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KRAS mutant NSCLC and Combinations to Overcome Resistance

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Atlanta Lung Cancer Symposium 2021
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DISCLOSURES

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

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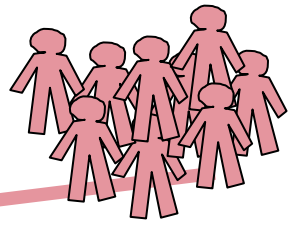
KRAS mutant NSCLC: subgroups based on alleles and co-mutations

NSCLC



KRAS mutant ~25%

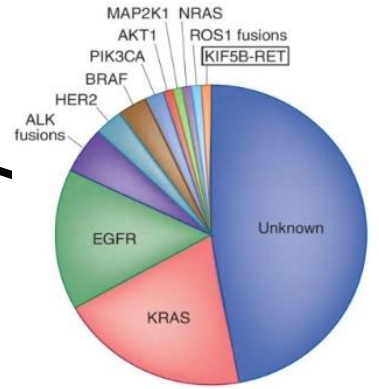
G12C ~13%

G12V ~6%

G12D ~3%

Other

Driver positive: the genomic pie (40-50%)



KRAS Alleles in NSCLC

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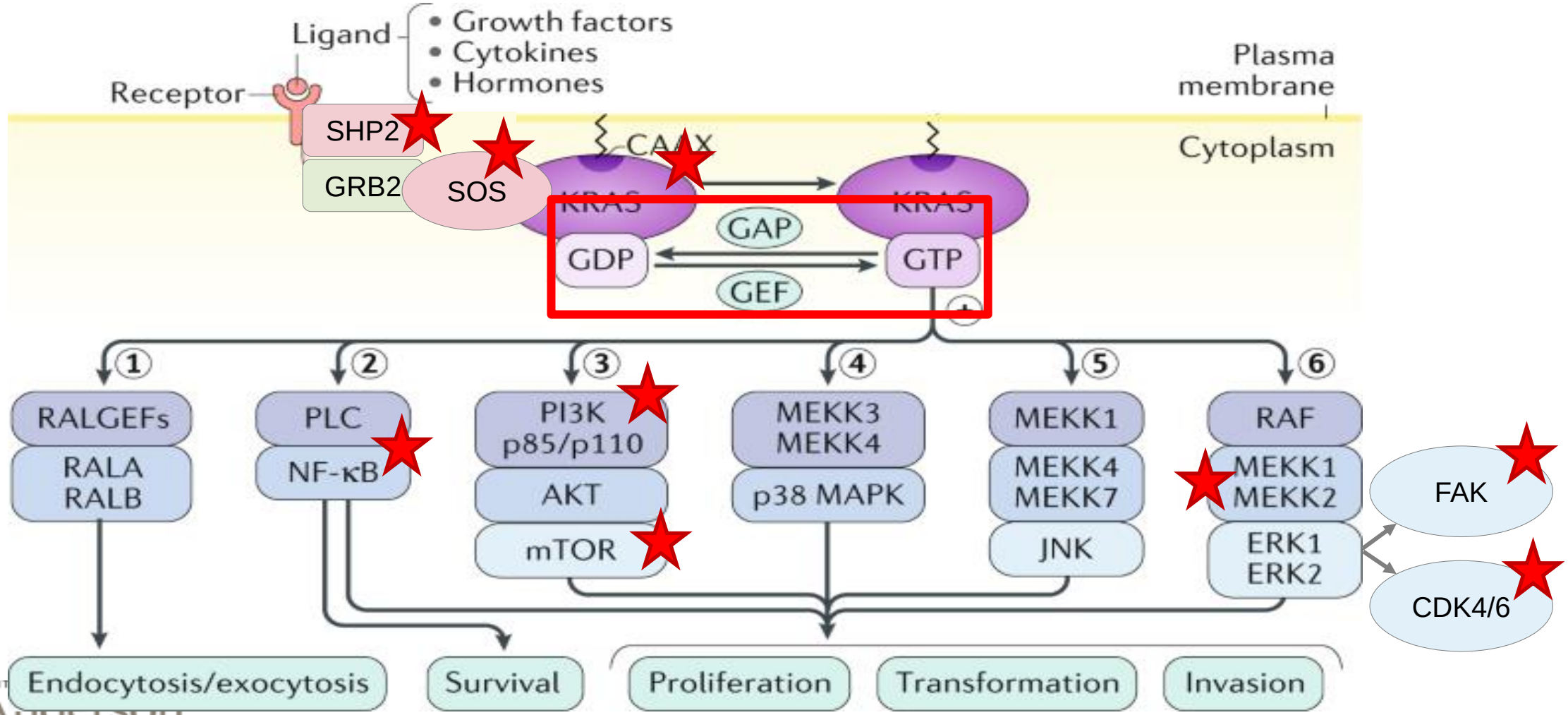
Skoulidis and Heymach, Nat Rev Cancer 2019

KRAS signaling: combinations with KRAS G12Ci



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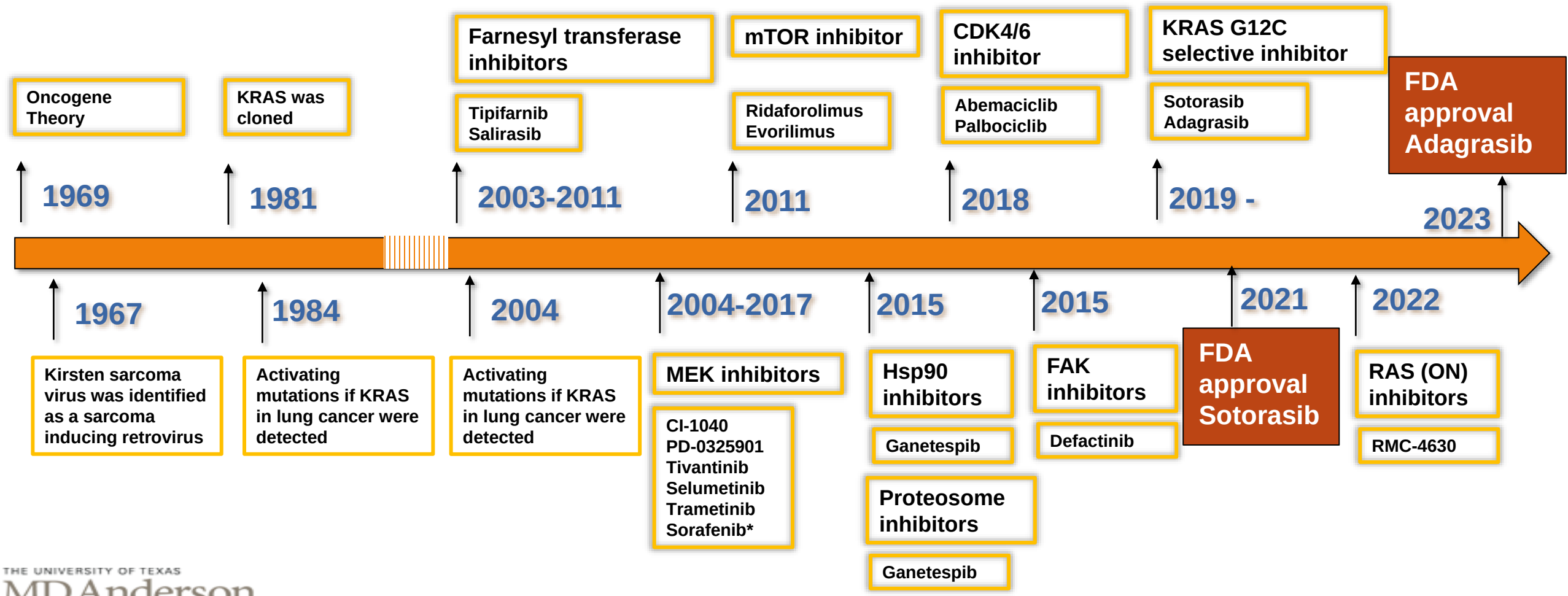
Adapted from Buscail, L., *Nat Rev Gast Hep* 2020

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

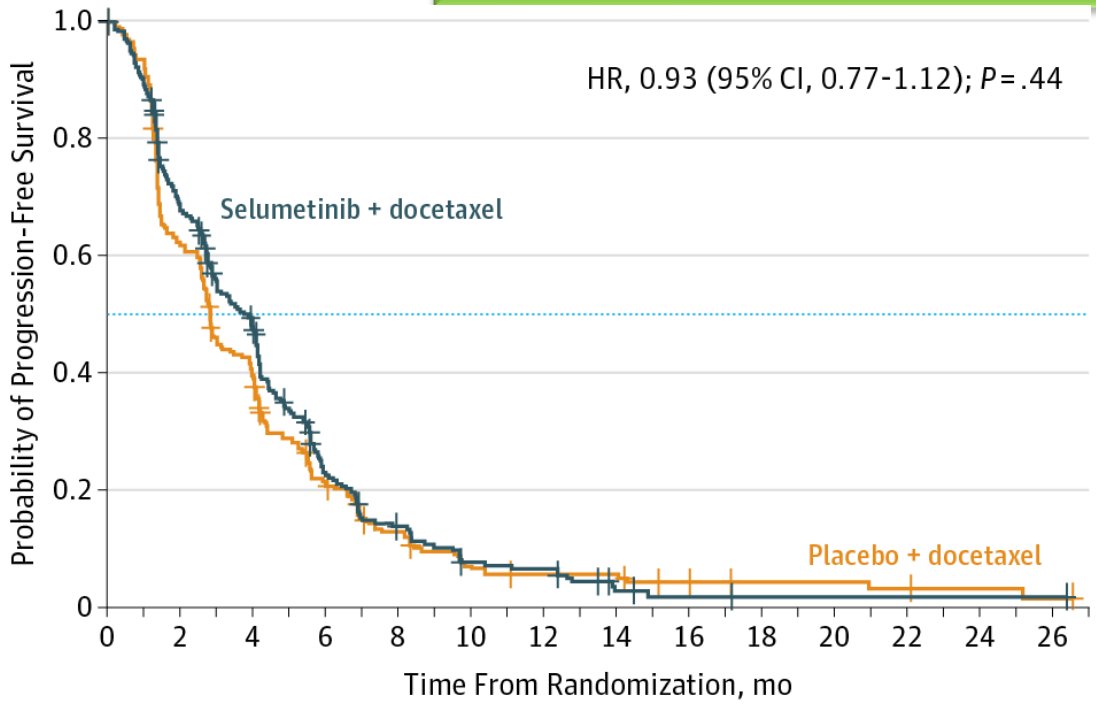
R

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

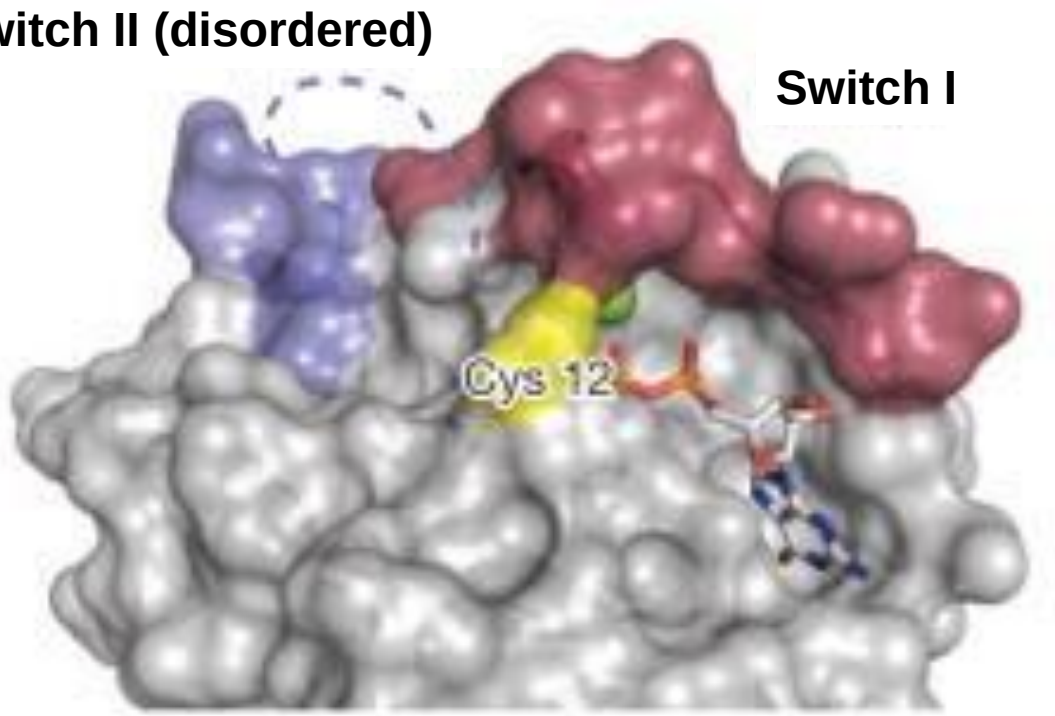
nature

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

Phase 2 CodeBreaK 100 trial evaluating sotorasib in pretreated KRAS p.G12C mutated

The NEW ENGLAND JOURNAL of MEDICINE

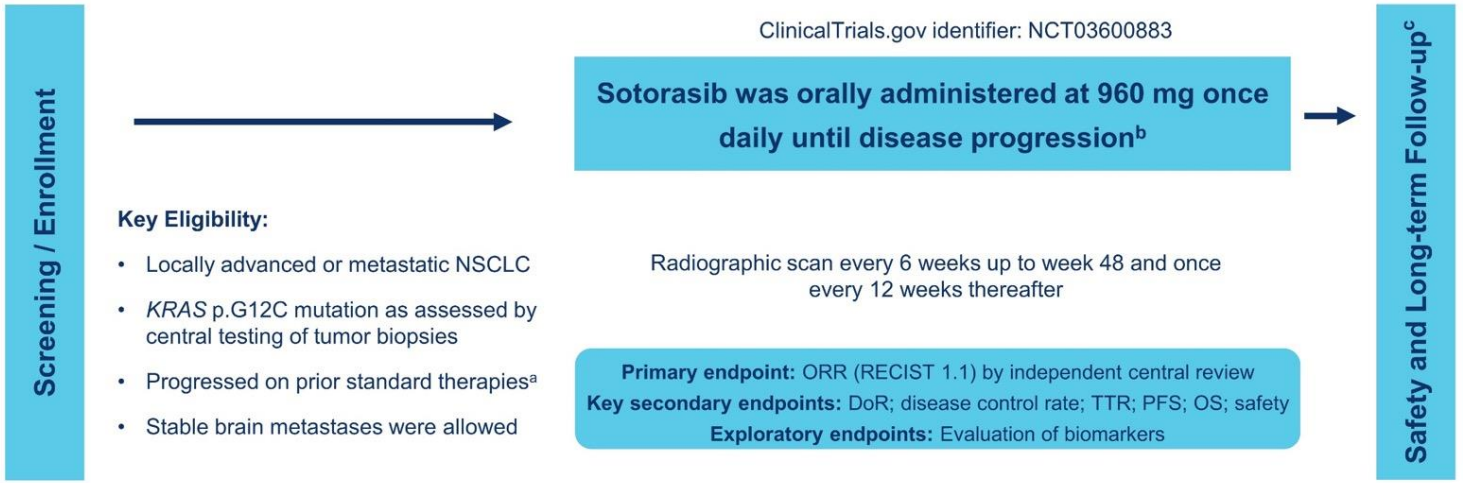
ESTABLISHED IN 1812 JUNE 24, 2021 VOL. 384 NO. 25

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

Skoulidis NEJM 2021

Phase 2 CodeBreaK100 Trial Design



Skoulidis ASCO 2021

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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

The NEW ENGLAND JOURNAL of MEDICINE
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Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

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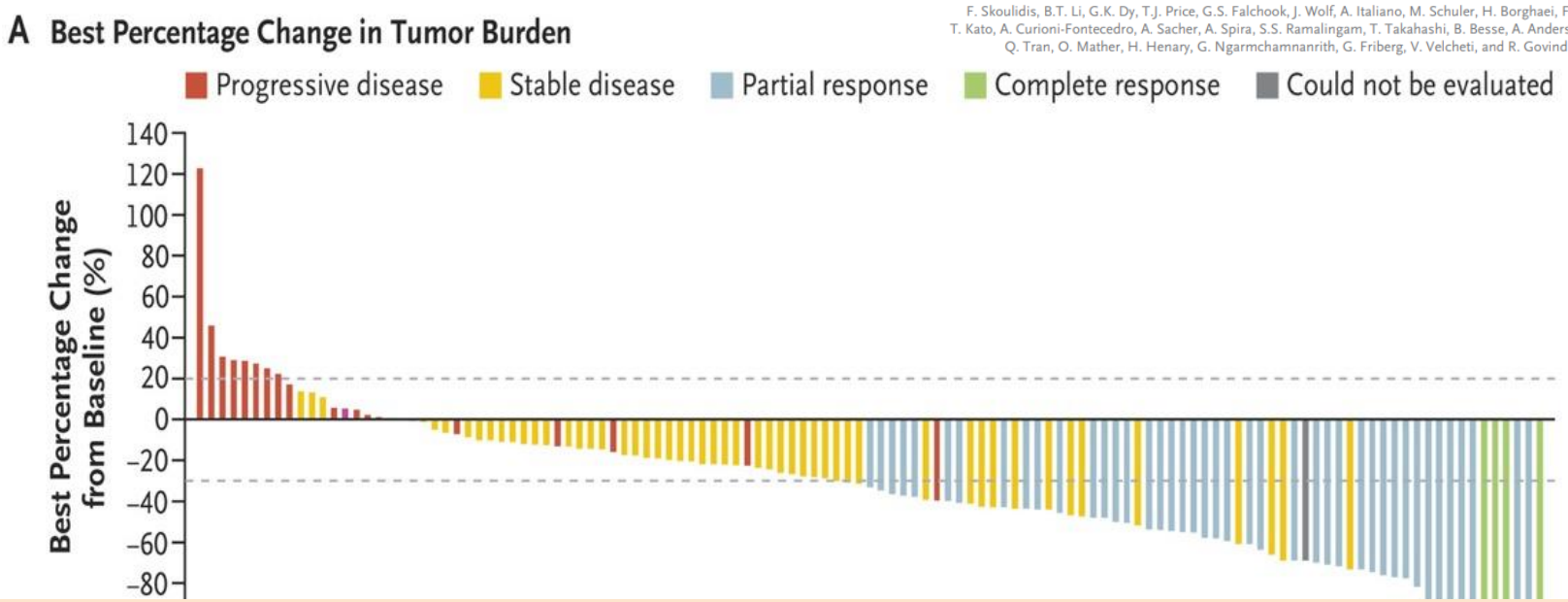

May 28, 2021: FDA granted accelerated approval for sotorasib for advanced NSCLC patients with KRAS G12C mutation who received one prior systemic therapy.

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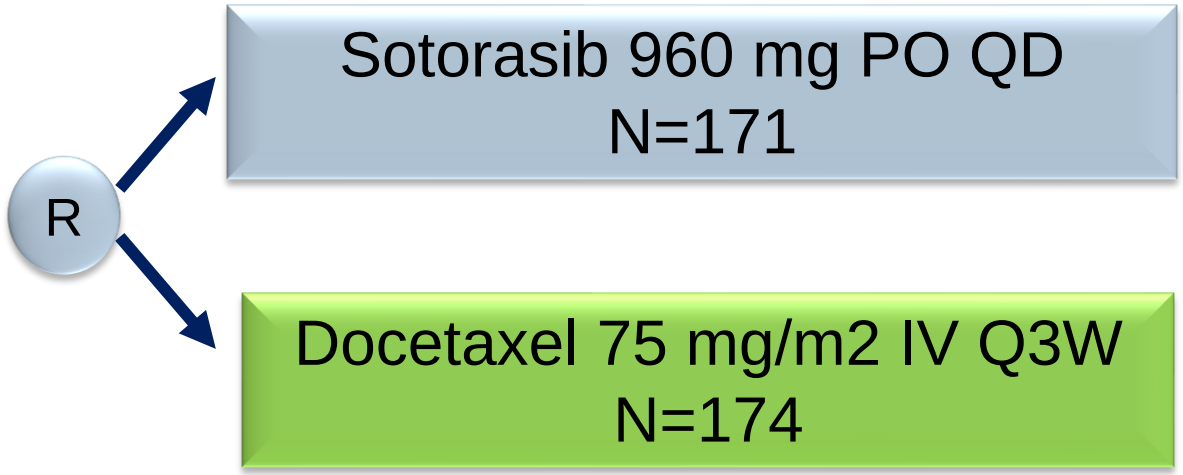
Skoulidis NEJM 2021

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



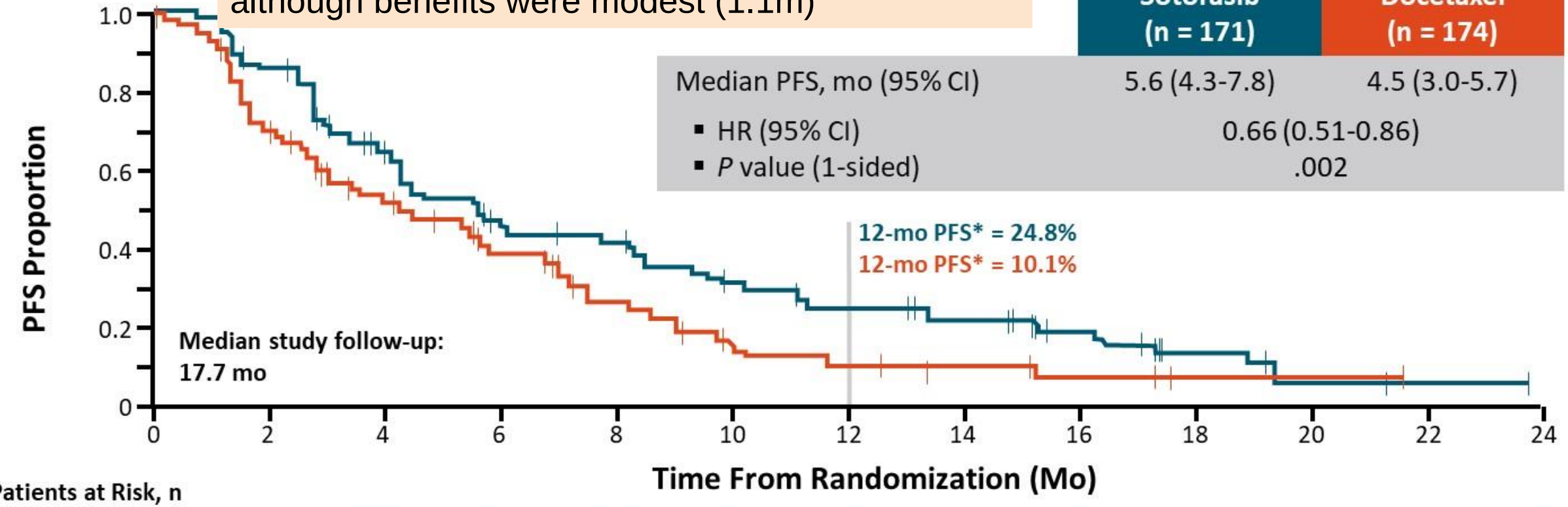
Protocol amended to reduce enrollment to 330 and allow crossover from docetaxel to sotorsib

Johnson ESMO 2022 LBA10

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

Study met its primary endpoint (PFS; P=.002) although benefits were modest (1.1m)

	Sotorasib (n = 171)	Docetaxel (n = 174)
Median PFS, mo (95% CI)	5.6 (4.3-7.8)	4.5 (3.0-5.7)
▪ HR (95% CI)	0.66 (0.51-0.86)	
▪ *P* value (1-sided)	.002	



Patients at Risk, n

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	15	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	7	

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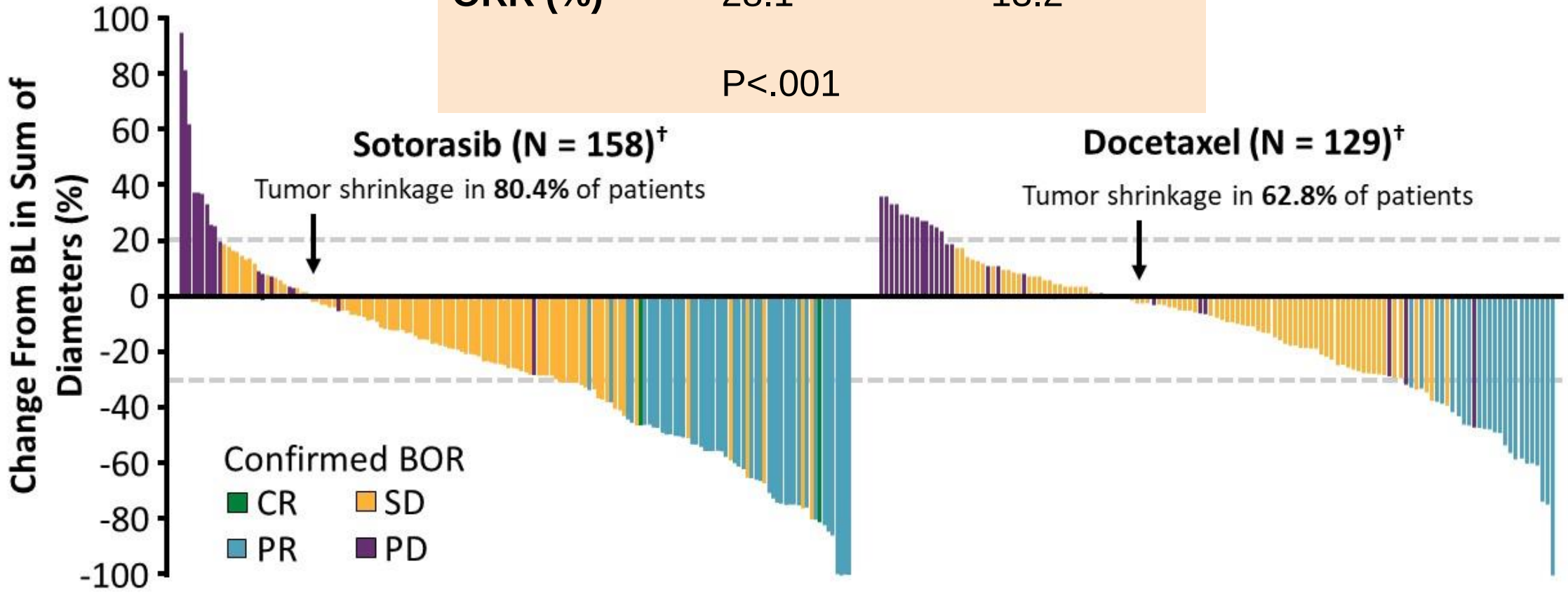
Johnson ESMO 2022 LBA10

CodeBreaK 200: Significantly higher ORR for sotorasib vs docetaxel

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



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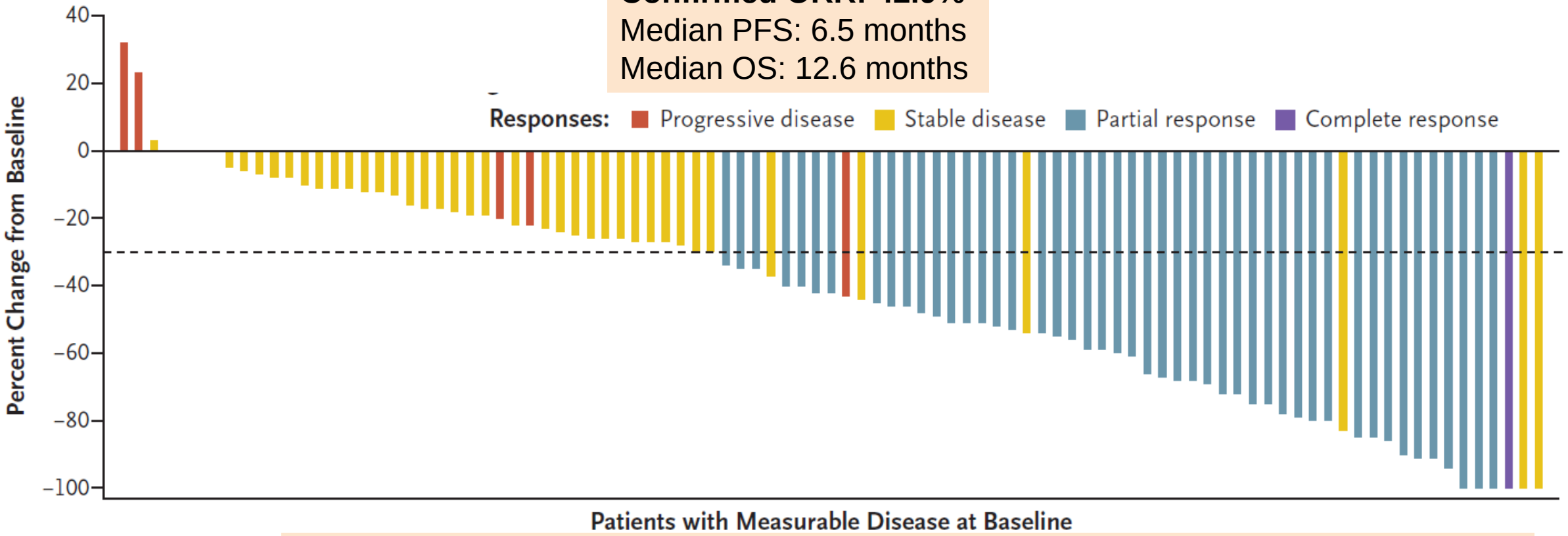
Johnson ESMO 2022 LBA10

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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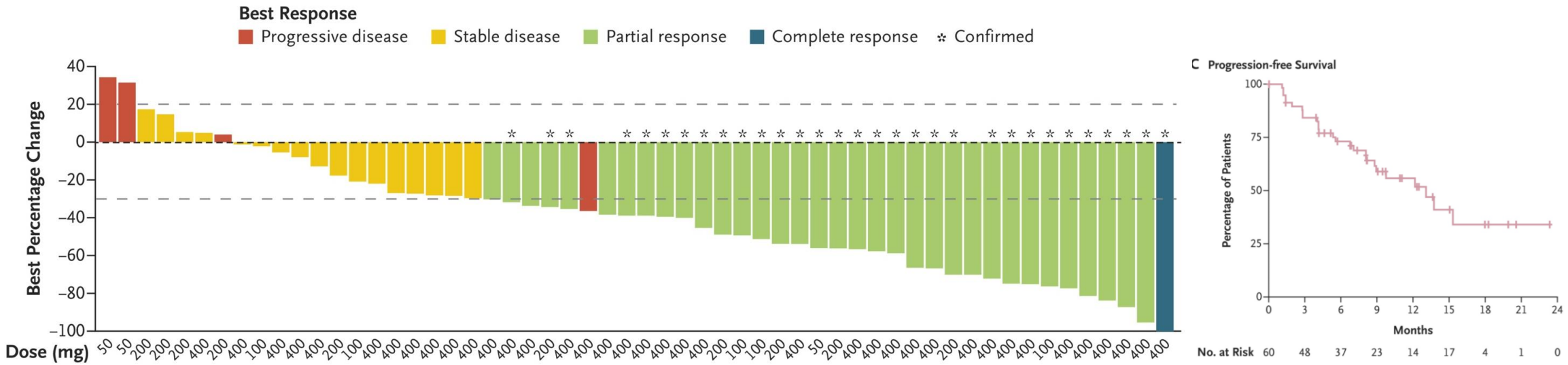
Jänne et. al., NEJM, 2022

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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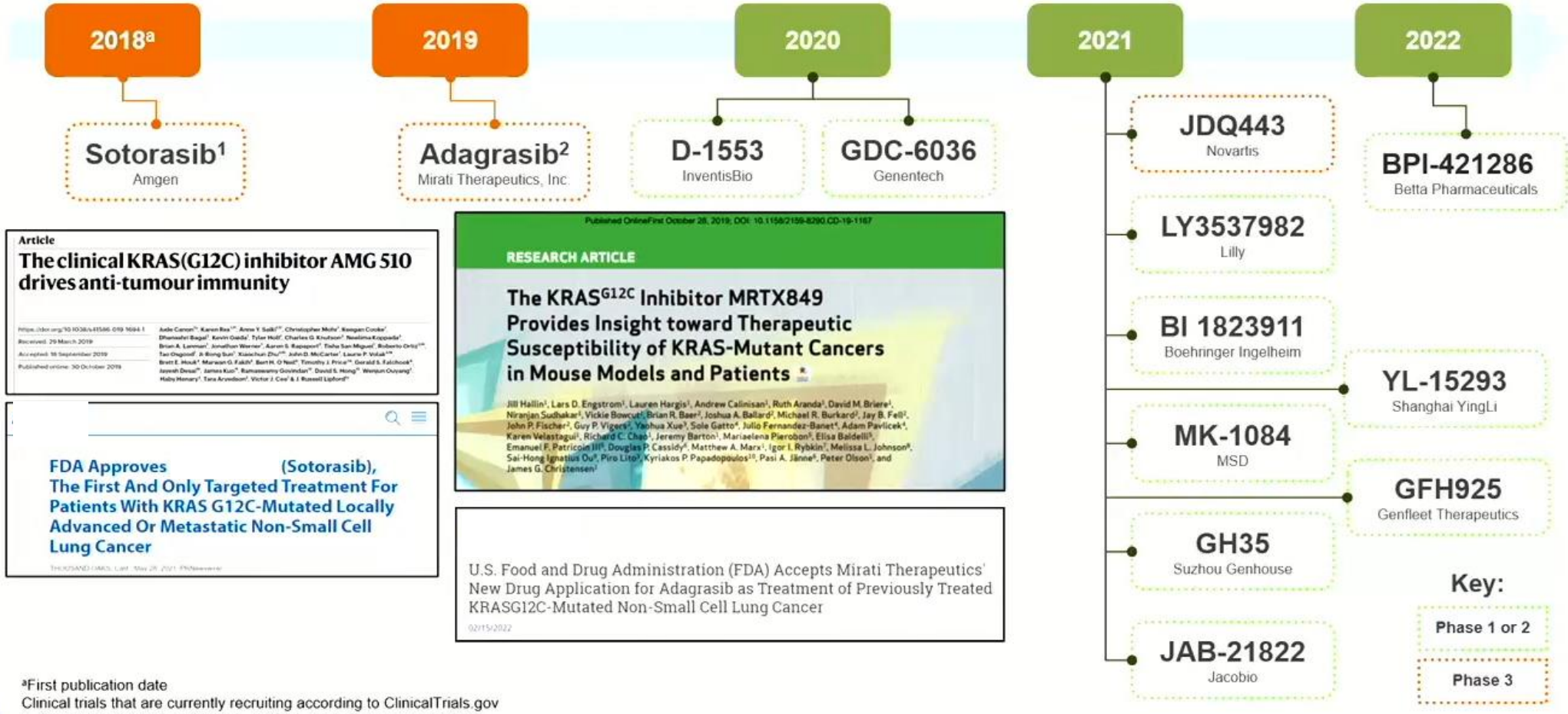
Sacher et. al., NEJM, 2023

Ongoing studies of direct Kras G12C inhibitors

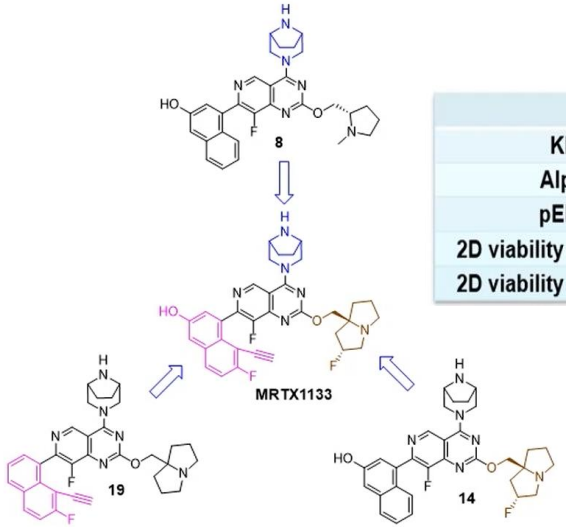


[a]First publication date
Clinical trials that are currently recruiting according to ClinicalTrials.gov
1. Canon J, et al. Nature 2019. 2. Hallin J, et al. Cancer Discov 2020
ClinicalTrials.gov. Accessed August 4, 2022

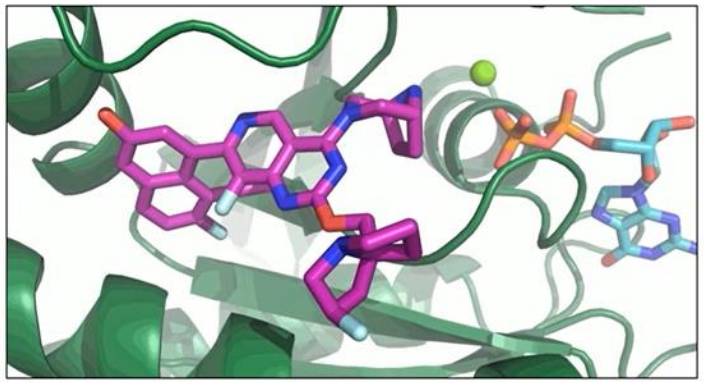
Adapted from Garassino et al, IASLC 2022

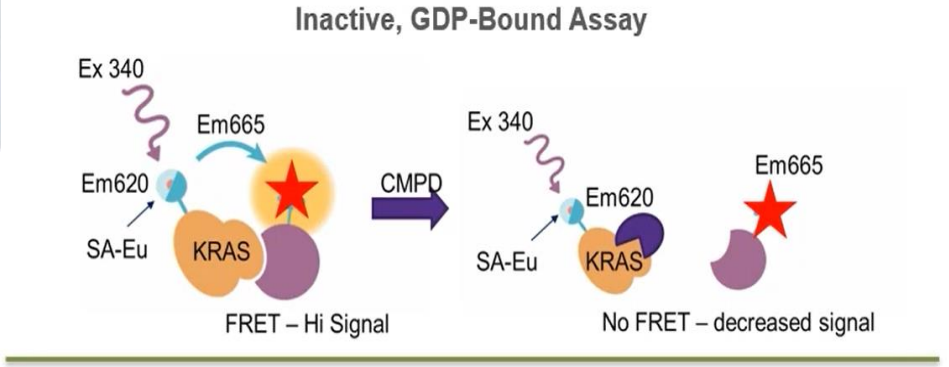
Other types of direct RAS inhibitors

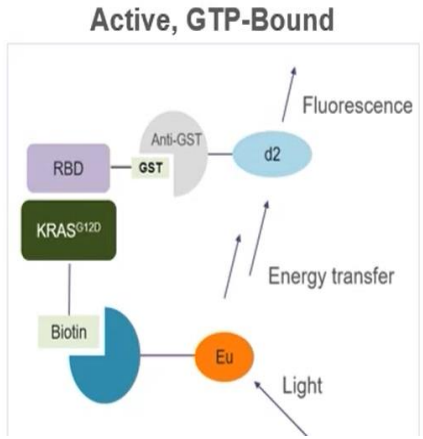
MRTX1133: a novel KRAS^{G12D} inhibitor that binds the inactive and active states of KRAS^{G12D}



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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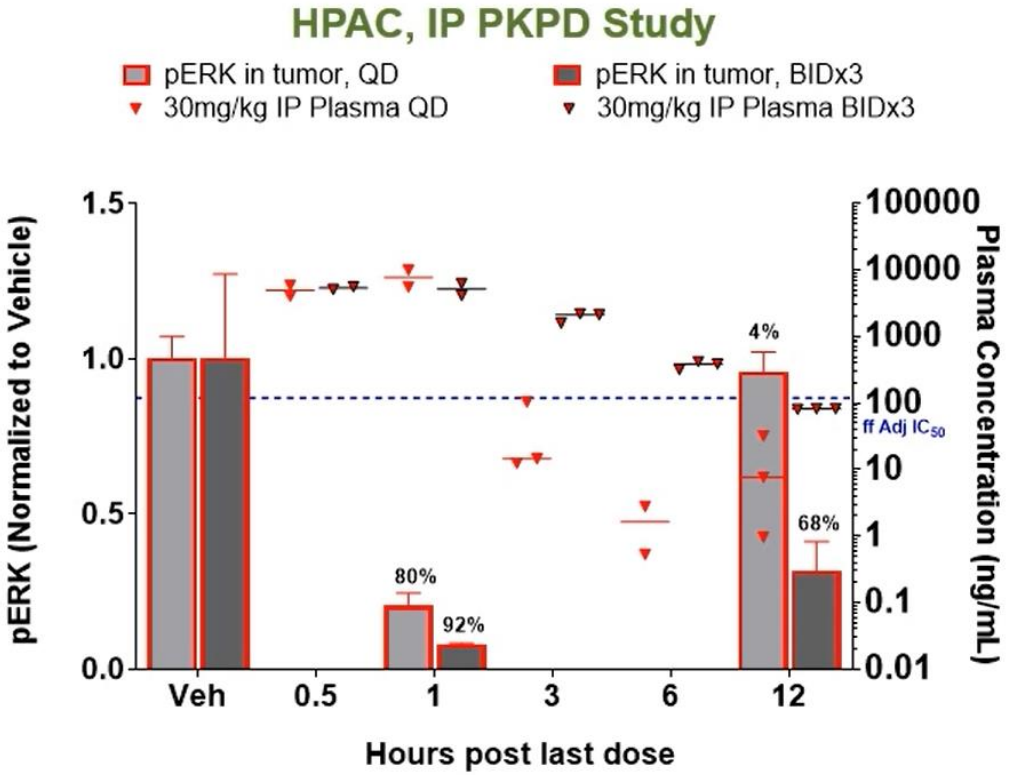
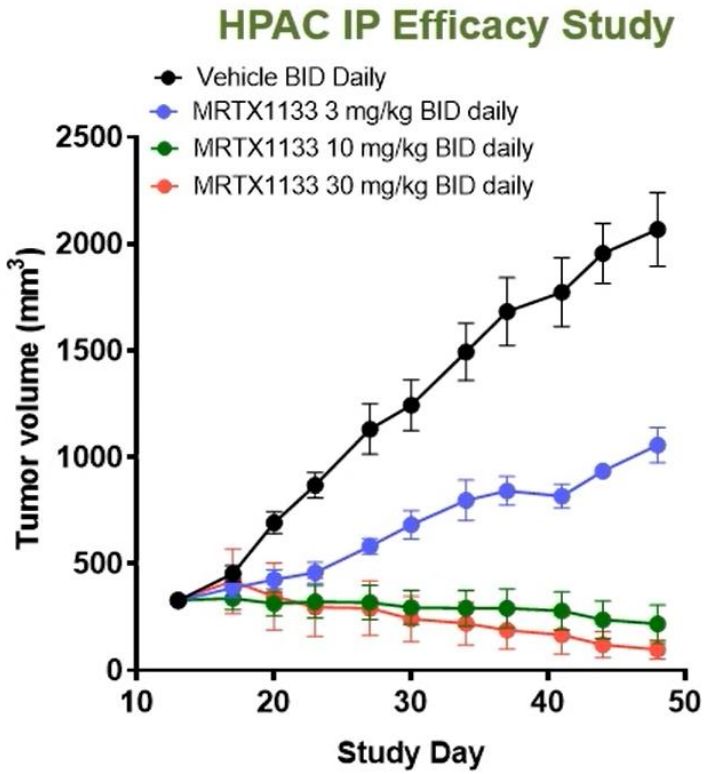
Efficacy of MRTX1133 in xenograft models





- 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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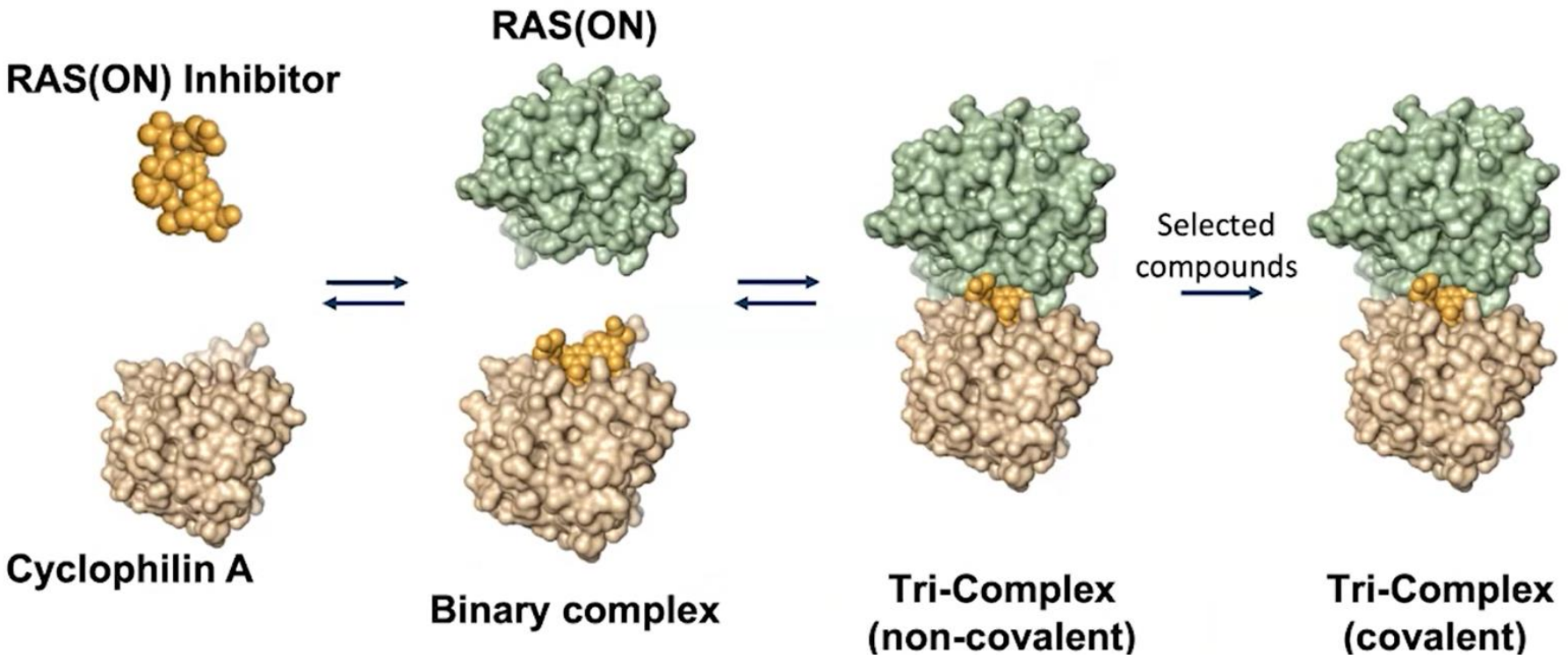
James G. Christensen, Mirati Therapeutics, AACR-NCI-EORTC 2021

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



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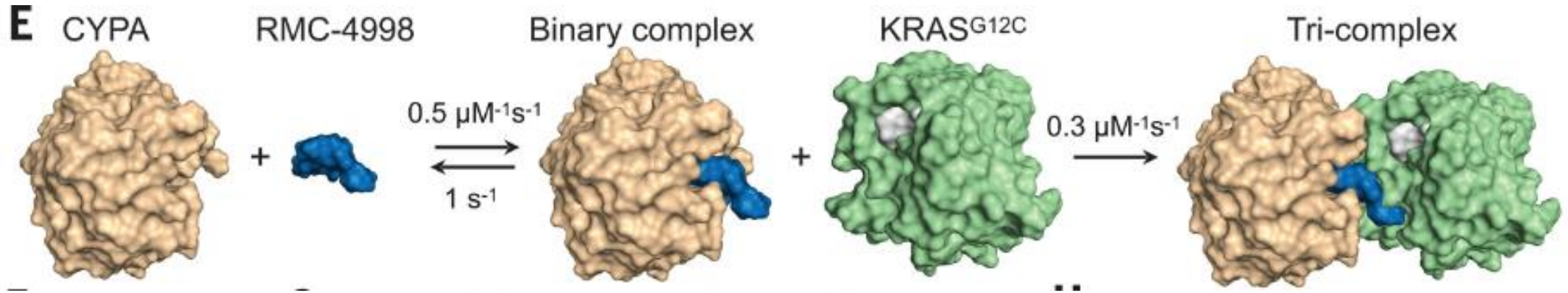
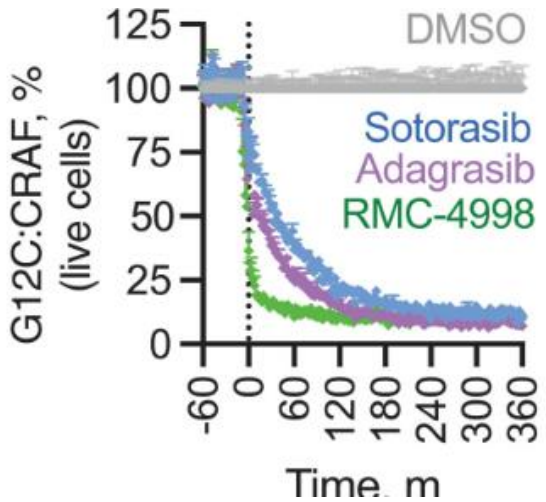
Stephen Kelsey, Revolution Medicines, AACR-NCI-EORTC 2021

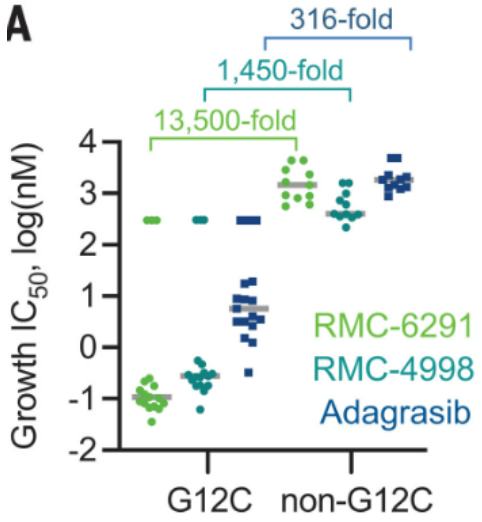
The tricomplex inhibitory strategy of mutant KRAS: RMC-4998 for KRAS G12C mutant NSCLC



Kinetics of target inhibition



3D cell viability



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C. Schulze, et al, *Science* 2023

RMC-6236: tri-complex RAS-MULTI(ON) inhibitor in patients with KRAS mutant PDAC and NSCLC

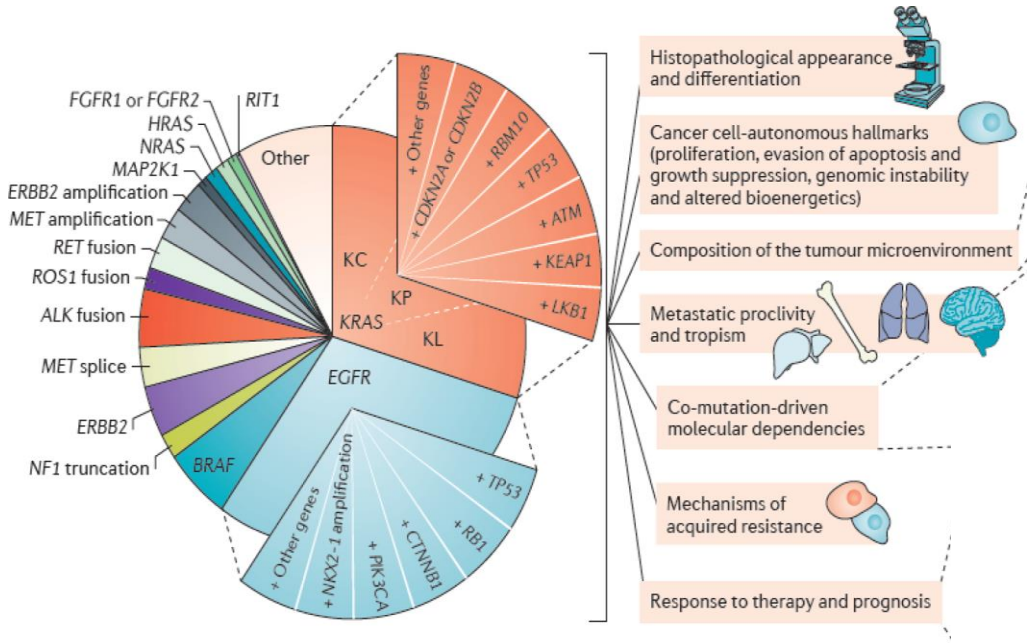
- 33 patients with KRAS G12X mutations and PDAC or NSCLC:
  - 11 NSCLC: 5 G12D, 4 G12V, 2 G12A
  - 22 PDAC: 13 G12D, 7 G12V, 2 G12R
- ORR 36% (confirmed and unconfirmed) among 14 evaluable patients (10 PDAC, 4 NSCLC) dosed at least 8 weeks prior to the data cut-off date
- 2/10 PDAC and 3/4 NSCLC.
- Treatment-related adverse events (TRAEs) occurring in ≥10% of patients were rash (52%), diarrhea (21%), nausea (21%), and vomiting (15%).

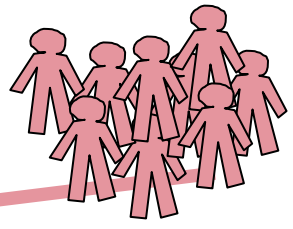
Arbour, et al, ESMO 2023, abstract 6520

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

NSCLC

KRAS co-mutations





KRAS mutant ~25%

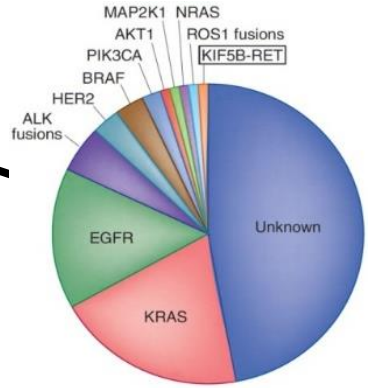
G12C ~13%

G12V ~6%

G12D ~3%

Other

Driver positive: the genomic pie (40-50%)



KRAS Alleles in NSCLC

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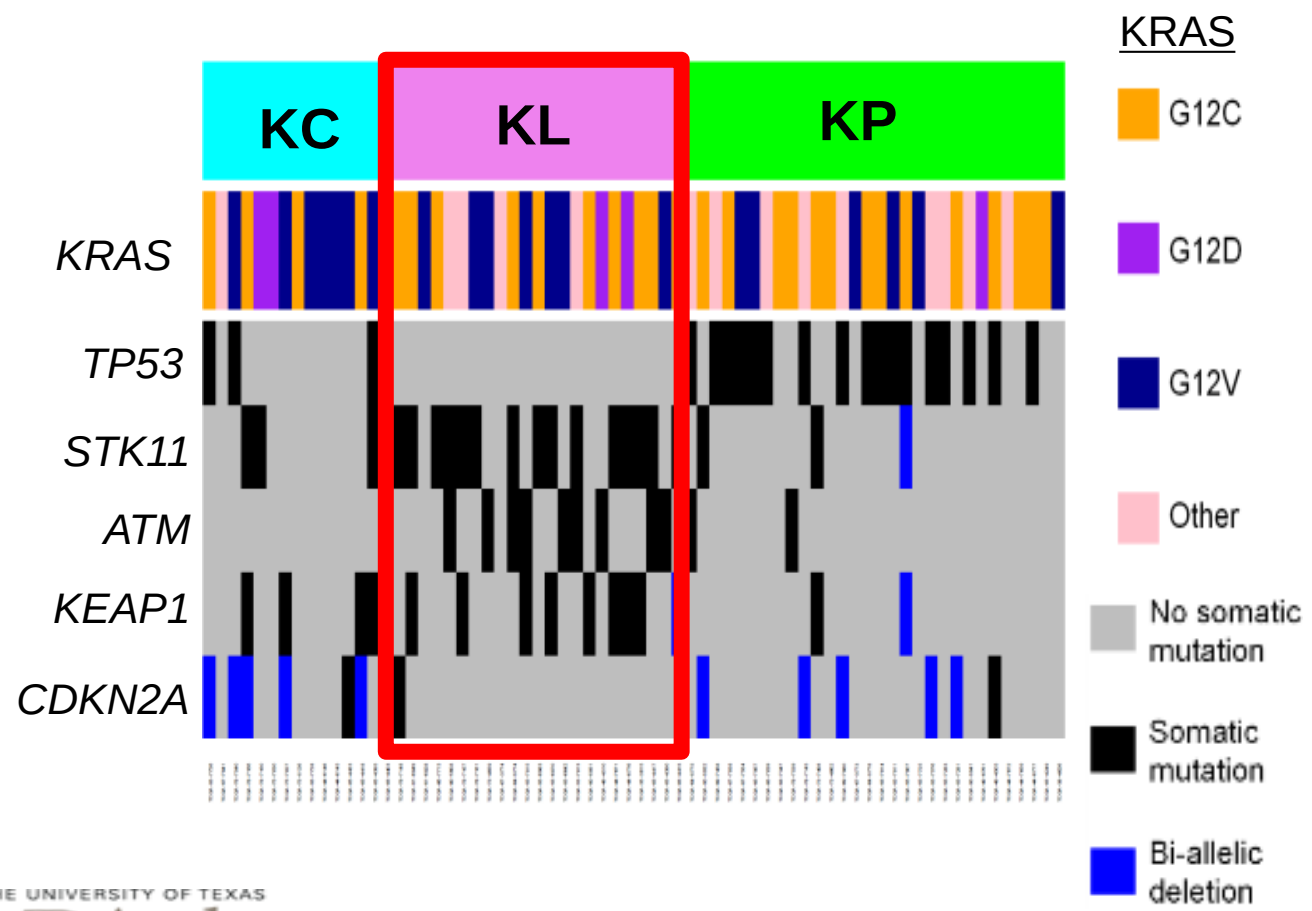
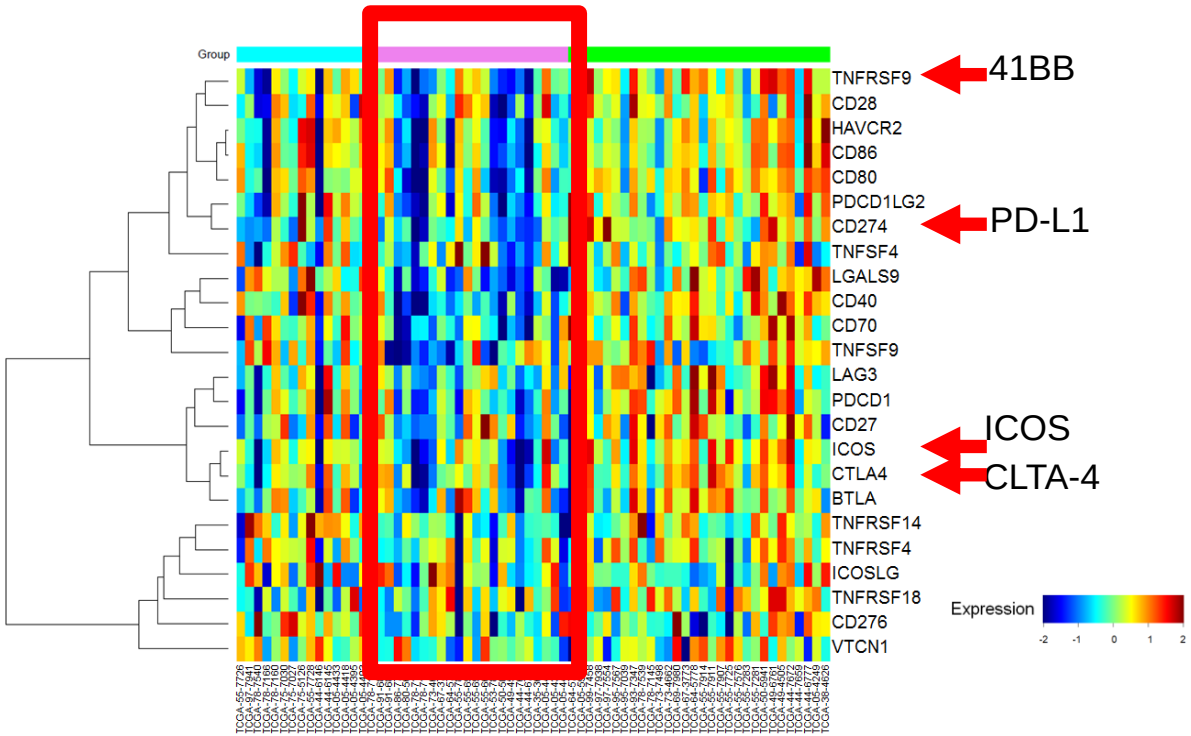
Skoulidis and Heymach, Nat Rev Cancer 2019

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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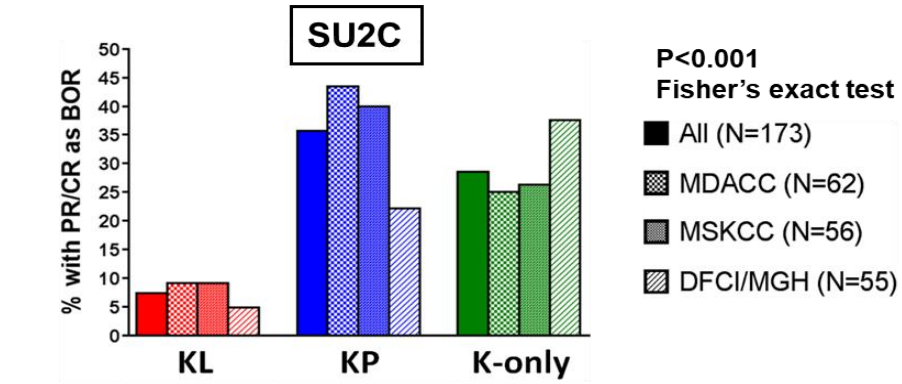
Skoulidis et al., Cancer Discov, 2015

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

Clinical study

Mouse study

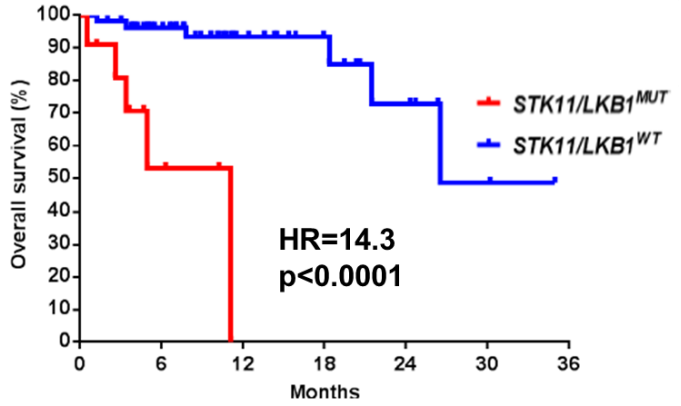
A



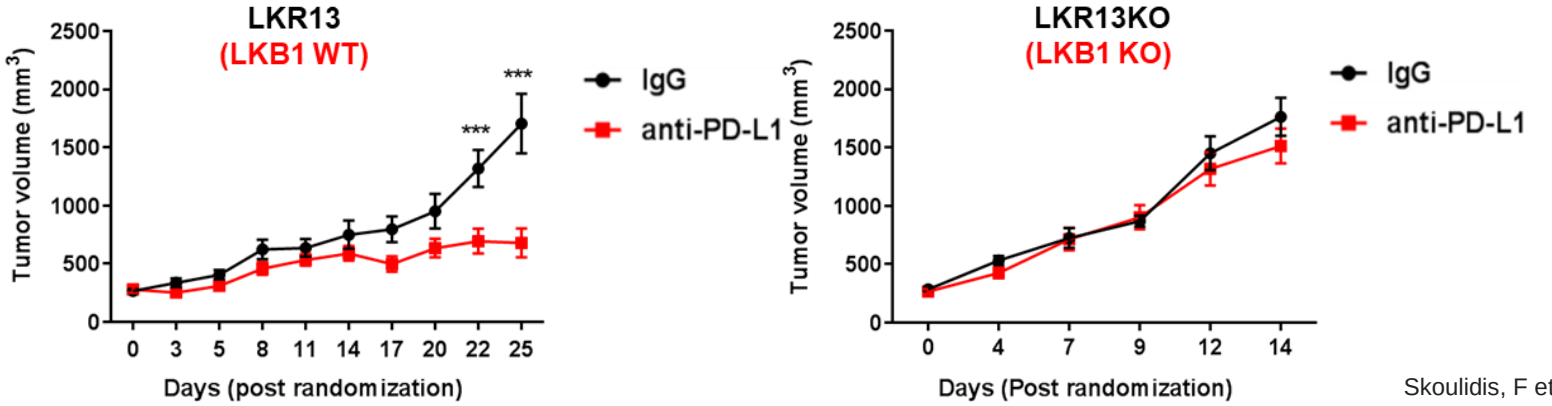
Group	KL	KP	K-only
ORR	7.4% (4/54)	35.7% (20/56)	28.6% (18/63)

B

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



C



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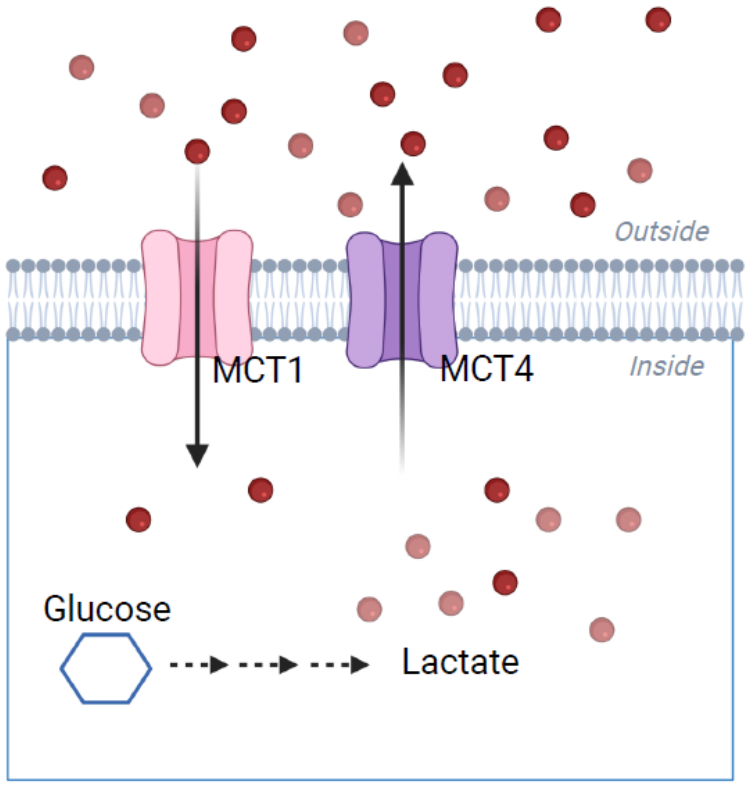
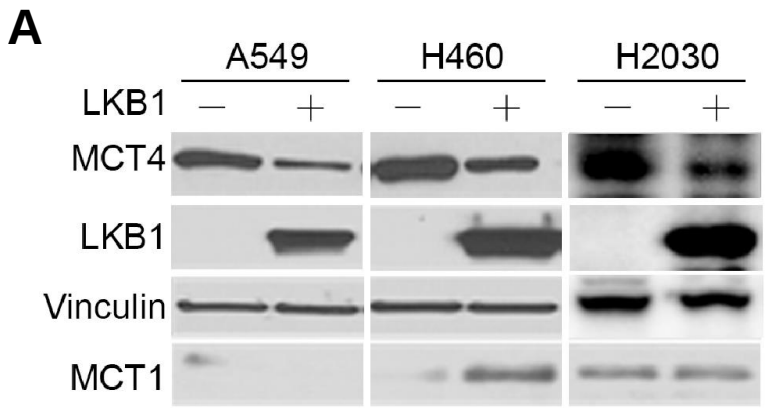
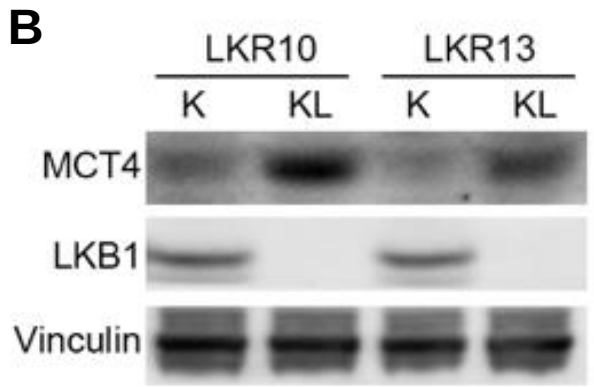
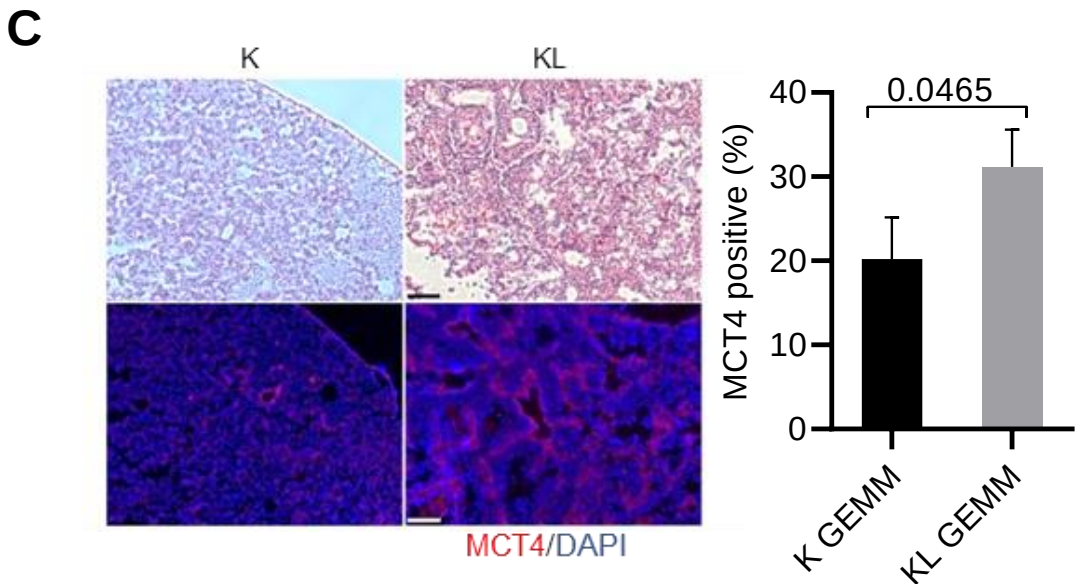
Skoulidis, F et al. *Cancer Discov* (2018)

LKB1 deficiency upregulates monocarboxylate transporter 4 (MCT4) lactate transporter









Qian et al, Cancer Cell 2023

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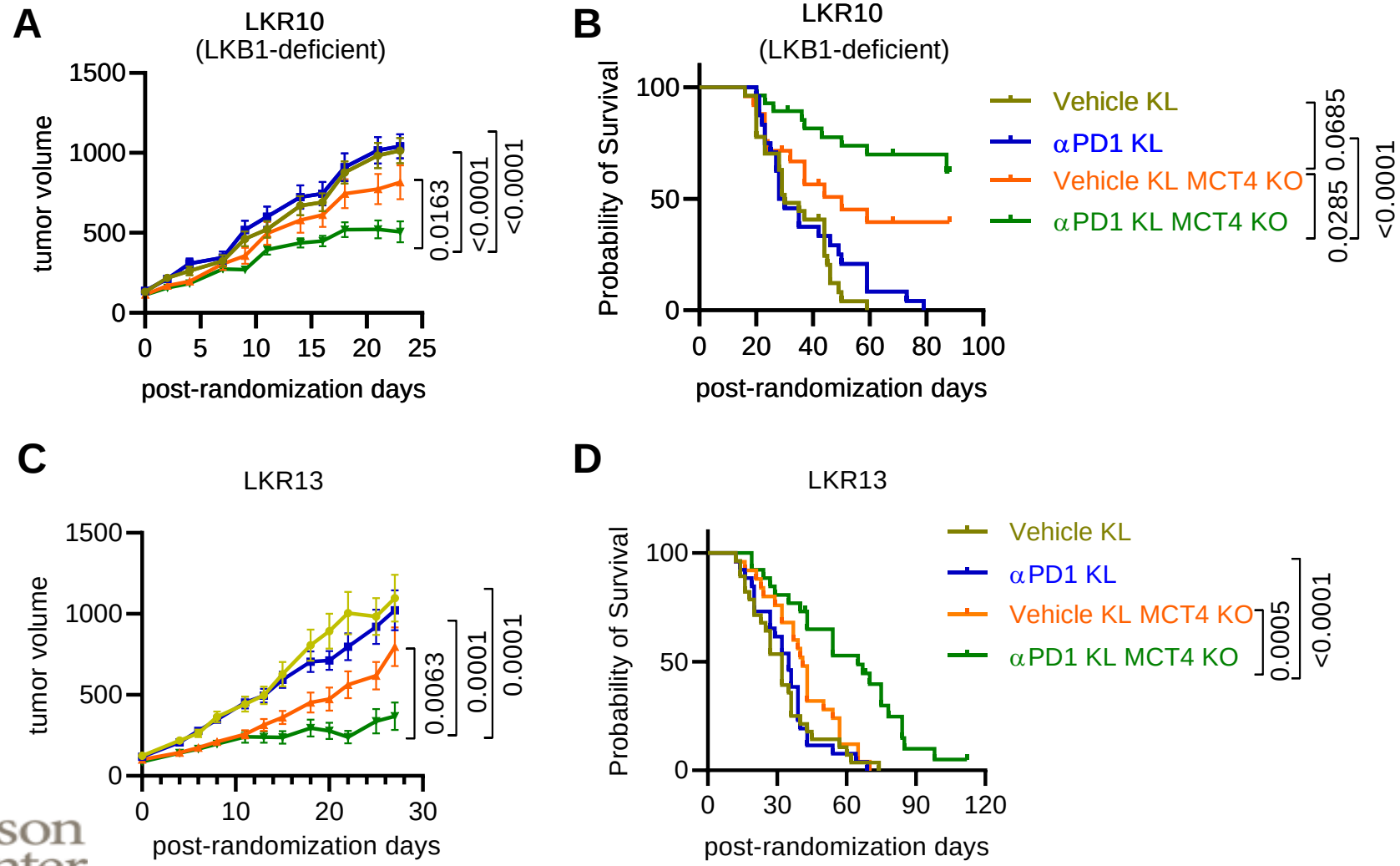
MCT4 KO enhances immunotherapy response in KL tumors



Qian et al, Cancer Cell 2023

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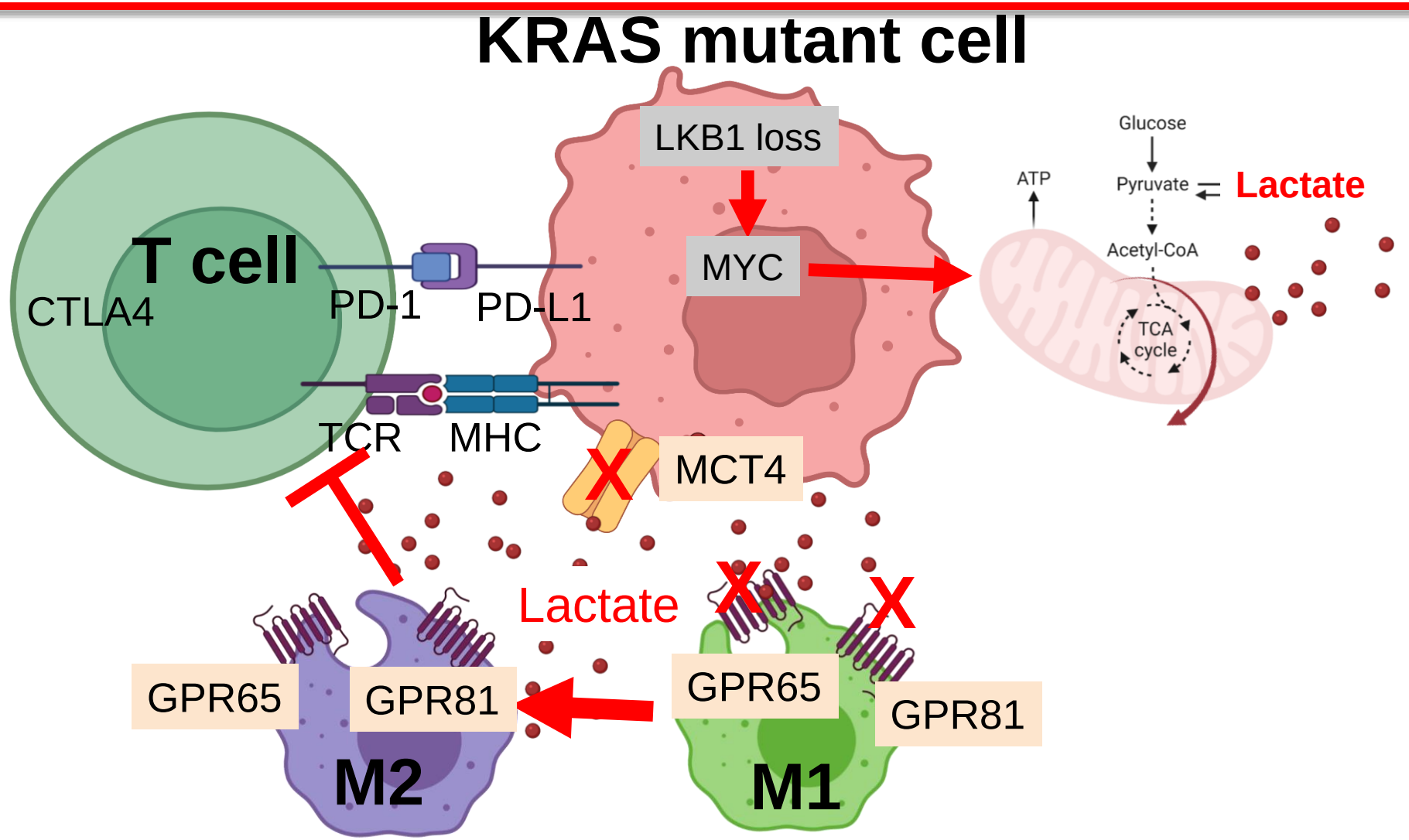
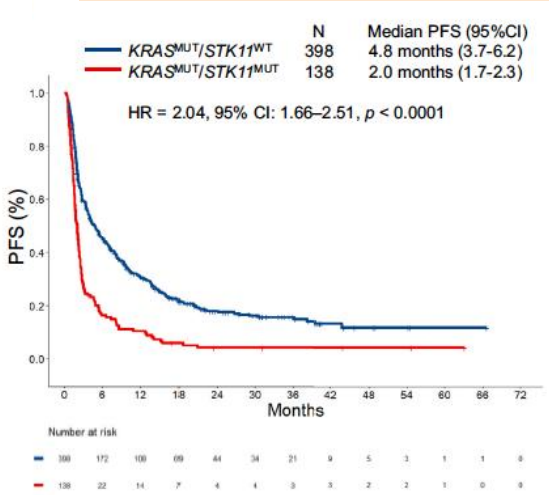
LKB1 loss enhances lactate production and promotes and immunosuppressive tumor microenvironment



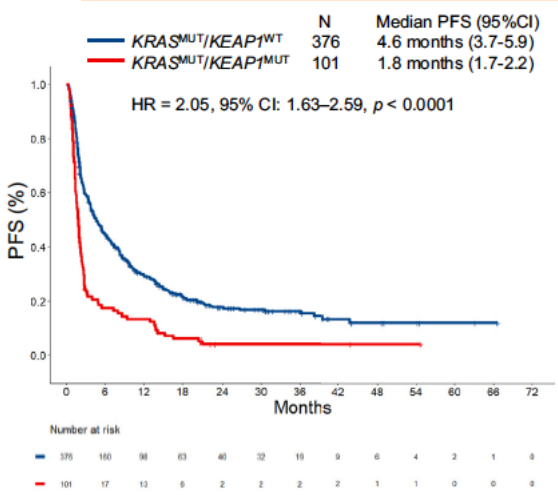
Adapted from Qian et al, Cancer Cell 2023

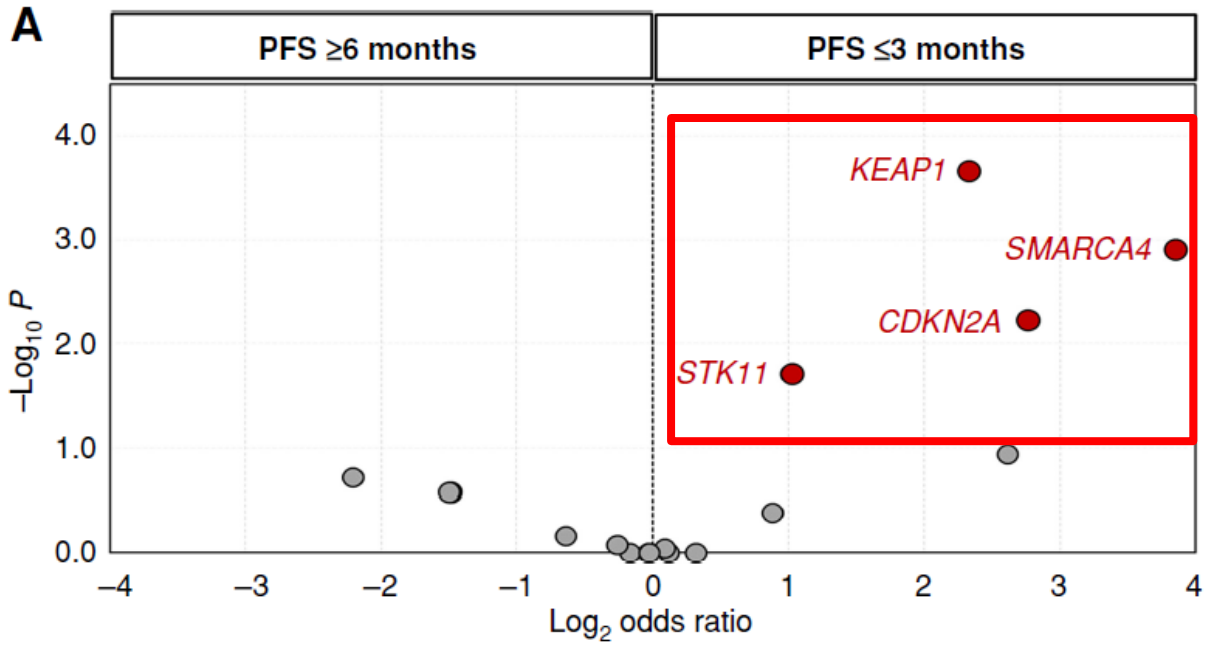
Impact of KRAS co-mutations on response to KRAS G12C inhibitors

STK11 mutations
PFS HR 2.04



KEAP1 mutations
PFS HR 2.05





Since these co-mutations are associated with different drug sensitivities, they may be useful for guiding KRAS G12C inhibitor combinations

Negrao et al, *Cancer Dis 2023*

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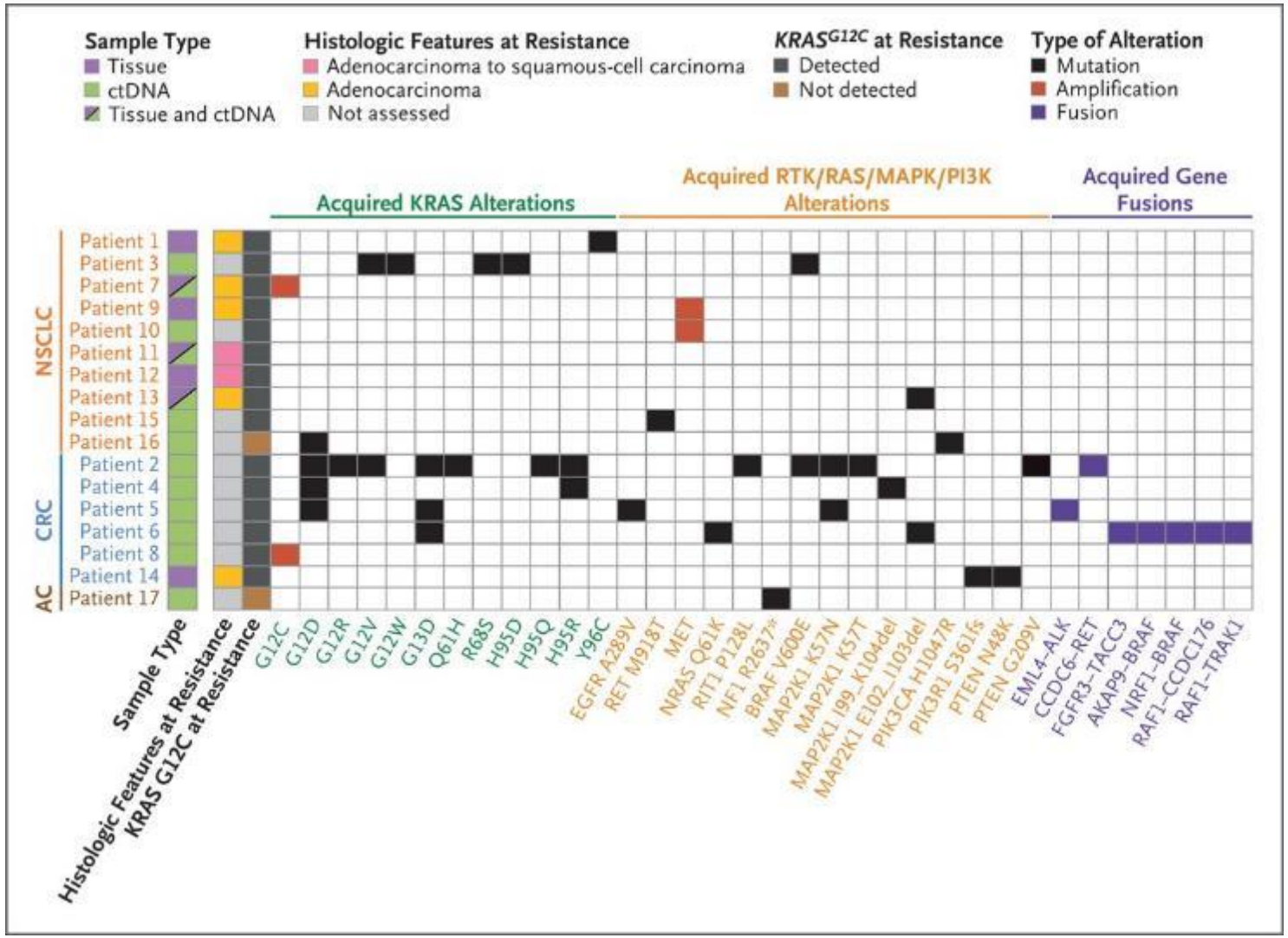
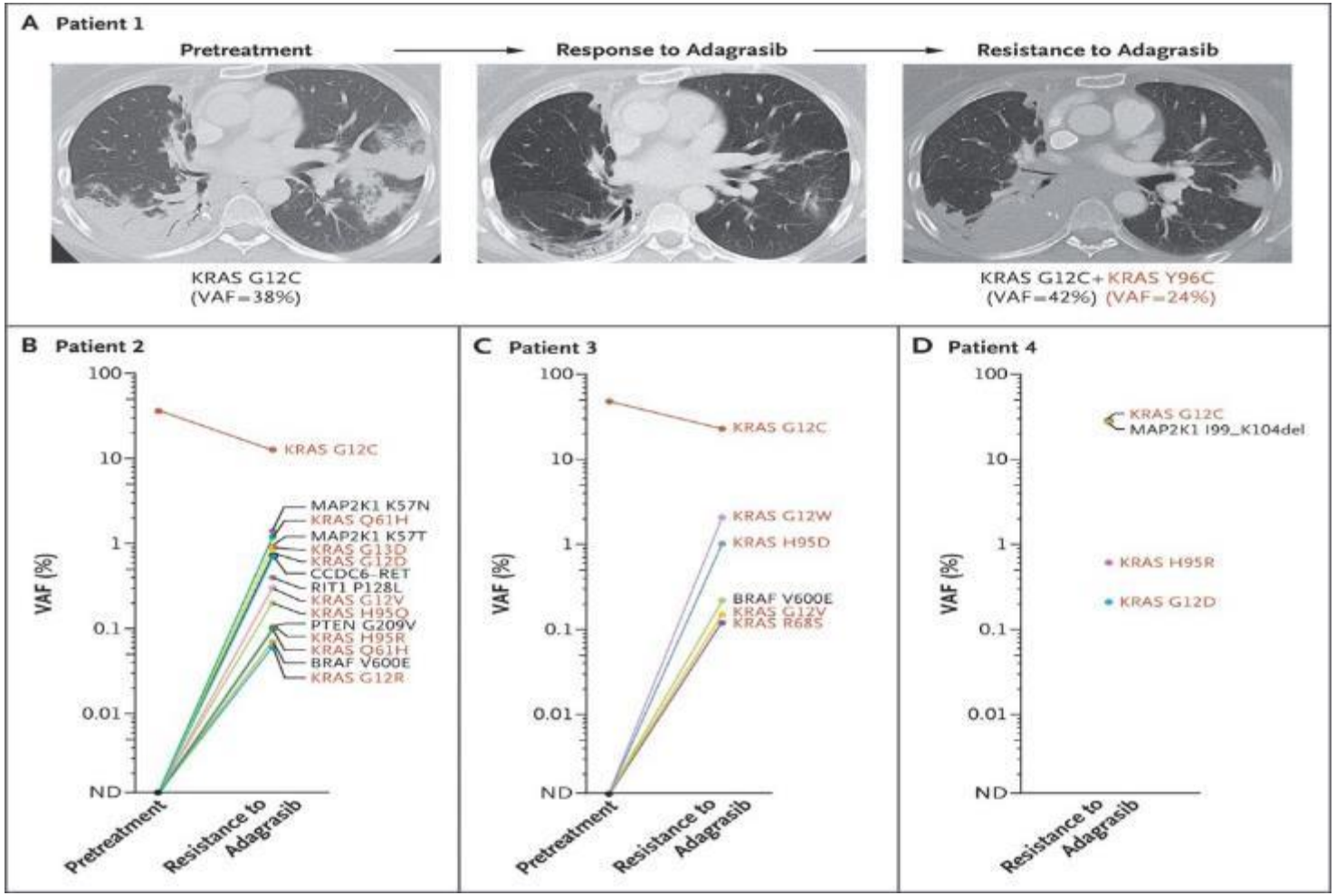
Mechanisms of resistance to G12C inhibitors and potential combinations to overcome them

Summary of putative mechanisms of acquired resistance to adagrasib treatment



Awad et al, NEJM 2021

Resistance to Adagrasib Conferred by Acquired *KRAS* Mutations



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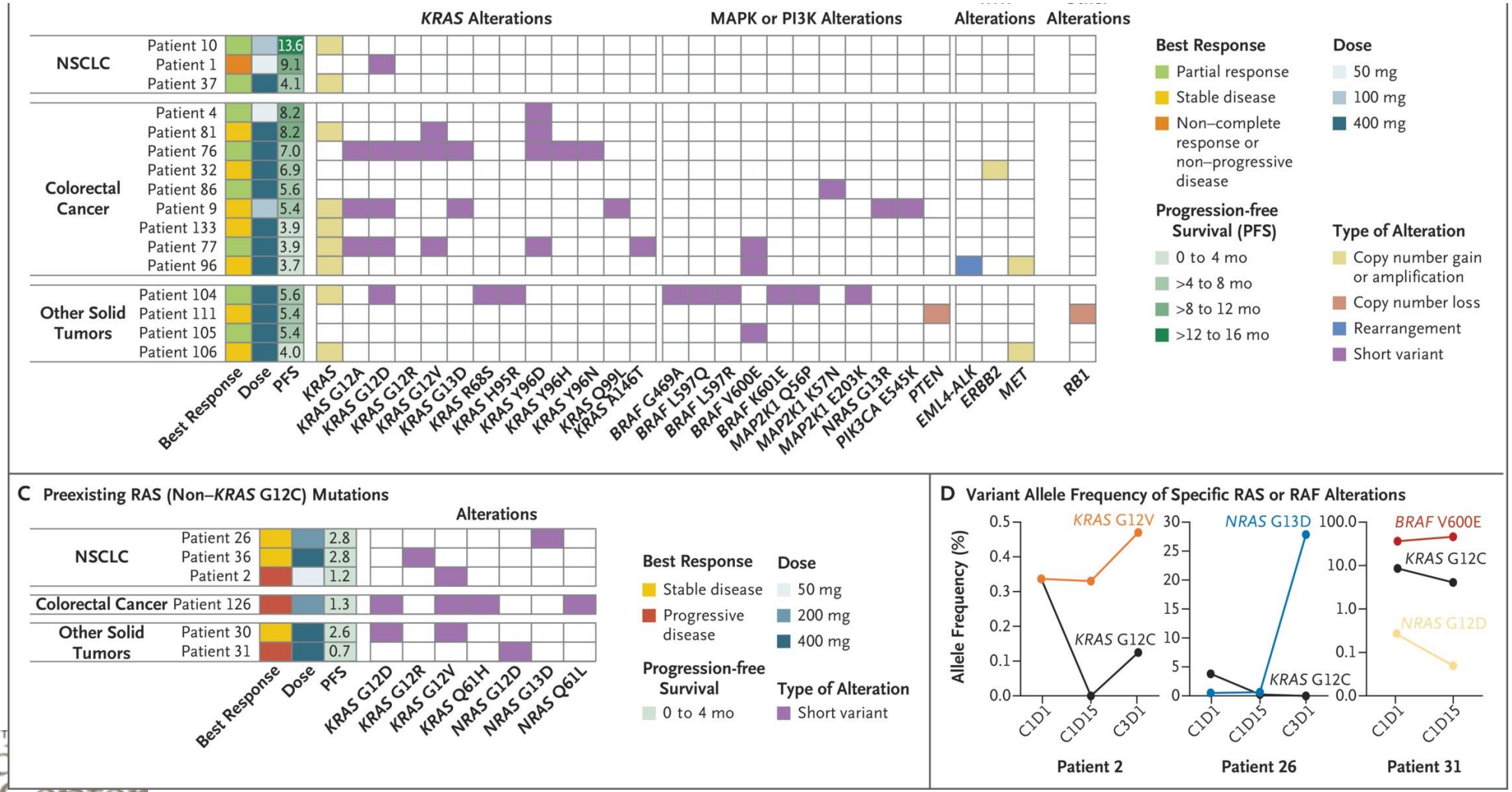
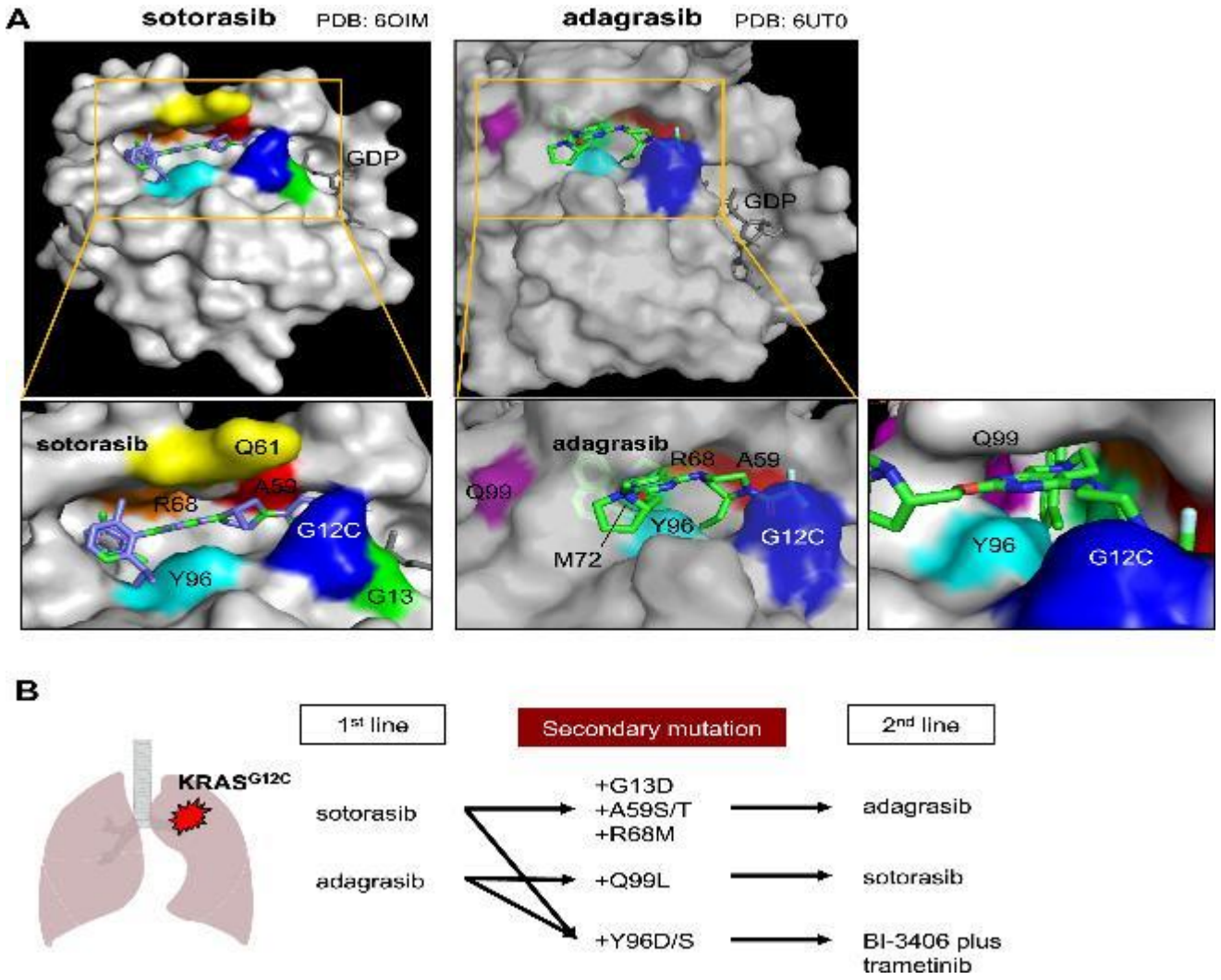
Awad et al, NEJM 2021

Diverse mechanisms of resistance to divarasib in $KRAS^{G12C}$ mutant tumors



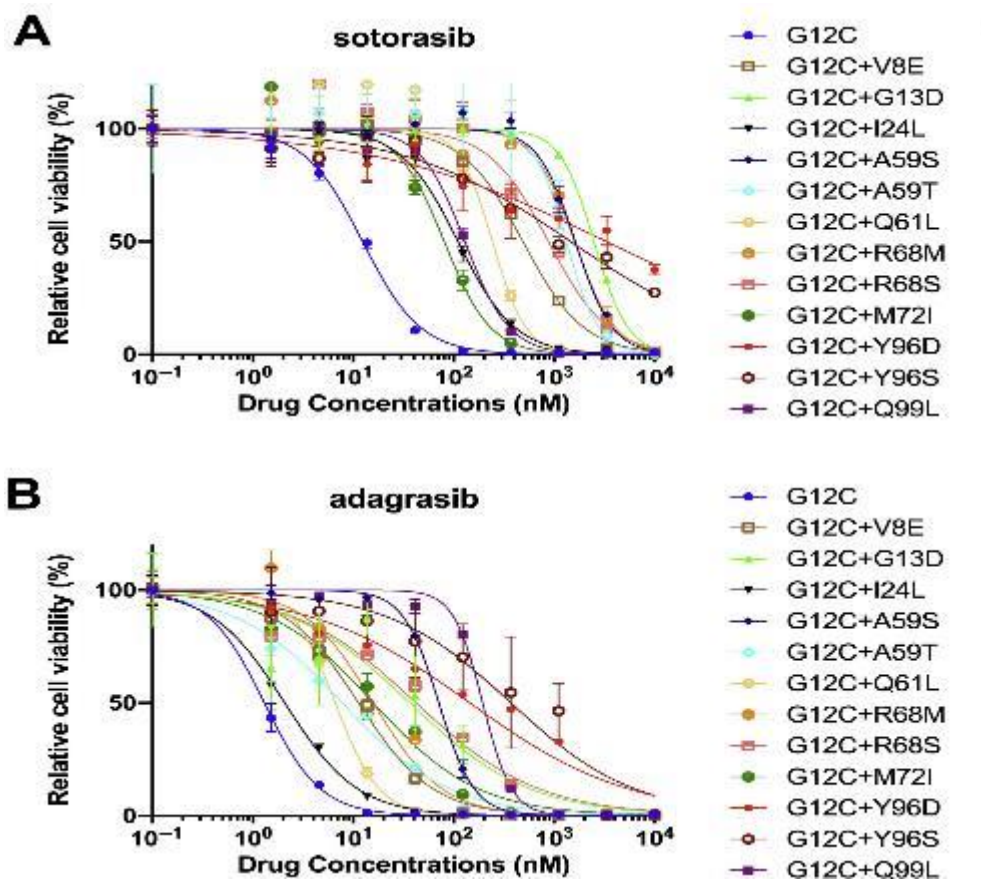
Sacher et. al., NEJM, 2023

Structural analysis of secondary KRAS mutations affecting the interaction between KRASG12C and sotorasib or adagrasib



Koga et al., JTO 2021

KRAS Secondary Mutations That Confer Acquired Resistance to KRAS G12Ci



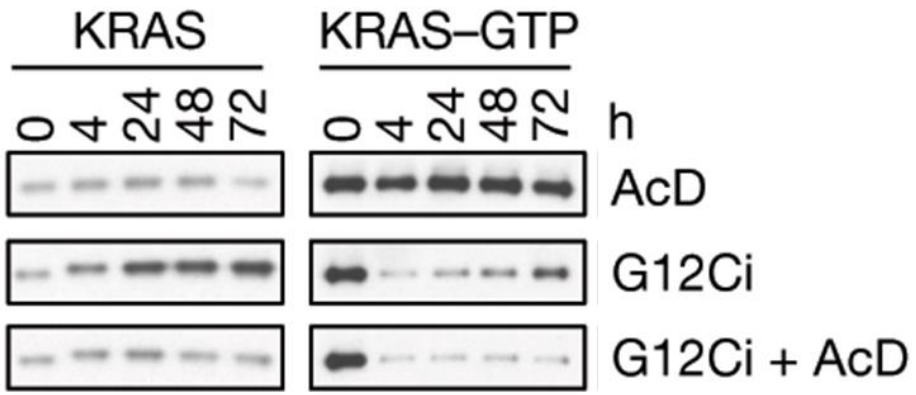
C

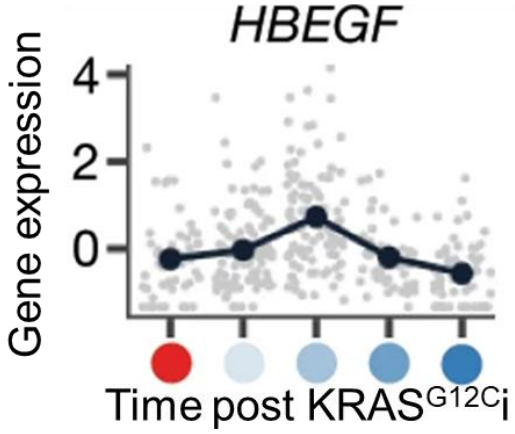
	sotorasib	adagrasib
G12C	1	1
G12C+V8E	39.5	8.7
G12C+G13D	202	28.2
G12C+I24L	8.9	1.6
G12C+A59S	131	54.8
G12C+A59T	107	6.0
G12C+Q61L	19.6	5.1
G12C+R68M	129	12.2
G12C+R68S	71.1	32.5
G12C+M72I	6.5	12.2
G12C+Y96D	268	111
G12C+Y96S	112	286
G12C+Q99L	10.4	150

Resistance index (RI)
<10
10–100
100<

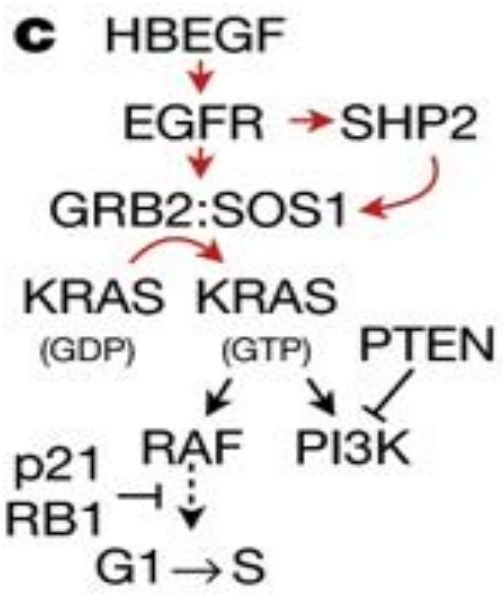
Koga et al., JTO 2021

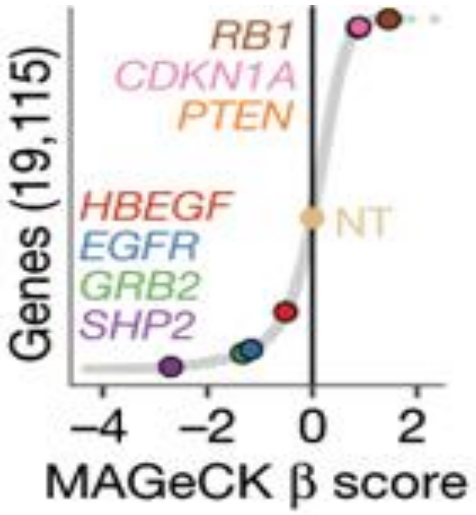
KRASG12C inhibitor adaptation correlates with upregulation of EGFR signaling





HB-EGF activates EGFR and HER4





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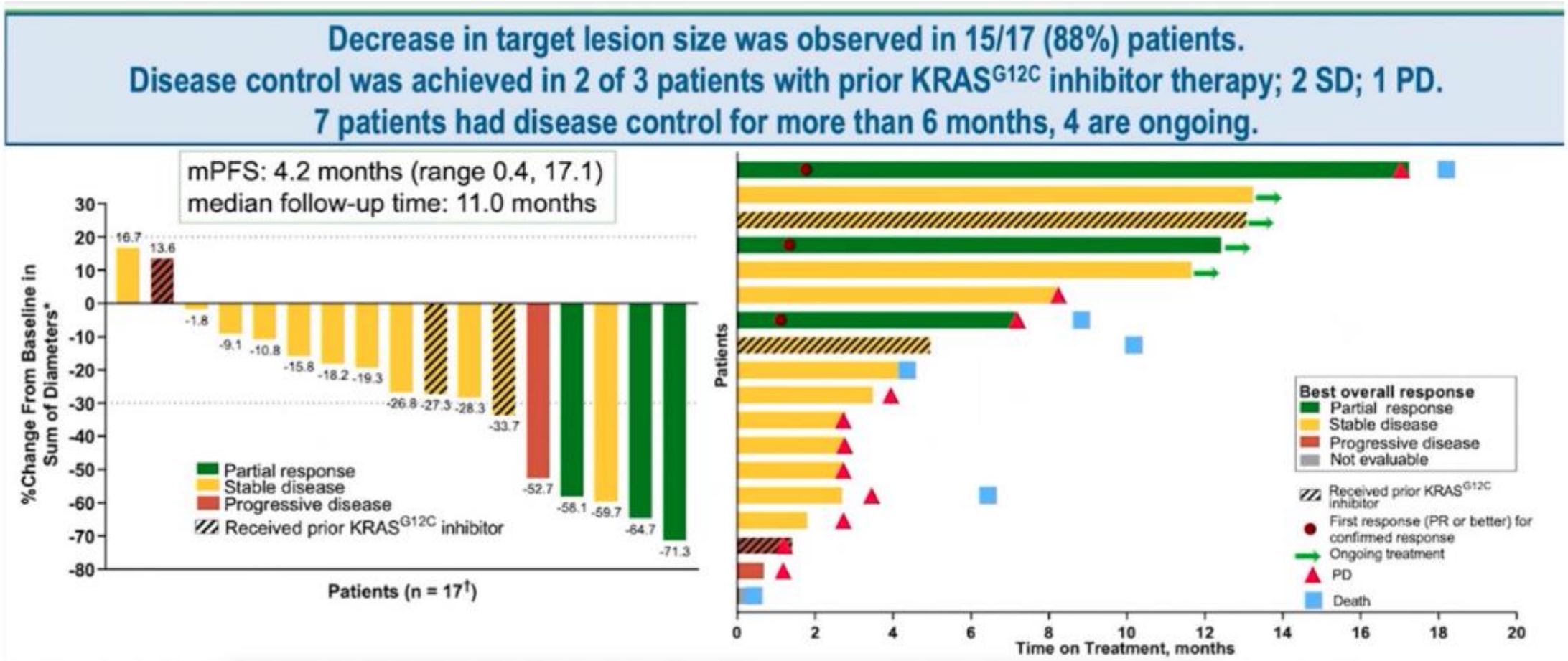
Xue et al Nature 2020

Sotorasib + trametinib combination in NSCLC: more effective in patients receiving prior KRAS^{G12Ci} therapy



Codebreak 101 subprotocol
Ramalingam, AACR-NCI-EORTC 2021

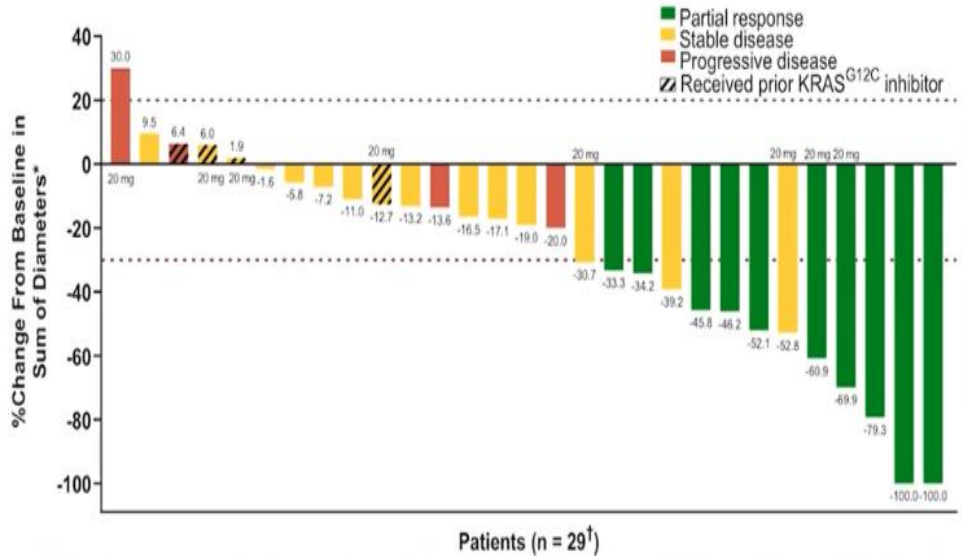
Efficacy of sotorasib + afatinib combination in NSCLC

Response assessed by investigator	Sotorasib 960 mg + Afatinib 20 mg (n = 10)*	Sotorasib 960 mg + Afatinib 30 mg (n = 23)†	Sotorasib 960 mg PO QD + Afatinib 20 mg or 30 mg QD Combined Cohorts (N = 33)
ORR,‡ % (95% CI)	**20.0 (2.5, 55.6)**	**34.8 (16.4, 57.3)**	**30.3 (15.6, 48.7)**
Best overall response, n (%)			
Partial response, confirmed	2 (20.0)	8 (34.8)	10 (30.3)
Stable disease	5 (50.0)	10 (43.5)	15 (45.5)
Progressive disease	1 (10.0)	4 (17.4)	5 (15.2)
Not done	2 (20.0)	1 (4.3)	3 (9.1)
Disease control rate, n (%)	**7 (70.0)**	**18 (78.3)**	**25 (75.8)**

*Includes 4 patients who had received prior sotorasib treatment. †Includes 1 patient who had received prior sotorasib treatment. ‡ORR analysis set includes all patients who received ≥ 1 dose of investigational product, have ≥ 1 measurable lesions at baseline assessed using RECIST 1.1, and have the opportunity to be followed for ≥ 7 weeks starting from day 1.
AE, adverse event; ORR, objective response rate; PD, progressive disease; PO, oral; QD, daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

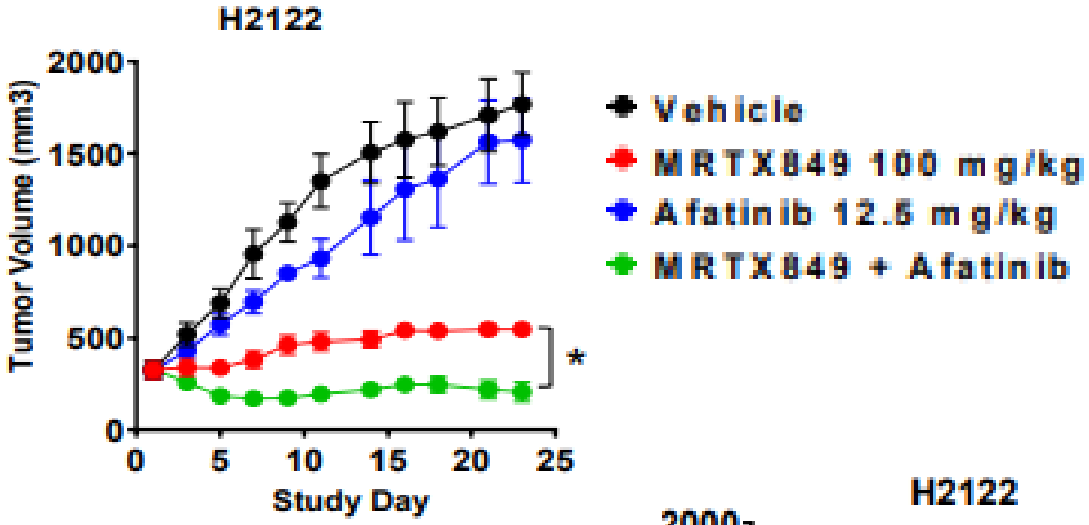
Overall, 10 of 33 (30%) of patients achieved partial response and 25 of 33 (76%) achieved disease control. For patients receiving prior KRAS^{G12C} inhibitor, 3 had SD, 1 had PD, and 1 withdrew due to an AE.

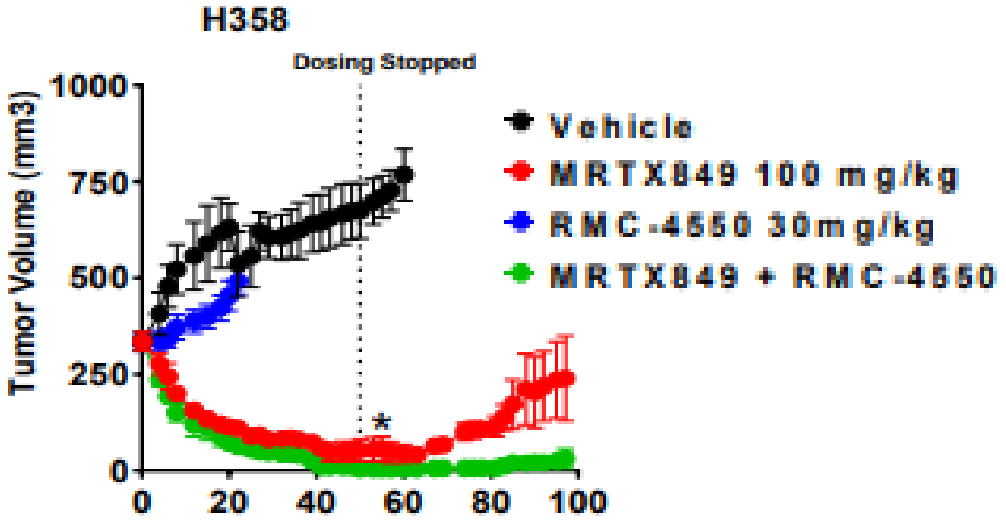
Tumor Response: Sotorasib 960 mg + Afatinib 20 or 30 mg combined cohorts

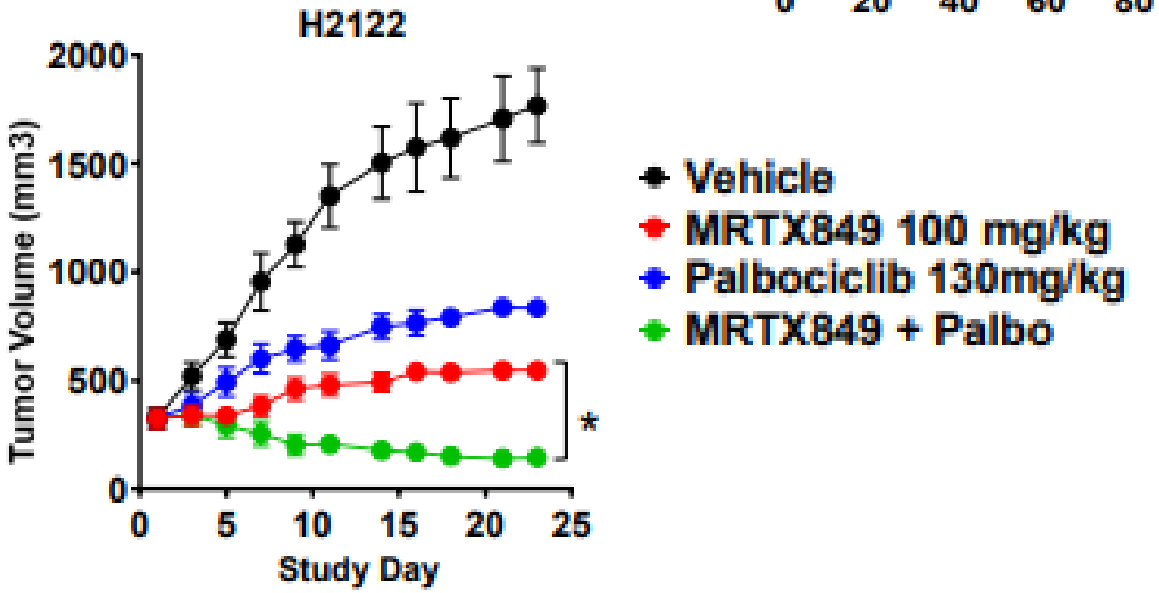


Codebreak 101 subprotocol D
Gandara, AACR-NCI-EORTC 2021

EGFR/HER2 family, SHP2, and CDK4/6 inhibitor combinations further increased anti-tumor responses







Hallin, J. Cancer Discov. 2019

KRAS inhibitors: the bottom line

1. Direct KRAS G12D inhibitors have finally arrived!
   - Sotorasib, adagrasib have FDA accelerated approval
   - Divarasib and others show promising activity
2. New types of KRAS inhibitors (G12D, tricomplex, others) can potentially broaden the patient population that can be treated
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

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