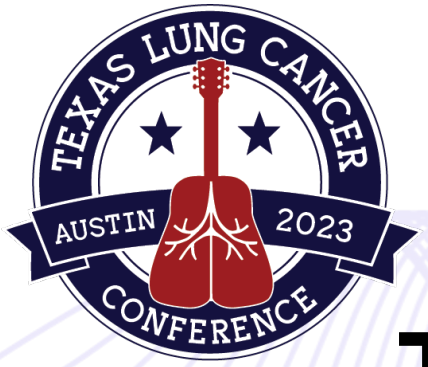


Targeting *KRAS*-mutant NSCLC

Ferdinandos Skoulidis, M.D., Ph.D

Associate Professor

Department of Thoracic/Head and Neck Medical Oncology

The University of Texas MD Anderson Cancer Center

April 1, 2023

Endorsed by

IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Thoracic Cancers Worldwide

Accredited by

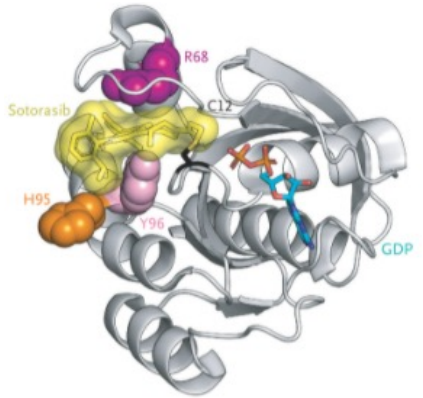
MEC THE MEDICAL EDUCATOR CONSORTIUM

Presented by

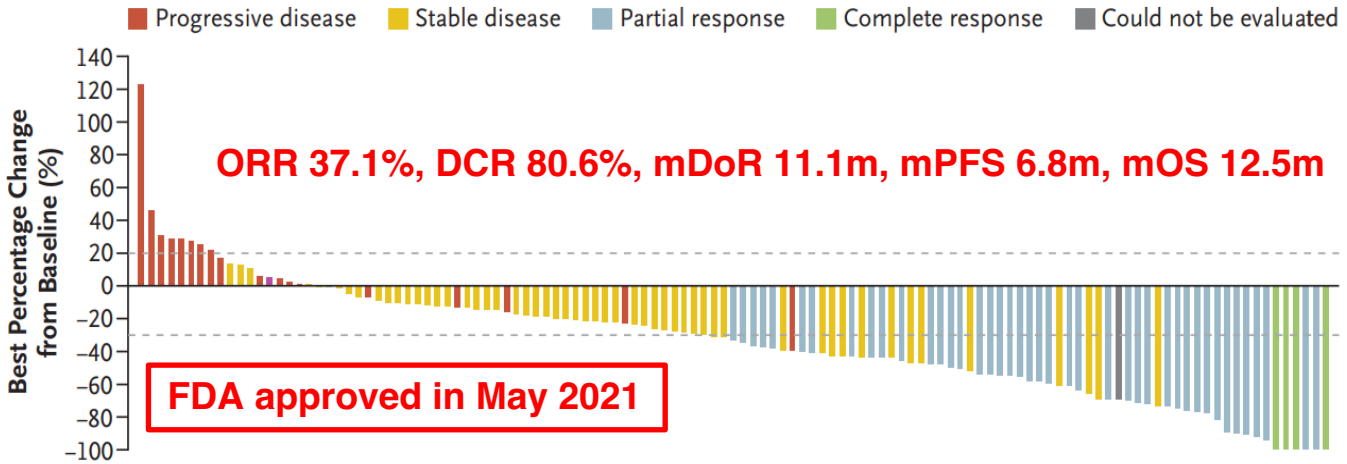
IDEOlogy Health
Creating Aha! Moments In Healthcare

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

A. Sotorasib (AMG 510)

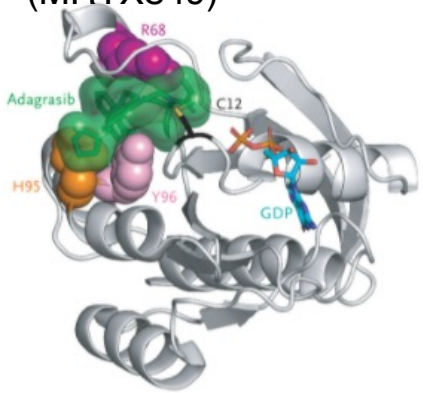


Awad MM et al. *N Engl J Med* 2021 Jun24;384(25):2382-2393

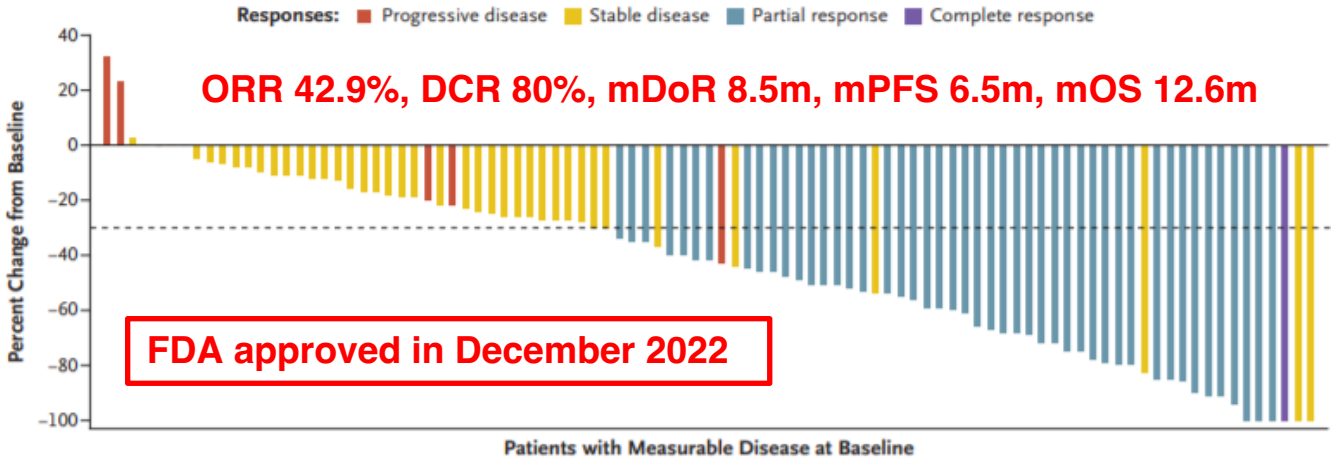


Skoulidis F et al. *N Engl J Med* 2021 Jun 24;384(25):2371-2381

B. Adagrasib (MRTX849)



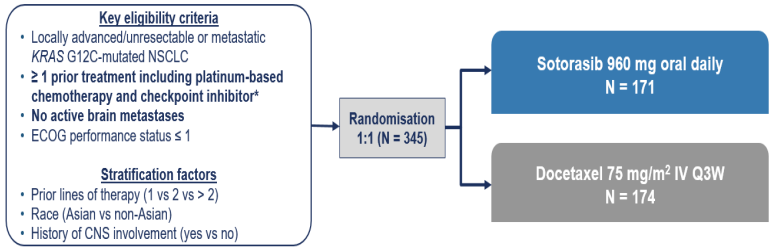
Awad MM et al. *N Engl J Med* 2021 Jun24;384(25):2382-2393



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

CodeBreaK200 : Phase III RCT of sotorasib vs docetaxel in previously treated advanced *KRAS*^{G12C}-mutant NSCLC

A.



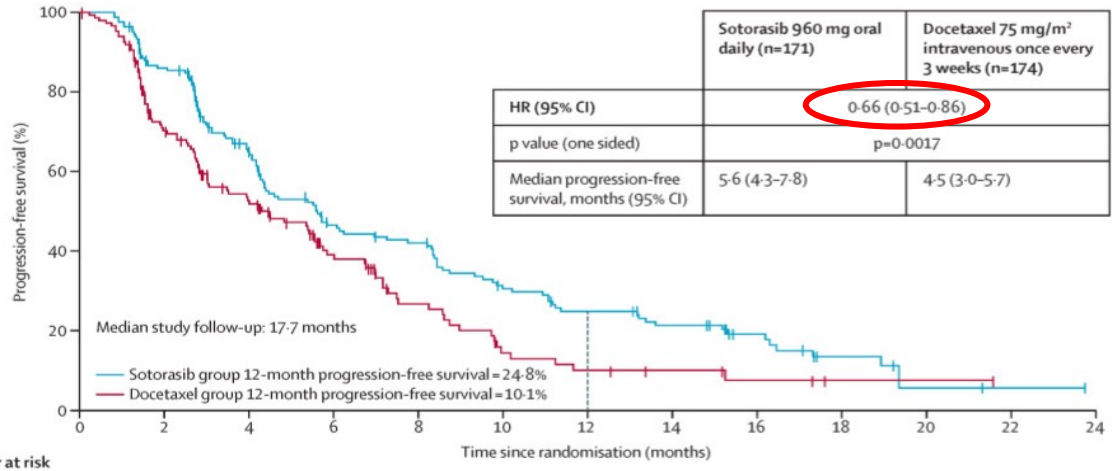
Per regulatory guidance, protocol was amended to reduce planned enrolment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted.

Primary Endpoint: PFS by BICR
Secondary Endpoints: Efficacy (OS†, ORR, DOR, TTR, DCR), **safety/tolerability, PRO**
ITT population analysis included all randomised patients

Enrollment period: June 4, 2020 to April 26, 2021; protocol amendment: February 15, 2021; data cutoff: August 2, 2022.

Johnson ML et al., ESMO Congress, 2022

B.

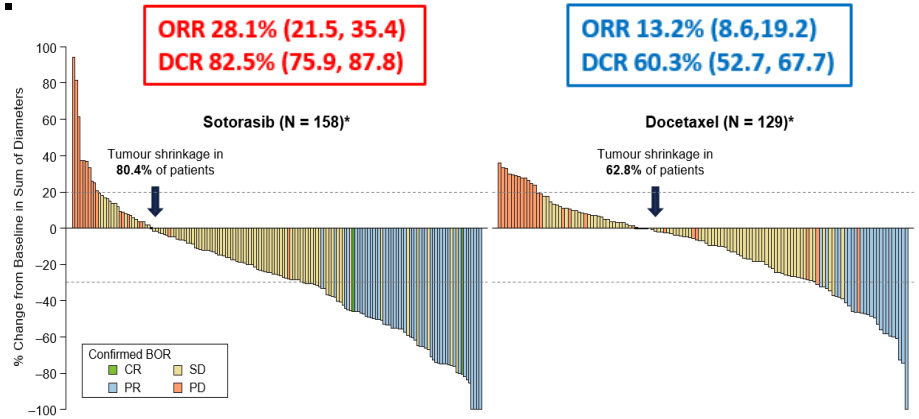


	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
HR (95% CI)	0·66 (0·51–0·86)	
p value (one sided)	p=0·0017	
Median progression-free survival, months (95% CI)	5·6 (4·3–7·8)	4·5 (3·0–5·7)

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)	..

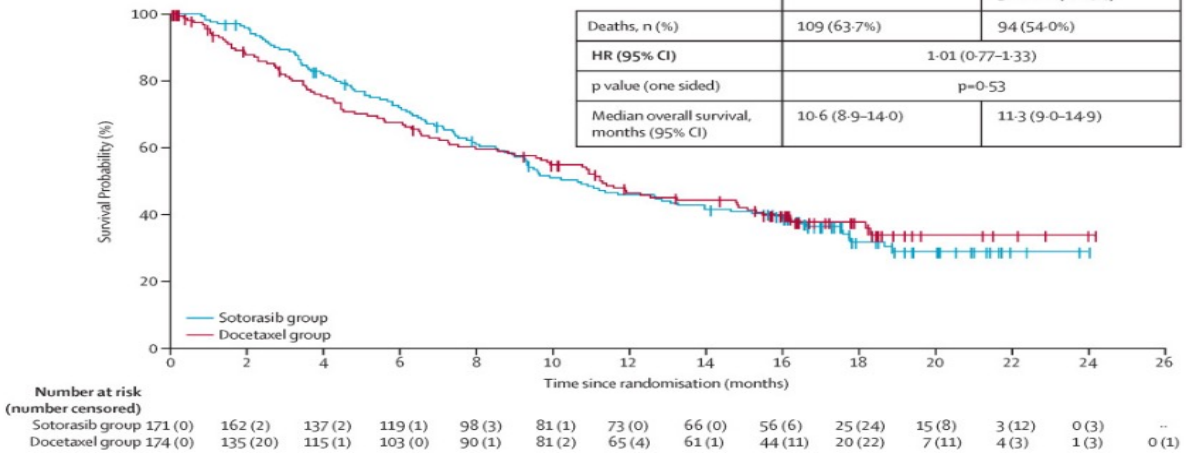
de Langen AJ et al., *Lancet.* 2023 Mar 4;29(3):593-604. Epub 2023 Mar 16

C.



Johnson ML et al., ESMO Congress, 2022

D.



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

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

de Langen AJ et al., *Lancet.* 2023 Mar 4;29(3):593-604. Epub 2023 Mar 16

Treatment-related adverse events

Sotorasib (CodeBreaK100)

Treatment-Related Adverse Events (TRAEs) Occurring in > 5%	Any Grade N = 126 n (%)	Grade 3 N = 126 n (%)
Any TRAEs	88 (69.8)	25 (19.8)
Diarrhea	40 (31.7)	5 (4.0)
Nausea	24 (19.0)	0
ALT increase	19 (15.1)	8 (6.3)
AST increase	19 (15.1)	7 (5.6)
Fatigue	14 (11.1)	0
Vomiting	10 (7.9)	0
Blood alkaline phosphatase increase	9 (7.1)	1 (0.8)
Maculopapular rash	7 (5.6)	0

- 0.8% G4 TRAEs (pneumonitis and dyspnea). No G5 TRAEs
- Dose modification due to TRAEs in 22.2%
- Treatment discontinuation due to TRAEs in 7.1%

Skoulidis F et al., ASCO 2021

Warnings and Precautions

- Hepatotoxicity
- Interstitial Lung Disease/Pneumonitis

Adagrasib (KRYSTAL-1)

	Adagrasib Monotherapy (N=116) Capsule, Fasted	
TRAEs, n (%)	**Any Grade**	**Grades 3–4**
Any TRAEs	113 (97%)	50 (43%)
Most frequent TRAEs[a], n (%)		
Diarrhea	73 (63%)	1 (<1%)
Nausea	72 (62%)	5 (4%)
Vomiting	55 (47%)	1 (<1%)
Fatigue	47 (41%)	5 (4%)
ALT increase	32 (28%)	5 (4%)
Blood creatinine increase	30 (26%)	1 (<1%)
AST increase	29 (25%)	4 (3%)
Decreased appetite	28 (24%)	4 (3%)

- 2 G5 TRAEs (cardiac failure, pulmonary hemorrhage)
- Dose reduction due to TRAEs in 52% and interruption in 61%
- Treatment discontinuation due to TRAEs in 7%

Spira A et al., ASCO 2022

Warnings and Precautions

- GI adverse reactions
- QTc Interval Prolongation
- Hepatotoxicity
- Interstitial Lung Disease/Pneumonitis

Intracranial activity of sotorasib in *KRAS*^{G12C}-mutant NSCLC with stable brain metastases (CodeBreaK100)

- Per central RANO BM review, 16/174 (9.2%) patients had baseline and ≥1 on-treatment evaluable scans*:
  - Nine patients had 1 lesion; 2 had 4 lesions; 5 had ≥ 5 lesions

Best Response by RANO, n (%)	Patients with Target and Non-target CNS Lesions Sotorasib 960 mg (n = 3)	Patients with only Non-target CNS Lesions Sotorasib 960 mg (n = 13)	All Patients with Evaluable BM Sotorasib 960 mg (N = 16)†
Complete response	0	2 (15)	2 (13)
Stable disease	1 (33)	11 (85)	12 (75)
Progressive disease	2 (67)	0	2 (13)

- Overall, intracranial disease control was achieved in 14/16 patients (88%) with evaluable BM

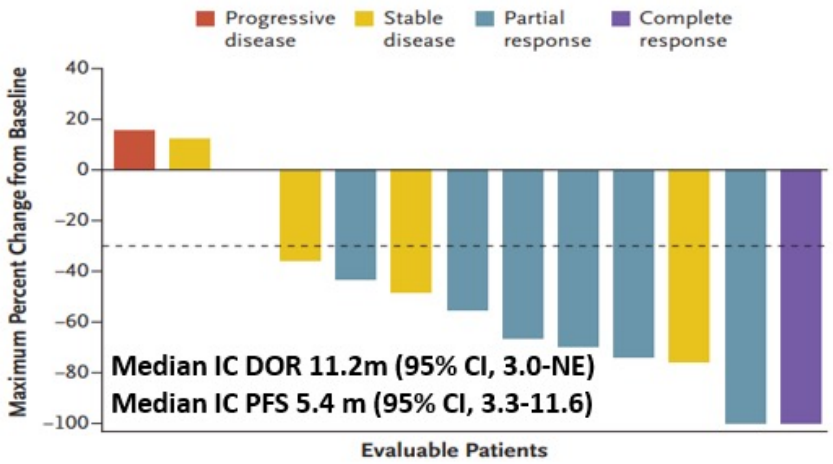
*Forty patients were identified by investigator as having BM; 16 patients with evaluable BM were identified per central review.
†Nine patients had 1 lesion; 2 had 4 lesions; 5 had ≥ 5 lesions.
BM, brain metastases; CNS, central nervous system; RANO, Response Assessment in Neuro-Oncology.

Intracranial activity of adagrasib in *KRAS*^{G12C}-mutant NSCLC

Previously treated and stable brain mets

Best Overall Response	Overall (n=33)[b]	Patients with Non-target Lesions Only (n=19)	Patients with Target Lesions (n=13)[c]
IC ORR, n (%)	11 (33%)	4 (21%)	7 (54%)
Complete response	5 (15%)	4 (21%)	1 (8%)
Partial response	6 (18%)	-	6 (46%)
Stable disease	17 (52%)	13 (68%)	4 (31%)
IC DCR, n (%)	28 (85%)	17 (89%)	11 (85%)

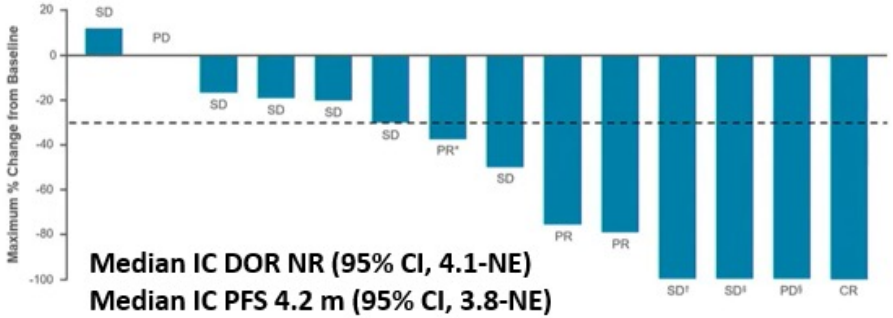
Spira A et al., ASCO 2022



Jänne PA al. *N Engl J Med* 2022

Active, untreated brain mets

Efficacy Outcome	Patients with Non-target Lesions Only (n=4)	Patients with Target Lesions (n=15)[a]	Overall (n=19)[b]
Objective response rate, n (%)	2 (50%)	4 (27%)	6 (32%)
Best overall response, n (%)			
Complete response (CR)	2 (50%)	1 (7%)	3 (16%)
Partial response (PR)	0	3 (20%)[c]	3 (16%)[c]
Stable disease (SD)	2 (50%)	8 (53%)	10 (53%)
Progressive disease (PD)	0	2 (13%)	2 (11%)
Not evaluable	0	1 (7%)[d]	1 (5%)[d]
Disease control rate, n (%)	4 (100%)	12 (80%)	16 (84%)



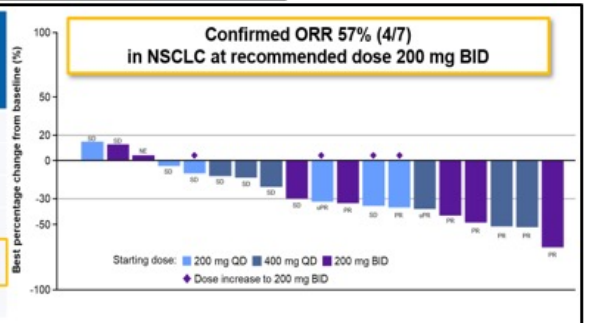
- Objective IC responses were observed in 32% (95% CI, 12.6–56.6)[a]
- IC DCR was 84% (95% CI, 60.4–96.6)

Sabari J et al., ASCO 2022

Other off state-selective KRAS^{G12C} inhibitors in clinical development

KontRASt-01: JDQ443

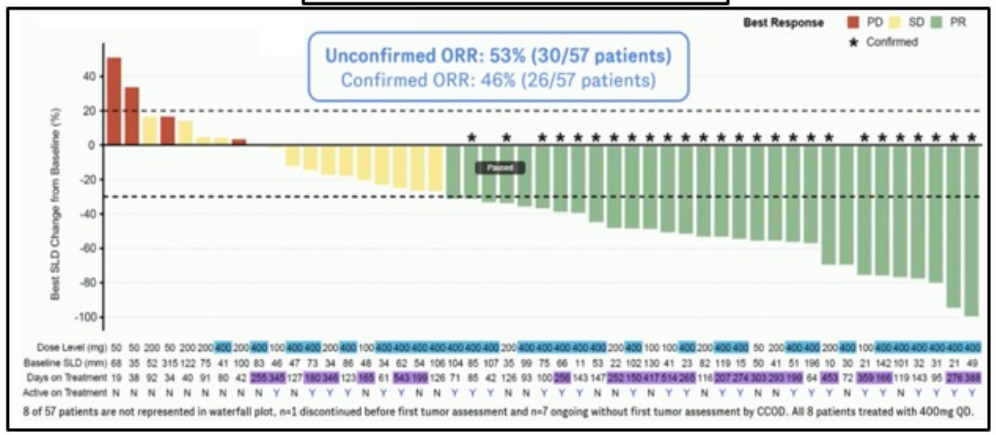
Best overall response, investigator assessed per RECIST v1.1	All patients with NSCLC, n=20, n (%)
PR (confirmed)	7 (35.0)
SD	11 (55.0)
PD	0
NE	2 (10.0)
ORR (confirmed and unconfirmed)	**9 (45.0)**
ORR (confirmed)	7 (35.0)



Data presented with a cut-off date of January 5, 2022. Waterfall plot: 19 (95.0%) NSCLC patients with available change from baseline tumor assessments; data are plotted out of N=20 NSCLC patients in JDQ443 single-agent cohorts. Responses are investigator assessed per RECIST v1.1. Two (10.0%) patients had a uPR, which contributed toward the ORR (confirmed and unconfirmed). uPR = unconfirmed PR pending confirmation, treatment ongoing with no PD. One of two patients with a uPR had confirmed PR after the data cut-off. BID, twice daily; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

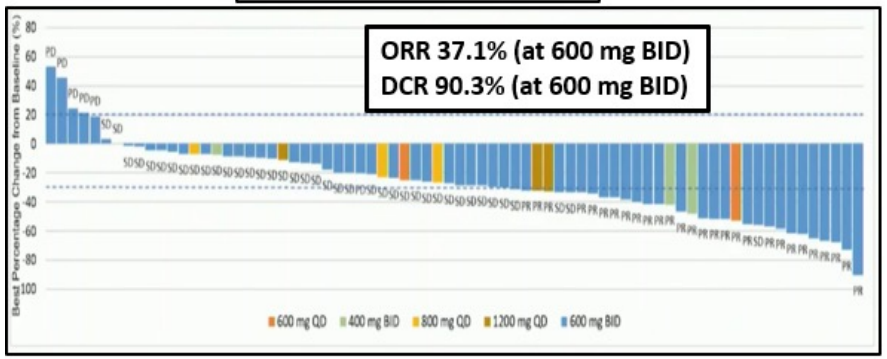
Tan DSW et al., AACR 2022

NCT04449874: GDC-6036



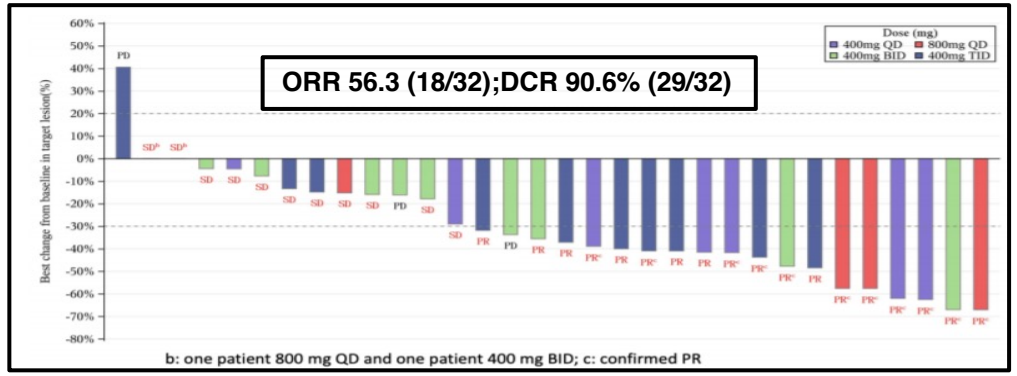
Sacher A et al., ESMO 2022

NCT03600883: D-1553



Lu S et al., WCLC 2022

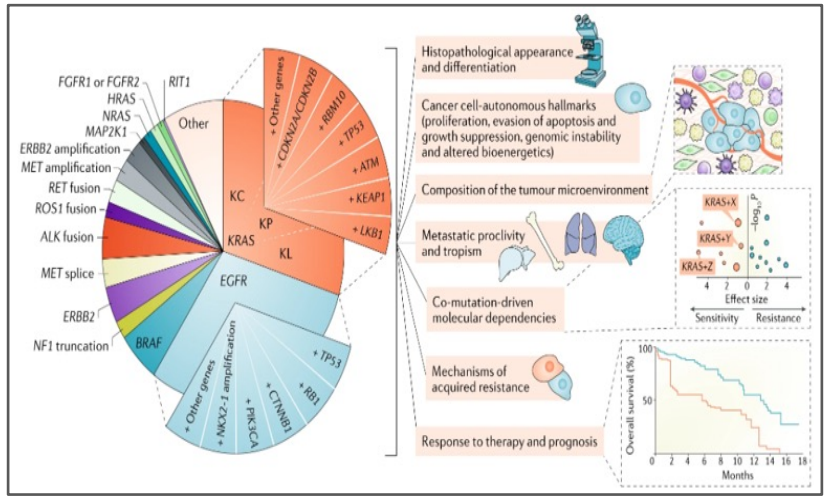
NCT05009329: JAB-21822 (Glecirasib)



Li J et al., ASCO 2022

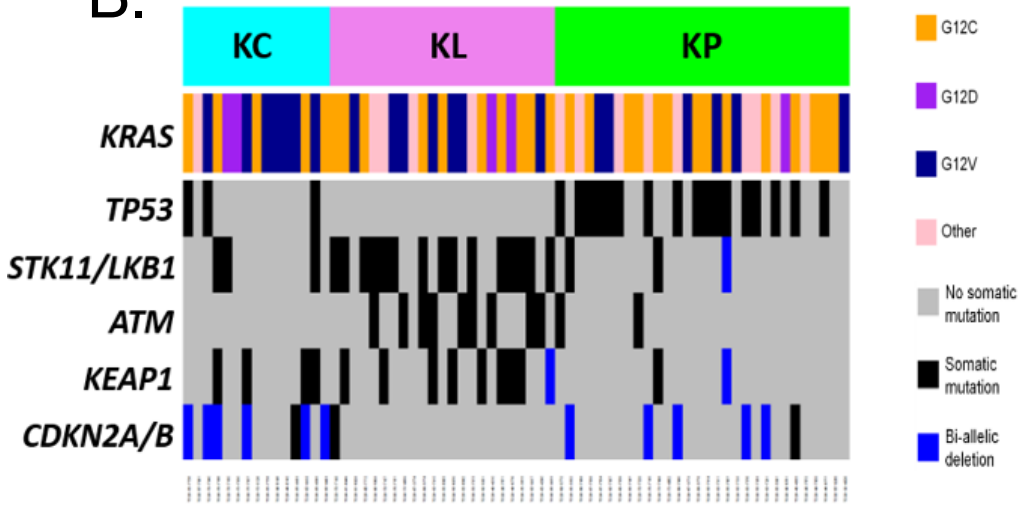
Barriers to the efficacy of KRAS G12Ci monotherapy : pervasive molecular diversity and variable oncogenic addiction

A.



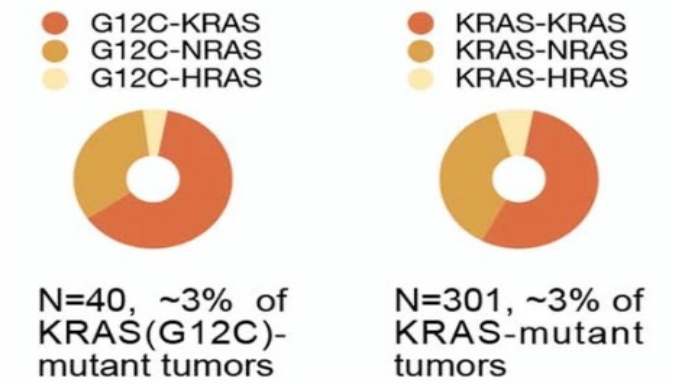
Skoulidis F, Heymach JV, *Nat Rev Cancer*, 2019

B.



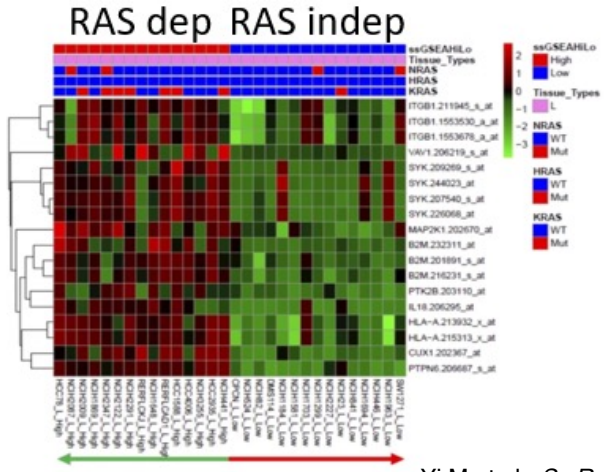
Skoulidis F et al., *Cancer Discov*, 2015

C.



Zhao Y et al., *Nature,* 2021

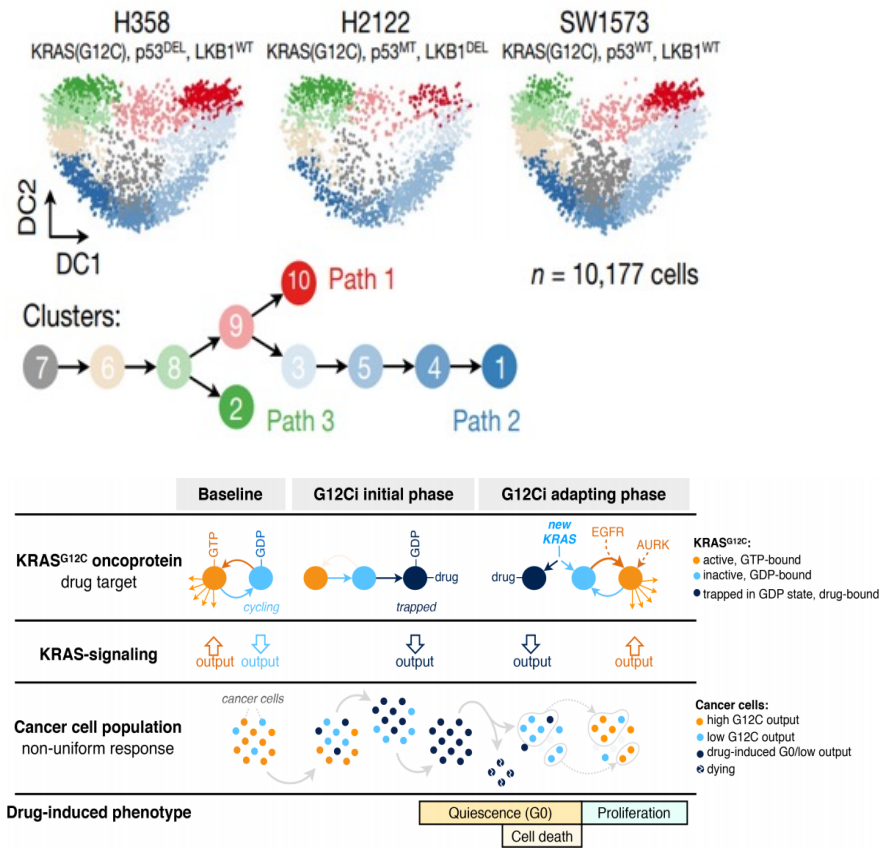
D.



Yi M et al., *Sc Rep,* 2020

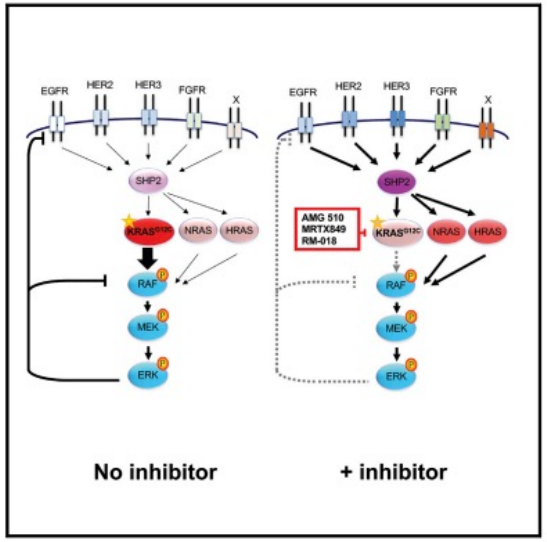
Barriers to the efficacy of inactive state-selective KRAS G12Ci : rapid molecular adaptation

A. Synthesis of new KRAS^{G12C} protein



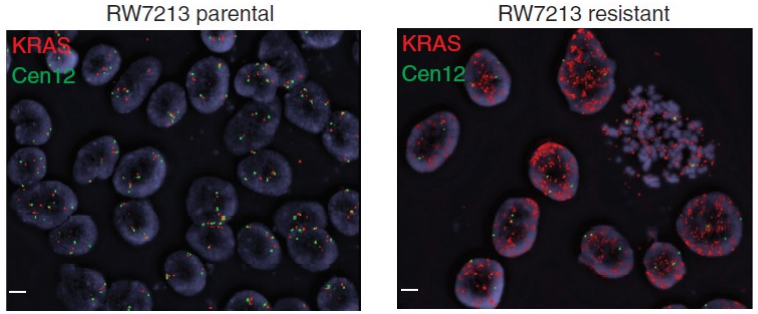
Xue JY et al., *Nature*, 2020

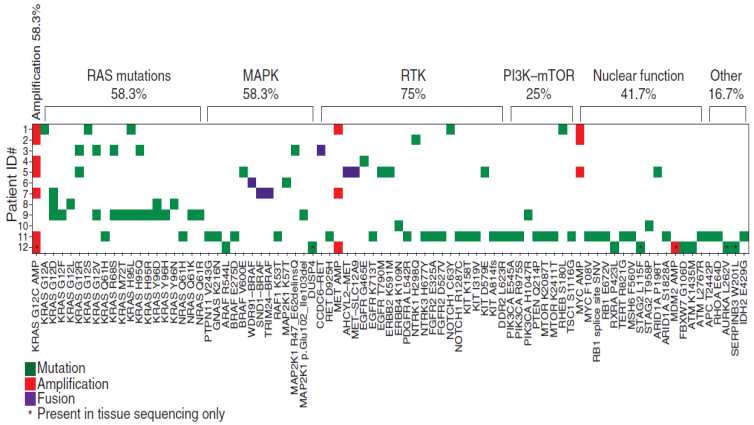
B. Increased RTK drive



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

C. KRAS^{G12C} amplification

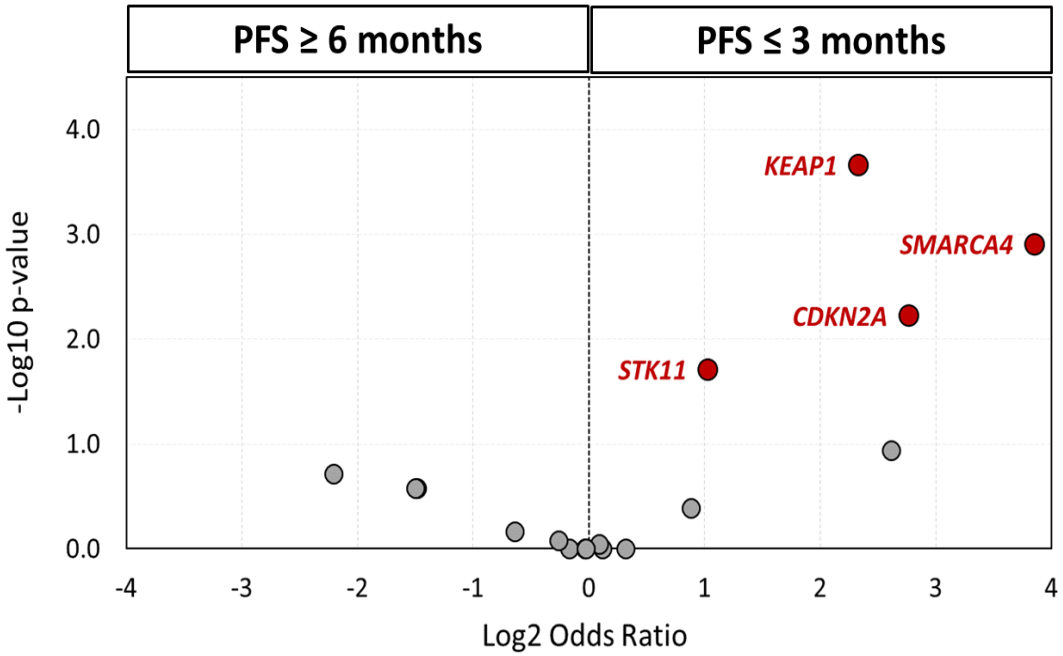




Yaeger R et al., *Cancer Discov*, 2023

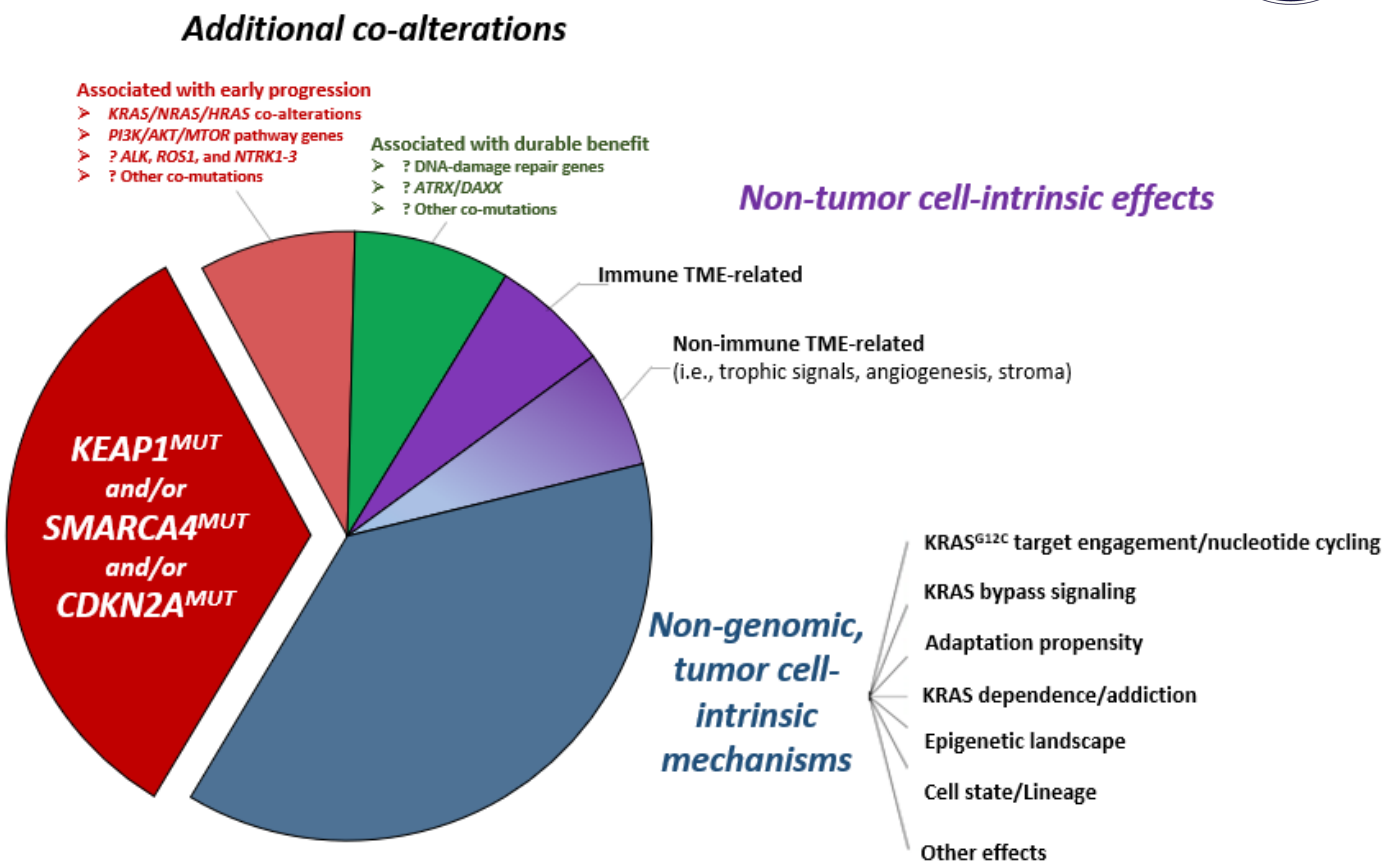
Molecular determinants/predictors of KRAS G12Ci efficacy

A.



Negrao MV et al., *Cancer Discovery*, in press

B.

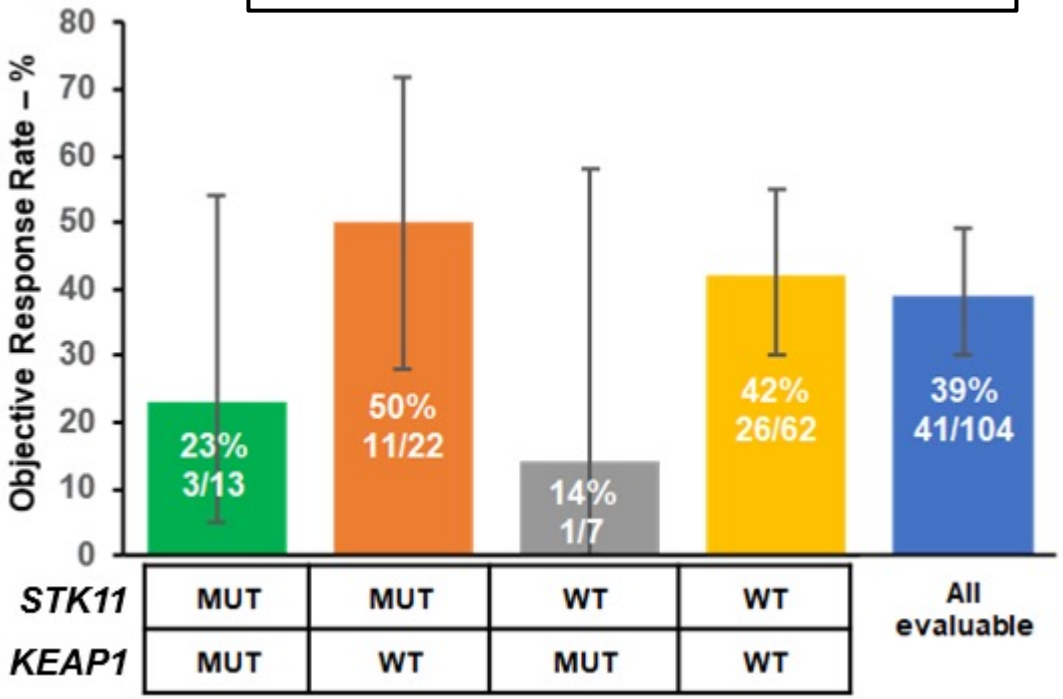


Urgent need to understand and chart mechanisms and determinants of primary resistance and adaptation to KRASi using model systems and clinical specimens

Impact of key co-mutations of sotorasib and adagrasib clinical efficacy

A.

Sotorasib (CodeBreaK100)

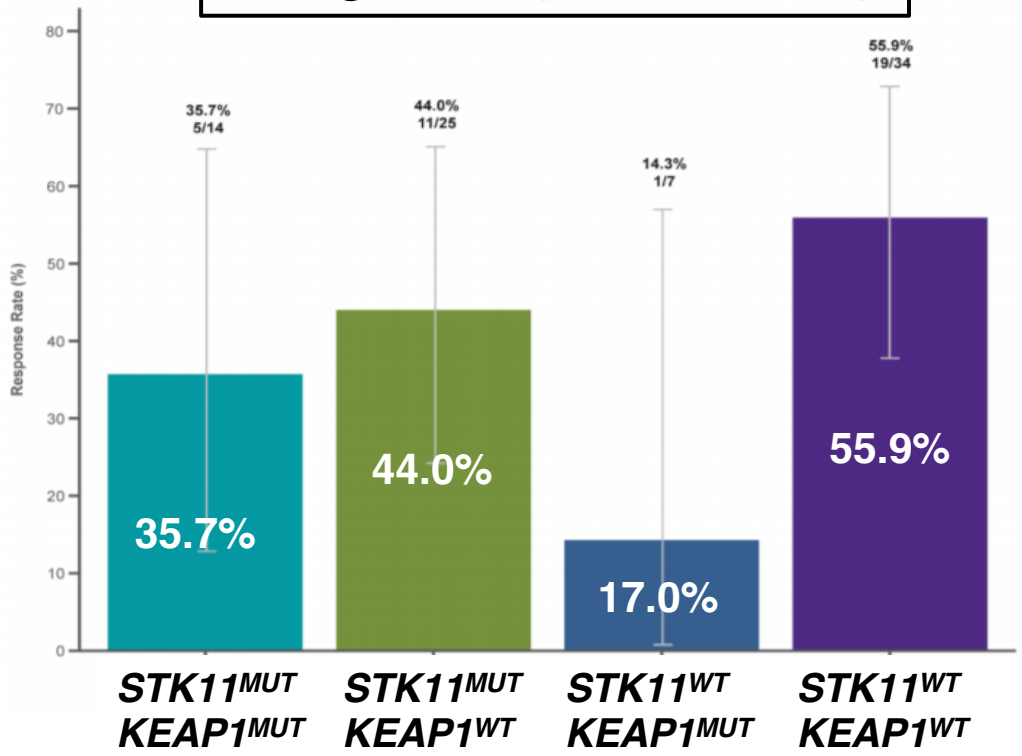


Skoulidis F et al., ASCO 2021

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

B.

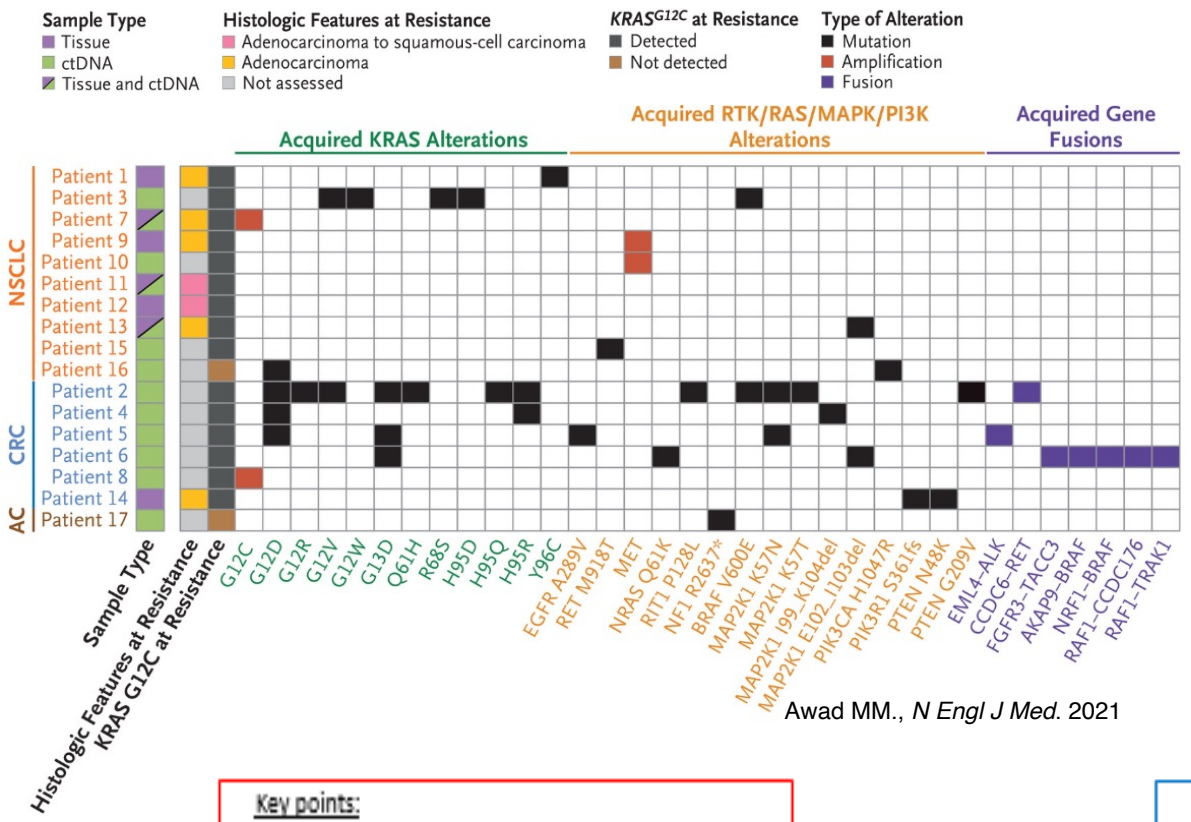
Adagrasib (KRYSTAL-1)



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

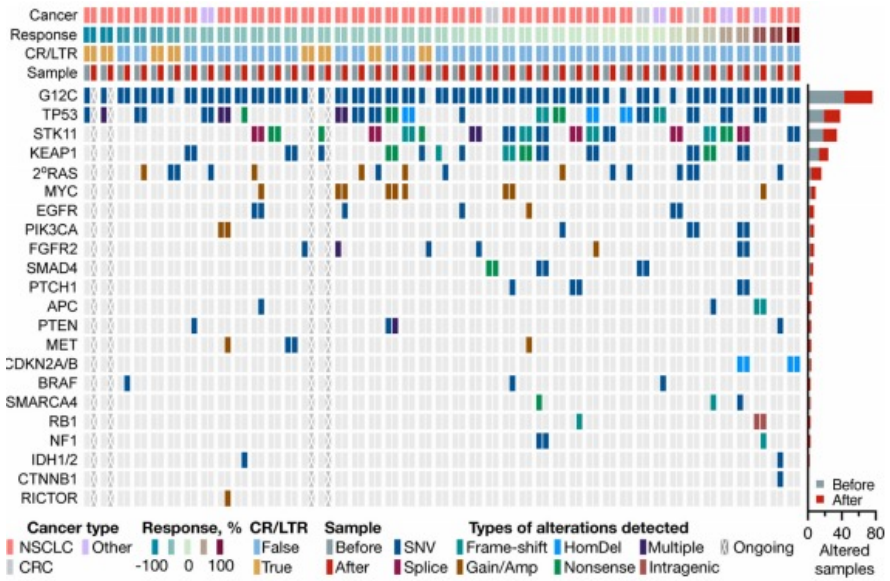
Emerging mechanisms of acquired resistance to KRAS p.G12C inhibitors

A.



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

B.



Zhao Y et al., *Nature*. 2021

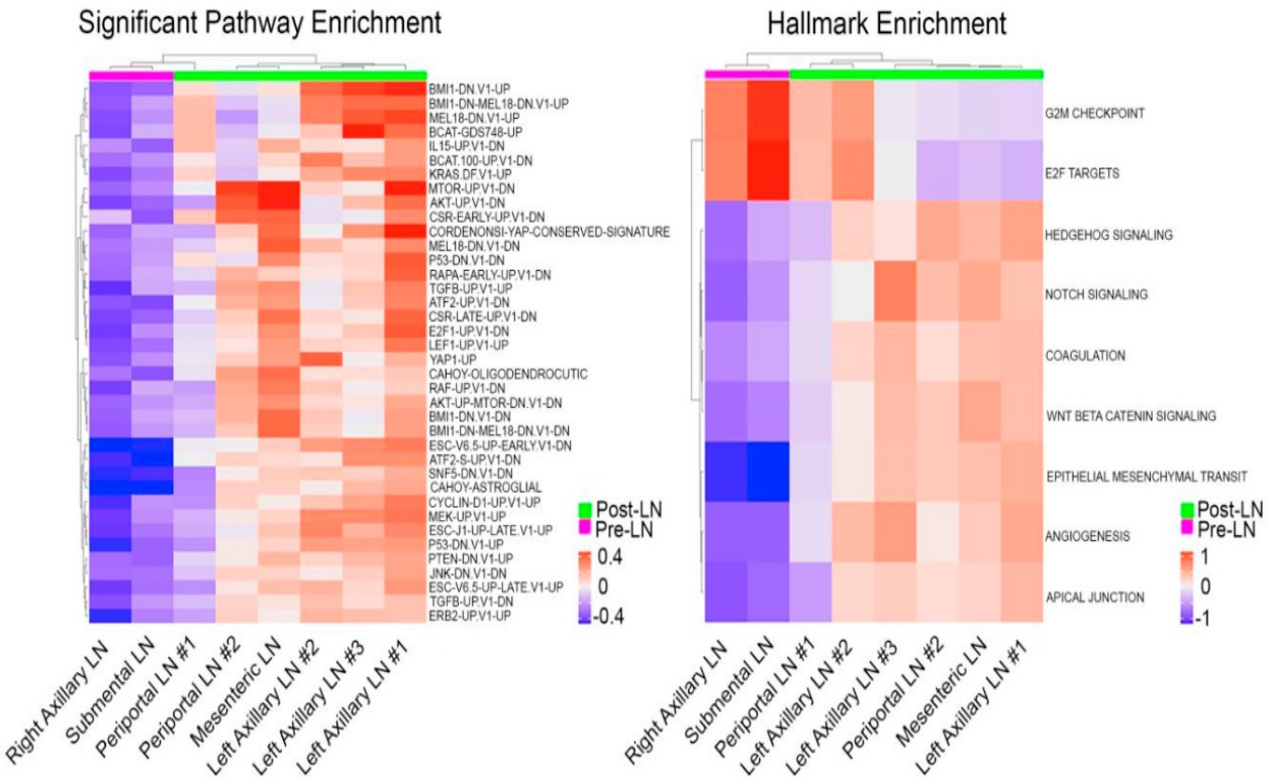
Key points:

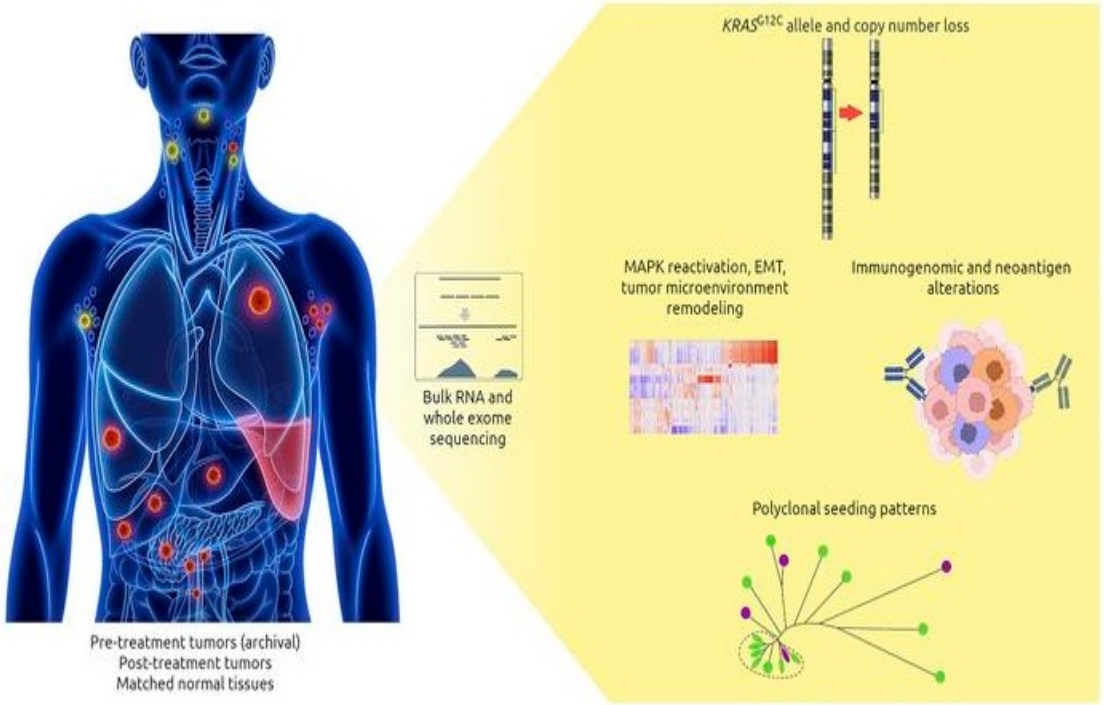
- Diverse mechanisms of acquired resistance
- Multiple mechanisms may coexist in the same patient (polyclonal res – convergent evolution)
- Some mechanisms may be unique to certain inhibitors (such as mutations involving H95)
- In many cases no mechanisms has been identified

Outstanding questions:

- Full spectrum of primary and acquired resistance mechanisms
- Is acquired resistance stochastic or predetermined?
- Why do some patient develop a single and others multiple mechanisms?
- Impact of DoR on patters of acquired resistance mechanisms?
- Impact of comutations on patterns of acquired resistance.
- Are secondary alterations at low MAF real drivers of resistance?
- Strategies to forestall or overcome clinical resistance

Non-genetic mechanisms of resistance to G12Ci

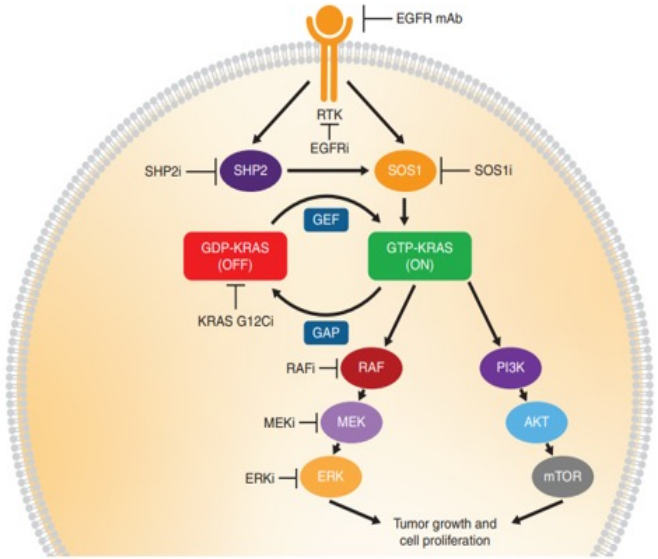




Tsai YS, *J Clin Invest*, 2022

KRAS^{G12C} inhibitor phase IB/II combination protocols

A.



Hofmann MH et al., *Cancer Discov*, 2022

B.

Sotorasib combinations

NSCLC	Mono	2L mono dose comparison	2
		2L mono v. docetaxel confirmatory	3
		1L mono STK11/PD-L1 neg biomarker	2
	Mono	Mono brain mets	1b
	PD1 Combo	PD-1 combo	1b
		PD-L1 combo	1b
	Chemo Combo	Chemo combo	1b
		1L Chemo combo in PD-L1 neg	3
	Novel Combo	Panitumumab combo	1b
		Palbociclib combo	1b
		SHP2i RevMed combo	1b
		SHP2i Novartis combo	1b
		SOS1 combo	1b

Corporate Update ESMO 2022, Amgen

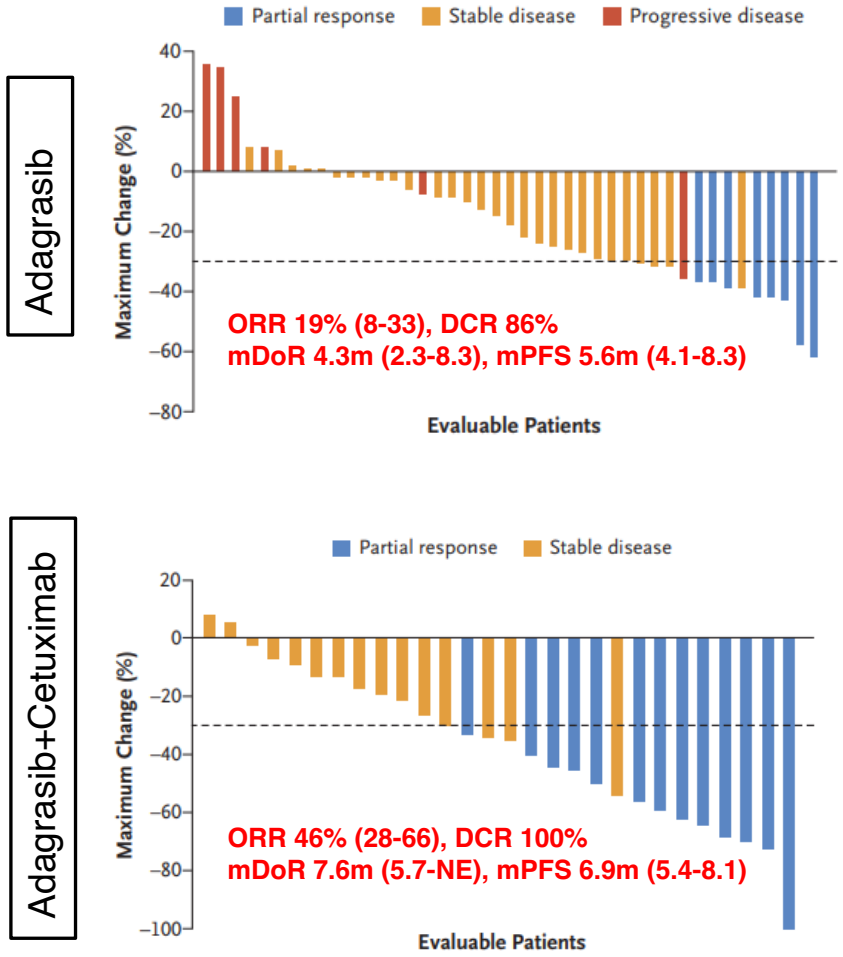
Adagrasib combinations

Adagrasib *KRAS G12C Inhibitor*	2L NSCLC	Monotherapy
		POC Combo: SHP2, SOS1, CDK4/6, Pan-EGFR, EGFR
	1L NSCLC	Monotherapy: STK11 co-mutations and TPS <1%
		Combo: Pembrolizumab (PD-1)
	2L CRC	Combo: Cetuximab (EGFR)
	3L+ CRC and Pancreatic	Monotherapy Combo: Cetuximab (EGFR)

Mirati Therapeutics Corporate Presentation September 2022

Addition of cetuximab significantly increases the ORR to adagrasib in previously treated *KRAS*^{G12C}-mutated metastatic CRC

A.



B.

Adverse Event	Adagrasib Monotherapy (N=44)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)				
Any event	41 (93)	10 (23)	16 (36)	13 (30)	2 (5)
Leading to dose discontinuation	0	—	—	—	—
Leading to dose interruption	20 (45)	—	—	—	—
Leading to dose reduction	17 (39)	—	—	—	—
Most frequent events†					
Diarrhea	29 (66)	16 (36)	10 (23)	3 (7)	0
Nausea	25 (57)	15 (34)	10 (23)	0	0
Vomiting	20 (45)	12 (27)	8 (18)	0	0
Fatigue	20 (45)	11 (25)	7 (16)	2 (5)	0
Anemia	7 (16)	2 (5)	1 (2)	4 (9)	0
Prolonged QT interval on ECG	7 (16)	2 (5)	3 (7)	2 (5)	0
Peripheral edema	7 (16)	6 (14)	1 (2)	0	0
Decreased appetite	8 (18)	4 (9)	4 (9)	0	0
Increased ALT	5 (11)	3 (7)	0	2 (5)	0
Increased AST	5 (11)	3 (7)	0	2 (5)	0

	Adagrasib plus Cetuximab (N=32)				
Any event	32 (100)	5 (16)	22 (69)	3 (9)	2 (6)
Leading to dose discontinuation					
Adagrasib	0	—	—	—	—
Cetuximab	5 (16)	—	—	—	—
Leading to dose interruption					
Adagrasib	14 (44)	—	—	—	—
Cetuximab	10 (31)	—	—	—	—
Leading to dose reduction					
Adagrasib	10 (31)	—	—	—	—
Cetuximab	1 (3)	—	—	—	—
Most frequent events†					
Nausea	20 (62)	13 (41)	7 (22)	0	0
Diarrhea	18 (56)	11 (34)	6 (19)	1 (3)	0
Vomiting	17 (53)	13 (41)	4 (12)	0	0
Dermatitis acneiform	15 (47)	11 (34)	3 (9)	1 (3)	0
Fatigue	15 (47)	8 (25)	7 (22)	0	0
Dry skin	13 (41)	11 (34)	2 (6)	0	0
Headache	10 (31)	7 (22)	3 (9)	0	0
Dizziness	8 (25)	4 (12)	4 (12)	0	0
Maculopapular rash	8 (25)	7 (22)	1 (3)	0	0
Stomatitis	7 (22)	5 (16)	1 (3)	1 (3)	0
Dyspepsia	6 (19)	4 (12)	2 (6)	0	0
Hypomagnesemia	6 (19)	3 (9)	3 (9)	0	0
Infusion-related reaction	6 (19)	1 (3)	4 (12)	0	1 (3)

Yaeger R et al., NEJM, 2023

Sotorasib and RMC-4630 (SHP2i) combination shows preliminary activity in KRAS^{G12C} inhibitor-naïve NSCLC patients

CodeBreaK101 Subprotocol C

- Phase 1b multicenter, open-label study (NCT04185883); data cutoff: April 11, 2022

Screening/Enrollment → **PART 1: Dose Exploration (N = 27)**

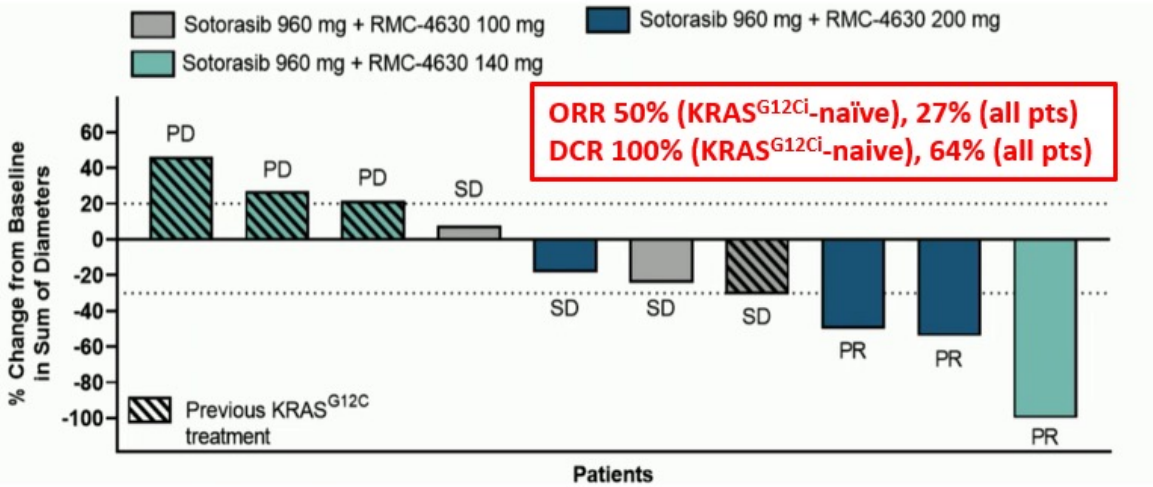
Key eligibility criteria*
- Locally advanced or metastatic *KRAS* p.G12C solid tumors
- Prior anti-PD(L)1 and/or platinum-based chemo and targeted therapy (NSCLC)
- Allowed prior KRAS^{G12C} inhibitor

Sotorasib (960 mg PO daily) + RMC-4630 (PO) at:
- 200 mg at days 1 and 2 Q7D
- 140 mg at days 1 and 2 Q7D
- 100 mg starting dose at days 1 and 2 or days 1 and 4 Q7D

Primary endpoints: Safety
- Dose-limiting toxicities
- TRAEs and TEAEs
- Changes in vital signs, ECGs, and clinical laboratory tests

Secondary endpoints
- Pharmacokinetics
- ORR, DOR, TTR, PFS, DCR, duration of stable disease per RECIST v1.1, OS

NSCLC patients



A study is underway (NCT05054725) to further define efficacy and safety of this combination in patients with mNSCLC who are KRAS^{G12C} inhibitor-naïve (WCLC 2022 e-poster #EP08.02-111)

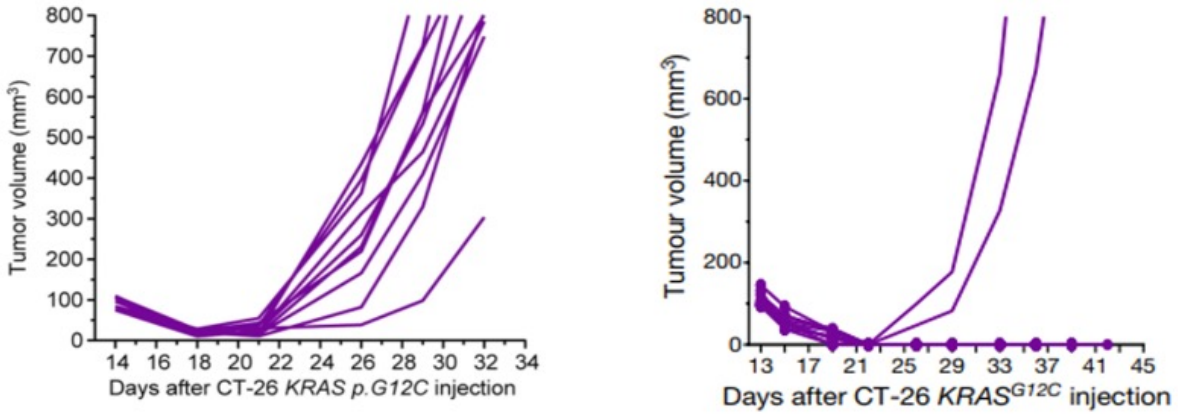
Falchook GS et al., WCLC 2022

Rationale for combining KRAS^{G12C} inhibitors with anti-PD-(L)1

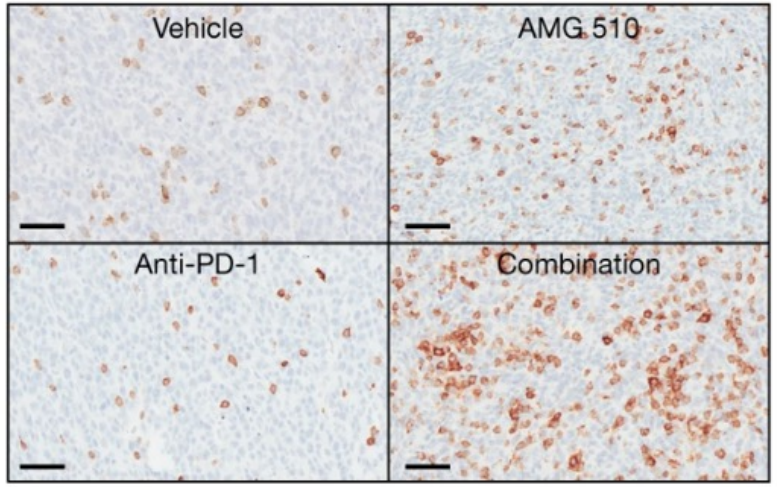
A.

BALB/c immune-deficient mice
sotorasib 200 mg/kg

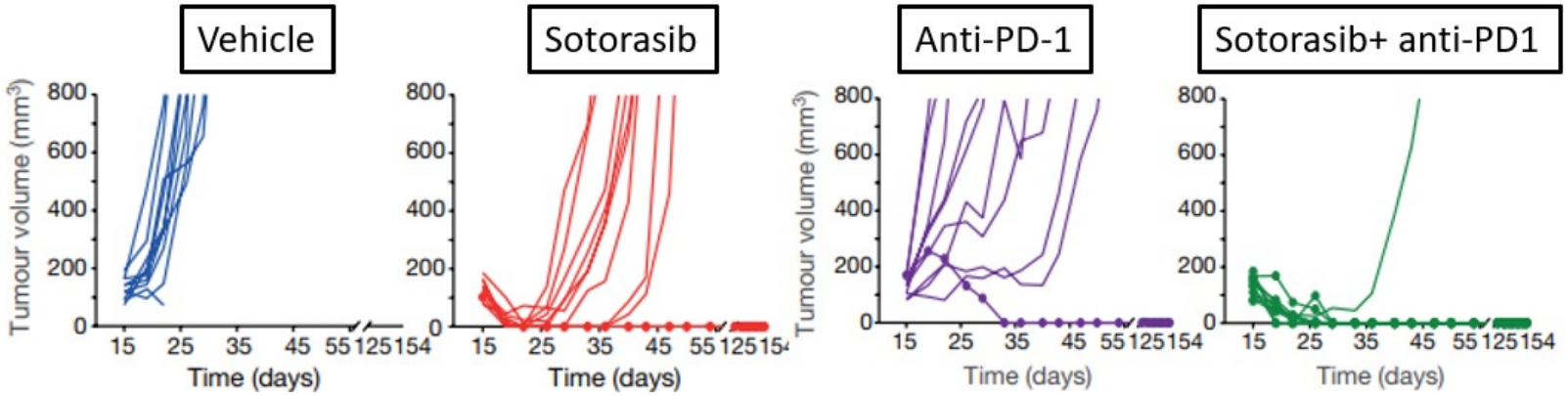
C57BL/6 immune-competent mice
sotorasib 200 mg/kg



C.



B.



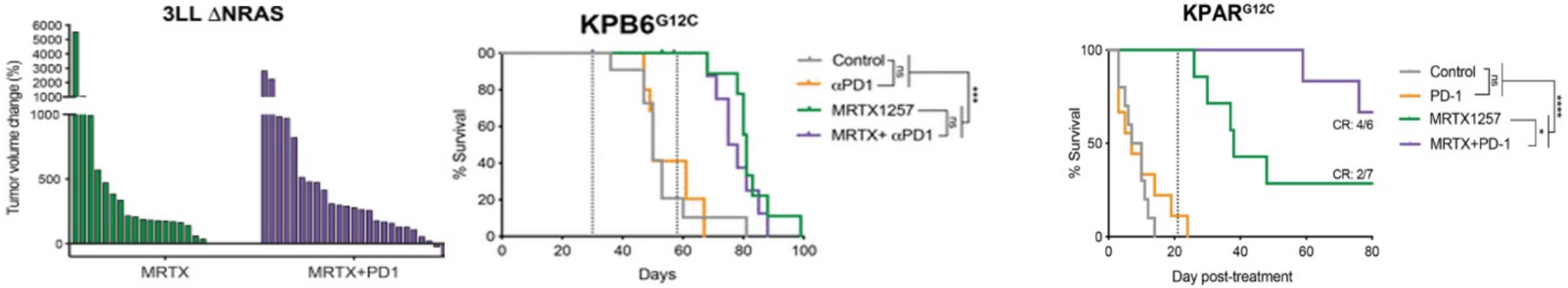
Canon J et al., *Nature*, 2019

Do all patients benefit from combinations of KRASi+aPD-(L)1?

A.

Low intrinsic immunogenicity

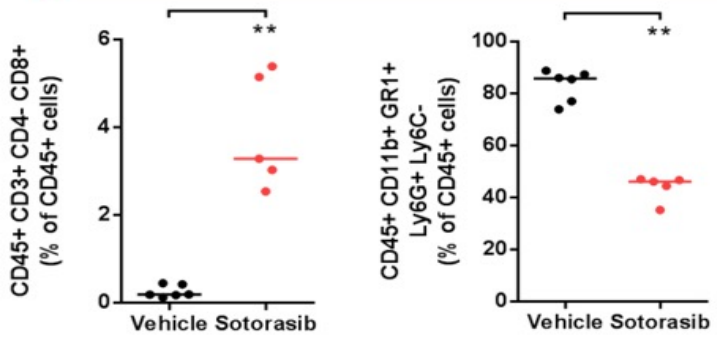
High intrinsic immunogenicity



Mugarza E et al., *Science Advances, 2022*

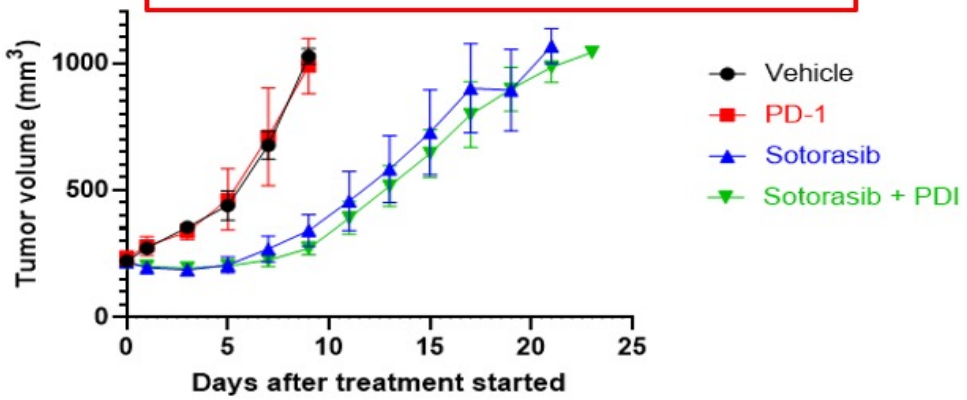
B.

STK11/LKB1 deficient $K^{G12C}L2A$ model



C.

STK11/LKB1 deficient $K^{G12C}L2A$ model



Skoulidis lab, unpublished data

Sotorasib in combination with pembrolizumab or atezolizumab in advanced *KRAS*^{G12C}-mutant NSCLC: CodeBreaK100/101

A.

CodeBreaK 100/101 Study Design

- Phase 1b multicenter, open-label studies

Key Eligibility
- Advanced *KRAS* p.G12C-mutated NSCLC
- Received (or refused) prior standard therapies
- No prior KRAS^{G12C} inhibitor
- No active brain mets

Screening/Enrollment →

Sotorasib* (oral daily) at:	Sotorasib lead-in 21d or 42d then combination (N = 29)	Concurrent treatment (N = 29)
960 mg	Atezolizumab 1200 mg Q3W (N = 10)	Atezolizumab 1200 mg Q3W (N = 10)
720 mg	OR	OR
360 mg	Pembrolizumab 200 mg Q3W (N = 19)	Pembrolizumab 200 mg Q3W (N = 19)
240 mg		
120 mg		

Primary endpoints: safety
Key secondary endpoints: ORR, DOR, DCR, PK

*Not all doses were tested for each cohort.
DCR, disease control rate; PK, pharmacokinetics; Q3W, every 3 weeks.

Snapshot: April 15, 2022

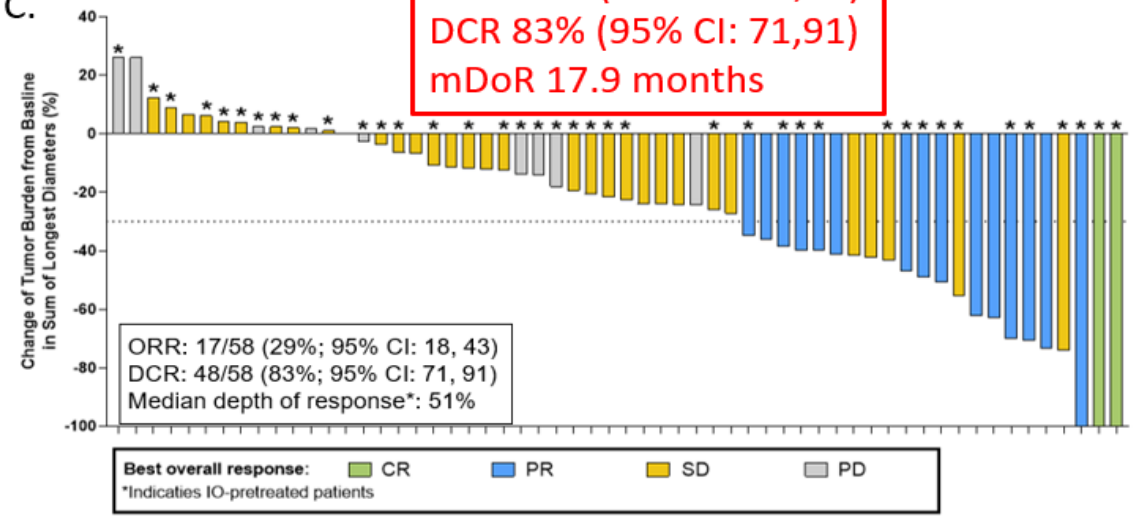
B.

Safety Summary: Lead-in versus Concurrent

	Sotorasib + Atezolizumab Lead-In (N = 10)	Sotorasib + Atezolizumab Concurrent (N = 10)	Sotorasib + Pembrolizumab Lead-In (N = 19)	Sotorasib + Pembrolizumab Concurrent (N = 19)
TRAE, any grade, n (%)	10 (100)	9 (90)	15 (79)	17 (89)
Grade 3	3 (30)	5 (50)	10 (53)	14 (74)
Grade 4*	0	1 (10)	0	1 (5)
TRAE leading to sotorasib and/or IO discontinuation, n (%)	1 (10)	5 (50)	6 (32)	10 (53)
Median duration of sotorasib, months (min, max)	6.5 (1, 18)	4.4 (1, 14)	2.8 (1, 15)	4.9 (2, 30)
Median duration of combination, months (min, max)‡	1.5 (0, 18)	2.5 (1, 14)	0.7 (1, 15)	2.3 (1, 9)
Hepatotoxicity grade ≥ 3, median onset, days (range)	50 (28, 93)	67 (36, 147)	73 (45, 127)	51 (29, 190)

C.

ORR 29% (95% CI: 18,43)
DCR 83% (95% CI: 71,91)
mDoR 17.9 months

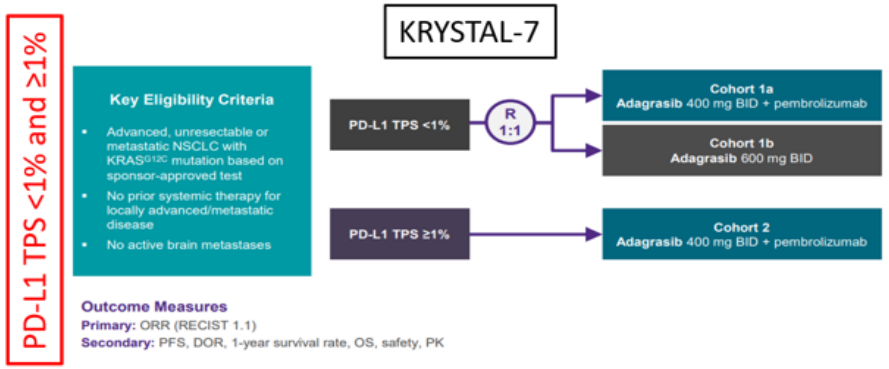


Hepatotoxicity with some KRAS^{G12C}i underscores need to optimize schedule, dose and patient selection

Li B et al., WCLC 2022

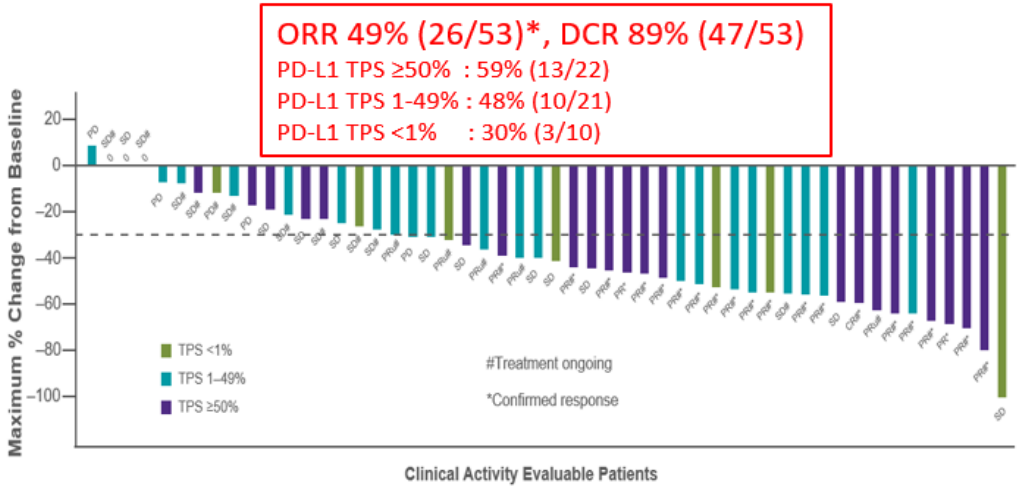
Adagrasib in combination with pembrolizumab in treatment-naïve *KRAS*^{G12C}-mutated NSCLC: KRYSTAL-7 phase 2 trial

A.



Mirati Therapeutics Corporate Presentation September 2022

B.



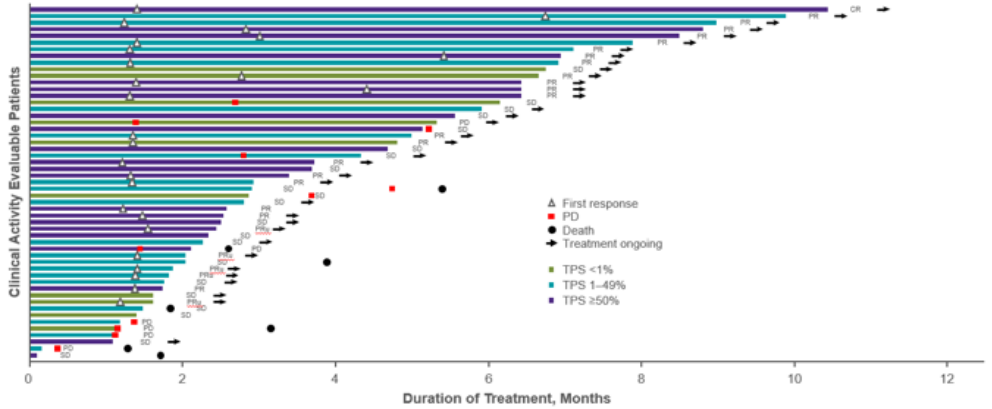
C.

Most Frequent TRAEs	Concurrent 400 mg BID Adagrasib + Pembrolizumab (n=75)				
TRAEs, %	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any TRAEs	83%	15%	24%	40%	4%[a]
Most frequent TRAEs[b], %					
Nausea	48%	24%	19%	5%	0%
Diarrhea	43%	33%	5%	4%	0%
Vomiting	24%	13%	9%	1%	0%
ALT increased	21%	7%	7%	8%	0%
AST increased	21%	7%	5%	9%	0%
Fatigue	21%	9%	8%	4%	0%
Decreased appetite	20%	11%	9%	0%	0%
Amylase increased	16%	5%	11%	0%	0%

- There were no Grade 5 TRAEs
- Median time to onset for ALT increase and AST increase was 26 and 37 days, respectively; only 1 patient experienced new onset treatment-related ALT/AST increase after 3 months
- TRAEs led to adagrasib dose reduction in 23/75 (31%) patients and to dose interruption in 31/75 (41%) patients
- TRAEs led to discontinuation of both drugs in 2/75 (3%) patients and only pembrolizumab in 2/75 (3%)[c] patients

D.

*Excludes 14 pts on study for <6 weeks (no post-baseline scan) and 8 pts that discontinued prior to first scan.

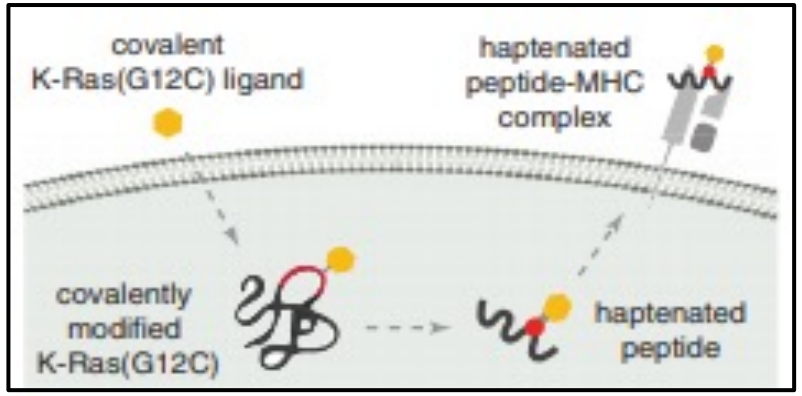


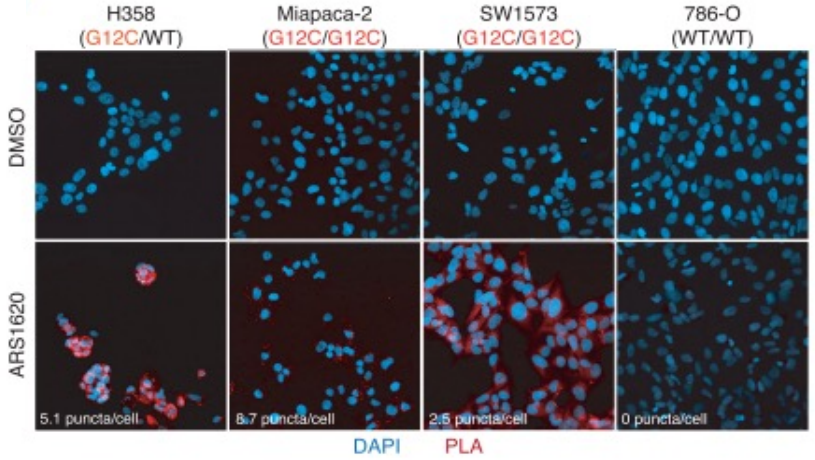
Jänne PA et al., ESMO Immuno-Oncology, 2022

Novel immunotherapy approaches to treat *KRAS*-mutant NSCLC

A.

KRAS^{G12C}i-induced MHC class I presentation of haptenated peptide neoepitopes

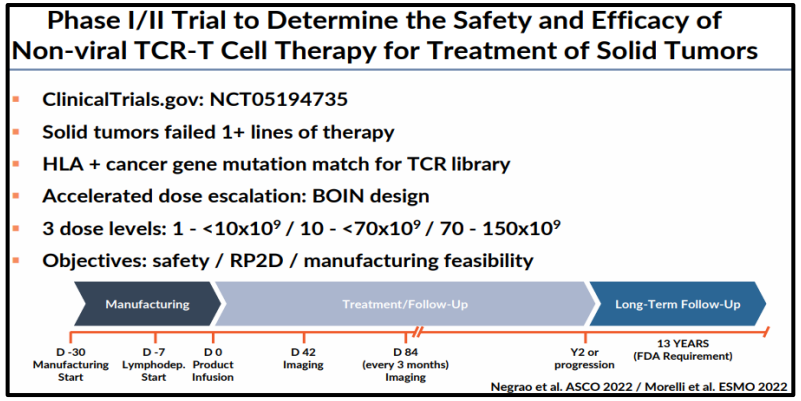


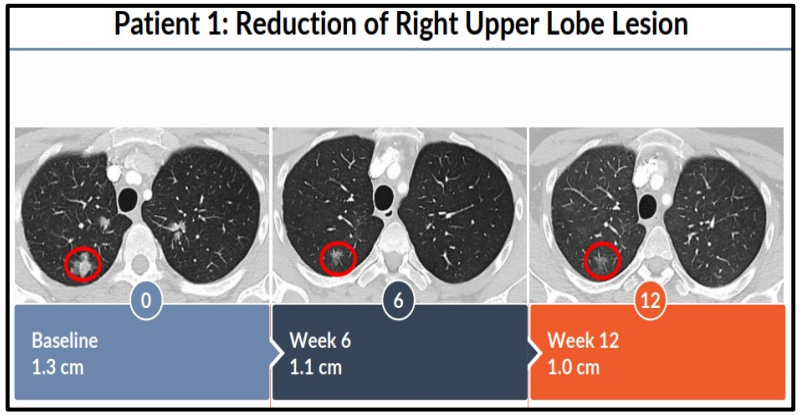


Zhang Z et al., *Cancer Cell*, 2022

B.

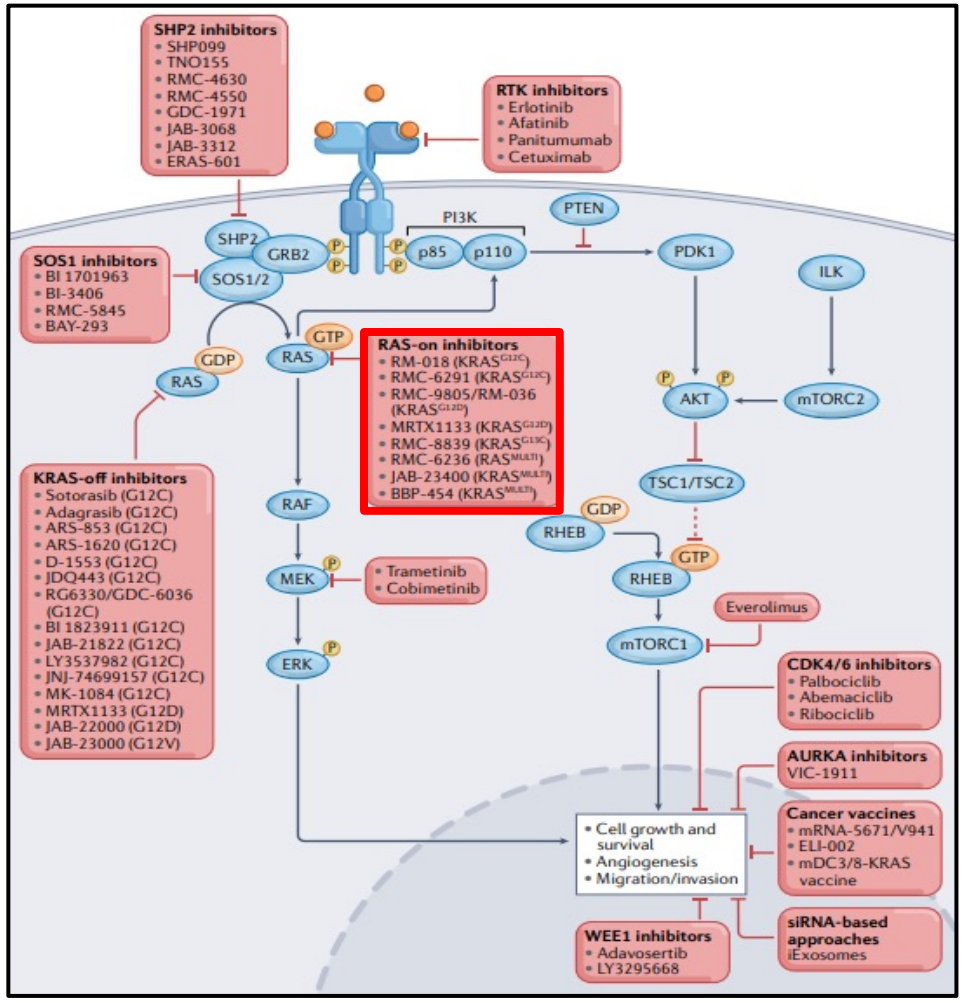
TCR T-cell therapy





Negrao MV et al., CICON, 2022

Emerging novel approaches to target *KRAS*-mutant tumors

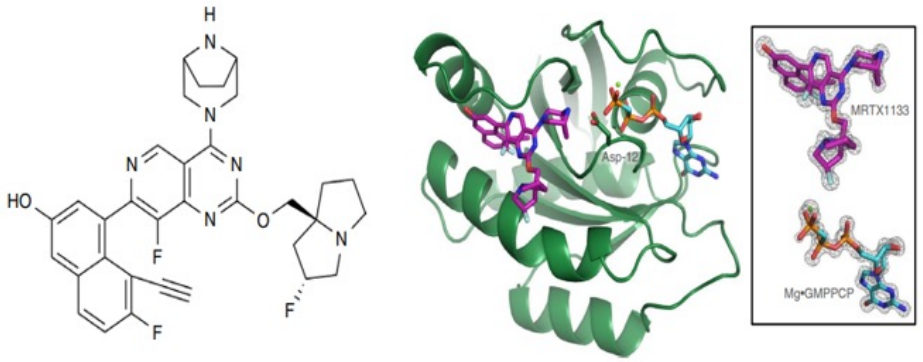


RAS degraders		
KRAS^{G12C}	LC-2 (PROTAC)	Preclinical studies
KRAS^{G12C}, KRAS^{G12D}, KRAS^{G12V} and KRAS^{Q61H}	K27-SPOP	Preclinical studies
RAS toxins		
Pan-RAS	RRSP-DT$_B$	Preclinical studies
Adoptive cell therapy		
KRAS^{G12V}	Specific TCRs	Clinical trials (NCT04146298)
KRAS^{G12D}	Specific TCRs	Preclinical studies
Cancer vaccines		
KRAS^{G12C}, KRAS^{G12D}, KRAS^{G12V} and KRAS^{G13D}	mRNA-5671/V941	Clinical trials (NCT03948763)
KRAS^{G12C}, KRAS^{G12V}, KRAS^{G12D}, KRAS^{G12A}, KRAS^{G13D} or KRAS^{G12R}	Mutant KRAS-targeted long-peptide vaccine	Clinical trials (NCT04117087)
KRAS^{G12C}, KRAS^{G12V}, KRAS^{G12D} or KRAS^{G12R}	mDC3/8-KRAS vaccine	Clinical trials (NCT03592888)
KRAS^{G12D} or KRAS^{G12R}	ELI-002 2P	Clinical trials (NCT04853017)
KRAS siRNAs		
Various mutant KRAS mRNAs	Various nanoparticle-based technologies	Preclinical studies
KRAS^{G12D} mRNA	iExosomes	Clinical trials (NCT03608631)

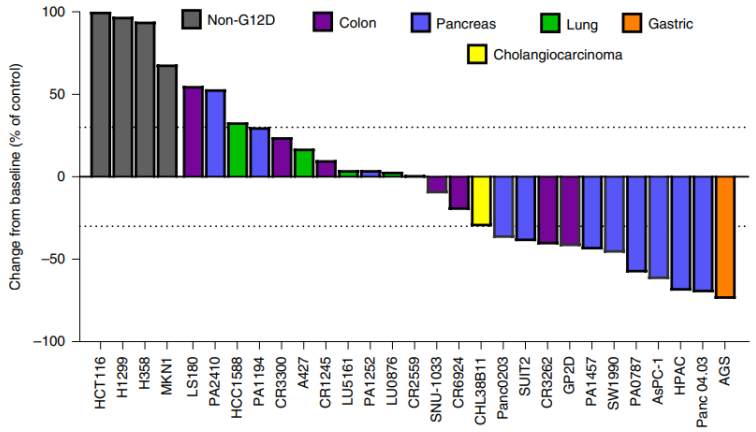
Punekar SR et al., *Nat Rev Clin Oncol* 2022

MRTX1133: A potent, selective, non-covalent inhibitor of KRAS^{G12D}

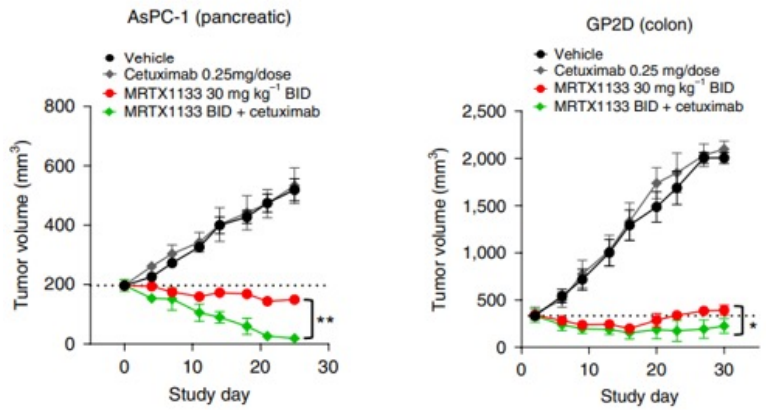
A.



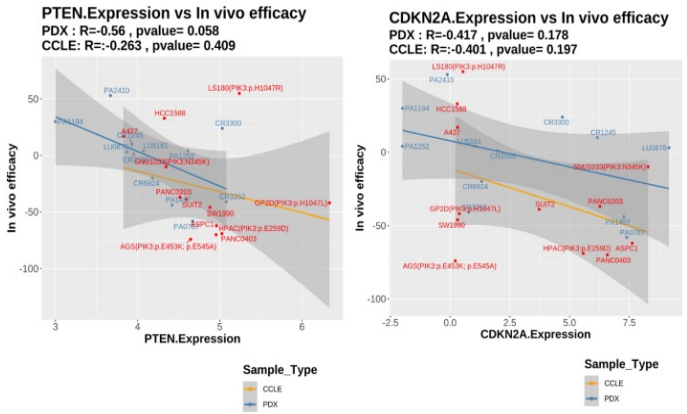
B.



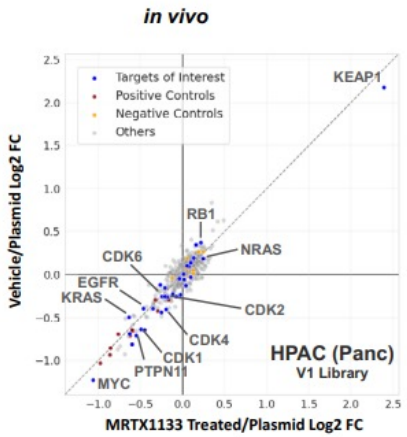
C.



D.



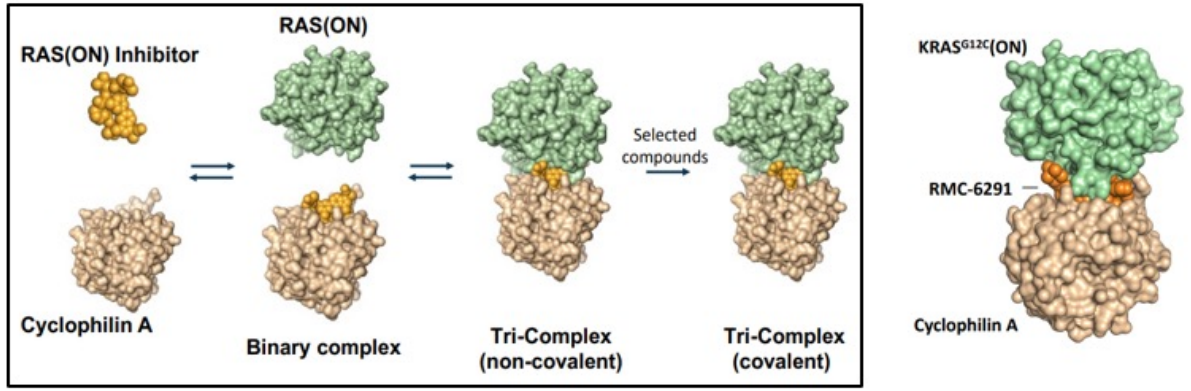
E.



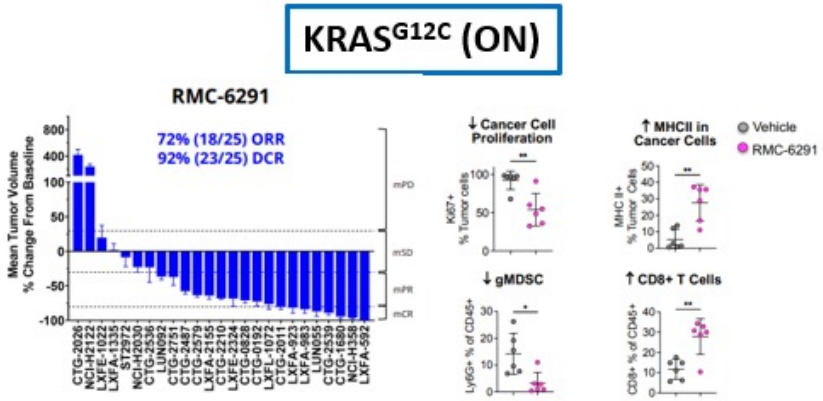
Hallin J et al., *Nat Med*, 2022

RAS(ON) Tri-complex inhibitors

A.

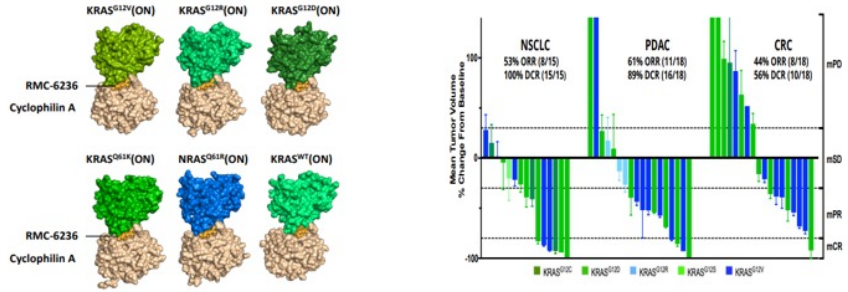


B.



Nichols RJ, AACR Annual Meeting, 2022

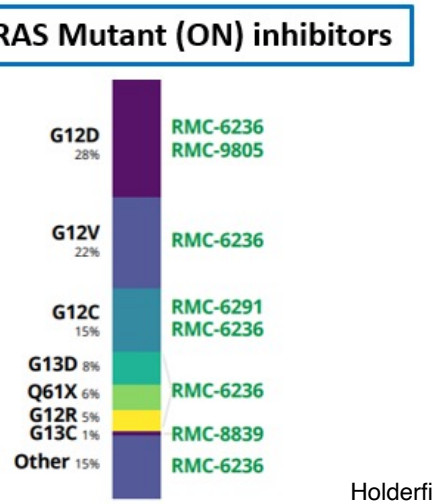
C.



Phase 1/1b Multicenter Open-Label Study of RMC-6236 in Subjects With Advanced Solid Tumors Harboring Specific Mutations in *KRAS* (NCT05379985)

Singh, AACR Annual Meeting, 2022

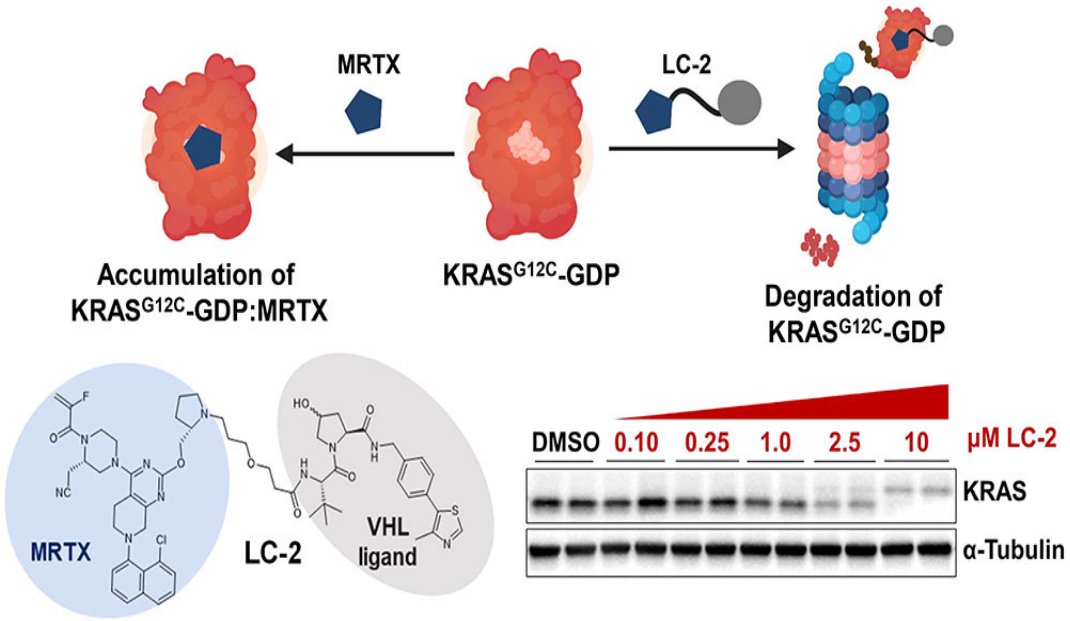
D.



Holderfield M, AACR Annual Meeting, 2022

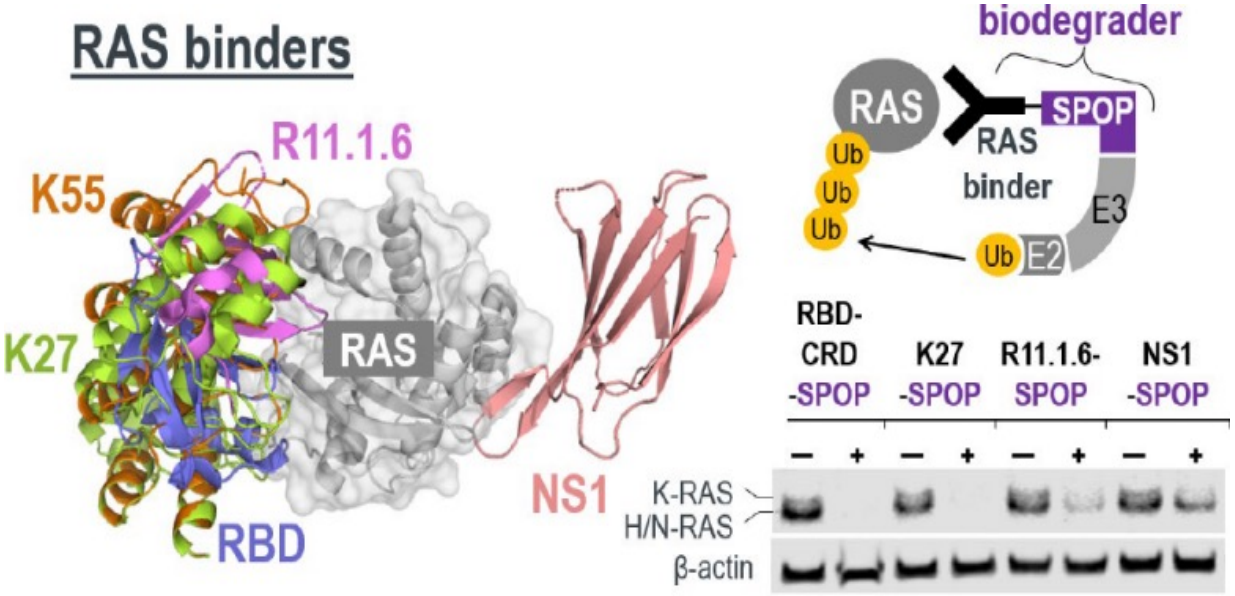
RAS degraders

LC-2 PROteolysis TArgeting Chimera (PROTAC)



Bond MJ, *ACS Cent Sci*, 2020

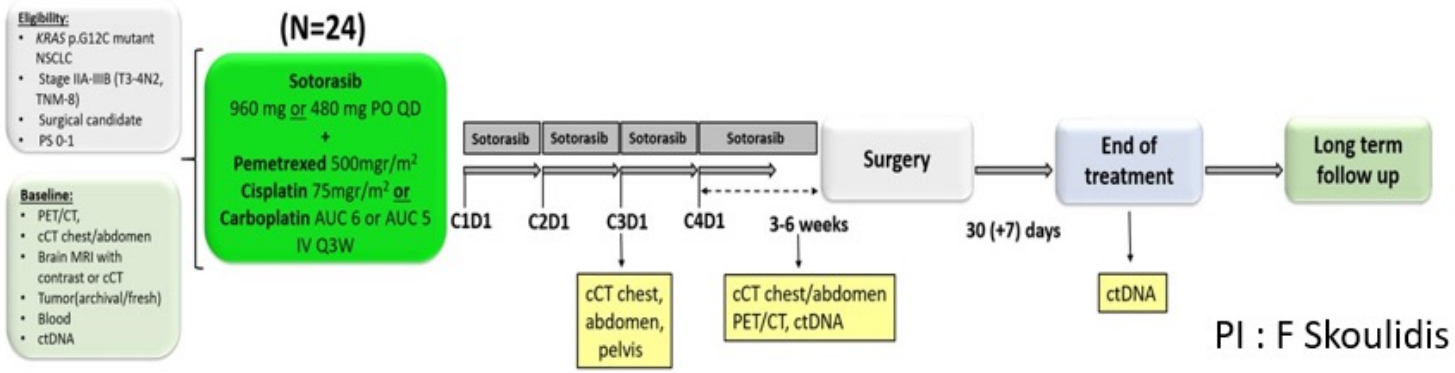
Anti-RAS Biodegraders



Lim S, *ACS Cent Sci*, 2021

Moving KRAS^{G12C} inhibitors to early-stage, surgically resectable NSCLC

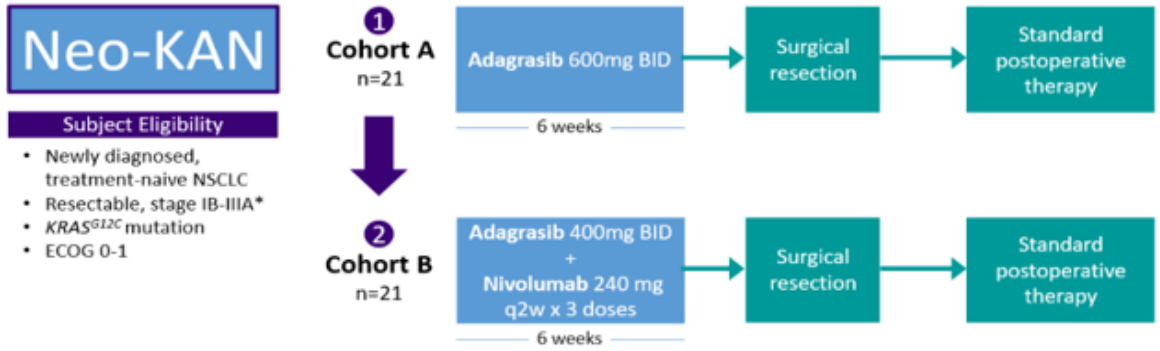
A Phase II Study of Neoadjuvant Sotorasib in Combination with Cisplatin or Carboplatin and Pemetrexed For Surgically Resectable Stage IIA-IIIB Non-Squamous Non-Small Cell Lung Cancer With a *KRAS p.G12C* Mutation (NCT05118854)



Recruiting

PI : F Skoulidis

Phase 2 Trial of Neoadjuvant KRAS G12C Directed Therapy With Adagrasib (MRTX849) With or Without Nivolumab in Resectable Non-Small Cell Lung Cancer (Neo-KAN) (NCT05472623)



Not yet recruiting

PI : K Marrone

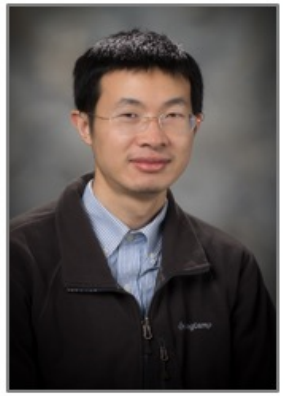
Conclusions and next steps

- Understanding mechanisms of *de novo* and acquired resistance
- Optimal and tailored therapeutic combinations to enhance the efficacy of KRAS G12C inhibitors
- Identification of biomarkers of response to monotherapy and distinct combinations
- First-line metastatic studies in combination with chemotherapy and/or immunotherapy
- Maximizing the immune sensitizing potential of KRAS inhibitors and optimizing combinations with ICIs
- Clinical development of novel mutant-selective inhibitors (both G12C and non-G12C) including RAS(ON) inhibitors
- Clinical development of mutant-selective RAS(ON) and pan-RAS inhibitors
- New approaches to extinguish oncogenic KRAS proteins (degraders, siRNA etc)
- Novel immunotherapy approaches (vaccines, adoptive cell therapy, KRASi-induced presentation of haptenated peptides that can be recognized by T cells etc)

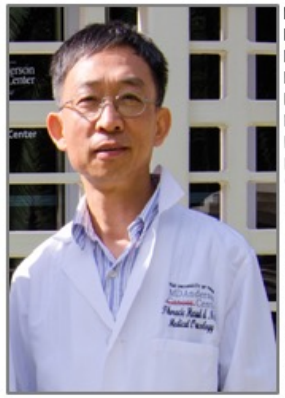
Acknowledgements

Skoulidis lab members


Haniel A. Araujo, MD


Teng Zhou, PhD


Minh-Truong Do, PhD


Richard Lee, MD

THNMO


Marcelo V. Negrao, MD


Neal Akhave, MD


John V. Heymach, MD, PhD

IPCT


David S. Hong, MD

Collaborators

- Dr Mark Awad, Dr Giuseppe Lamberti, Dr Biagio Ricciuti, Dr Joao V. Alessi
- Dr Rebecca Heist, Dr Alissa Cooper
- Dr Jhanelle Gray, Dr Kevin Hicks
- Dr Christine Bestvina, Dr Marina Garassino, Dr Jacobi Hines
- Dr Heather Wakelee, Dr Jacqueline Aredo
- Dr Pradnya Patil, Dr Lukas Delasos
- Dr Sandip Patel, Dr Michael Dennis
- Dr Collin Blakely, Dr Turja Chakrabarti
- Dr Jonathan Riess, Dr David Gandara
- Dr Catherine Su
- Dr Kristen Marrone, Dr Susan Scott
- Dr So Yeon Kim, Dr Sarah Goldberg
- Dr Federico Cappuzzo, Dr Gabriele Minuti
- Dr Mihaela Aldea, Dr Fabrice Barlesi
- Dr Ioannis Mountzios
- Dr Petros Christopoulos
- Dr Giorgio Scagliotti, Dr Paolo Bironzo
- Dr Amy Cummings
- Dr Dwight Owen
- Dr Matthias Scheffler, Dr Jurgen Wolf
- Dr Don Gibbons
- Dr Jianjun Zhang
- Dr Hai Tran

Funding

- 1 R01 CA262469-01 (Skoulidis)
- CPRIT IIRA RP200287 (Skoulidis)
- Tami Hissom Reseach Grant, Rexanna's Foundation for Fighting Lung Cancer
- Lung Cancer Moonshot

GEMINI team

Guardant Health

Biostatistics

- Dr J. Jack Lee
- Dr Yun Qing