KRAS and ERBB2 mutations in NSCLC

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New Orleans Summer Cancer Meeting

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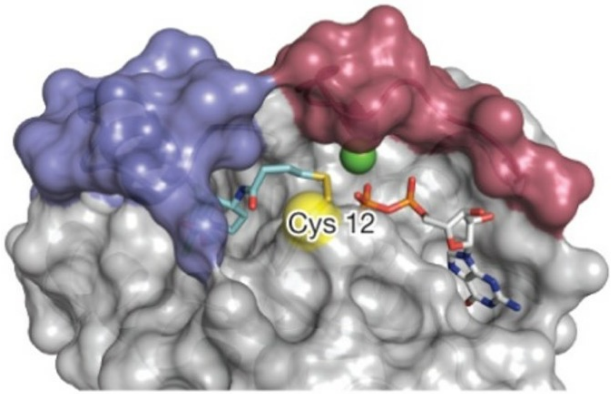
Development of covalent *KRAS*^{G12C} inhibitors: a breakthrough in targeted cancer therapy

A.



Ostrem et al., *Nature*, 2013

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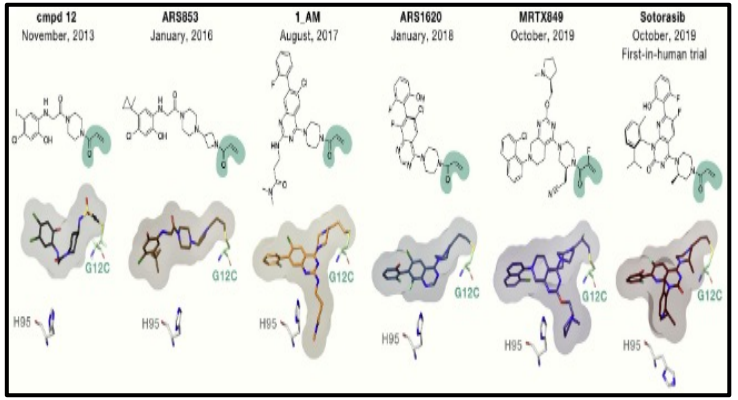

Kim D et al., *Cell*, 2020

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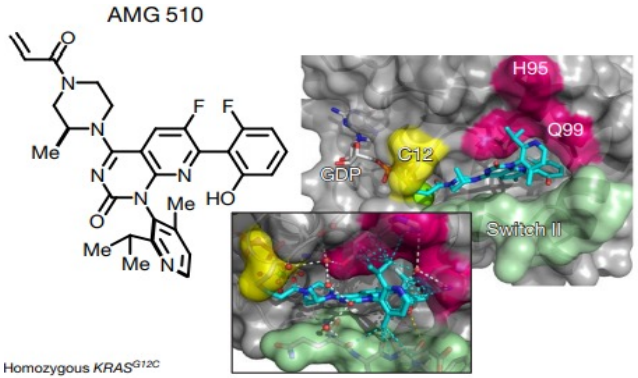

Canon J et al., *Nature*, 2019

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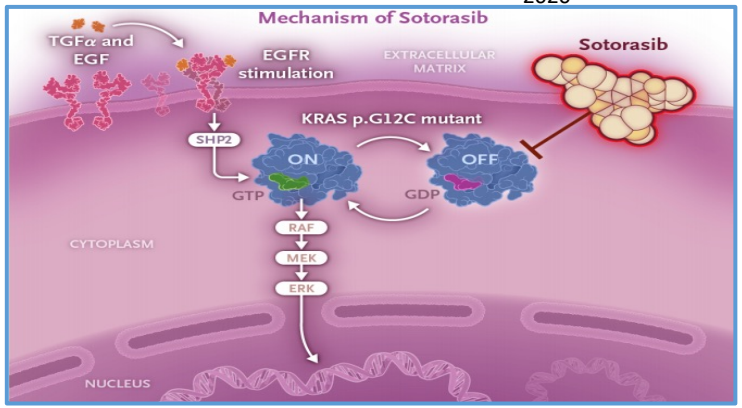
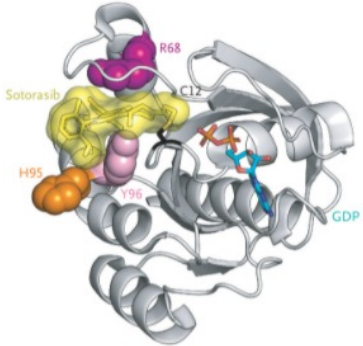


Skoulidis F et al. *N Engl J Med* 2021 Jun 24;384(25):2371-2381

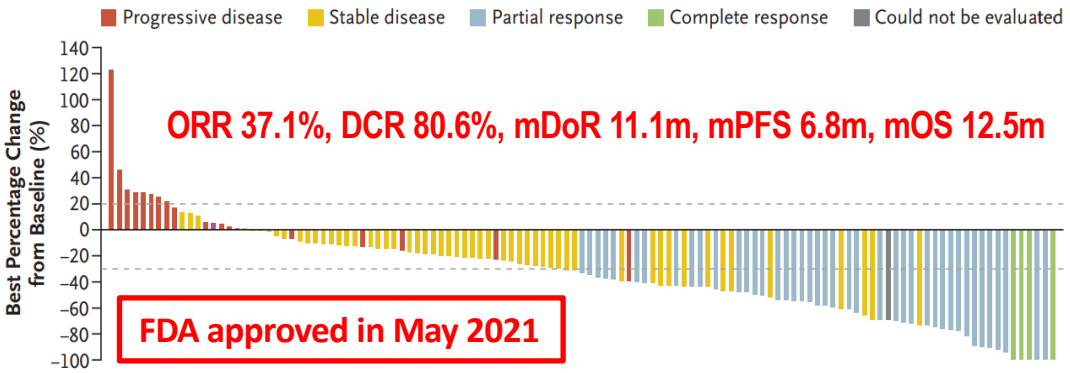
Covalent *KRAS*^{G12C} inhibitors: a breakthrough in targeted cancer therapy

A.

Sotorasib (AMG 510)



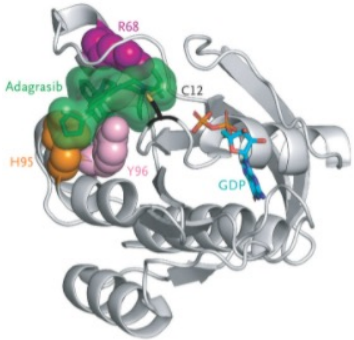
Awad MM et al. *N Engl J Med* 2021 Jun24;384(25):2382-2393



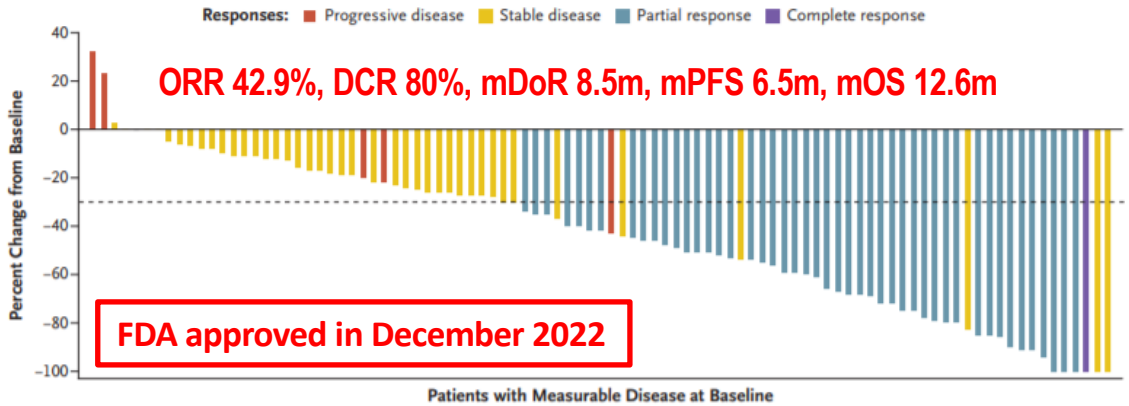
Skoulidis F et al. *N Engl J Med* 2021 Jun 24;384(25):2371-2381

B.

Adagrasib (MRTX849)



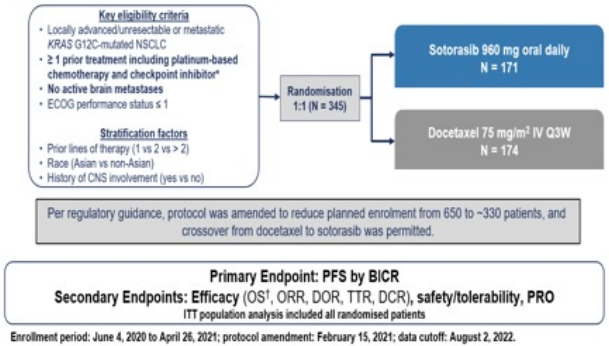
Awad MM et al. *N Engl J Med* 2021 Jun24;384(25):2382-2393



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.



Johnson ML et al., ESMO Congress, 2022

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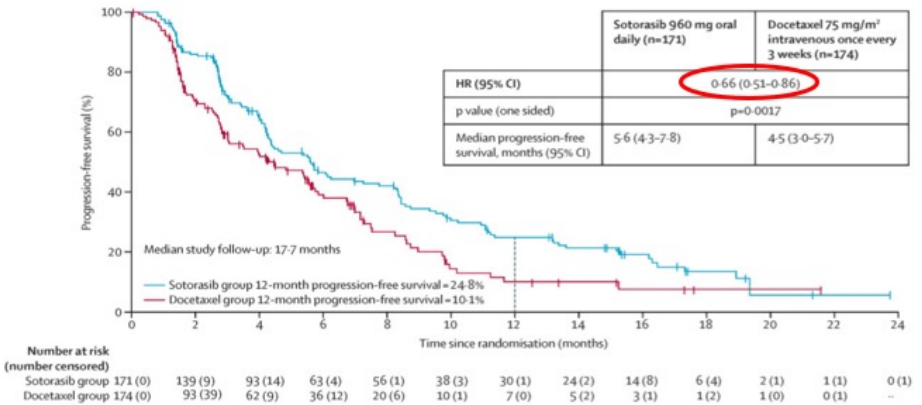
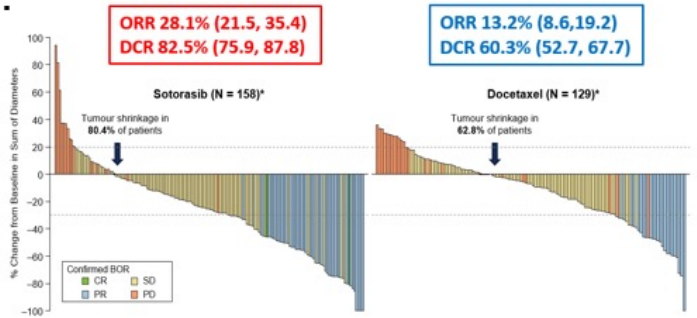


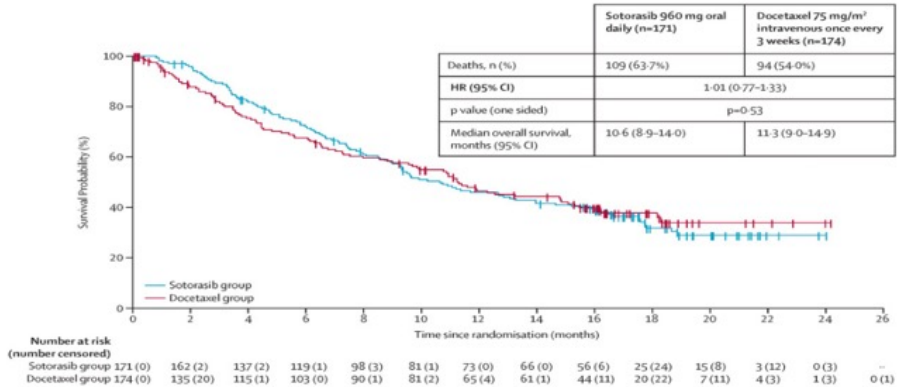
de Langen AJ et al., *Lancet*. 2023 Mar 4;29(3):593-604. Epub 2023 Mar 16

C.



Johnson ML et al., ESMO Congress, 2022

D.

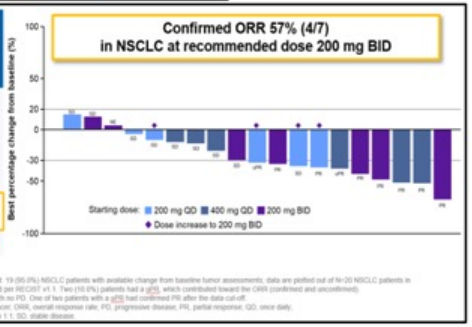


de Langen AJ et al., *Lancet*. 2023 Mar 4;29(3):593-604. Epub 2023 Mar 16

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

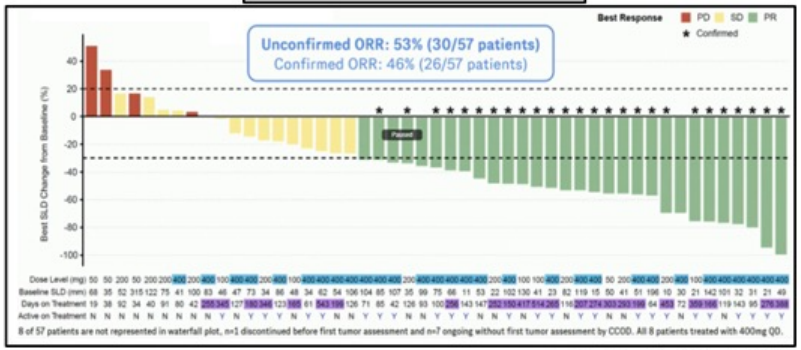
KontRASt-01: JDQ443

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)



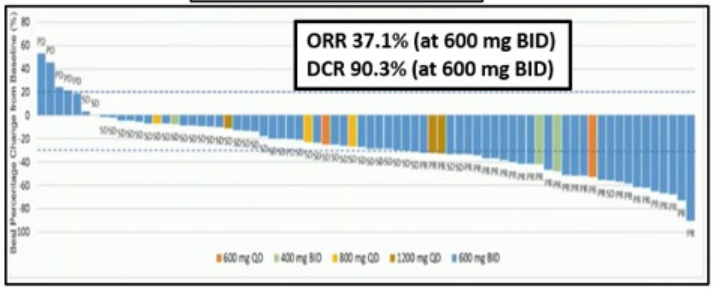
Tan DSW et al., AACR 2022

NCT04449874: GDC-6036



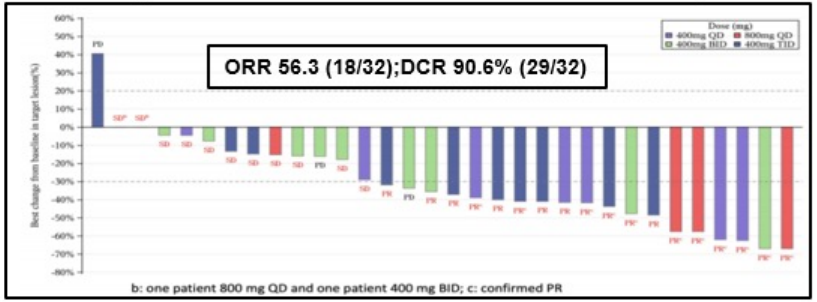
Sacher A et al., ESMO 2022

NCT03600883: D-1553



Lu S et al., WCLC 2022

NCT05009329: JAB-21822 (Glecirasib)



Li J et al., ASCO 2022

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

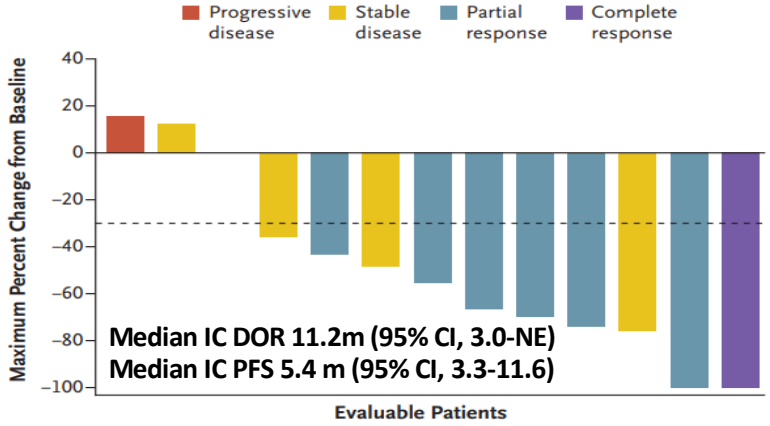
*Forty patients were identified by investigator as having BM; 16 patients with evaluable BM were identified per central review.
†Nine patients had 1 lesion; 2 had 4 lesions; 5 had ≥ 5 lesions.
BM, brain metastases; CNS, central nervous system; RANO, Response Assessment in Neuro-Oncology.

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%)

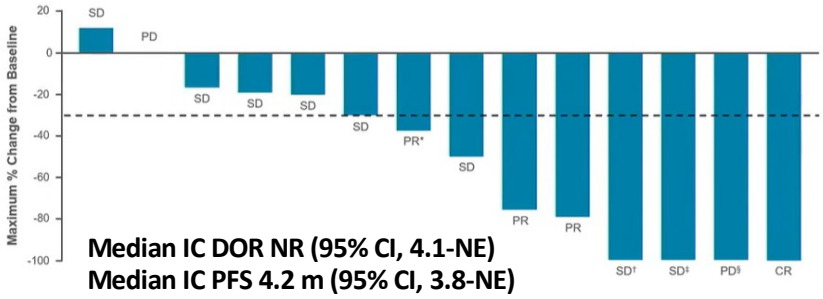
Spira A et al., ASCO 2022



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%)

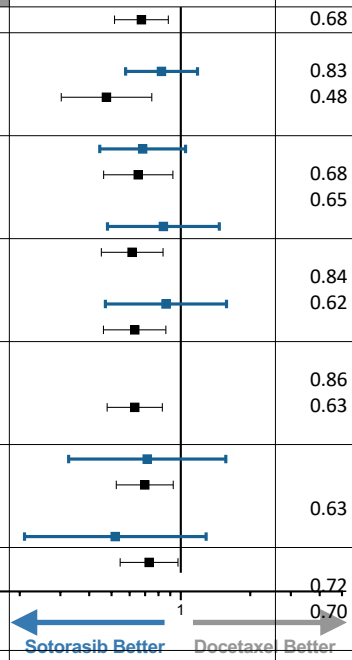


- Objective IC responses were observed in 32% (95% CI, 12.6–56.6)[a]
- IC DCR was 84% (95% CI, 60.4–96.6)

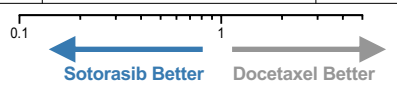
Sabari J et al., ASCO 2022

In the randomized Phase III CodeBreaK 200 trial, Sotorasib Retained PFS Benefit Versus Docetaxel Across Key Co-alteration Subgroups*

	Number of Patients		Hazard Ratio (95% CI)
	Sotorasib	Docetaxel	
All patients	164	154	0.68 (0.52, 0.88)
TP53			
Altered	89	92	0.83 (0.58, 1.18)
Wild-type	75	62	0.48 (0.30, 0.75)
STK11			
Altered	60	60	0.68 (0.45, 1.05)
Wild-type	104	94	0.65 (0.46, 0.92)
KEAP1			
Altered	46	36	0.84 (0.48, 1.47)
Wild-type	118	118	0.62 (0.45, 0.84)
EGFR			
Altered	31	35	0.86 (0.47, 1.58)
Wild-type	133	119	0.63 (0.46, 0.86)
BRAF			
Altered	7	9	–
Wild-type	157	145	0.63 (0.48, 0.83)
ALK			
Altered	19	15	0.72 (0.33, 1.57)
Wild-type	145	139	0.70 (0.53, 0.93)
MET			
Altered	18	21	0.52 (0.21, 1.29)



	Number of Patients		Hazard Ratio (95% CI)
	Sotorasib	Docetaxel	
ERBB2			
Altered	13	13	1.02 (0.40, 2.59)
Wild-type	151	141	0.67 (0.50, 0.88)
RET			
Altered	10	11	0.49 (0.16, 1.52)
Wild-type	154	143	0.68 (0.52, 0.90)
ROS1			
Altered	12	5	–
Wild-type	152	149	0.68 (0.52, 0.89)
NTRK1, 2, 3			
Altered	35	18	0.59 (0.29, 1.20)
Wild-type	129	136	0.66 (0.49, 0.88)
KRAS, NRAS			
Altered	11	17	0.62 (0.21, 1.82)
Wild-type	153	137	0.67 (0.50, 0.89)
PIK3CA			
Altered	16	14	0.88 (0.35, 2.21)
Wild-type	148	140	0.64 (0.49, 0.85)

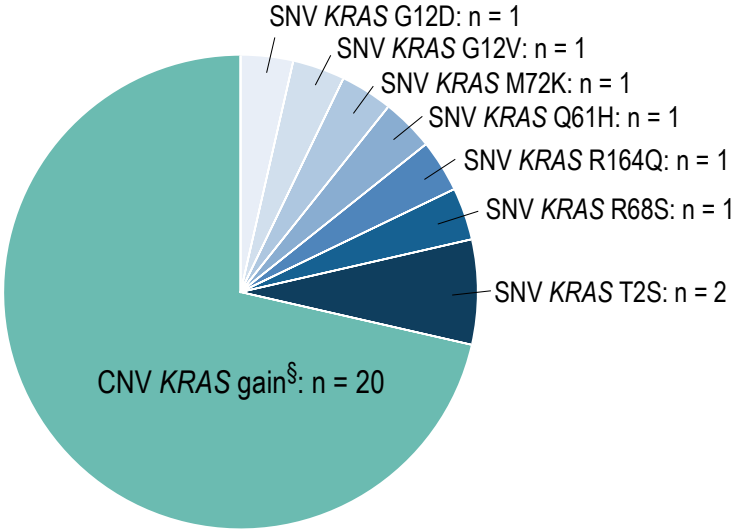


Additionally, sotorasib retained ORR benefit versus docetaxel independent of key co-alteration subgroups*

Analyses was performed for subgroups with n ≥ 10 patients per treatment arm; – indicates no analysis performed for this subgroup.
*Alterations include any somatic SNV, insertion or deletion, or CNV alterations and are not just actionable alterations.

KRAS Co-alterations Were Potentially Associated with Primary Resistance Irrespective of Treatment

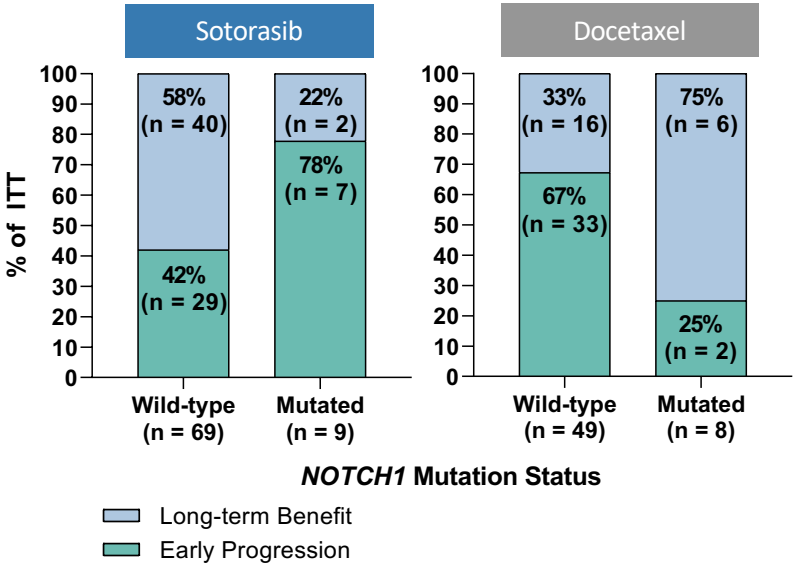
	Sotorasib (n = 164)	Docetaxel (n = 154)	Treatment Difference (*P*-value)
***KRAS* co-alteration*, n (%)**	**9 (5)**	**17 (11)**	
ORR†, n (%)	0	0	–
Median PFS (95% CI)†	1.8 (0.8, 3.0)	2.5 (1.4, 3.1)	0.016‡
HR (95% CI)‡	1.74 (0.84, 3.58)		

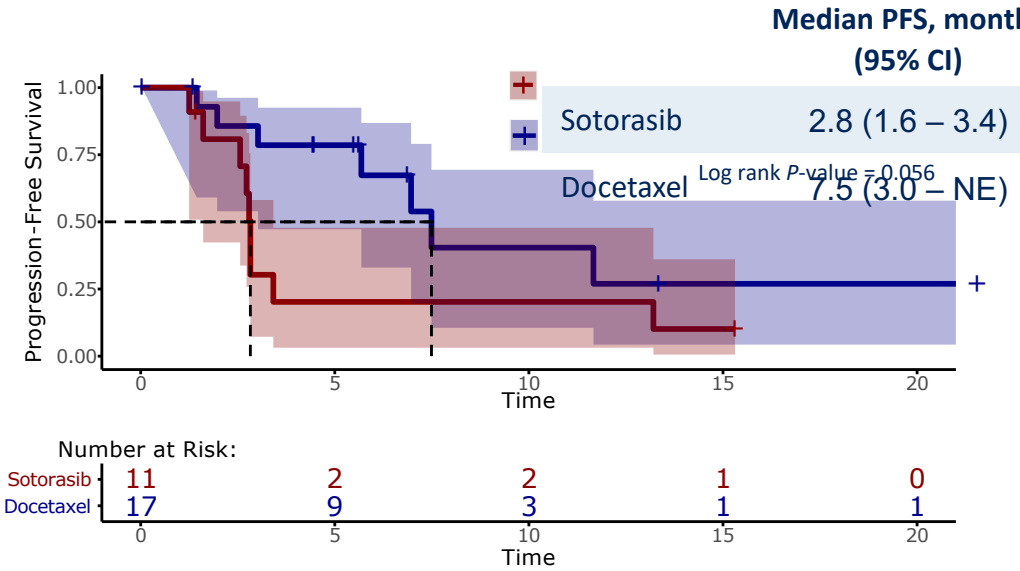


- **No response observed in patients with additional *KRAS* co-alterations in either treatment arm**
- **Outcomes align with preclinical data suggesting some non-G12C *KRAS* alterations mediate sotorasib resistance[8]**

*Excluding G12C.
†Medians were estimated using the Kaplan-Meier method. 95% CIs were estimated using the method by Klein and Moeschberger with log-log transformation.
‡Hazard ratios, 95% CIs, and *P*-values were estimated using a stratified Cox proportional hazards model with treatment, stratification factors, and co-alterations as covariates and treatment by co-alteration interaction. A hazard ratio <1.0 indicates a lower average event rate and a longer PFS for sotorasib versus docetaxel.
§Limit of detection for CNV was >2, all *KRAS* CNV were copy number gains.

In a Limited Data Set, *NOTCH1m* Had an Early Progression Signal With Sotorasib That Warrants Further Exploration

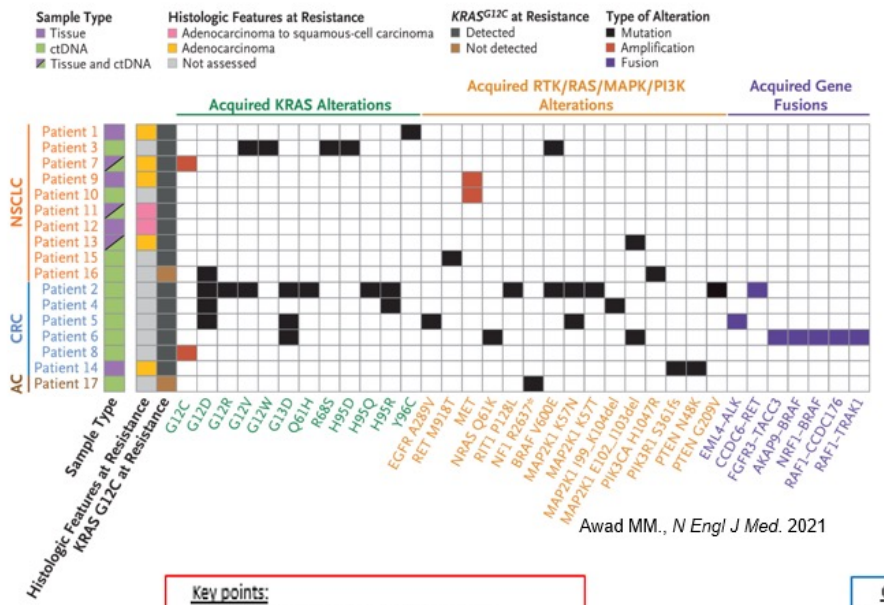




Long-term benefit defined as ≥ 6 months PFS; early progression defined as < 3 months PFS with no clinical responders (no complete/partial responders).
Left-hand figure includes patients with *NOTCH1* mutation or wild-type who were classified as having early progression or long-term benefit. Right-hand figure includes all biomarker-evaluable patients with *NOTCH1* mutation.

Barriers to the efficacy of OFF state-selective KRAS G12Ci : acquired resistance

A.



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

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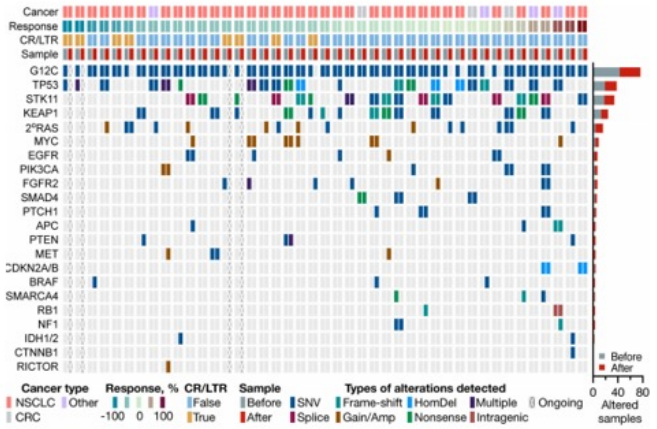


Zhao Y et al., *Nature*. 2021

Key points:

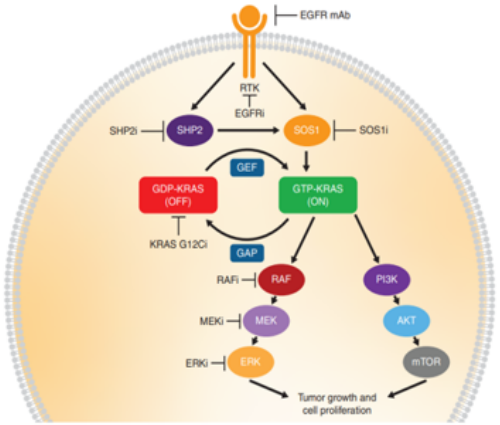
- Diverse mechanisms of acquired resistance
- Multiple mechanisms may coexist in the same patient (polyclonal res – convergent evolution)
- Some mechanisms may be unique to certain inhibitors (such as mutations involving H95)
- In many cases no mechanisms has been identified

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

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

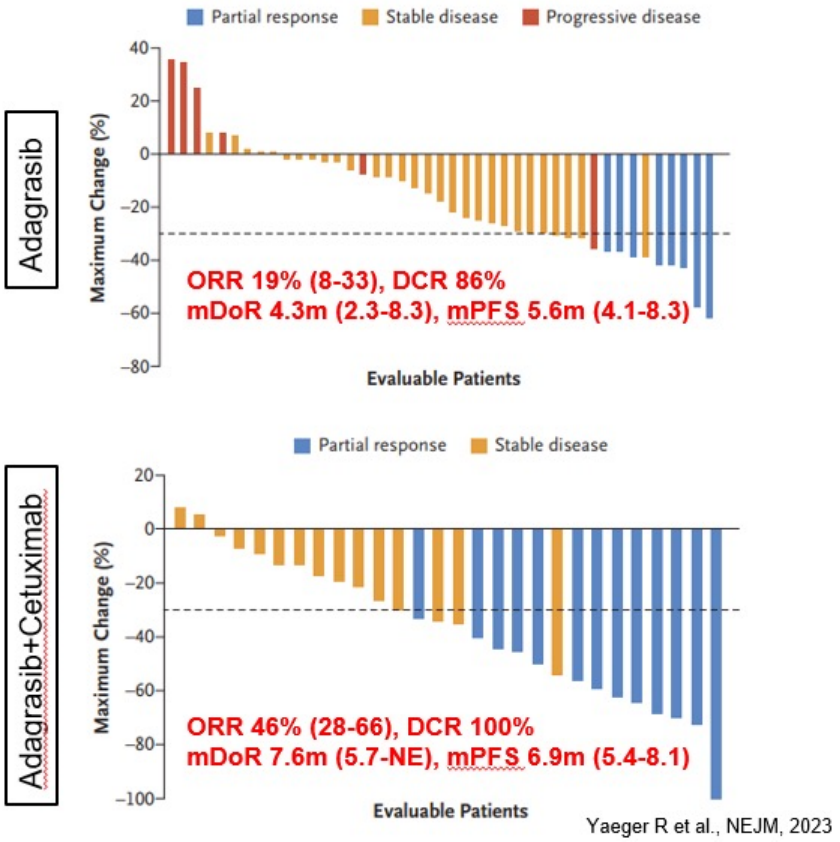
Adagrasib combinations

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.



Yaeger R et al., NEJM, 2023

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)

GDC-6036 + cetuximab in advanced CRC

A.

KEY ELIGIBILITY CRITERIA

- Locally advanced or metastatic solid tumors, including CRC, harboring a *KRAS G12C* mutation
- At least one prior treatment or intolerability of standard therapy
- Measurable or evaluable disease per RECIST
- Previously treated brain metastases only
- Prior KRAS G12C inhibitor treatment allowed

DOSE ESCALATION

GDC-6036 oral QD, 21-day cycles
200mg → 400mg *Max Admin Dose MTD not reached*
N=3 N=6
+ **cetuximab** 400 mg/m2 intravenously initially, then 250 mg/m2 weekly

DOSE EXPANSION

GDC-6036 oral QD, 21-day cycles
400mg
N=20
+ **cetuximab** 400 mg/m2 intravenously initially, then 250 mg/m2 weekly

KEY ENDPOINTS

- Safety (NCI-CTCAE v5)
- Pharmacokinetics
- Preliminary antitumor activity (RECIST v1.1)

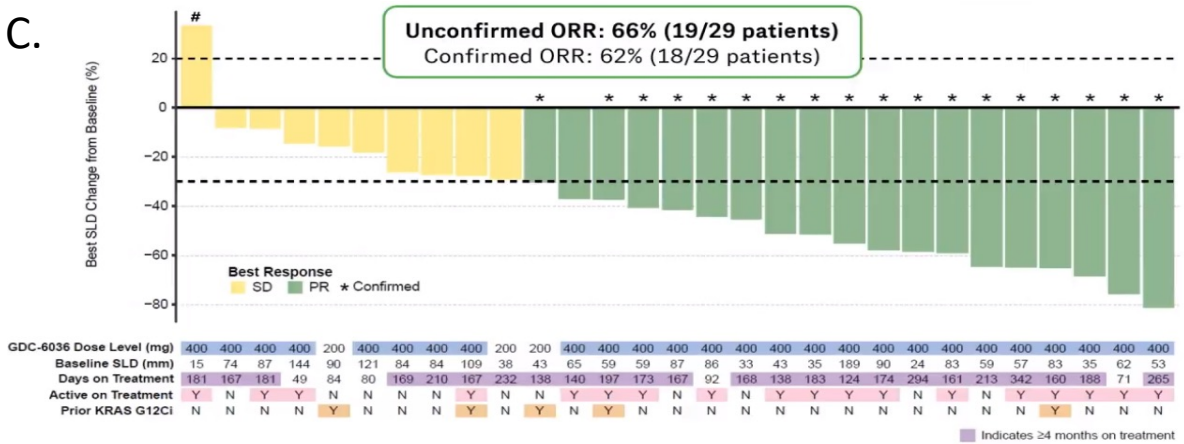
GO42144, NCT04449874 - Data presented as of CCOD 21 Nov 2022, patients enrolled by 07 Oct 2022. **Total N=29 CRC patients**

B.

TREATMENT-RELATED AEs (≥10% PATIENTS) OVERALL & CORRESPONDING GRADE 3-4 AEs	N=29	
	Related AEs	Related Grade 3-4 AEs
Patients with at least one AE	29 (100%)	12 (41.4%)
Rash (Grouped Term*)	27 (93%)	1 (3.4%)
Diarrhea	21 (72.4%)	3 (10.3%)
Nausea	19 (65.5%)	0
Vomiting	14 (48.3%)	0
Dry skin	8 (27.6%)	0
Paronychia	5 (17.2%)	1 (3.4%)
Hypomagnesaemia	4 (13.8%)	2 (6.9%)
Pruritus	4 (13.8%)	0
Infusion related reaction	4 (13.8%)	1 (3.4%)
Fatigue	3 (10.3%)	0
Pyrexia	3 (10.3%)	0
Dysgeusia	3 (10.3%)	0

*Rash Grouped Term = dermatitis, dermatitis acneiform, rash, rash pustular, rash follicular, rash maculopapular, rash papular.
No treatment-related grade 5 events were reported.

C.



Desai J et al., AACR Annual Meeting 2023

Efficacy, treatment duration and safety of LY3537982 in combination with cetuximab in CRC (Cohort C2)

A.

Treatment Emergent AEs, (>10%)[a], % (All Doses and Patients)					Treatment Related AEs[b], %			
	100 mg BID (n=13)		150 mg BID (n=7)		100 mg BID (n=13)		150 mg BID (n=7)	
Adverse Event	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Dermatitis acneiform	39%	-	71%	-	39%	-	43%	-
Diarrhea	23%	8%	43%	-	15%	8%	29%	-
Headache	31%	-	29%	-	31%	-	14%	-
Dry skin	39%	-	-	-	39%	-	-	-
Fatigue	23%	-	29%	-	8%	-	14%	-
Vomiting	23%	-	29%	-	8%	-	14%	-
AST increased	23%	-	14%	-	23%	-	14%	-
Nausea	23%	-	14%	-	8%	-	-	-
ALT increased	23%	8%	-	-	23%	8%	-	-
Blood CPK increased	15%	-	14%	-	8%	-	14%	-
Hypokalemia	15%	-	14%	-	8%	-	-	-
Hypomagnesaemia	15%	-	14%	-	15%	-	14%	-
Pruritus	15%	-	14%	-	15%	-	14%	-
Pyrexia	8%	-	29%	-	8%	-	14%	-

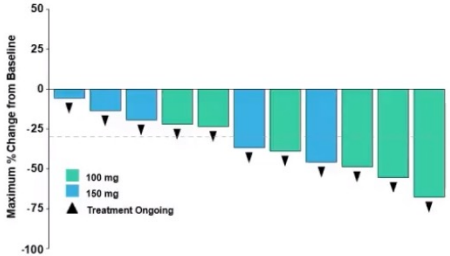
Median time on treatment was 1.8 months (range, 0.03-5.1 months)

1 DLT observed at 100 mg BID (grade 3 ALT/AST increase)

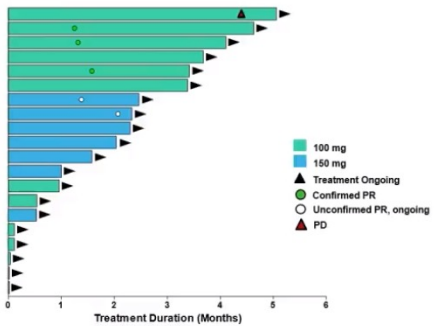
5% (n=1) dose reduced LY3537982 due to TRAEs

No patient permanently discontinued due to TRAEs

B.



Efficacy Evaluable Patients[a]	n = 11
Overall Response Rate[b]	**45% (5/11)**
Best Overall Response	
CR, n (%)	-
PR, n (%)[b]	5 (45)
SD, n (%)	6 (55)
PD, n (%)	-
DCR, n (%)	**11 (100)**



- **100% (11/11) of patients have treatment ongoing**
- **Median time to response was 1.3 months**

Murciano-Goroff YR et al., AACR Annual Meeting 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)**

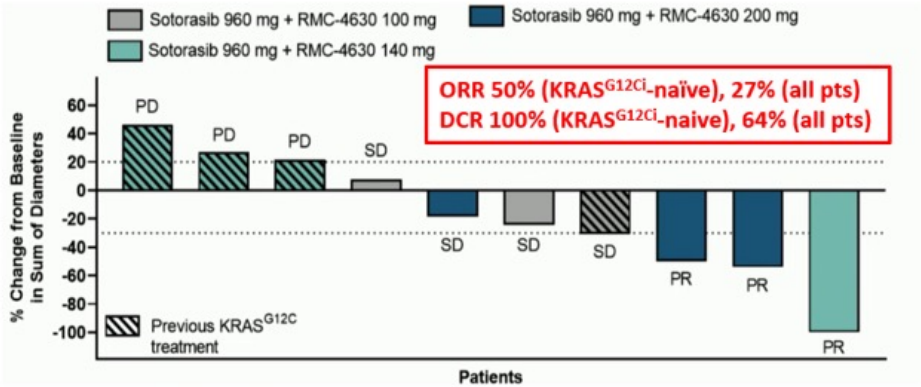
Key eligibility criteria*
- Locally advanced or metastatic *KRAS* p.G12C solid tumors
- Prior anti-PD(L)1 and/or platinum-based chemo and targeted therapy (NSCLC)
- Allowed prior KRAS^{G12C} inhibitor

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

Sotorasib in combination with pembrolizumab or atezolizumab in advanced *KRAS*^{G12C}-mutant NSCLC : CodeBreak 100/101

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		
360 mg	*OR*	*OR*
240 mg	Pembrolizumab 200 mg Q3W (N = 19)	Pembrolizumab 200 mg Q3W (N = 19)
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

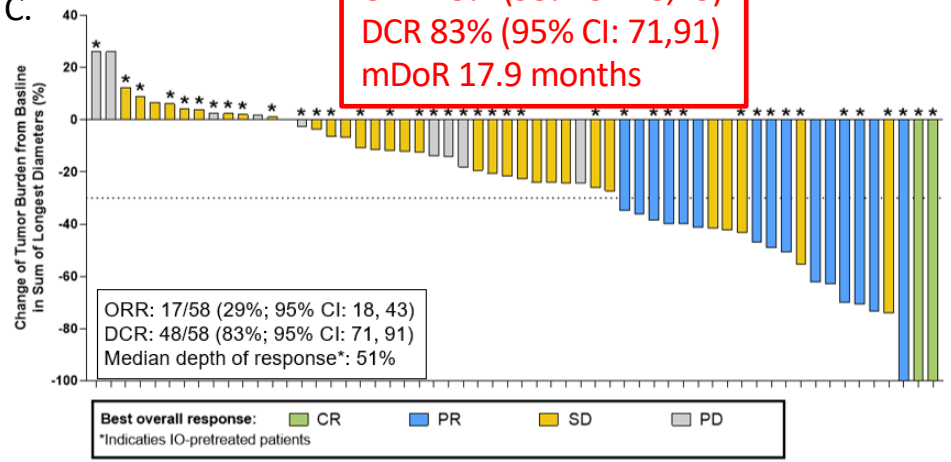
B.

Safety Summary: Lead-in versus Concurrent

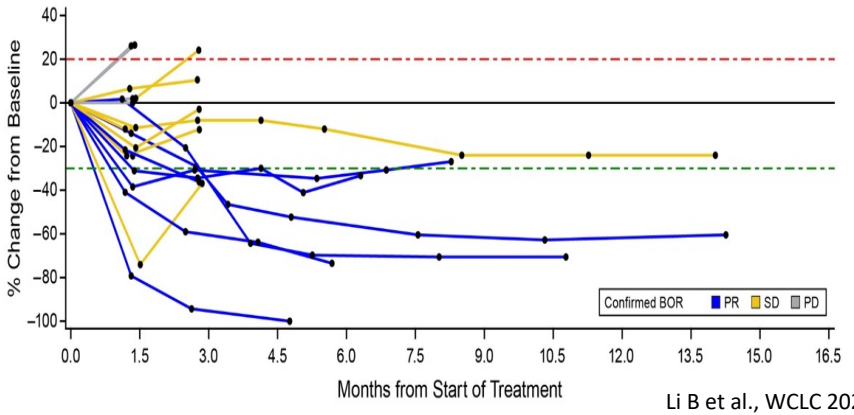
	Sotorasib + Atezolizumab Lead-In (N = 10)	Sotorasib + Atezolizumab Concurrent (N = 10)	Sotorasib + Pembrolizumab Lead-In (N = 19)	Sotorasib + Pembrolizumab Concurrent (N = 19)
TRAE, any grade, n (%)	10 (100)	9 (90)	15 (79)	17 (89)
Grade 3	3 (30)	5 (50)	10 (53)	14 (74)
Grade 4*	0	1 (10)	0	1 (5)
TRAE leading 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



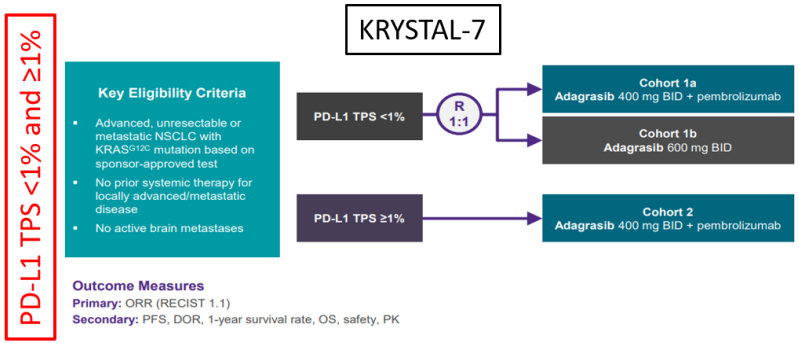
D.



Li B et al., WCLC 2022

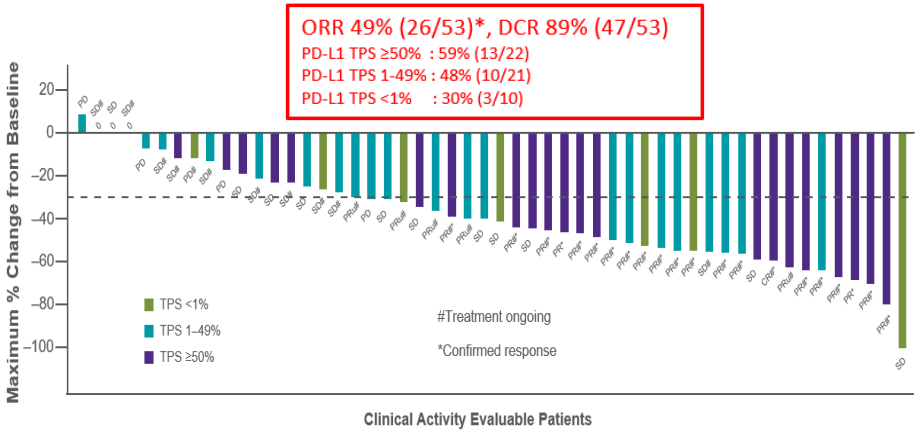
Adagrasib in combination with pembrolizumab in treatment-naïve *KRAS^{G12C}*-mutated NSCLC : KRYSTAL-7 phase 2 trial

A.



Mirati Therapeutics Corporate Presentation September 2022

B.



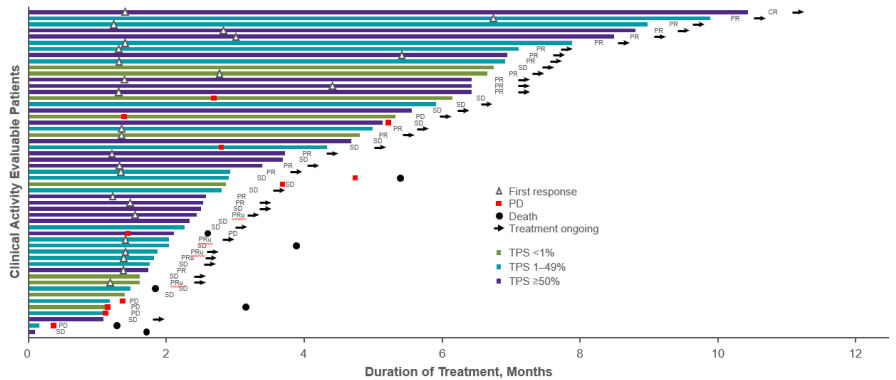
C.

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.

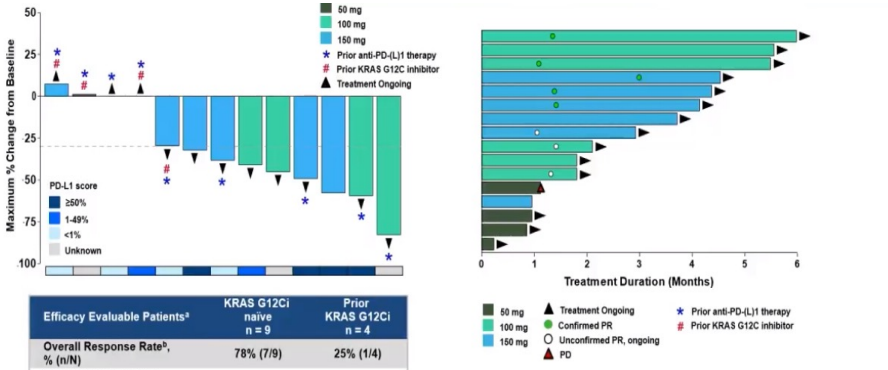
*Excludes 14 pts on study for <6 weeks (no post-baseline scan) and 8 pts that discontinued prior to first scan.



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

Efficacy, treatment duration and safety of LY3537982 in combination with pembrolizumab in NSCLC (Cohort B4)

A.



Efficacy Evaluable Patients[a]	KRAS G12Ci naive n = 9	Prior KRAS G12Ci n = 4
Overall Response Rate[b], % (n/N)	78% (7/9)	25% (1/4)
Best overall response		
CR, n (%)	-	-
PR, n (%)	7 (78)	1 (25)
SD, n (%)	2 (22)	2 (50)
PD, n (%)	-	1 (25)
DCR, n (%)	9 (100)	3 (75)

- 100% (8/8) of responding patients have treatment ongoing[a]
- Median time to response was 1.4 months
- Of the 7 KRAS G12C inhibitor naïve responders, 3 had PD-L1 score ≥50%

Data cutoff date of 03 Jan 2023. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment before the first post-baseline response assessment. [b]ORR includes patients with a best response

B.

Treatment Emergent AEs, (>10%)[a], % (All Doses and Patients)					Treatment Related AEs[b], %			
	50 mg BID (n=4) + 100 mg BID (n=6)		150 mg BID (n=6)		50 mg BID (n=4) + 100 mg BID (n=6)		150 mg BID (n=6)	
Adverse Event	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhea	30%	10%	50%	-	30%	10%	50%	0
Nausea	20%	-	33%	-	10%	-	17%	-
ALT increased	-	-	50%	33%	-	-	50%	33%
AST increased	-	-	50%	33%	-	-	50%	33%
Vomiting	20%	-	17%	-	-	-	17%	-
Abdominal pain	-	-	33%	-	-	-	17%	-
Arthralgia	10%	-	17%	-	10%	-	17%	-
Cough	-	-	33%	-	-	-	17%	-
Dyspnea	-	-	33%	-	-	-	17%	-
Flank pain	-	-	33%	-	-	-	-	-
Hypomagnesaemia	10%	-	17%	-	-	-	17%	-
Hypothyroidism	-	-	33%	-	-	-	33%	-
Pruritus	10%	-	17%	-	10%	-	17%	-

Median time on treatment was 2.5 months (range, 0.2-6 months)

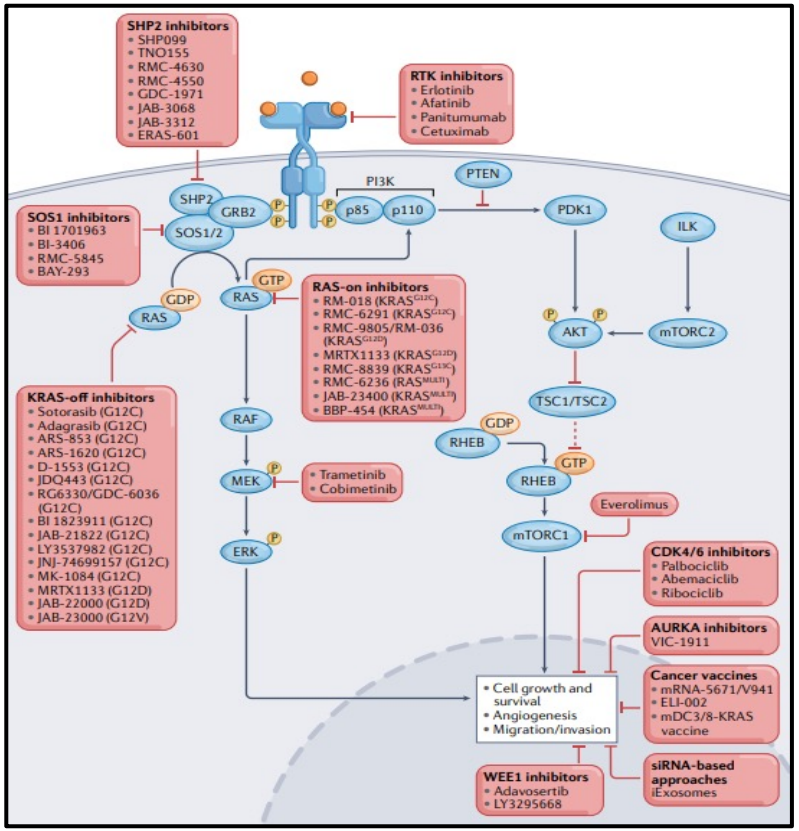
No DLTs observed, although delayed AST/ALT elevations observed at 150 mg BID

At 50 mg BID, 1 discontinuation occurred due to a TRAE

At 50 mg and 100 mg BID doses, there were no dose reductions

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

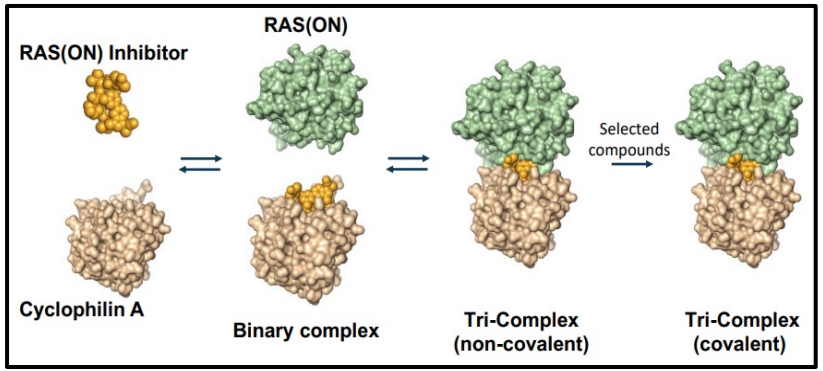
Emerging novel approaches to target *KRAS*-mutant tumors

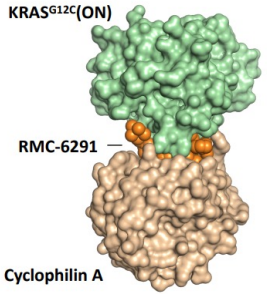


Punekar SR et al., *Nat Rev Clin Oncol* 2022

RAS(ON) Tri-complex inhibitors

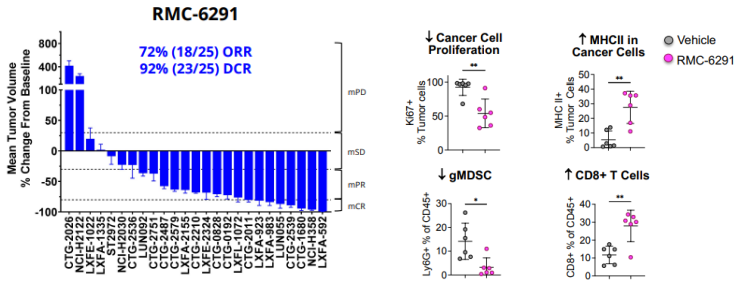
A.





B.

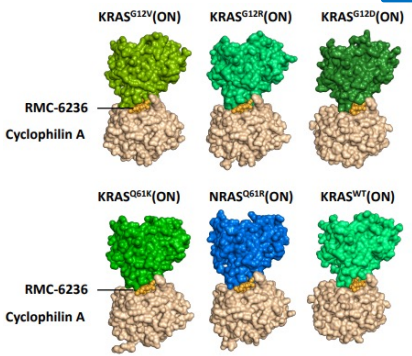
KRAS^{G12C} (ON)

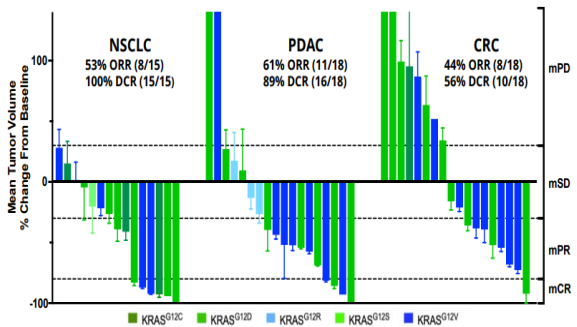


Nichols RJ, AACR Annual Meeting, 2022

C.

RAS^{MULTI} (ON)

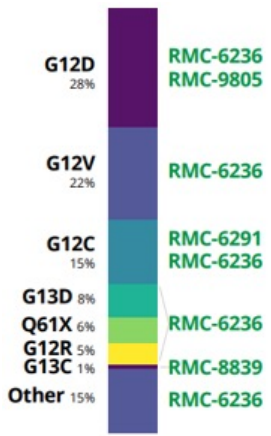




Singh, AACR Annual Meeting, 2022

D.

Other RAS Mutant (ON) inhibitors



Holderfield M, AACR Annual Meeting, 2022

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

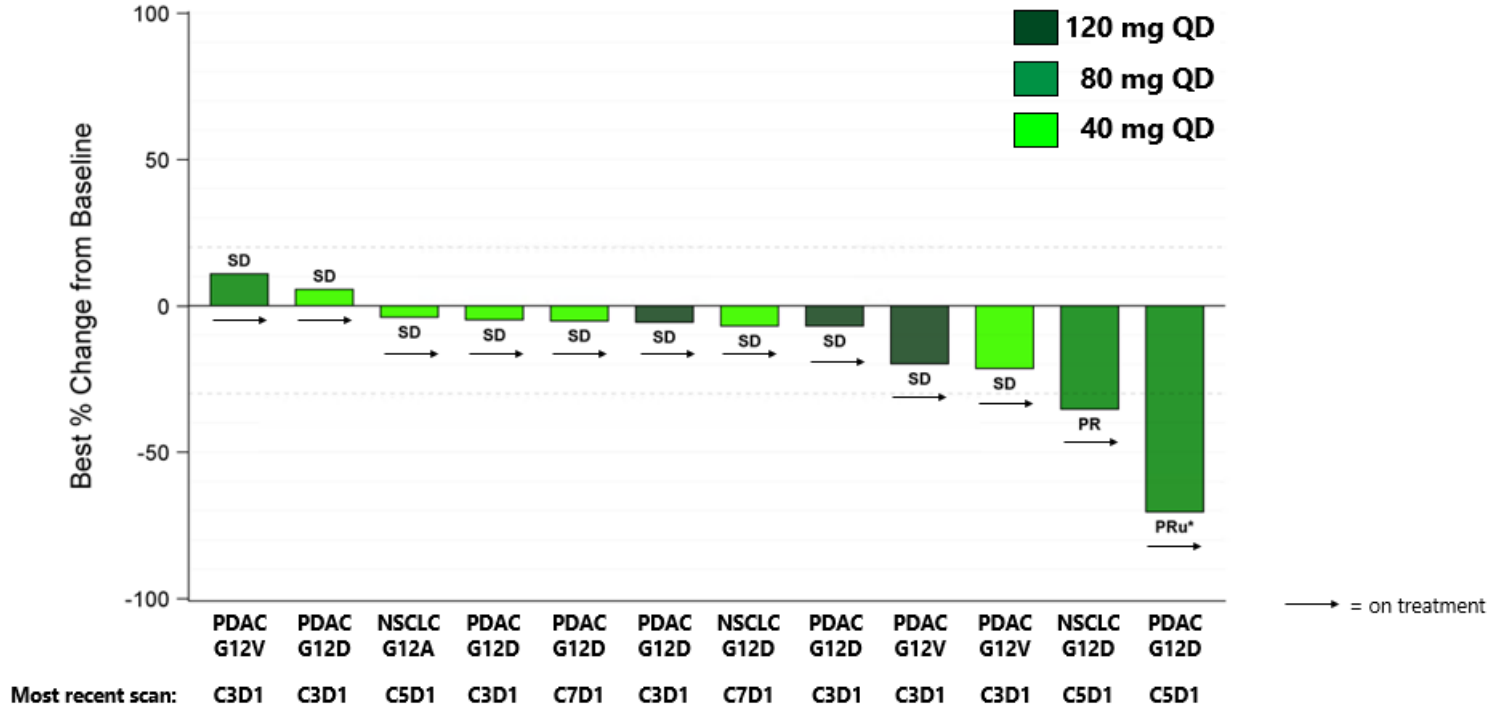
RMC-6236-001 Phase 1/1b Trial : Treatment-Related AEs Occurring in ≥ 10% of All Patients

	10 mg QD (N=3)		20 mg QD (N=13)		40 mg QD (N=9)		80 mg QD (N=7)		120 mg QD (N=4)		Overall (N=36)	
Preferred Term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Rash (CMQ)*	0	0	2 (15.4%)	0	4 (44.4%)	0	6 (85.7%)	0	4 (100%)	0	16 (44.4%)	0
Nausea	1 (33.3%)	0	2 (15.4%)	0	6 (66.7%)	0	2 (28.6%)	0	1 (25.0%)	0	12 (33.3%)	0
Diarrhea	0	0	1 (7.7%)	0	2 (22.2%)	0	1 (14.3%)	0	2 (50.0%)	0	6 (16.7%)	0
Fatigue	0	0	0	0	2 (22.2%)	0	0	0	2 (50.0%)	0	4 (11.1%)	0
Vomiting	0	0	1 (7.7%)	0	2 (22.2%)	0	0	0	1 (25.0%)	0	4 (11.1%)	0

One related grade 4 adverse event of bowel perforation (also considered a serious adverse event) was reported in a patient receiving 80 mg daily. The likely cause of the perforation was considered to be shrinkage of metastatic $KRAS^{G12V}$ pancreatic cancer at the site of full-thickness bowel infiltration.

EDC data as of 02/17/2023
CMQ = Customized MedDRA Query
*Consists of dermatitis acneiform, dermatitis psoriasiform, palmar-plantar erythrodysesthesia syndrome, rash maculo-papular, and rash pustular.

RMC-6236-001: Change in Tumor Burden from Patients with KRAS^{G12X} NSCLC or Pancreatic Cancer Treated at ≥ 40 mg Daily



EDC data as of 02/17/2023; efficacy evaluable patients defined as those in this data set with at least one post baseline response assessment or who have died or have experienced clinical progression prior to the first post baseline scan (n=12). Cycle time is 21 days. SD = stable disease, PR = partial response. NSCLC = non-small cell lung cancer; PDAC = pancreatic ductal adenocarcinoma.

*PR unconfirmed as of 02/17/2023.

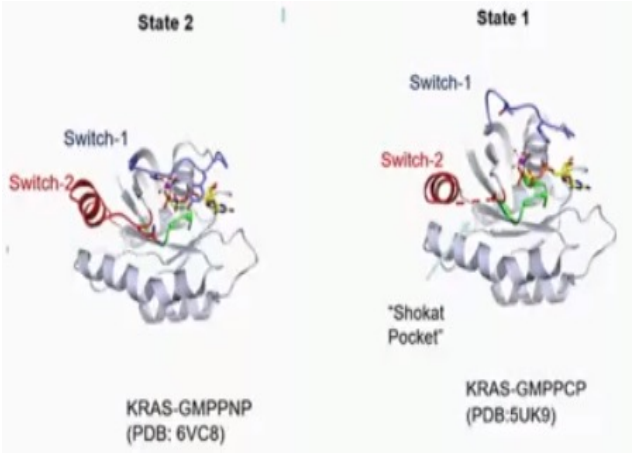
Slide courtesy of Revolution Medicines

BBO-8520: a dual state selective covalent inhibitor of KRAS^{G12C} that traps KRAS GTP in the non-productive State 1 configuration

A.

			BBO-8520	Sotorasib	Adagrasib
% modified	KRAS^{G12C} GTP (active)	15'	100	0	0
		60'	100	0	0
	KRAS^{G12C} GDP (inactive)	15'	91	80	73
		60'	100	82	84
KRAS^{G12C} : RAF1 Effector Binding IC_{50} (nM)			33	>100,000	20,000
H358 pERK IC_{50} @ 30' (nM)			4	50	310
H358 kinact/Ki (M*s)-1			43,000	776	1064

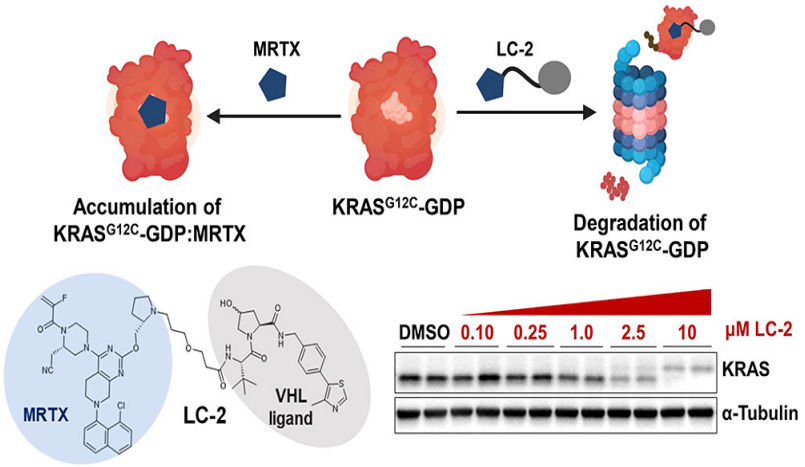
B.



McCormick F, AACR Annual Meeting 2023

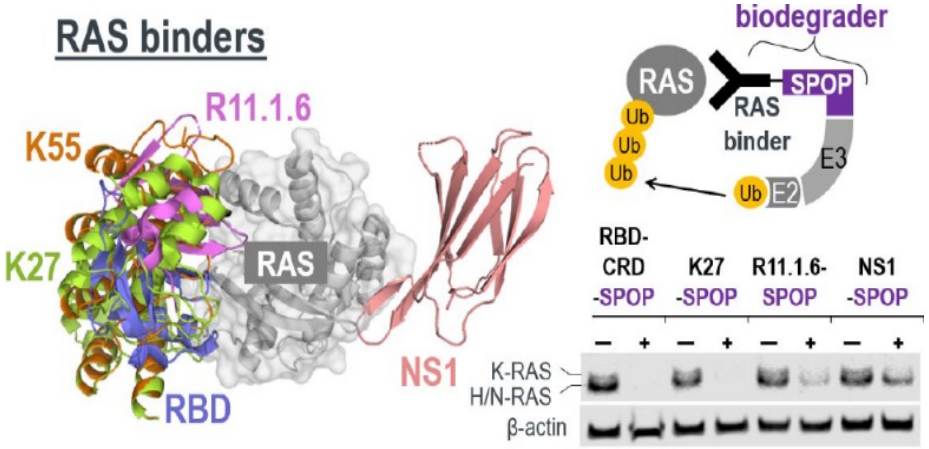
RAS degraders

LC-2 PROteolysis TArgeting Chimera (PROTAC)



Bond MJ, *ACS Cent Sci*, 2020

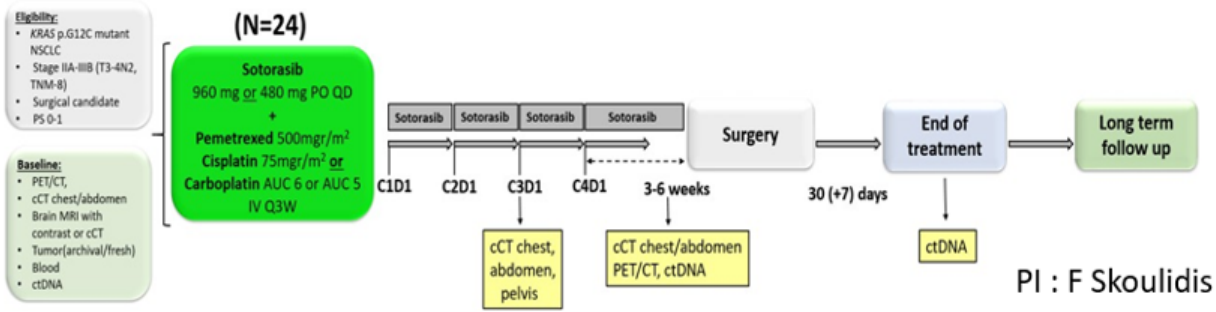
Anti-RAS Biodegraders



Lim S, *ACS Cent Sci*, 2021

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

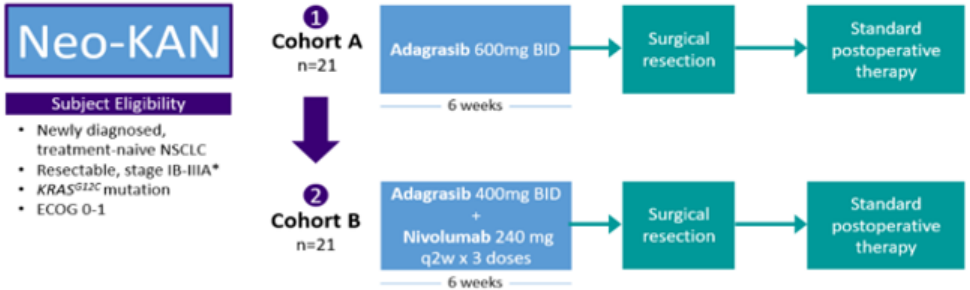
A Phase II Study of Neoadjuvant Sotorasib in Combination with Cisplatin or Carboplatin and Pemetrexed For Surgically Resectable Stage IIA-IIIB Non-Squamous Non-Small Cell Lung Cancer With a *KRAS p.G12C* Mutation (NCT05118854)



PI : F Skoulidis

Recruiting

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)

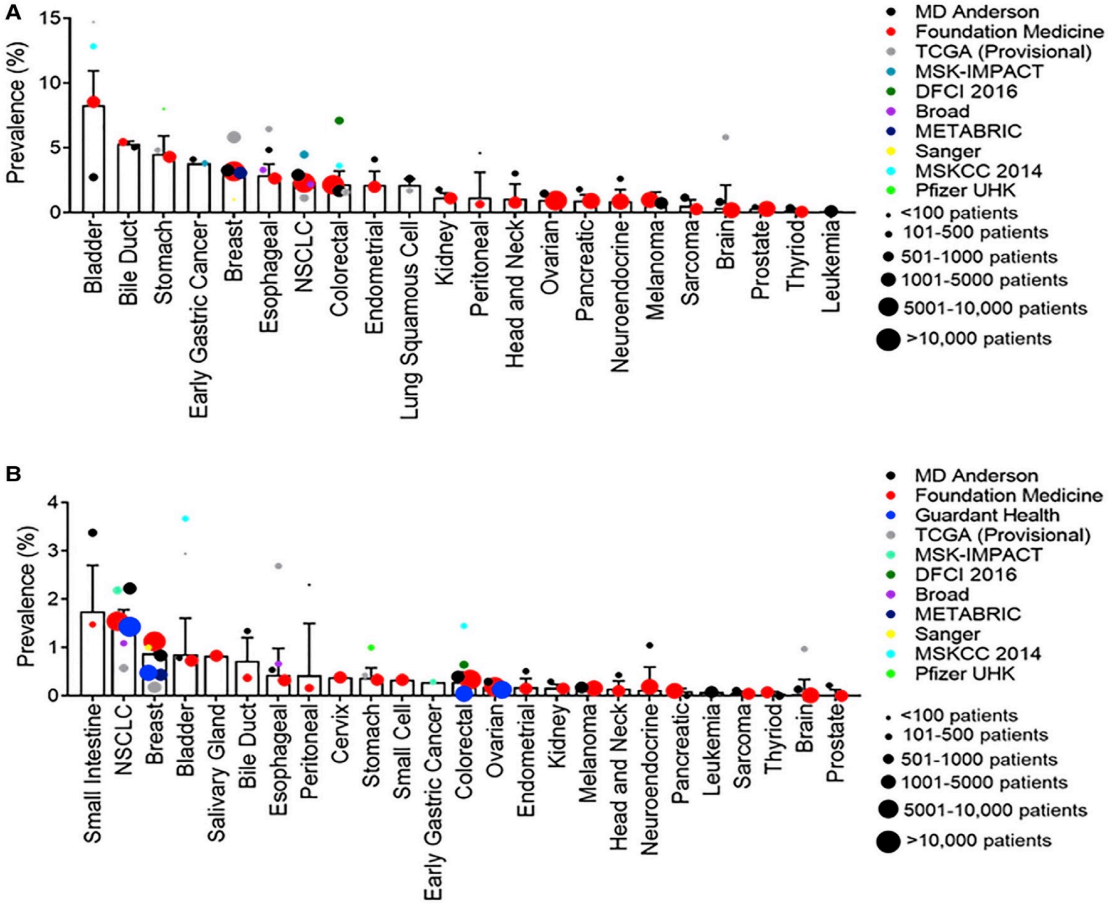


PI : K Marrone

Not yet recruiting

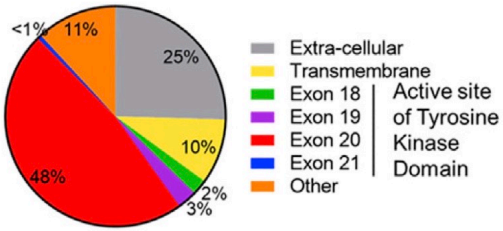
HER2 mutations

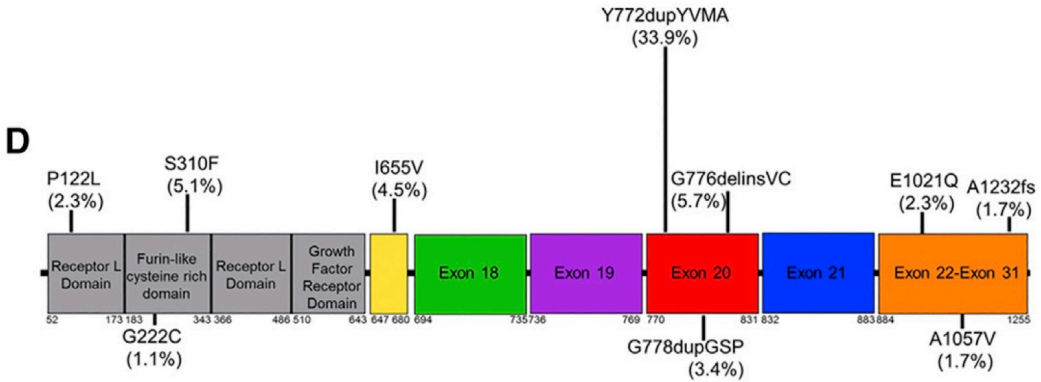
ERBB2 mutations occur in a variety of cancer types



Robichaux et al. Cancer cell 2019

ERBB2 mutation hotspots in NSCLC





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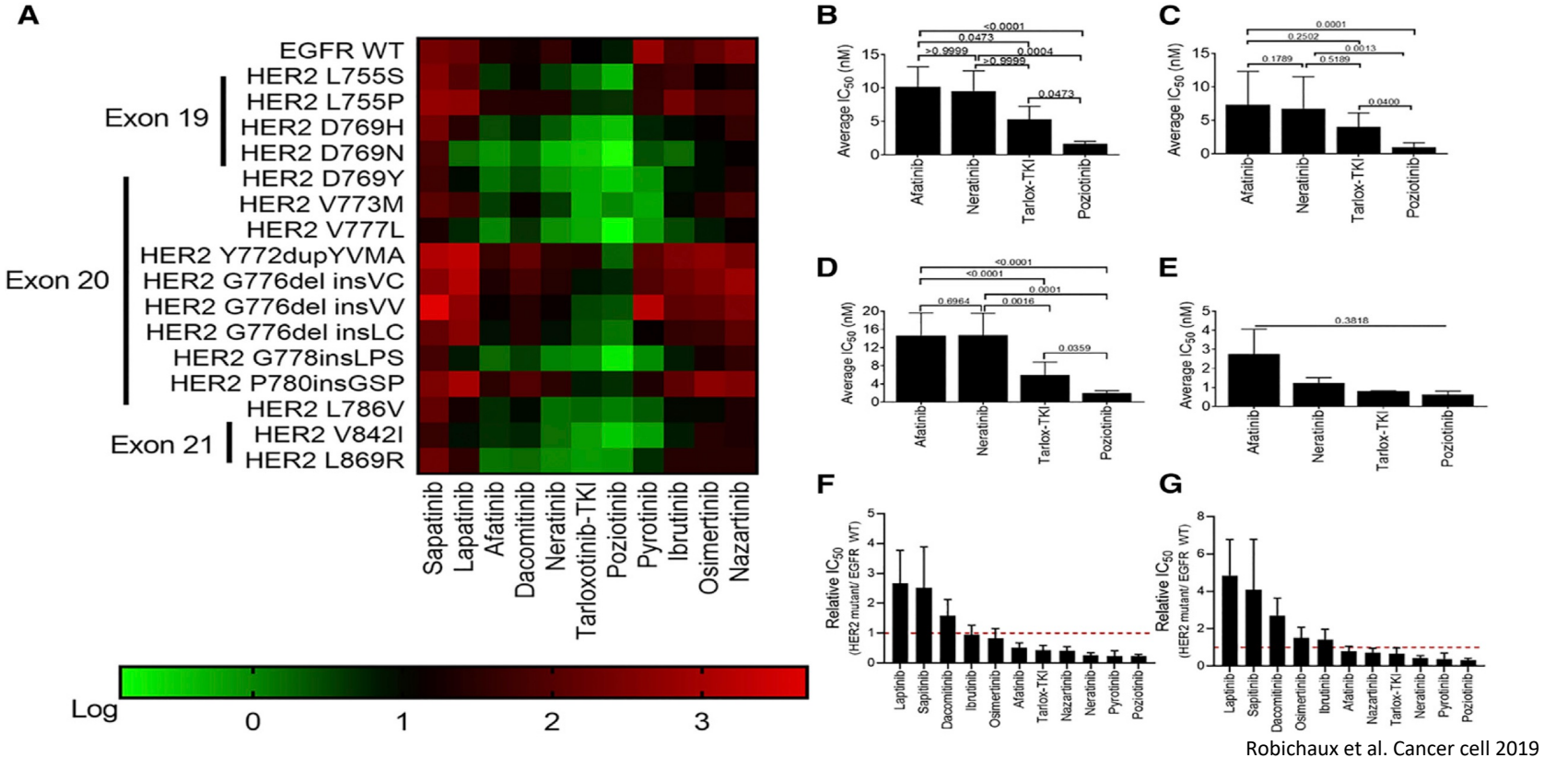
Potency of TKIs in Ba/F3 cells expressing HER2 mutations



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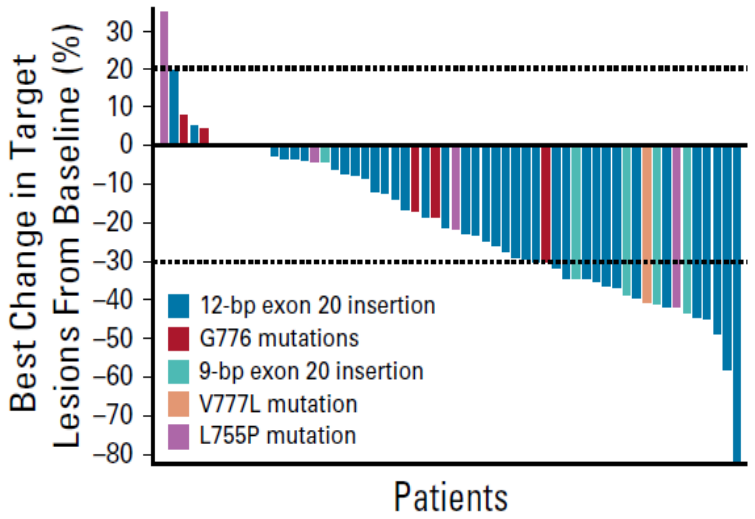
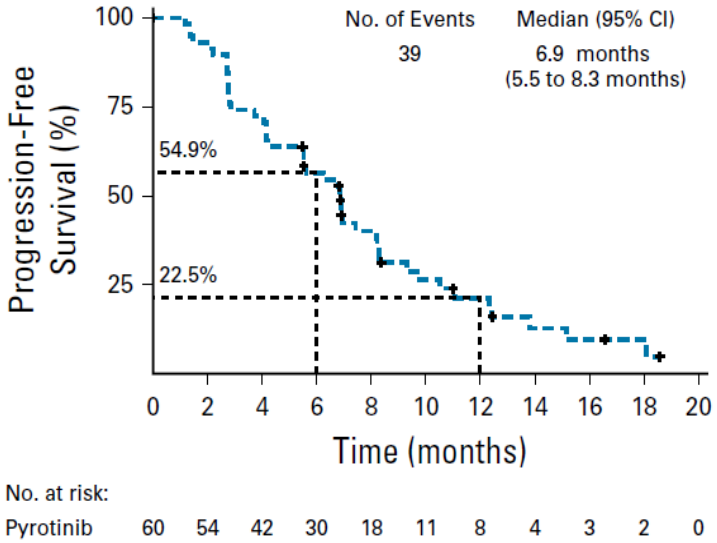
Pyrotinib in HER2 mutations

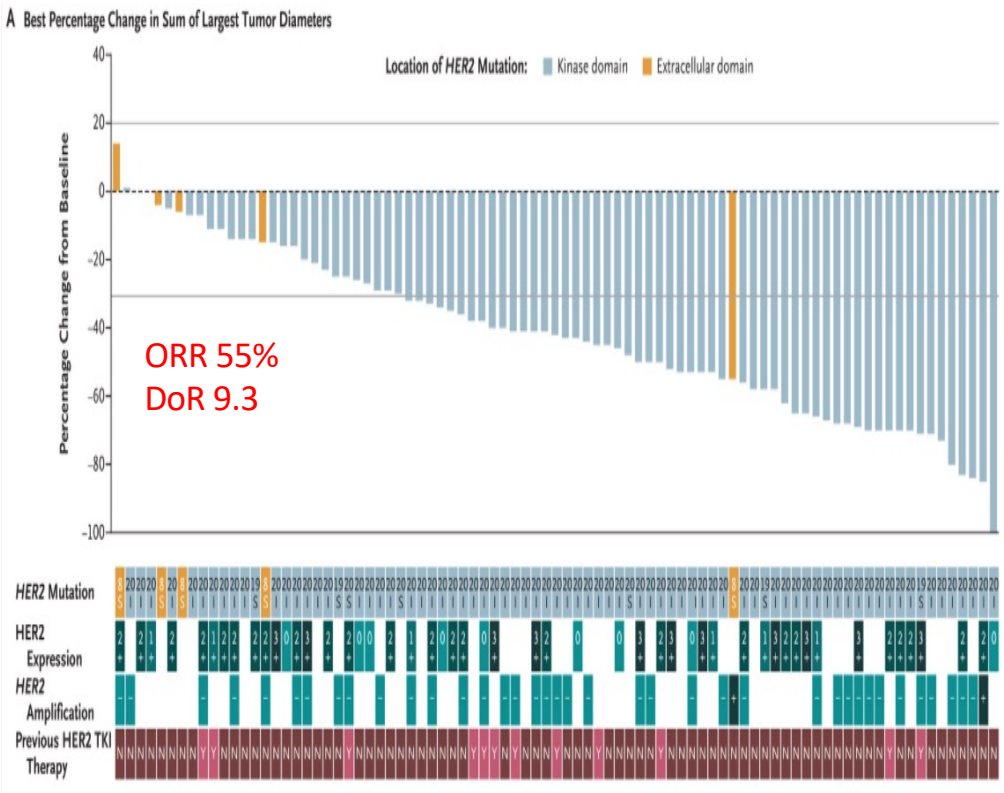


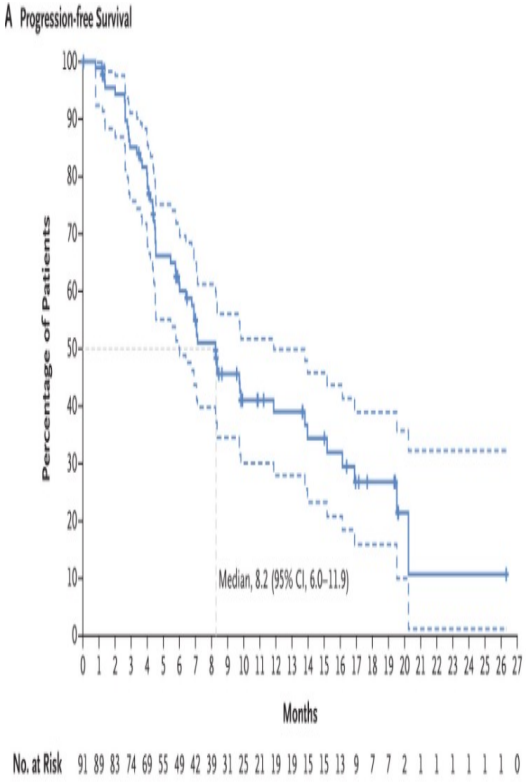
Objective response rate	18 (30.0)
95% CI	18.8 to 43.2
Median duration of response, months	6.9 (4.9 to 11.1)



Zhou J Clin Oncol 2020

Trastuzumab Dertuxtecan in HER2 mutant NSCLC





Li et al. NEJM 2021

Trastuzumab Dertuxtecan in HER2 mutant NSCLC

Table S5. Adjudicated Drug-related Interstitial Lung Disease.

	Patients (N = 91)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Adjudicated drug-related interstitial lung disease, n (%)*	3 (3.3)	15 (16.5)	4 (4.4)	0	2 (2.2)†	24 (26.4)

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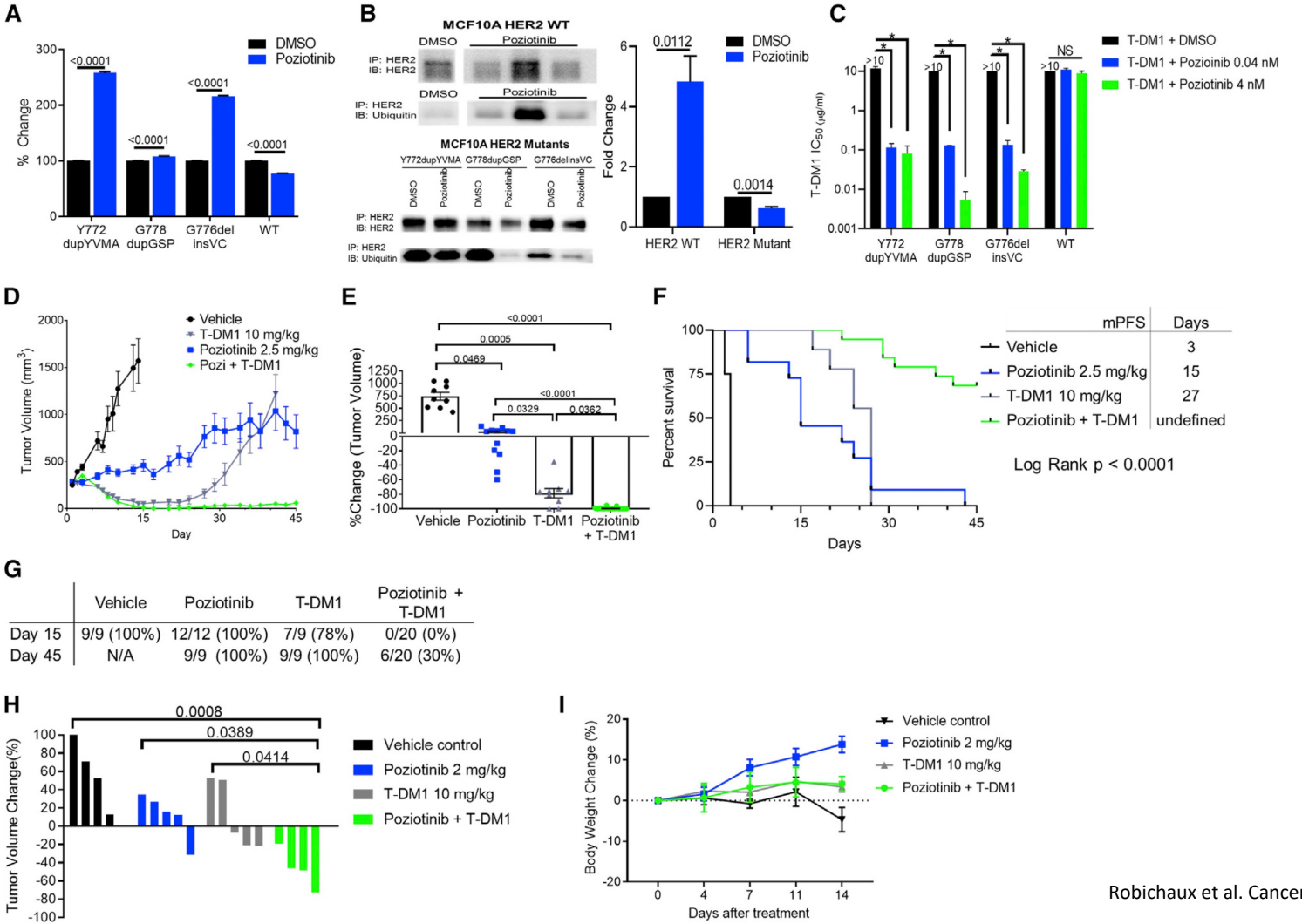

Robichaux et al. Cancer cell 2019