Spectrum Pharmaceuticals, Takeda

Research Support – AstraZeneca, Boehringer-Ingelheim, Mirati, Bristol-Myer Squibb and Takeda

Licensing/Royalties – Spectrum

KRAS mutant NSCLC: subgroups based on alleles and co-mutations

KRAS alleles (G12C, G12V, etc)



KRAS G12C 12%

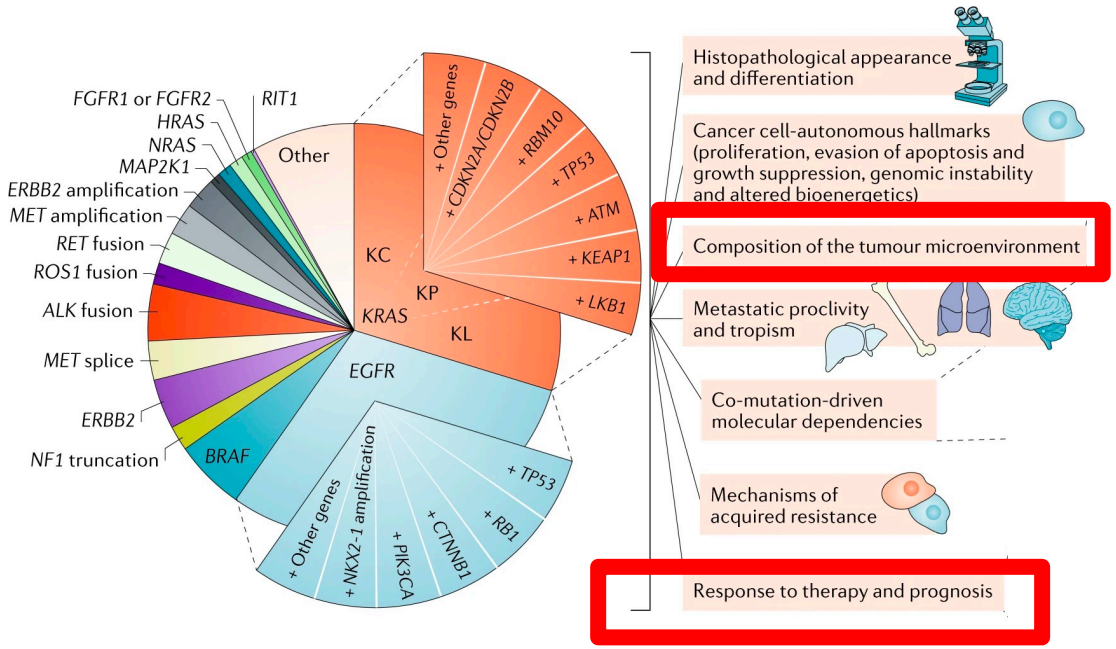
KRAS G12V 6%

KRAS G12D 3%

other

KRAS co-mutations (STK11, p53, etc)

Co-occurring alterations in tumor suppressors (STK11/LKB1, KEAP1, etc) impact biology and response to treatment



Skoulidis and Heymach, Nat Rev Cancer 2019; Skoulidis et al, Cancer Discovery 2018

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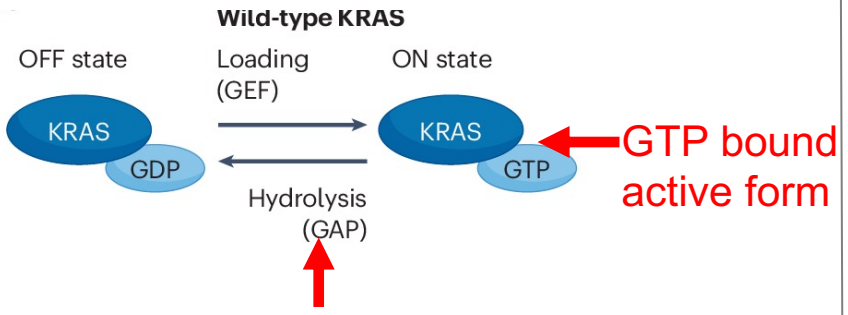
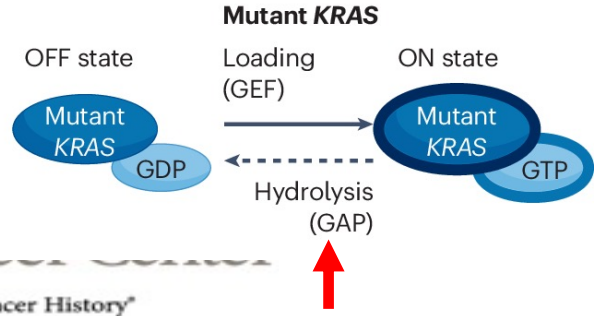
KRAS mechanism of activation and signaling

GTP hydrolysis determines on/off state: GTP on, GDP off

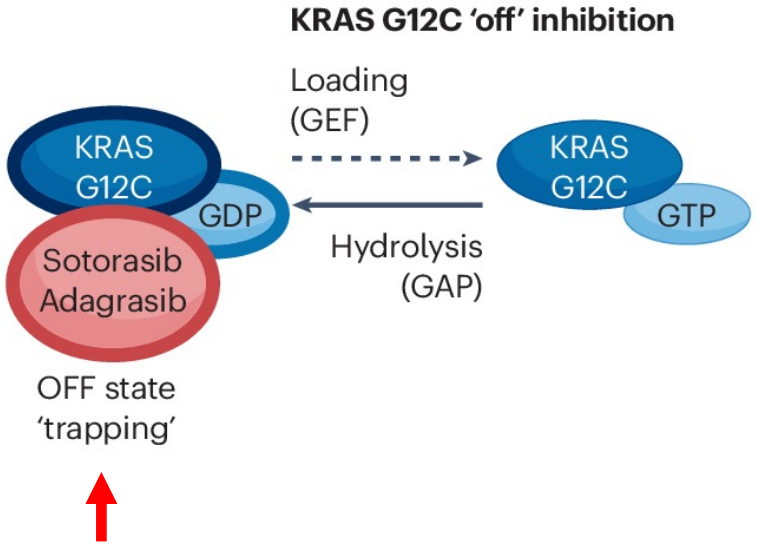


GEFs (e.g. SOS1) vs GAPs shift balance

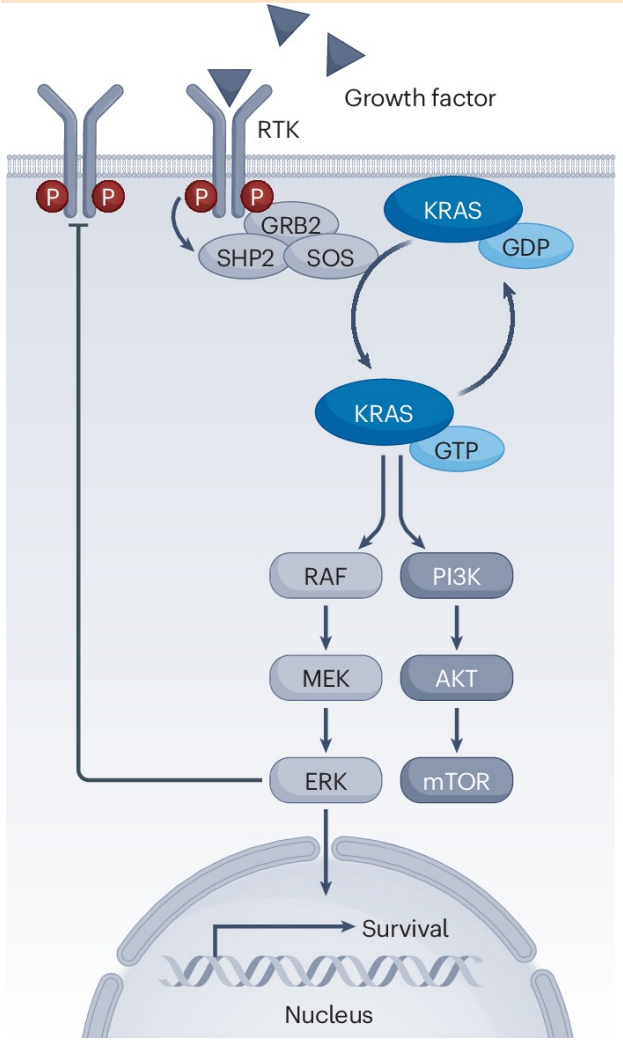
KRAS mutations shift balance (usually less hydrolysis or GAP activity)



KRAS G12C inhibitors lock KRAS in GDP-bound "off" state

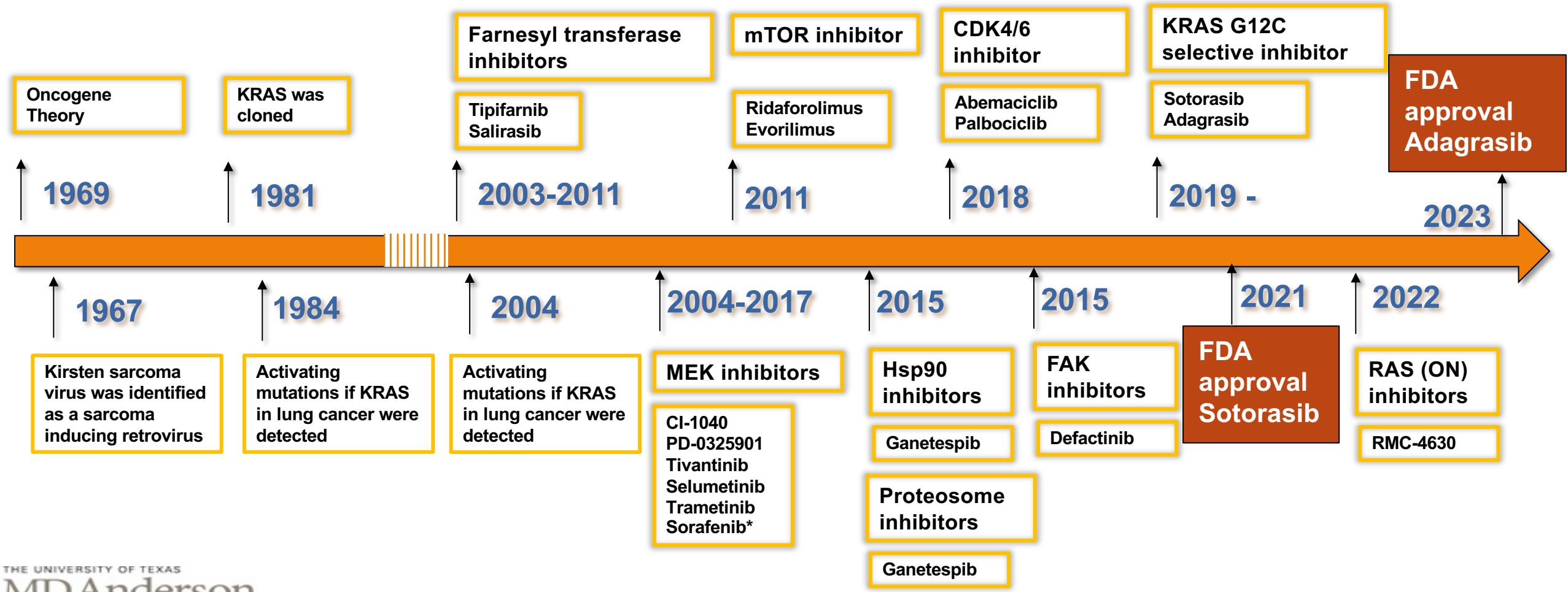


RTK signaling via wt KRAS



Singhal et al, Nat Med 2024

Historical Overview of KRAS Targeted Therapies



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Addition of MEK inhibitor selumetinib to docetaxel does not improve outcomes in 2L KRAS mutant NSCLC: the SELECT-1 study

2L KRAS mutant NSCLC
N=510 patients
Primary endpt: PFS

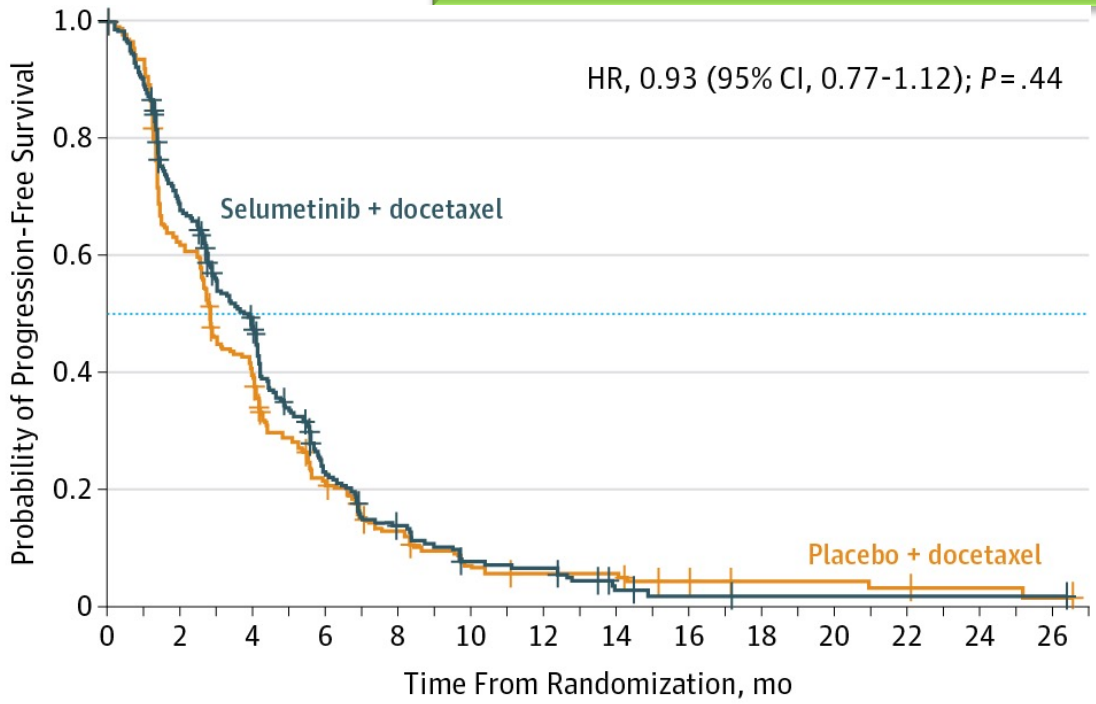
R

Docetaxel + selumetinib

Docetaxel + placebo

mPFS
Doc+sel: 3.9m
Doc+placebo: 2.8m

PFS HR: 0.93
P=.44



No. at risk

Selumetinib + docetaxel	254	164	109	48	27	15	13	4	2	1	1	1	1	1
Placebo + docetaxel	256	154	97	50	28	13	10	10	6	4	4	3	2	1

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Janne et al JAMA 2017

Direct targeting of KRAS G12C

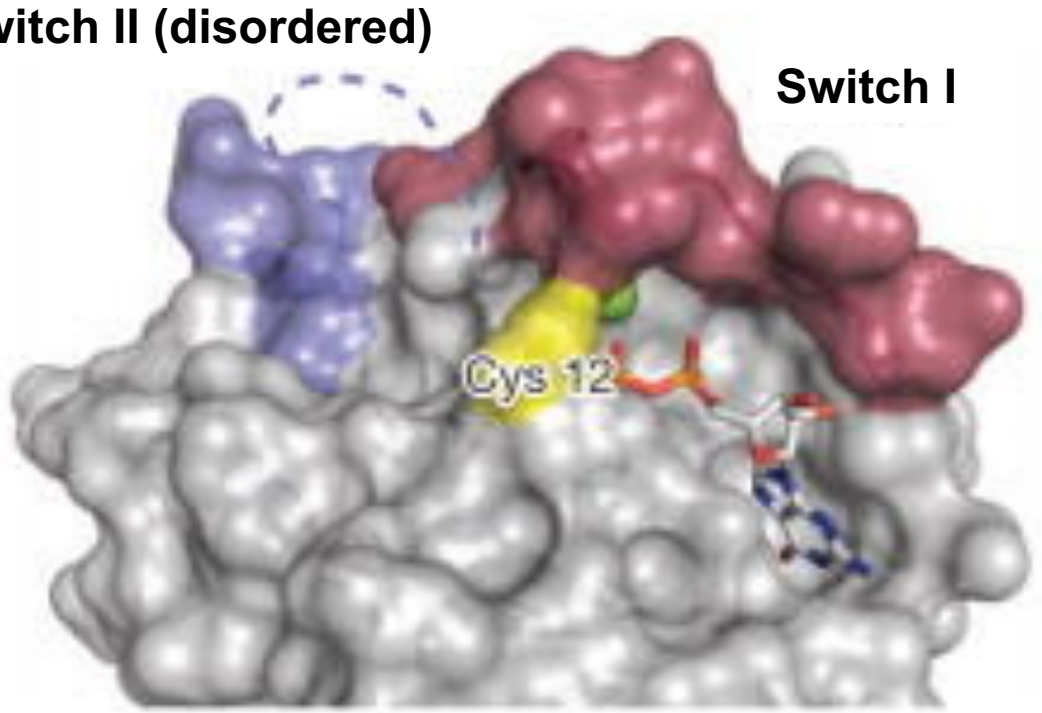
nature

Published: 20 November 2013

K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions

Jonathan M. Ostrem, Ulf Peters, Martin L. Sos, James A. Wells & Kevan M. Shoka

Ostrem, J et al., Nature 2013



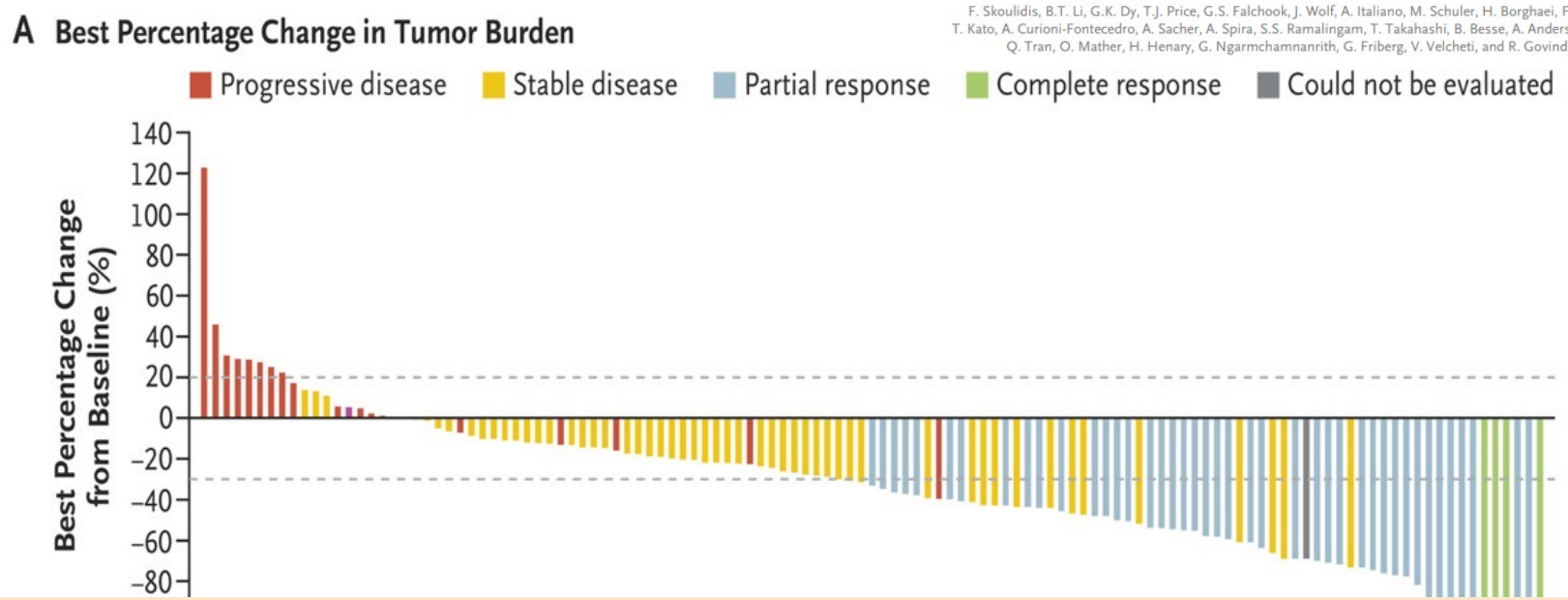
Small molecules that irreversibly bind to K-RAS G12C in the GDP state

Sotorasib therapy led to a durable clinical benefit in KRAS G12C mutant NSCLC (Codebreak 100)

ORR 37.1%
mPFS 6.8m; mDOR 11.1m
mOS 12.5m

Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. Govindan



May 28, 2021: FDA granted accelerated approval for sotorasib for advanced NSCLC patients with KRAS G12C mutation who received one prior systemic therapy.

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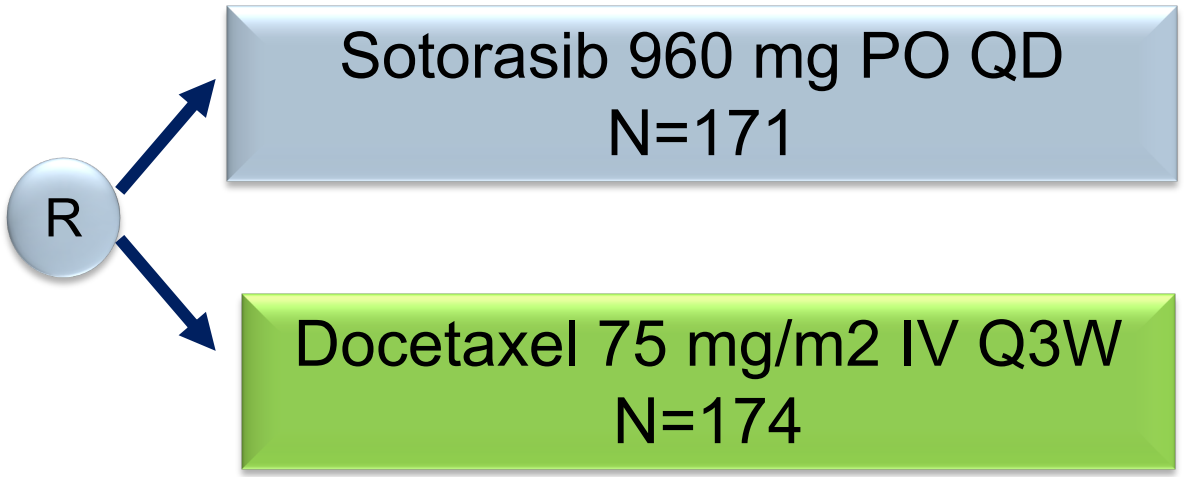
Skoulidis NEJM 2021

CodeBreaK 200: A randomized phase III study of sotorasib vs docetaxel in 2L KRAS G12C NSCLC

N=345
KRAS G12C mutant NSCLC
>1 prior systemic therapy including platinum and CPI
-PS 0-1; no active BM

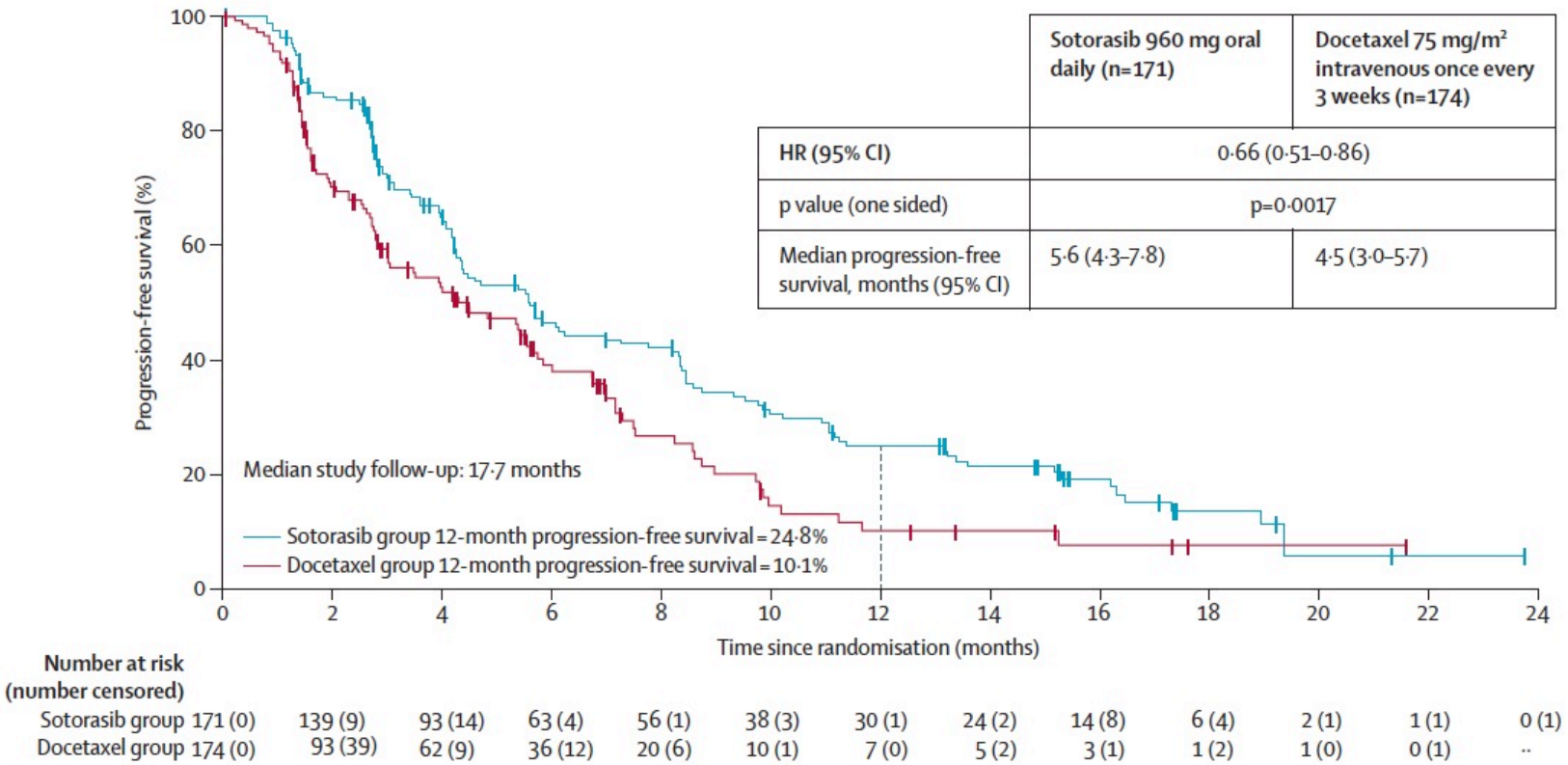
Primary Endpoint: PFS by BICR
Secondary: OS, ORR, DoR, TTR, DCR, safety, tolerability, PRO



Protocol amended to reduce enrollment to 330 and allow crossover from docetaxel to sotorsib

Johnson ESMO 2022 LBA10

CodeBreaK 200: sotorasib improves PFS vs docetaxel in 2L KRAS G12C mutant NSCLC



	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)

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)	..

	Soto	Doc
mPFS (mo)	5.6	4.5

PFS HR 0.66 (p-0.0017)

Bottom line: Met its primary endpoint (PFS; P=.002) although benefits modest (1.1 m)

de Langen et al, Lancet 2023

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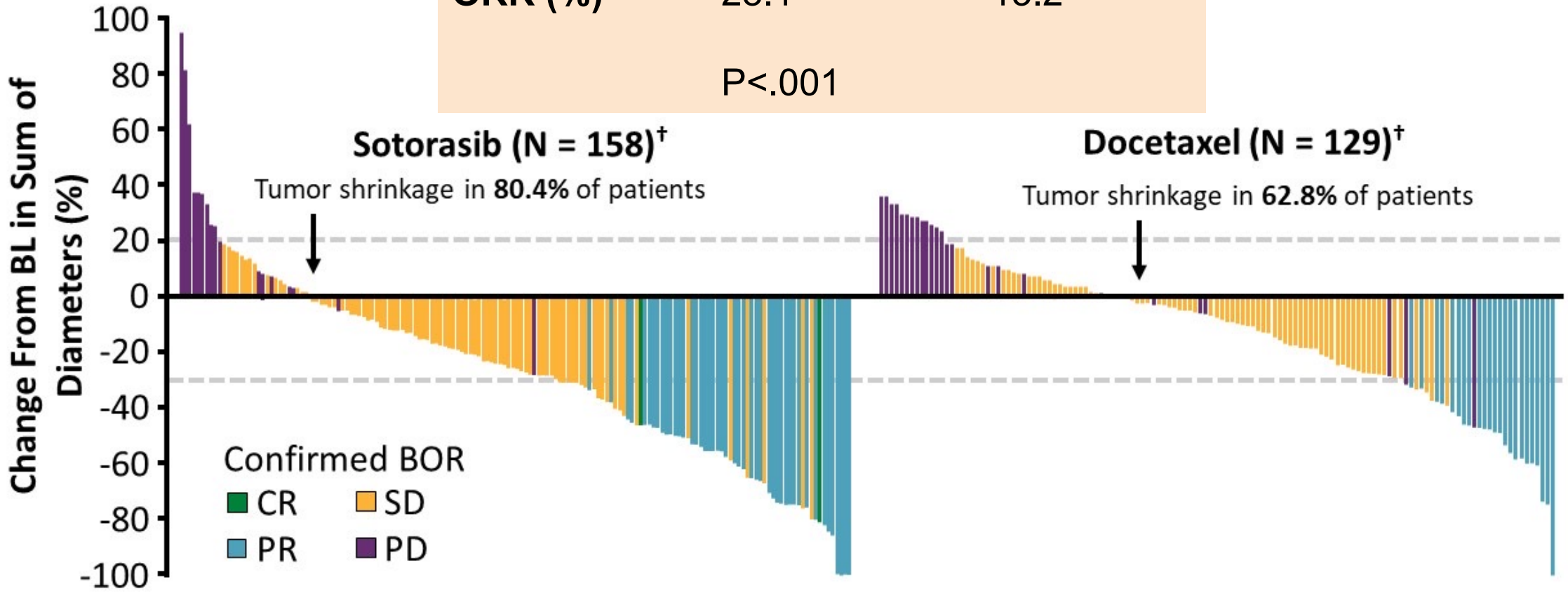
CodeBreaK 200: Significantly higher ORR for sotorasib vs docetaxel

	sotorasib	docetaxel
ORR (%)	28.1	13.2
	P<.001	



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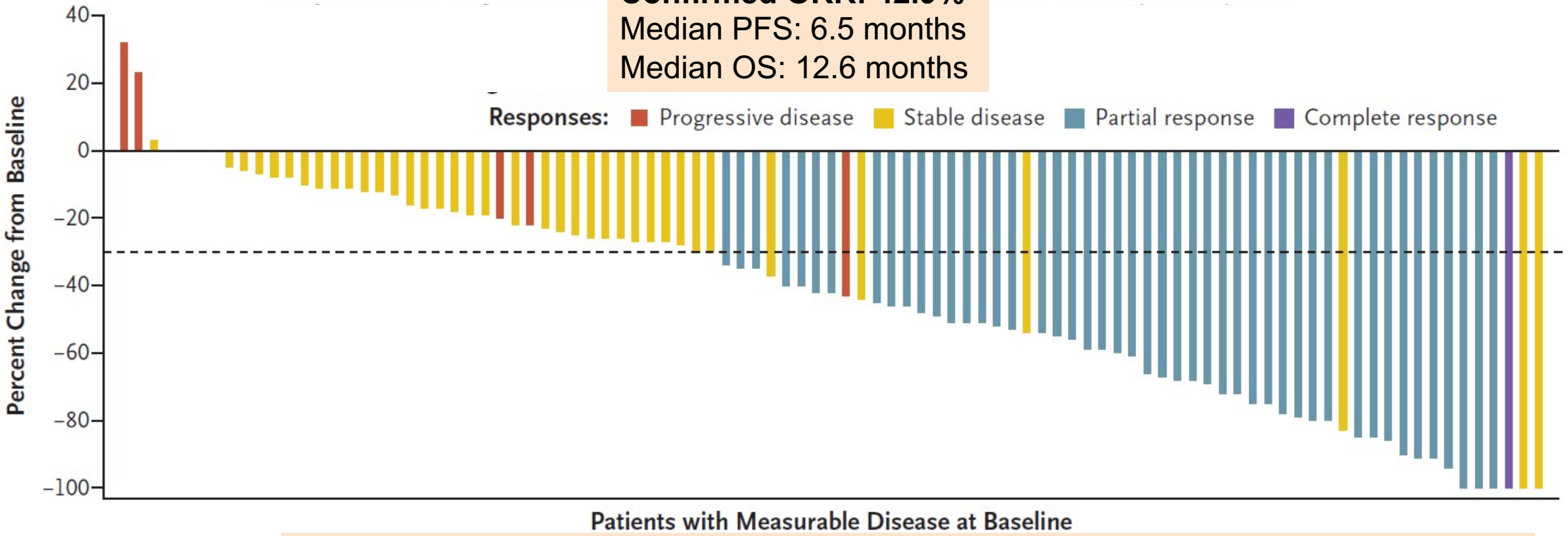
Johnson ESMO 2022 LBA10

Adagrasib in KRAS^{G12C} mutant NSCLC: Efficacy

Confirmed ORR: 42.9%
Median PFS: 6.5 months
Median OS: 12.6 months



December 12, 2022: FDA granted accelerated approval for adagrasib for advanced NSCLC patients with KRAS G12C mutation who received one prior systemic therapy.

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Jänne et. al., NEJM, July 14, 2022

Adagrasib in Non–Small-Cell Lung Cancer Harboring a KRAS^{G12C} Mutation: adverse events

Event	Any Grade	Grade ≥3
	no. of patients (%)	
Any adverse event	116 (100)	95 (81.9)
Adverse event leading to dose reduction or interruption	96 (82.8)	—
Adverse event leading to discontinuation of therapy	18 (15.5)	—
Adverse event of any grade that occurred in >10% of patients or that was grade ≥3 in >1 patient†		
Diarrhea	82 (70.7)	1 (0.9)
Nausea	81 (69.8)	5 (4.3)
Fatigue	69 (59.5)	8 (6.9)
Vomiting	66 (56.9)	1 (0.9)

57-71% rates of GI toxicity (mainly Grade 1 /2) at approved doses but also significant CNS activity reported and feasibility of PD1 inhibitor combos

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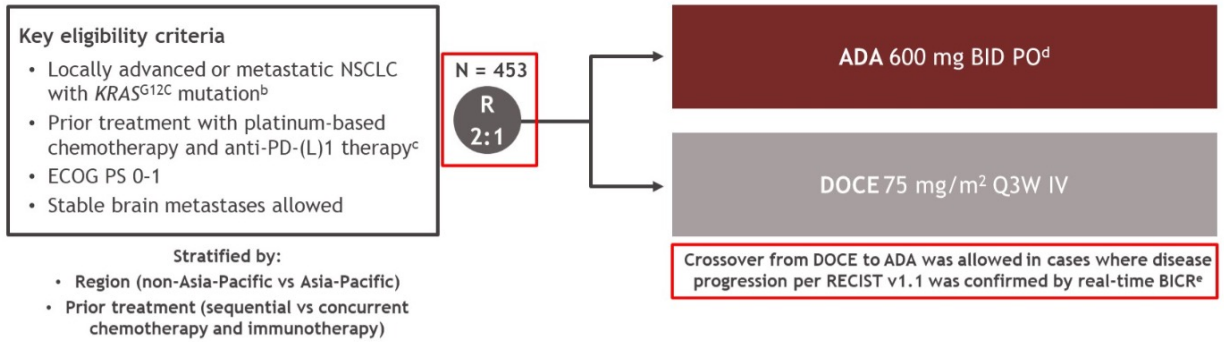
Jänne et. al., NEJM, 2022

KRYSTAL-12: RP3 of adagrasib vs docetaxel in previously treated KRAS G12C mutant NSCLC

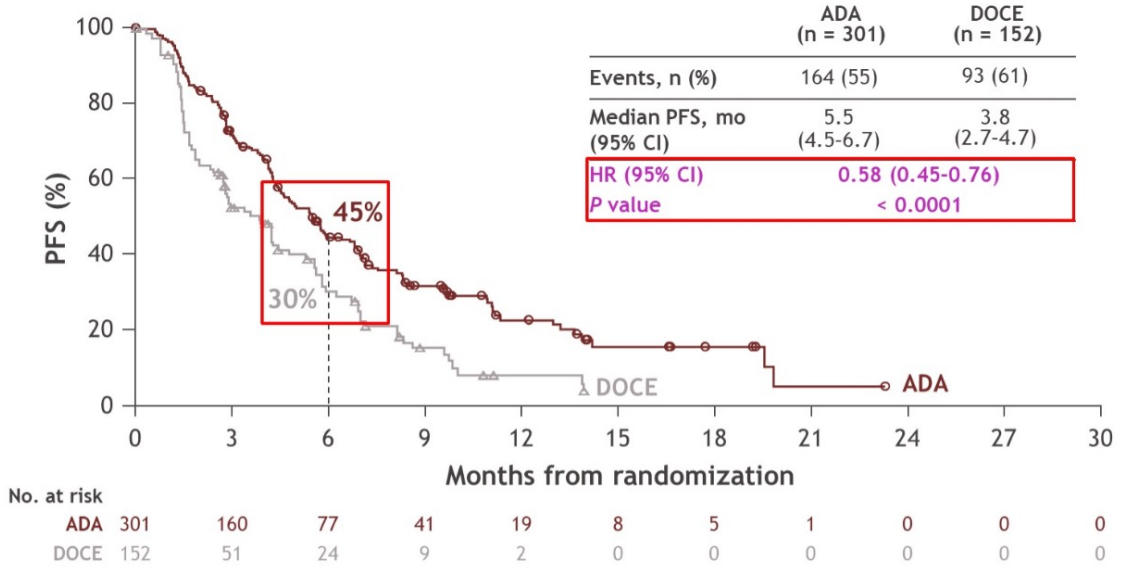
	Ada	Doc
mPFS (mo)	5.5	3.8

PFS HR 0.58 (p<0.001)

KRYSTAL-12 RP3 design



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



	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	

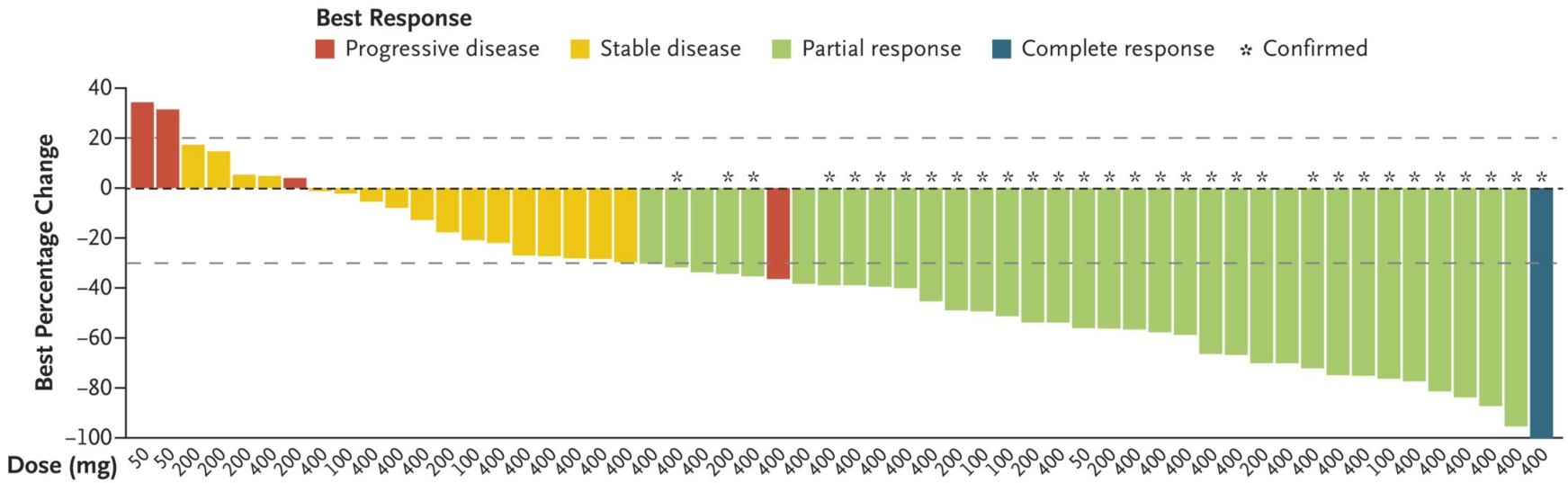
Median follow-up: 7.2 months.
[a]Time from randomization to the date of disease progression per BICR or death due to any cause, whichever occurs first. For patients who started a subsequent anticancer therapy prior to disease progression or death, PFS was censored at the date of the last tumor assessment prior to the start of the new therapy.

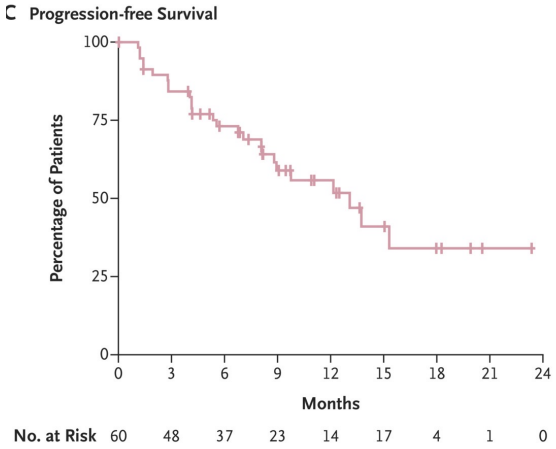
Bottom line: Met its primary endpoint; slightly larger improvement in mPFS (1.7m) than CB200

Mok et al, ASCO 2024

Divarasib in KRAS^{G12C} mutant NSCLC: Efficacy

N=60 with 2L+ NSCLC (66% with 1-2 prior tx)
Confirmed ORR: 53.4% (CI, 39.9-66.7)
median PFS: 13.1 months (CI, 8.8-NR)





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Sacher et. al., NEJM, 2023

Divarasib in KRAS^{G12C} mutant tumors: TRAEs

Table 2. Treatment-Related Adverse Events in 10% or More of Patients.

Treatment-Related Adverse Event	NSCLC (N=60)		Colorectal Cancer (N=55)		All Patients (N=137)	
	Any Grade	Grade 3–5*	Any Grade	Grade 3–5*	Any Grade	Grade 3–5*
	number of patients (percent)					
At least one event	56 (93)	11 (18)	53 (96)	4 (7)	127 (93)	16 (12)
Nausea	47 (78)	1 (2)	43 (78)	0	101 (74)	1 (1)
Diarrhea	36 (60)	2 (3)	38 (69)	3 (5.5)	84 (61)	5 (4)
Vomiting	38 (63)	0	32 (58)	0	80 (58)	1 (1)
Fatigue	16 (27)	1 (2)	11 (20)	0	30 (22)	1 (1)
Decreased appetite	11 (18)	0	6 (11)	0	18 (13)	0
Aspartate aminotransferase level increased	9 (15)	4 (7)	3 (5.5)	0	14 (10)	4 (3)

* No grade 5 treatment-related adverse events (death) were reported.

58-74% with nausea, vomiting, diarrhea (mainly Gr 1 /2)

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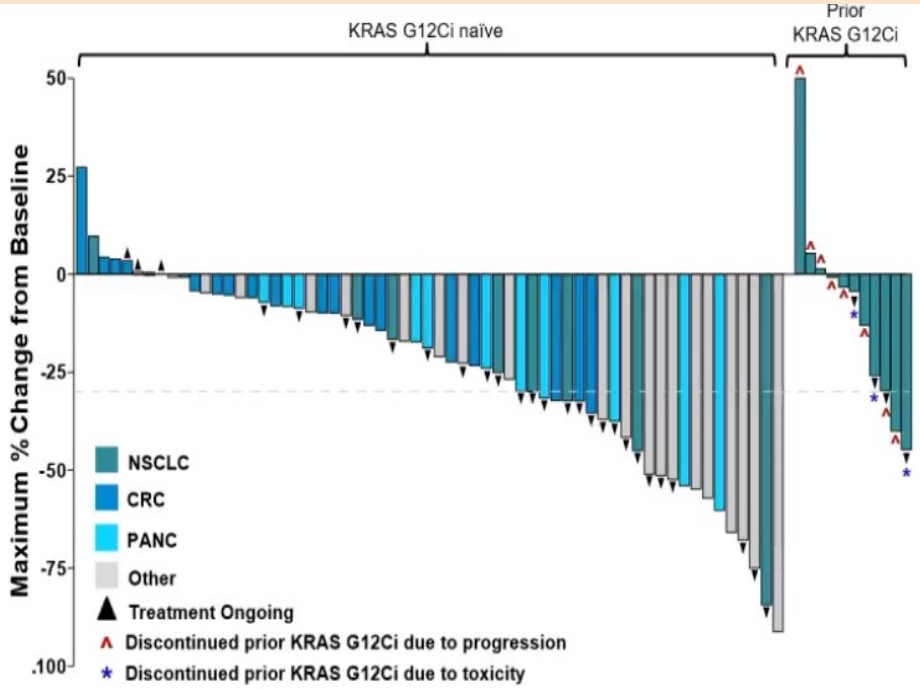
Sacher et. al., NEJM, 2023

LOXO-RAS-20001: LY3537982 (Olomorasib)

NSCLC ORR: 38% (G12Ci naïve)



Efficacy Evaluable Patients[a] (n = 75)	ORR[b]	DCR[b]
NSCLC (G12Ci naïve)	38% (3/8)	88% (7/8)
NSCLC (prior G12Ci)	7% (1/14)	64% (9/14)
Colorectal	10% (2/20)	90% (18/20)
Pancreatic	42% (5/12)	92% (11/12)
Other[c]	52% (11/21)	95% (20/21)

Treatment-emergent- and -related AEs

All Doses and Patients (50 mg BID – 200 mg BID, N = 84)							
	Treatment-Emergent AEs (>10%), %					Treatment-Related AEs, %	
Adverse Event	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade ≥3
Diarrhea	36%	29%	6%	-	1%[a]	25%	-
Fatigue	17%	14%	2%	-	-	8%	-
Constipation	16%	14%	1%	-	-	5%	-
Nausea	16%	14%	1%	-	-	10%	-
AST increased	12%	10%	1%	1%	-	7%	-

-No DLTs and MTD not reached
-36% diarrhea (mainly Gr1)
-rates of ≥Gr3 toxicities low

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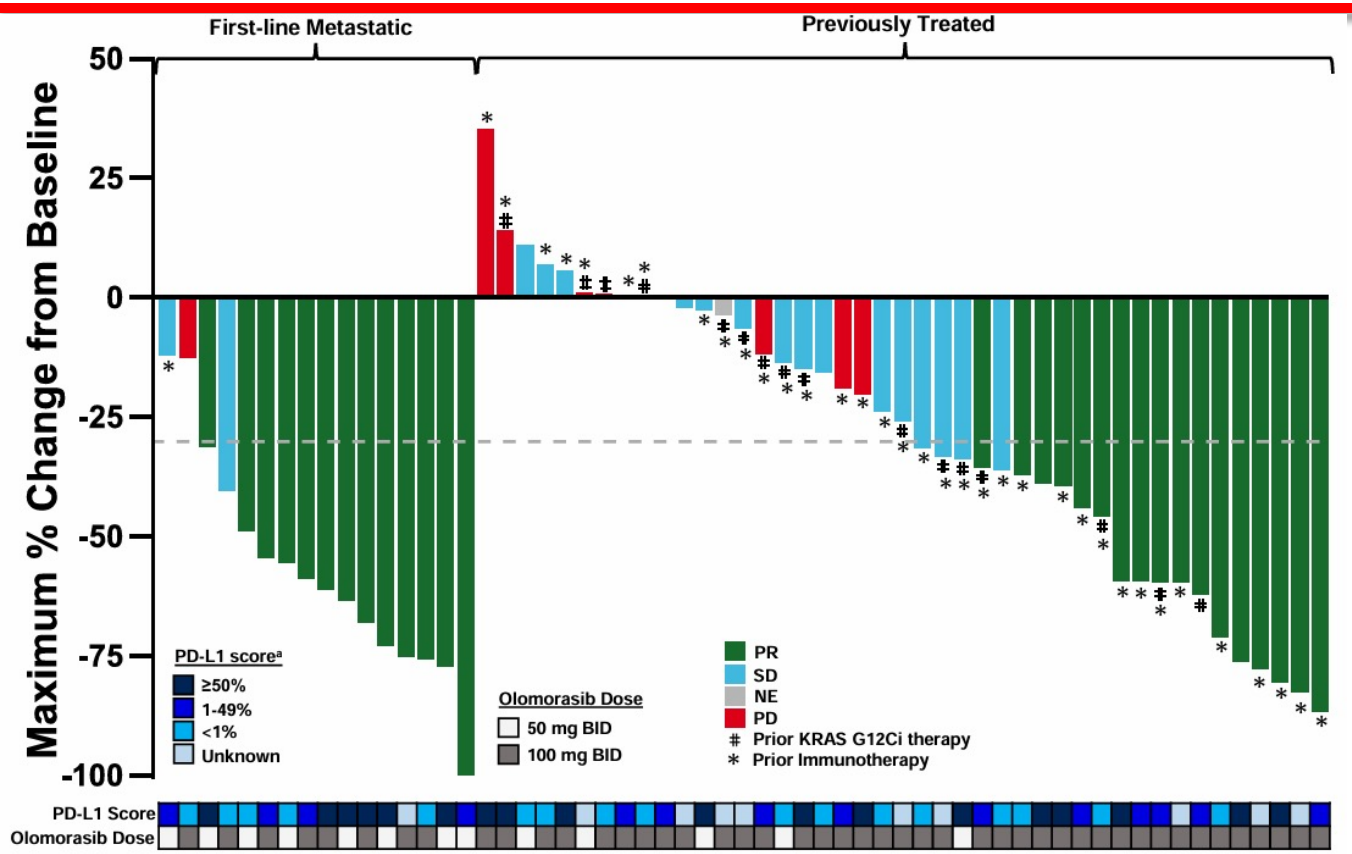
Murciano-Goroff YR et al., AACR Annual Meeting 2023

Combination of olomorasib and pembrolizumab shows promising efficacy for treatment-naïve *KRAS*^{G12C}-mutant NSCLC patients



Efficacy Evaluable Patients[b]	First-line Metastatic (N=17)	Previously Treated (N=43)
Objective Response Rate[c], % (n/N)	**77% (13/17)**	**40% (17/43)**
Best overall response		
CR, n (%)	-	-
PR, n (%)	13 (77)	17 (40)
SD, n (%)	2 (12)	18 (42)
PD, n (%)	1 (6)	7 (16)
NE, n (%)	1 (6)	1 (2)
DCR, % (n/N)	**88% (15/17)**	**81% (35/43)**

- **Median time to response: 1.4 months**
- **Median DOR: not reached**

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Burns. ASCO 2024

The combination of pembrolizumab and olomorasib at 50-100mg bid dose was safe for treatment of *KRAS*^{G12C}-mutant NSCLC

All Doses and Patients (50 + 100 mg BID, N = 64)							
	Treatment-Emergent AEs (>10%), %		Treatment-Related AEs[a], %				
Adverse Event	Any grade	Grade ≥3	Any grade	Grade 1	Grade 2	Grade 3	Grade 4[b]
Any AE	86%	47%	70%	20%	23%	25%	2%
Diarrhea	28%	13%	23%	8%	3%	13%	-
Fatigue	27%	-	16%	8%	8%	-	-
ALT increased	25%	8%	20%	11%	3%	6%	-
Pruritus	25%	3%	19%	11%	5%	3%	-
Nausea	23%	-	14%	6%	8%	-	-
Arthralgia	19%	-	8%	8%	-	-	-
AST increased	17%	8%	16%	6%	2%	8%	-
Vomiting	17%	-	8%	5%	3%	-	-
Anemia	16%	2%	3%	3%	-	-	-
Decreased appetite	14%	2%	9%	8%	-	2%	-
Cough	13%	-	-	-	-	-	-
Dyspnea	11%	5%	-	-	-	-	-
Headache	11%	-	2%	2%	-	-	-
Hypokalemia	11%	3%	-	-	-	-	-

- Grade 3 AST/ALT: < 10% / no grade 4-5
- Grade 2+ diarrhea: 92% resolved to G≤1 with dose reduction and supportive care
- Olomorasib dose hold and reduction: 25% / 17%
- Olomorasib only discontinuation: 3%
- Olomorasib and pembrolizumab discontinuation: 5%

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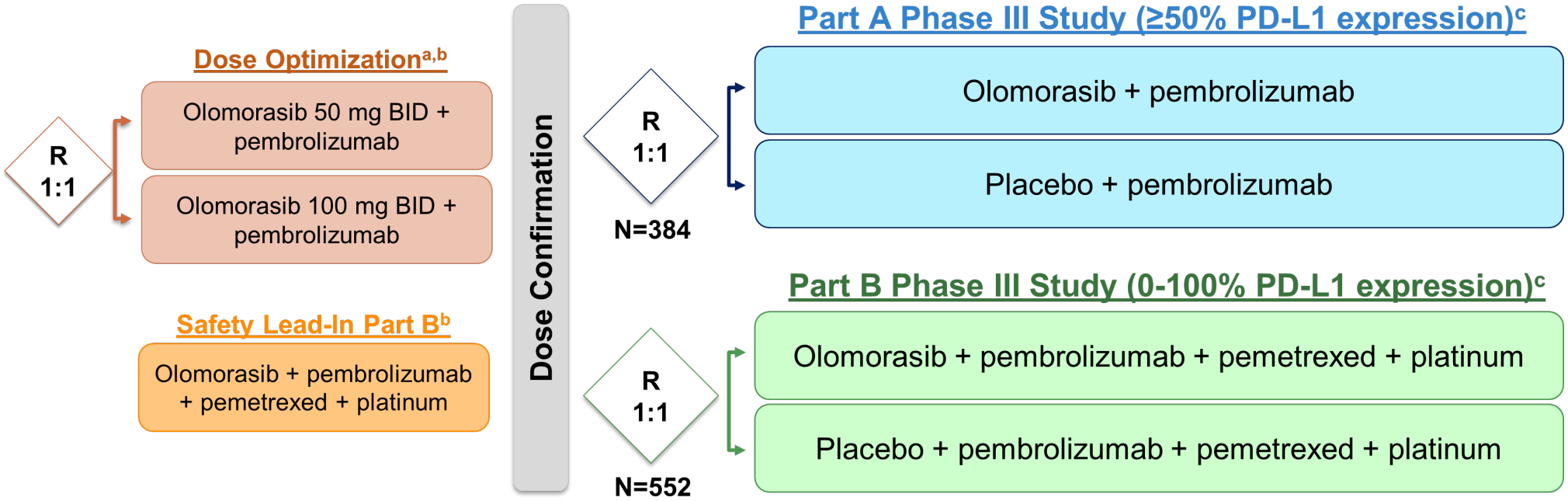
Burns. ASCO 2024

Efficacy of frontline olomorasib is under investigation in the Sunray-1 trial (NCT06119581)

SUNRAY-01 is a pivotal, global, phase 3 study in 1L advanced KRAS G12C-mutated NSCLC (NCT06119581)



- Olomorasib/placebo are administered orally, twice daily
- Pembrolizumab, pemetrexed, and platinum (cisplatin or carboplatin) are each administered intravenously per label. After completing 4 cycles of chemotherapy without disease progression, patients will receive maintenance therapy with olomorasib/placebo, pembrolizumab and pemetrexed

[a]Participants should be suitable for pembrolizumab monotherapy
[b]PD-L1 expression 0-100%, N~40 for each study part (randomized Dose Optimization and Safety Lead-In Part B)
[c]Participants with PD-L1 ≥50% are eligible to be enrolled to Part A or Part B at the discretion of the investigator

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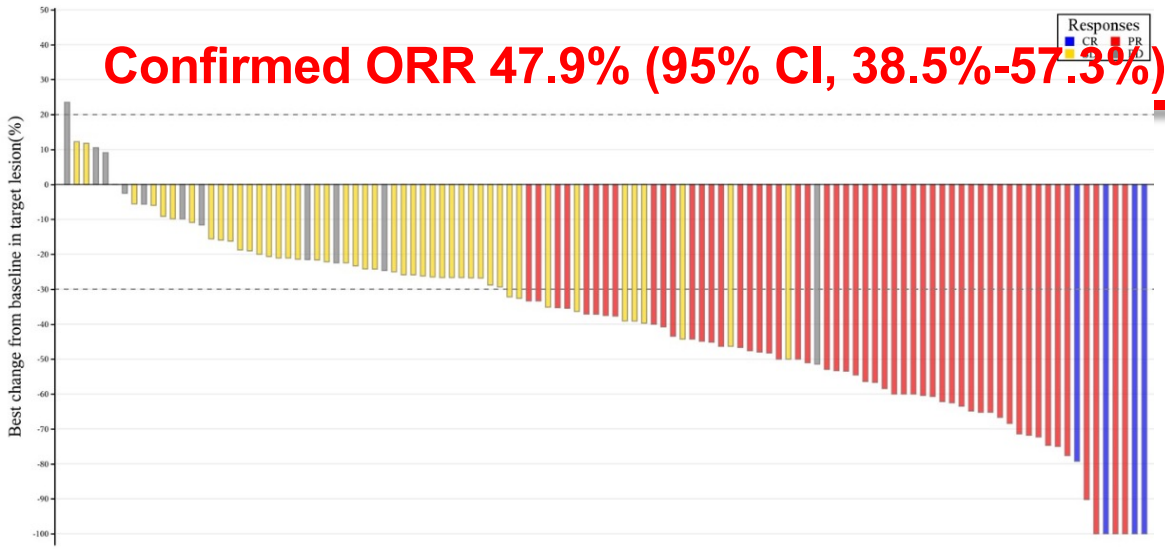
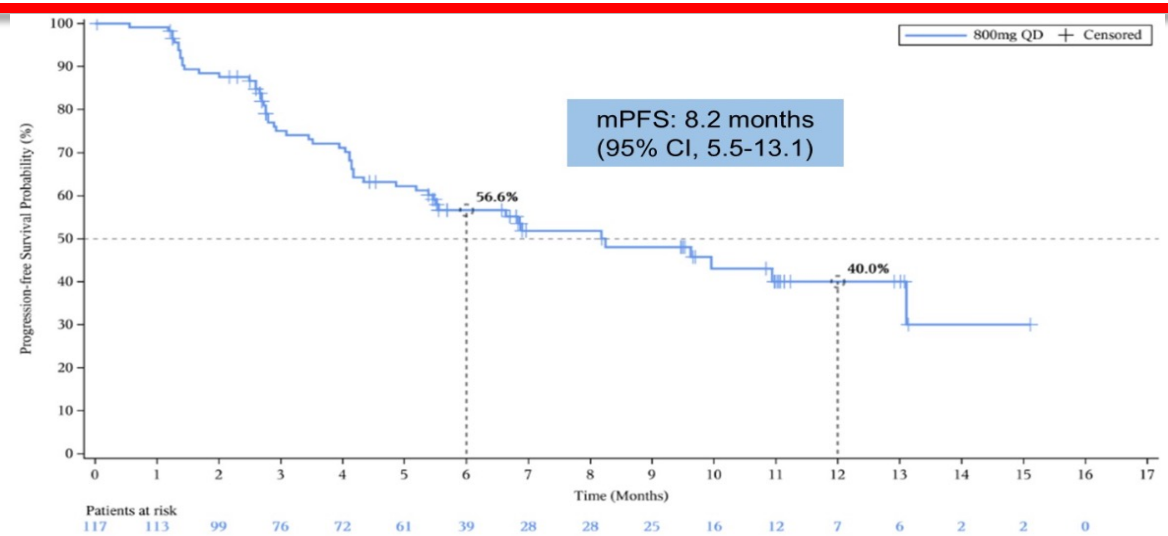
Negrao. ASCO 2024

Pivotal Phase II study of glecirasib (JAB-21822) in patients with advanced, previously treated *KRAS*^{G12C}-mutant NSCLC

A.



B.



C.

Common TRAEs in ≥ 10% of Patients (n=119)

Adverse Event	All Grade n (%)	Grade 3-4 n (%)
Anemia	67 (56.3%)	5(4.2%)
Blood bilirubin increased	58 (48.7%)	8(6.7%)
Alanine aminotransferase increased	42 (35.3%)	13(10.9%)
Aspartate aminotransferase increased	42 (35.3%)	13(10.9%)
Hypertriglyceridemia	34 (28.6%)	9(7.6%)
Gamma-glutamyltransferase increased	18 (15.1%)	7(5.9%)
Bilirubin conjugated increased	16 (13.4%)	2(1.7%)
Weight decreased	15 (12.6%)	0
Anorexia	15 (12.6%)	2(1.7%)
ALP increased	14 (11.8%)	0
White blood cell count decreased	14 (11.8%)	2(1.7%)
Neutrophil count decreased	12 (10.1%)	5(4.2%)
Hypoalbuminemia	12 (10.1%)	0
Proteinuria	12 (10.1%)	0

- Glecirasib resulted in minimal GI toxicities (Grade 1/2 TRAE): 5.9 % of nausea, 7.6% vomiting, 3.4% diarrhea .
- Only one (0.8%) patient had grade 3 nausea.

Low rates of GI tox (all Gr1/2):
Nausea 5.9%
Vomiting 7.6%
Diarrhea 3.4%

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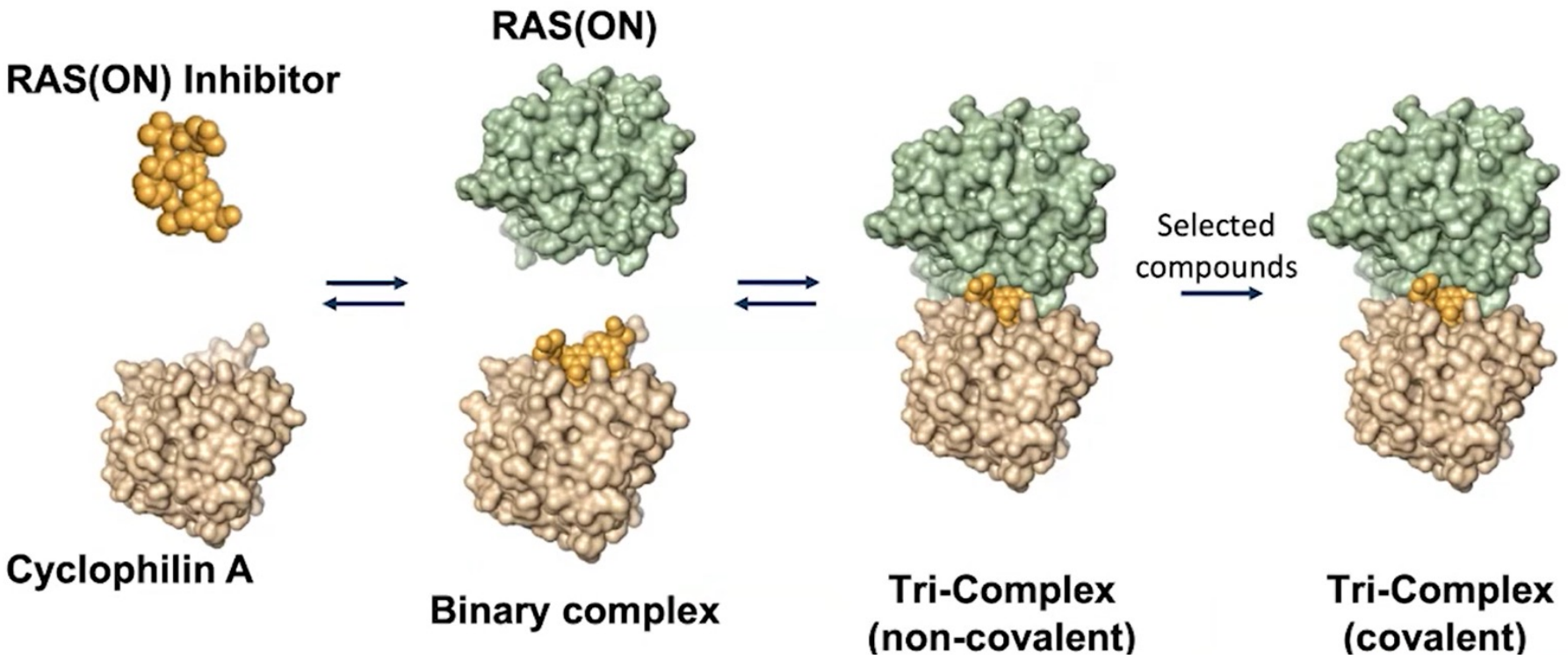
Shi Y et al., ASCO plenary series 2024; slide courtesy of F. Skoulidis

Other types of direct RAS inhibitors

RAS(ON) inhibitors block signaling through formation of inhibitory tri-complexes



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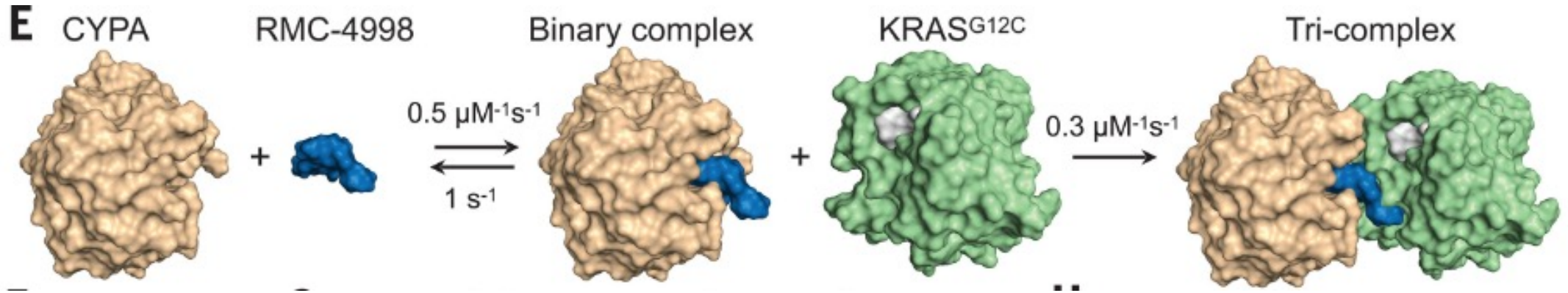
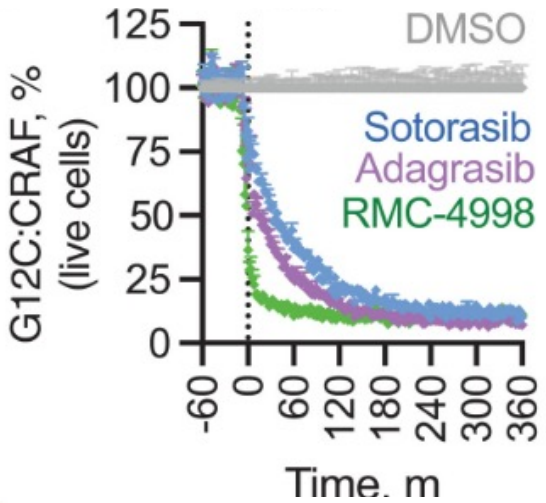
Stephen Kelsey, AACR-NCI-EORTC 2021

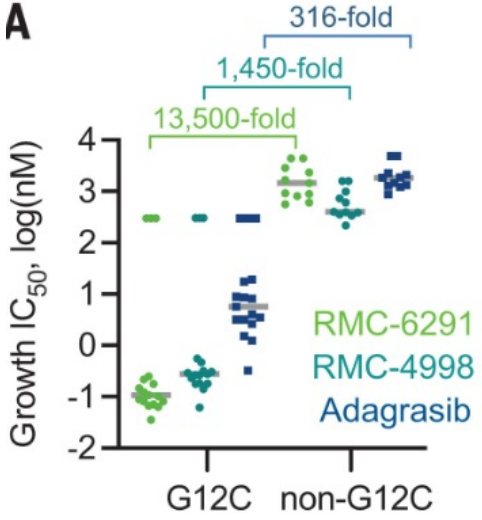
The tricomplex inhibitory strategy of mutant KRAS: RMC-4998 for KRAS G12C mutant NSCLC



Kinetics of target inhibition



3D cell viability



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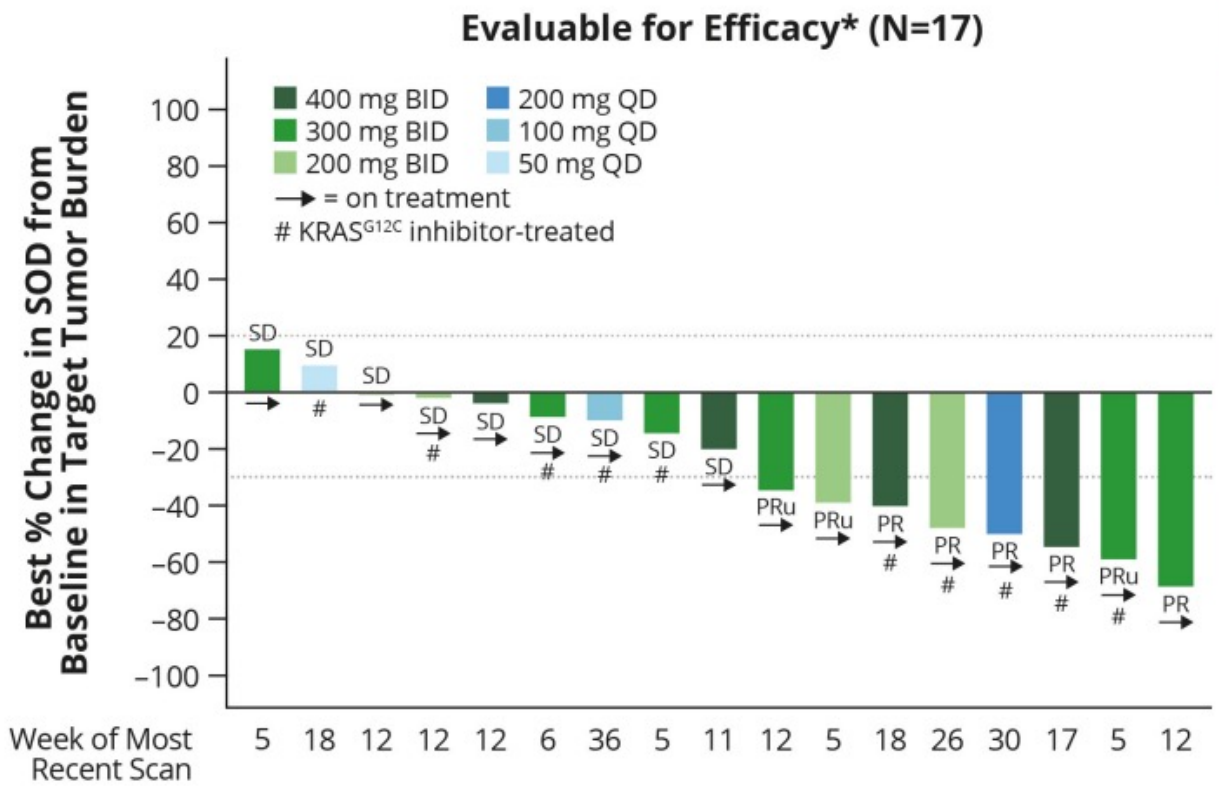
C. Schulze, et al, *Science* 2023

RMC-6291 is a first-in-class potent covalent tricomplex KRASG12C (ON) inhibitor



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)

*All treated patients who received a first dose of RMC-6291 at least 8 weeks prior to data extract date; †PR includes 5 confirmed and 3 unconfirmed.
CR, complete response; DCR, disease control rate; G12Ci, G12C inhibitor; PD, progressive disease; PR, partial response; PRu, unconfirmed partial response; SD, stable disease; SOD, sum of diameters; ORR objective response rate; DCR, disease control rate; RECIST, response evaluation criteria in solid tumors.

Data Extracted 05 October 2023.

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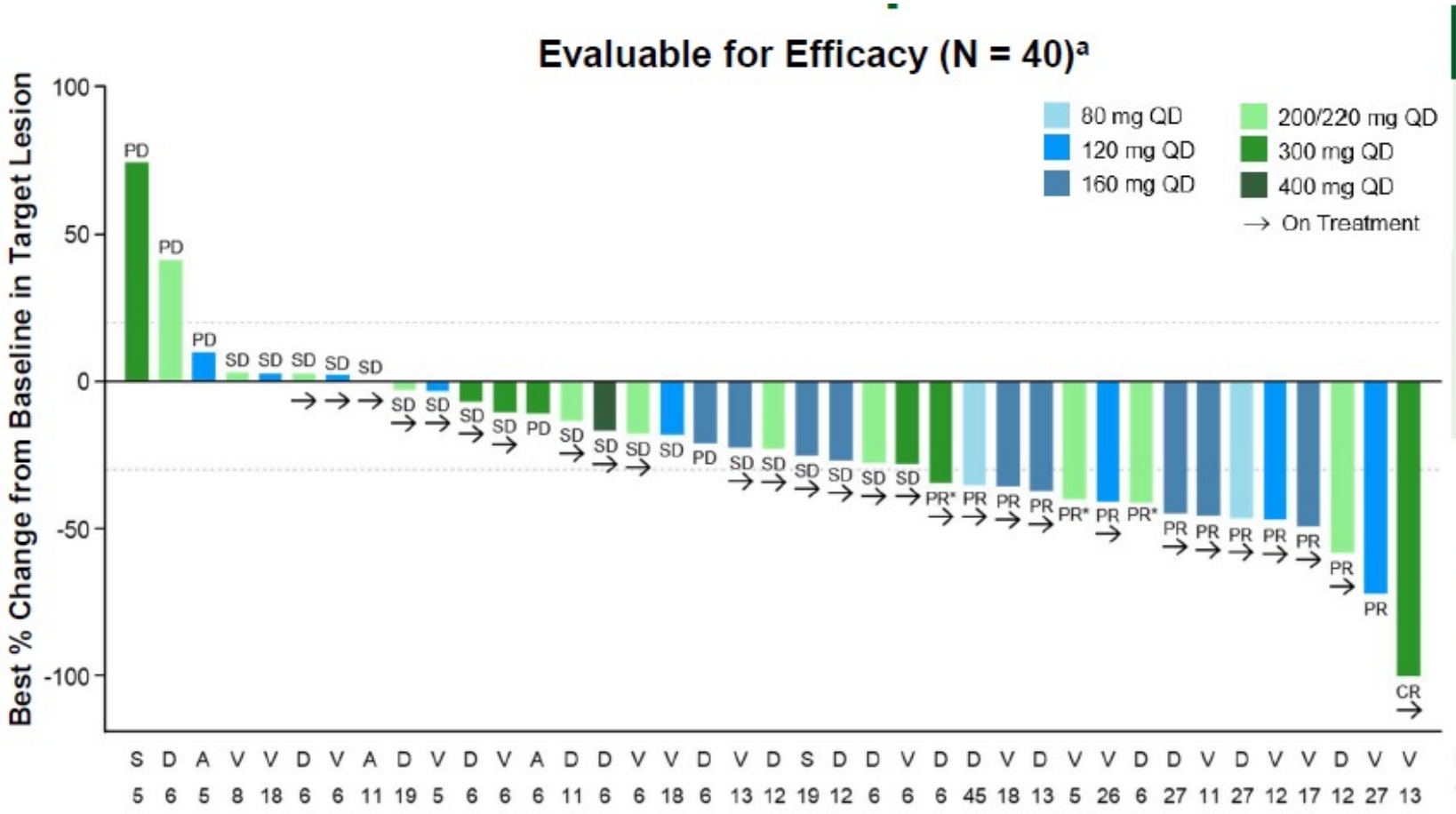
Janne PA et al, AACR-NCI-EORTC Meeting 2023; slide courtesy of F. Skoulidis

Tricomplex RMC-6236 efficacy in KRASG12X NSCLC



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.

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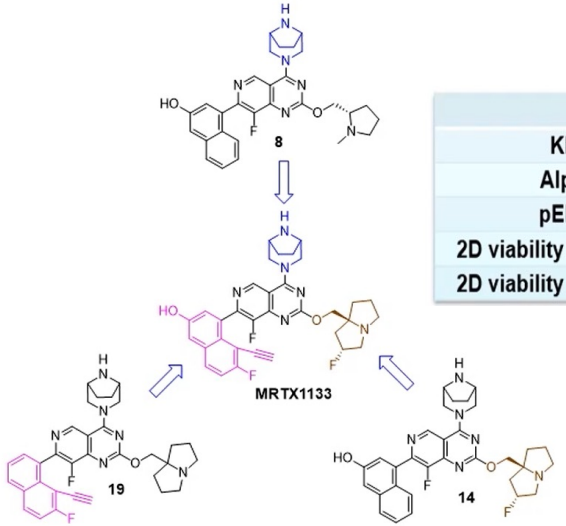
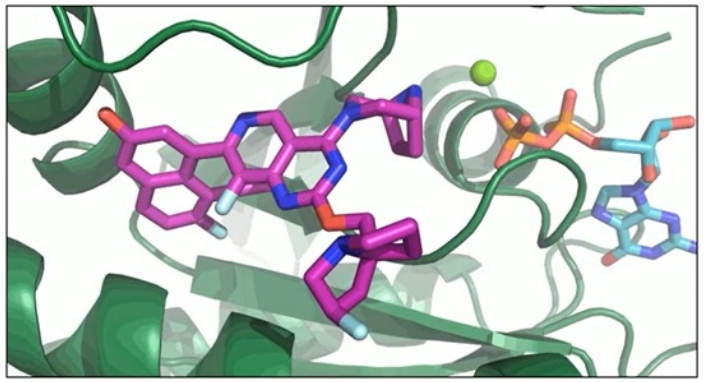
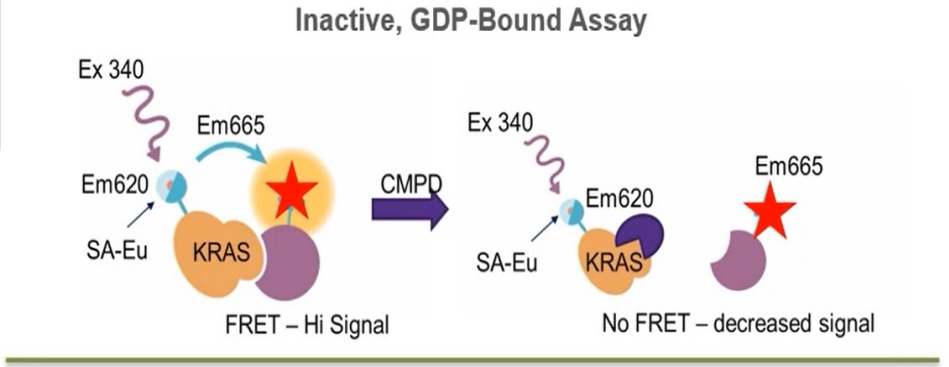
Arbour KC et al., 2023 ESMO Annual Meeting

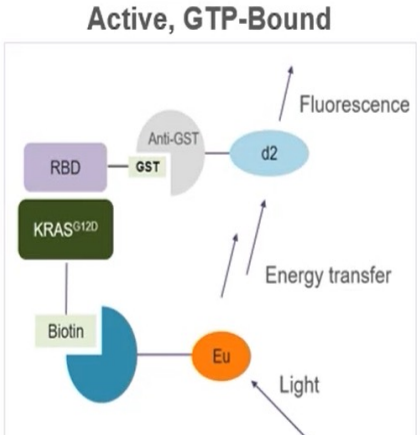
MRTX1133: a novel KRAS^{G12D} inhibitor that binds the inactive and active states of KRAS^{G12D}



Assay	Activity
KRAS^{G12D} K_D (nM)	~0.0002*
AlphaLISA IC_{50} (nM)	5
pERK AGS IC_{50} (nM)	2
2D viability AGS (KRAS^{G12D}) IC_{50} (nM)	6
2D viability MKN1 (KRAS^{WT}) IC_{50} (nM)	>3000







KRAS Protein	MRTX1133		
	Inactive IC_{50} (nM)	Active IC_{50} (nM)	SPR (pM)
G12D	<2*	9	0.2
WT	2.4	112	140

*MRTX1133 bottoms out the inactive assay

- MRTX1133 Binds the inactive, GDP-bound KRAS^{G12D} with high affinity (<2nM)
- Ability to inhibit binding of active KRAS^{G12D} to RBD binding may contribute to the pharmacological MOA

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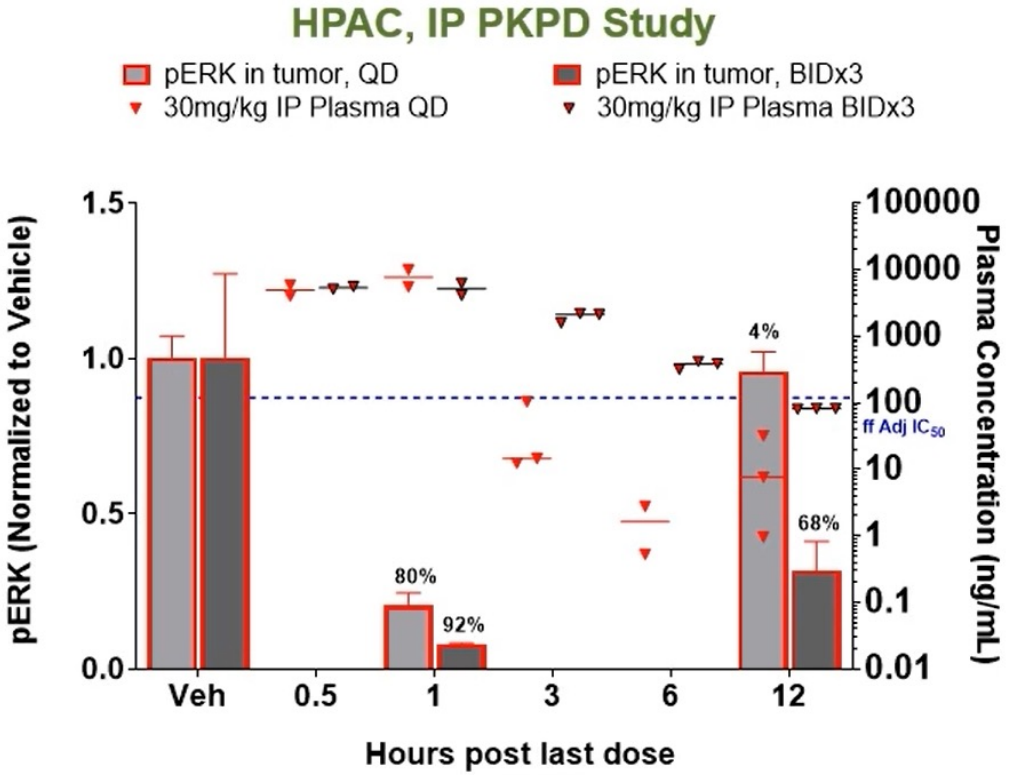
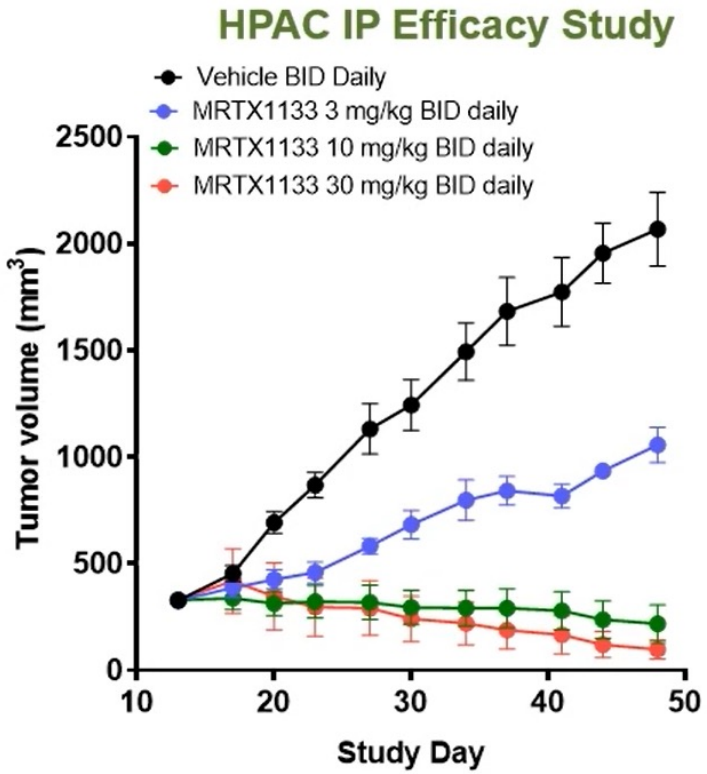
James G. Christensen, AACR-NCI-EORTC 2021

Efficacy of MRTX1133 in xenograft models





- Near maximal pERK inhibition after a single dose of MRTX1133
- BIDx3 administration demonstrates robust pERK inhibition for entire dose interval and correlates with maximal antitumor efficacy

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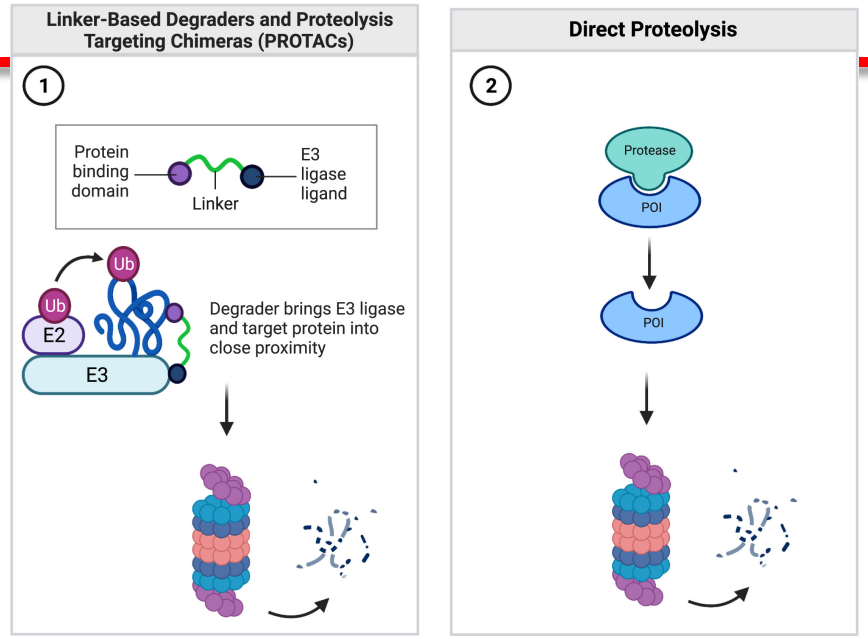
James G. Christensen, AACR-NCI-EORTC 2021

RAS degraders

A.



Escher TE and Satchell KJF. *Molecular Therapy*, 2023

B.

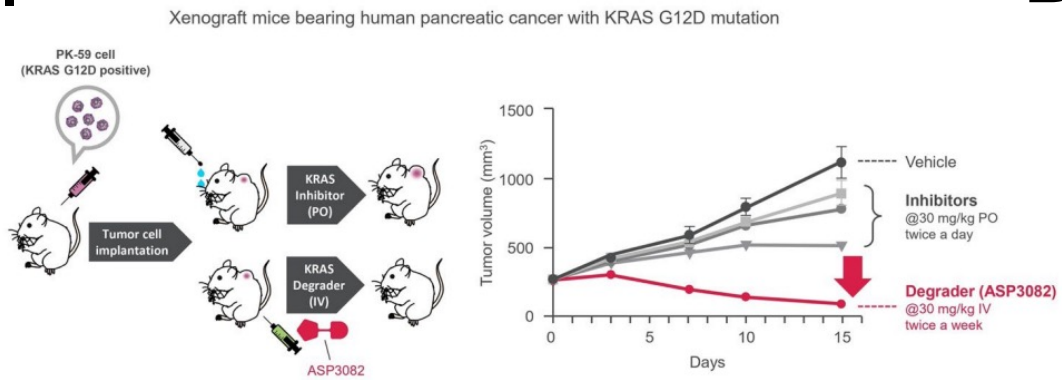
Table 2. Summary of selected RAS degraders

Compound	RAS Targets	Concentration	*In vitro* studies	*In vivo* studies
RRSP	KRAS, NRAS, HRAS	1-300 pM	Induces apoptosis or senescence in pancreatic, breast, and colon cancer	Tumor regression in pancreatic, breast, and colon xenografts
ASP3082	PROTAC against KRAS G12D	NA	ND	*In vivo* results not disclosed but a phase I clinical trial began in June 2022
RC-U	KRAS, NRAS, HRAS	transfection	Reduced RAS levels upon transfection in HEK293T cells	Transfection reduced tumor size
VHL-KRAS DARPin K19	KRAS	transfection	Reduced KRAS levels in mutant KRAS cells	Doxycycline-inducible expression reduced tumor size
UBOX-Pan-RAS iDab	KRAS, NRAS, HRAS	transfection	Reduced RAS levels in mutant KRAS cells	Doxycycline-inducible expression reduced tumor size
BIpanKRAS3	KRAS, KRAS G12D	19–91 nM	Cleaved KRAS and reduced pERK levels in NCI-H2122 and SW837 cells	$KRAS^{G12/13D}$ mutant CDX xenograft models a 30-mg/kg dose caused tumor regression
Compound 13 (XY-4-88)	KRAS G12C	>0.410 μM	Did not degrade endogenous RAS	NA
LC-2	KRAS G12C	0.25–0.76 μM	Degraded endogenous KRASG12C and ERK	NA
$FKBP12^{F36V}$-$KRAS^{G12V}$ + dTAG13	KRAS G12V	transfection	Reduced KRAS G12V levels	NA
VHL-aHRAS AdPROM	KRAS, NRAS, HRAS	transfection	Reduced K,N,H-RAS in CRISPR-Cas9 HEK293 and U2OS cells	NA
DARPin K27-SPOP and others	various	plasmid and mRNA transfection	Several RAS degraders and E3 ligases reduced RAS expression and inhibited cell proliferation specific to each compound	NA
BIKRASdegrader1	KRAS mutants	2–116 nM	Degraded KRAS, reduced pERK levels and reduced cell proliferation	NA
Engineered subtilisin	KRAS	transfection	Cleaved eGFP-KRAS after doxycycline induction	NA

ND-not disclosed, NA-information is not available

Escher TE and Satchell KJF. *Molecular Therapy*, 2023

C.



D.

A Study of ASP3082 in Adults With Previously Treated Solid Tumors

ClinicalTrials.gov ID NCT05382559

Sponsor Astellas Pharma Inc

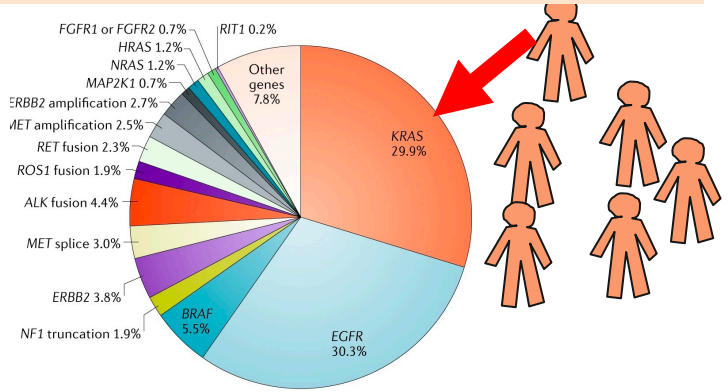
Information provided by Astellas Pharma Inc (Responsible Party)

Last Update Posted 2024-01-08 ClinicalTrials.gov

https://www.astellas.com/en/system/files/rdmeeting221209_pre_en_2.pdf; Slide courtesy of F. Skoulidis

KRAS mutant NSCLC: subgroups based on alleles and co-mutations

KRAS alleles (G12C, G12V, etc)



KRAS G12C 12%

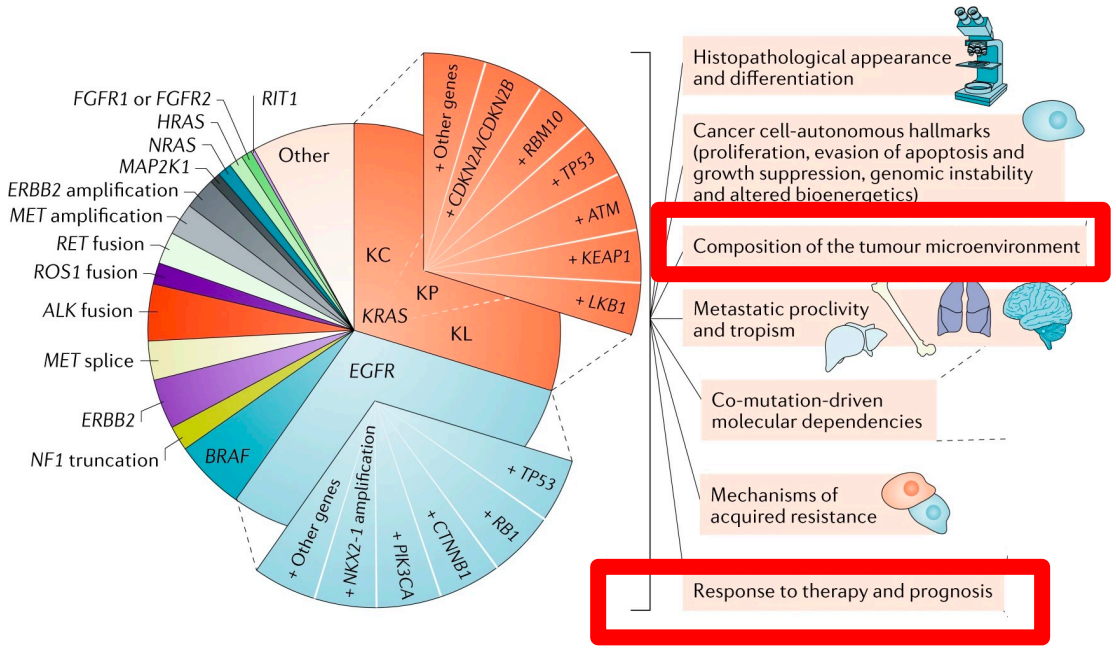
KRAS G12V 6%

KRAS G12D 3%

other

KRAS co-mutations (STK11, p53, etc)

Co-occurring alterations in tumor suppressors (STK11/LKB1, KEAP1, etc) impact biology and response to treatment



Skoulidis and Heymach, Nat Rev Cancer 2019; Skoulidis et al, Cancer Discovery 2018

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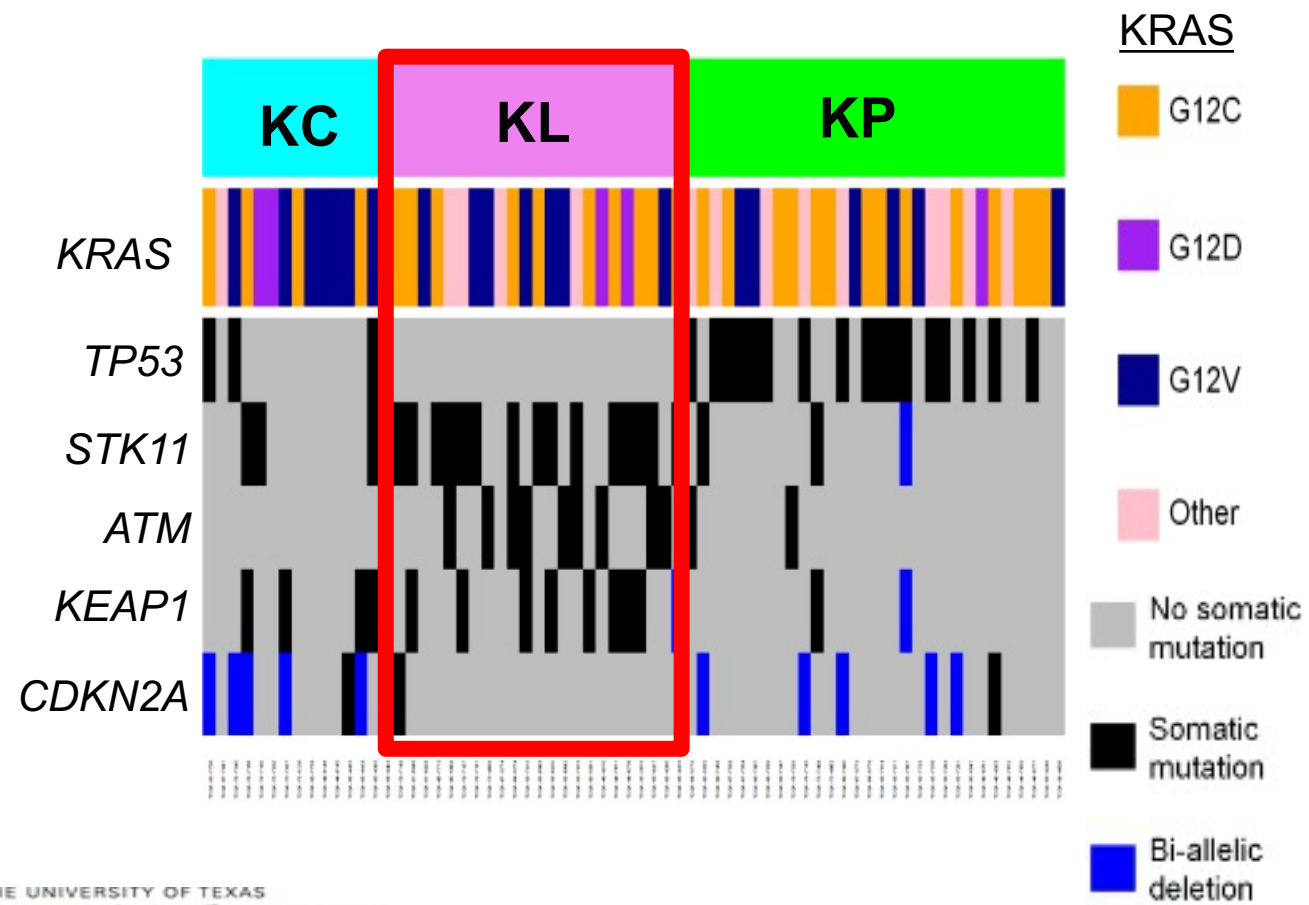
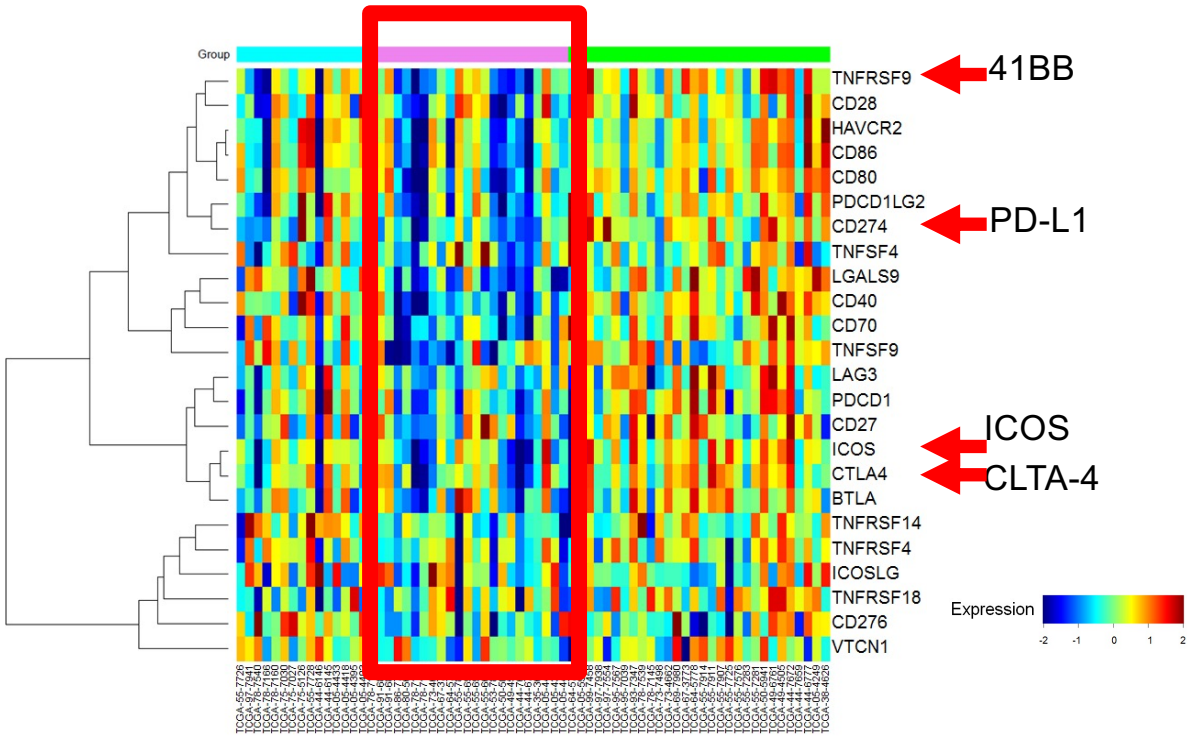
KRAS mutant tumors often have co-occurring alterations in STK11/LKB1 (KL), KEAP1, P53 (KP), or CDKN2A



Distinct patterns of immune system engagement: KL appears immunologically “inert”



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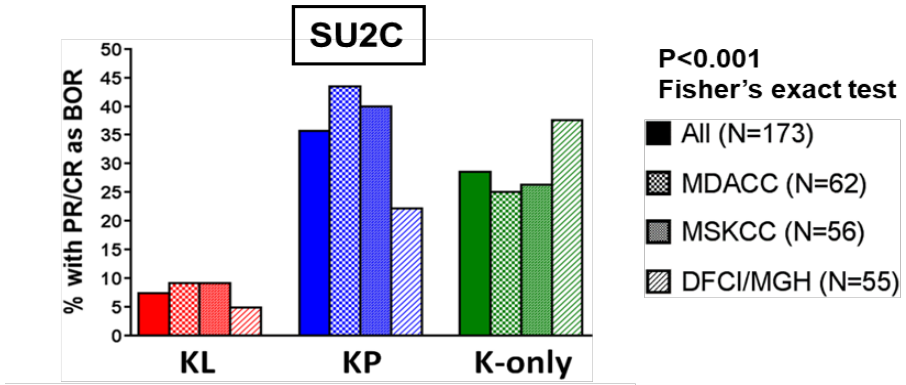
Skoulidis et al., Cancer Discov, 2015

STK11/LKB1 co-mutations (KL) predict inferior response to immunotherapy in PDL1^{+} LUADs

Clinical study

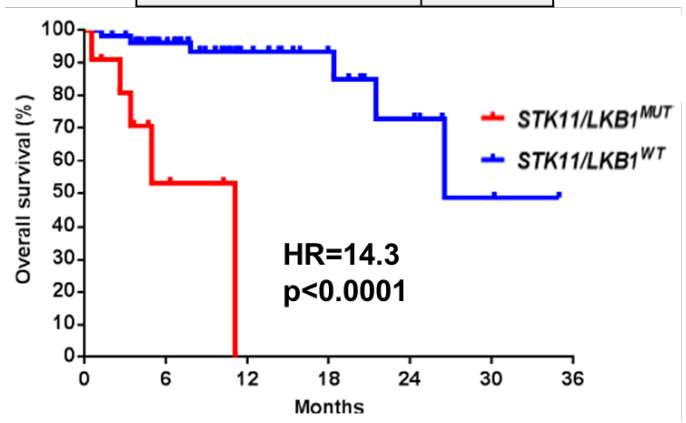
A



Group	KL	KP	K-only
ORR	7.4% (4/54)	35.7% (20/56)	28.6% (18/63)

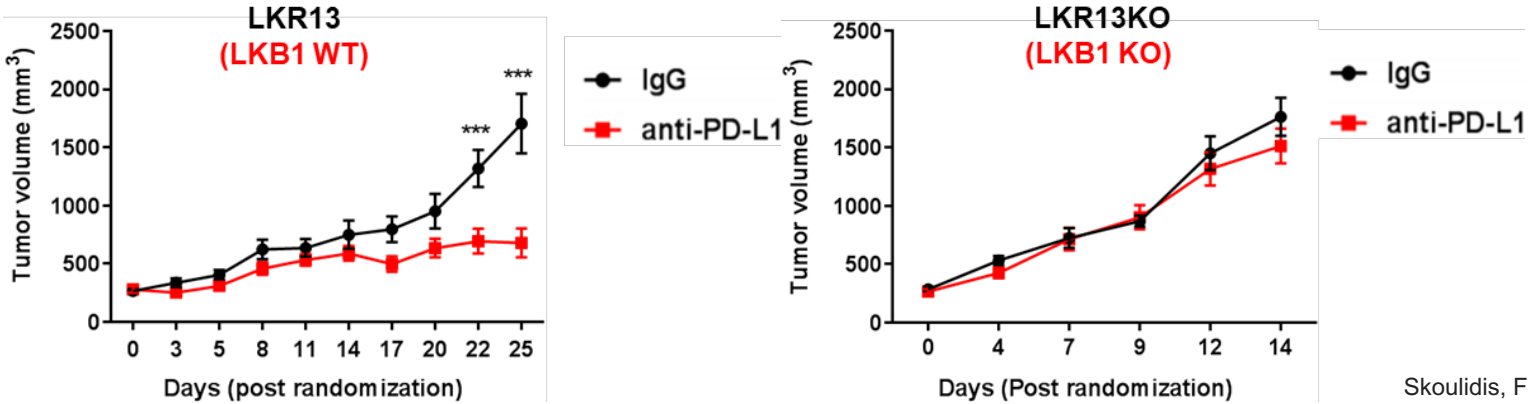
B

GROUP	mOS
STK11/LKB1 mutant	11.1m
STK11/LKB1 wt	26.5m



Mouse study

C



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Skoulidis, F et al. *Cancer Discov* (2018)

Article

CTLA4 blockade abrogates *KEAP1/STK11*-related resistance to PD-1 and PD-L1 inhibitors

Poseidon RP3: CT vs durva-CT (DCT) vs tremi-CT (DTCT)

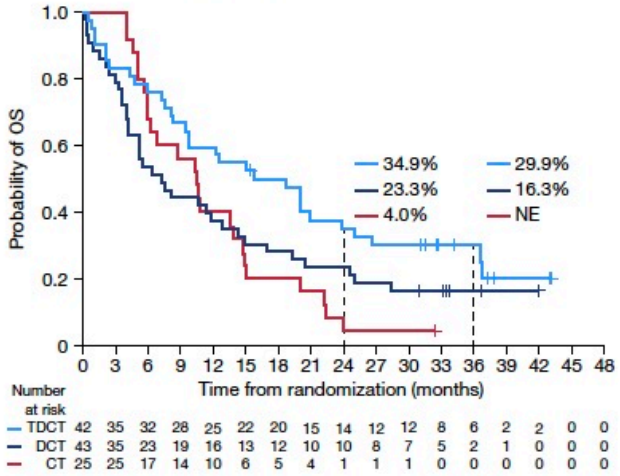
What is benefit for adding CTLA4? (DCT vs TDCT)
OS HR in STK11/KEAP1 mutant : 0.64
OS HR in STK11 wt and KEAP1 wt: 0.90--→ almost all OS benefit for adding CTLA4 comes in the STK11/KEAP1 groups

Preclinical models

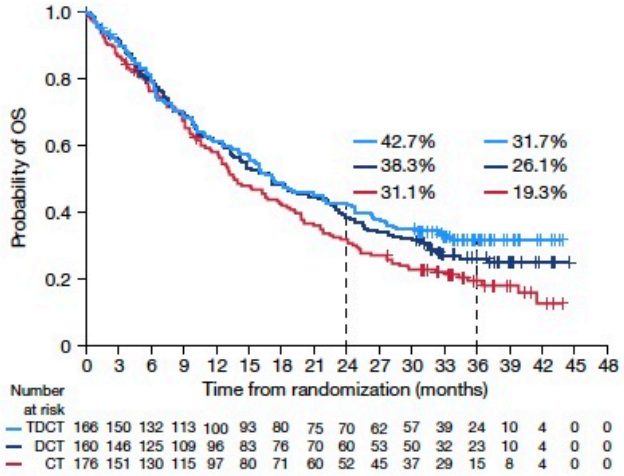
KRAS/STK11 (KL), KRAS/KEAP1 (KK), or KRAS/STK11/KEAP1 groups are all PD-(L)1 inhibitor resistant and CTLA4 inhibitor reponsive

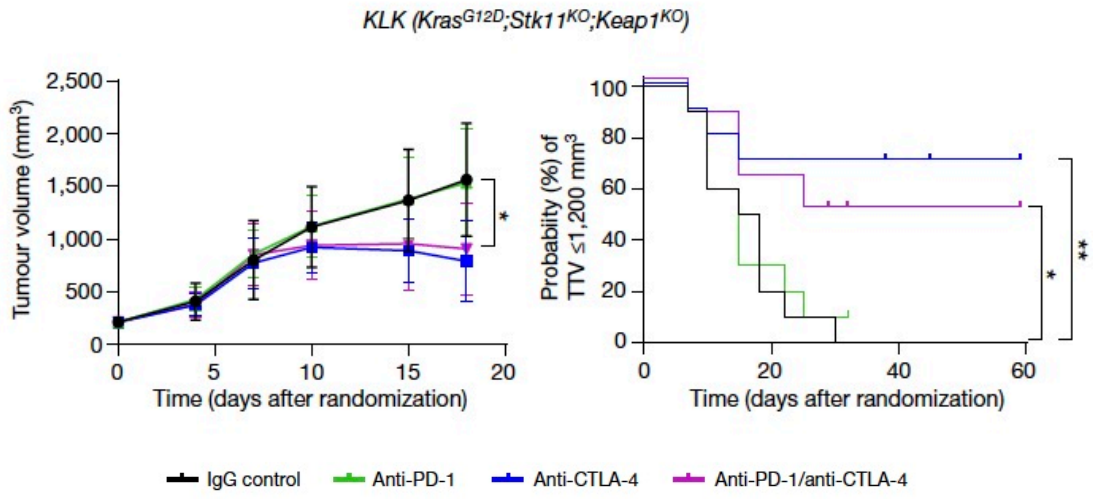
b

	TDCT	DCT	CT
mOS (months) (95% CI)	15.8 (9.5–23.8)	7.3 (4.2–12.9)	10.5 (6.0–14.7)
HR versus CT (95% CI)	0.50 (0.29–0.87)	0.90 (0.53–1.52)	–
HR versus DCT (95% CI)	0.64 (0.40–1.04)	–	–



	TDCT	DCT	CT
mOS (months) (95% CI)	17.2 (14.2–24.1)	17.1 (13.3–22.6)	13.7 (12.0–17.8)
HR versus CT (95% CI)	0.74 (0.58–0.95)	0.81 (0.63–1.04)	–
HR versus DCT (95% CI)	0.90 (0.69–1.17)	–	–





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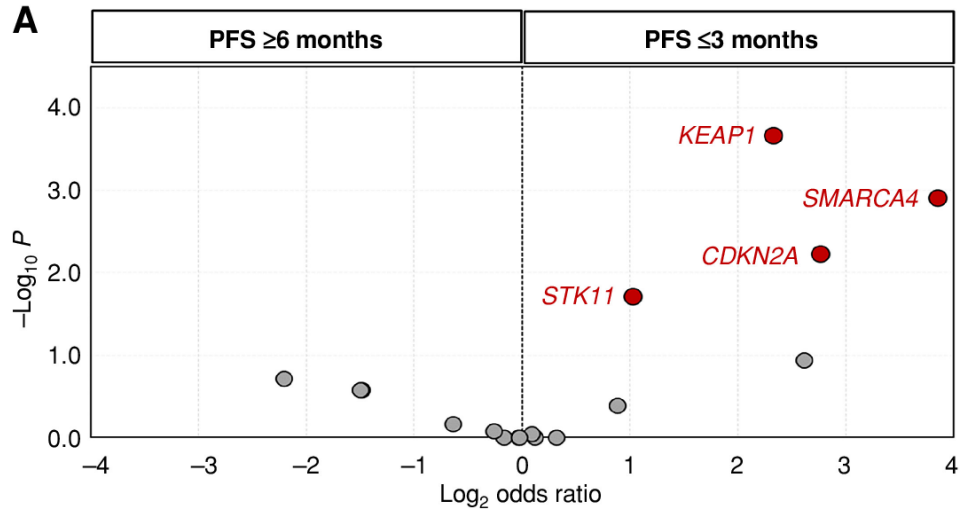
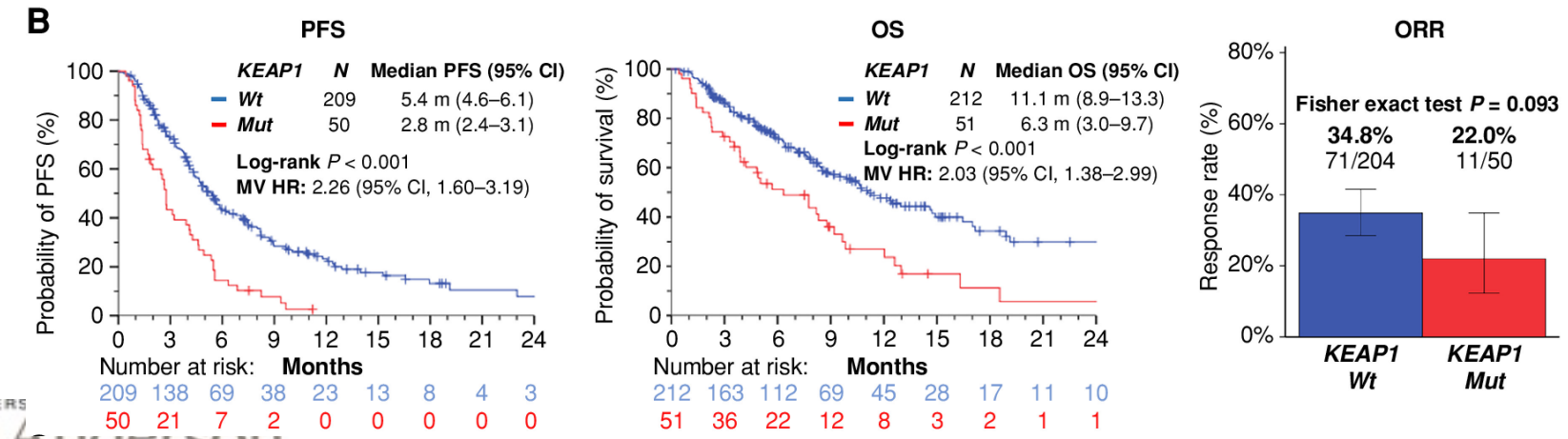
Skoulidis et al Nature 2024

KEAP1 and STK11 mutations are associated with shorter PFS in patients treated with KRAS G12C inhibitors



If STK11 and KEAP1 are associated with resistance to G12C inhibitors, but sensitivity to MDM2i, would combinations of G12Ci+MDM2i be highly effective in the KRASG12C/STK11 or KEAP1 mut+/P53wt group (roughly 1/3 of G12C)?

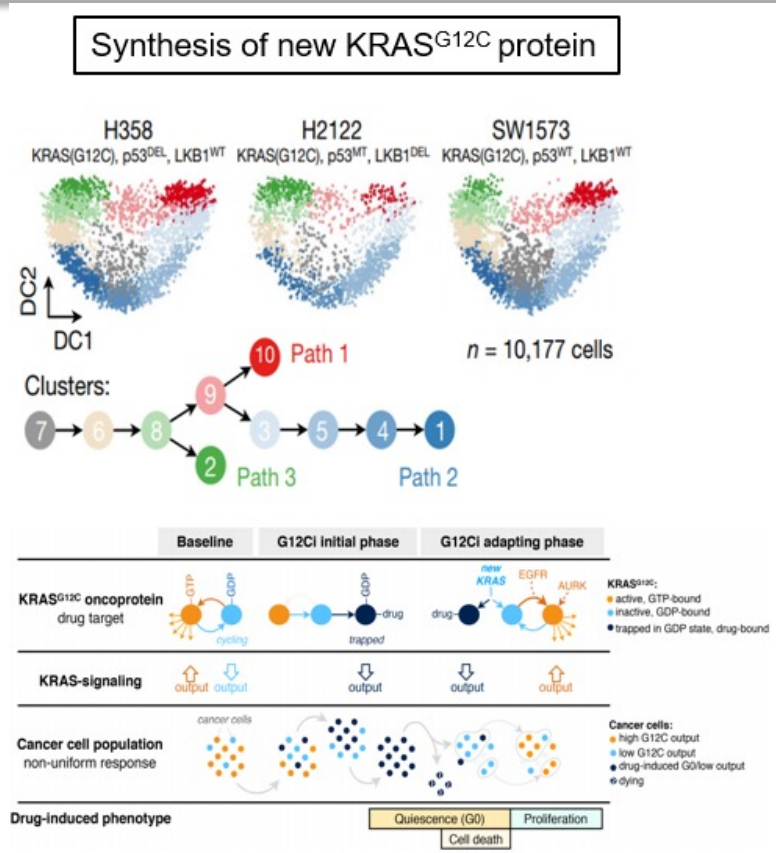
If this combo is effective, could it be developed with all KRAS G12D and other combos?



Negrao et al, Cancer Discov. 2023;13(7):1556-1571

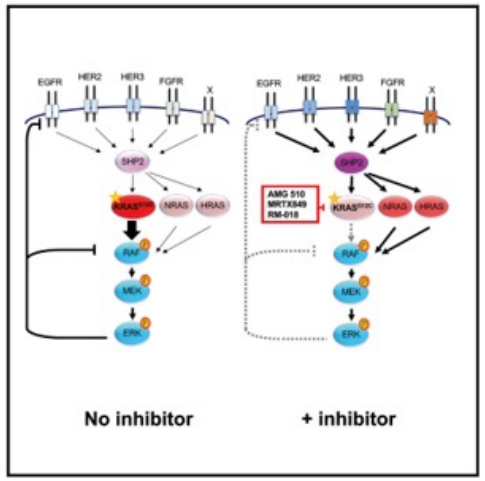
Mechanisms of innate, adaptive and acquired resistance to OFF state-selective KRAS G12Ci frequently converge on accumulation of "active" $KRAS^{G12C}$-GTP

A. Synthesis of new $KRAS^{G12C}$ protein



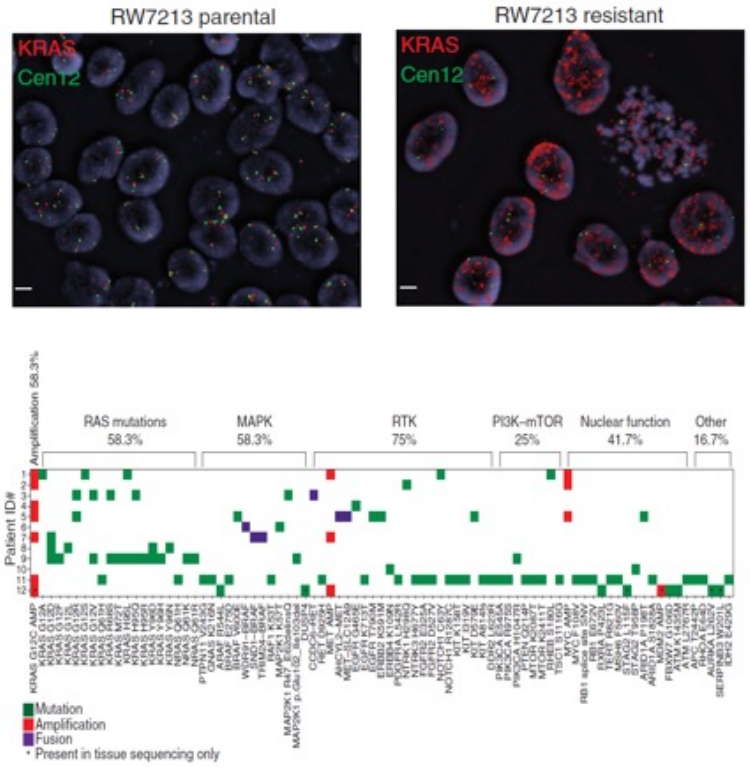
Xue JY et al., *Nature*, 2020

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

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KRAS inhibitors: the bottom line

1. Direct KRAS G12C inhibitors have finally arrived!
   - Sotorasib, adagrasib have FDA accelerated approval
   - Divarasib, olomorasib, glecirasib and others show promising activity
2. New types of KRAS inhibitors (G12D, tricomplex, others) can potentially broaden the patient population that can be treated
   - RMC6236 is a promising tricomplex RAS (ON) inhibitor
3. Co-mutations (STK11, KEAP1, CDKN2A, SMARCA4) can impact response and may help guide combinations
4. Diverse (but no dominant) MOR for G12Ci, including other KRAS mutations and RAF/MEK pathway alterations.
   - Combinations with ICB, MEK, EGFRi appear promising thus far