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oncology therapeutics

BBO-8520, a first-in-class, direct inhibitor of KRAS^{G12C} (ON)

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5th Annual RAS-Targeted Drug Development Summit

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RAS INITIATIVE

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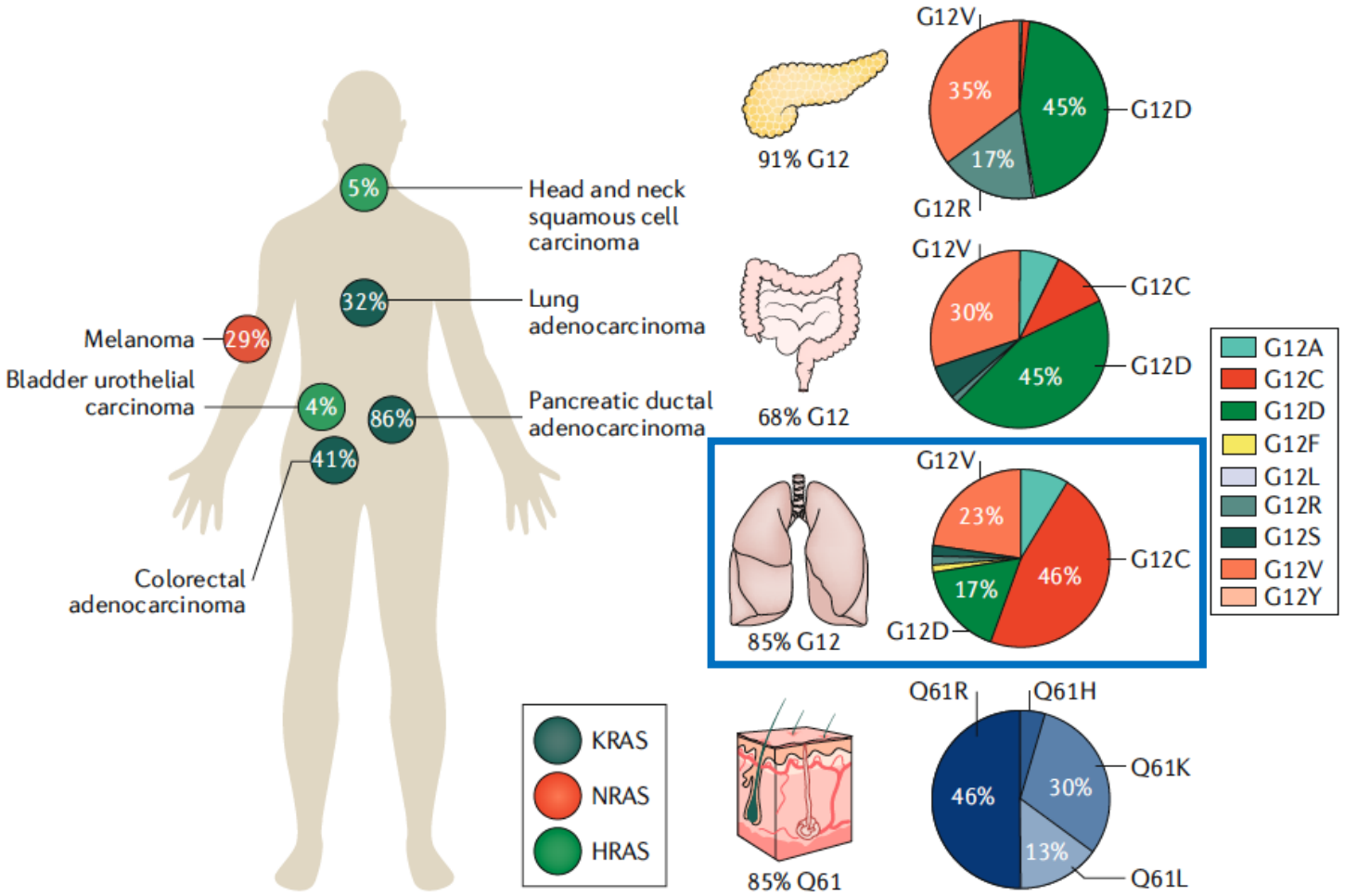
Disclosures

- Current shareholder and employee of BridgeBio Pharma
- Current shareholder and ex-employee of Amgen, Inc

KRAS^{G12C} is the most common mutated KRAS isoform found in NSCLC



Lung cancer is the second most common cancer in the US with greater than 235K in new cases and 130K deaths a year

Lung cancer is the second leading cause of death in US and, by far, the leading cause of cancer death – 25% of all cancer deaths are from lung cancer

Non-small cancer lung cancer (NSCLC) accounts for ~85% of lung cancer

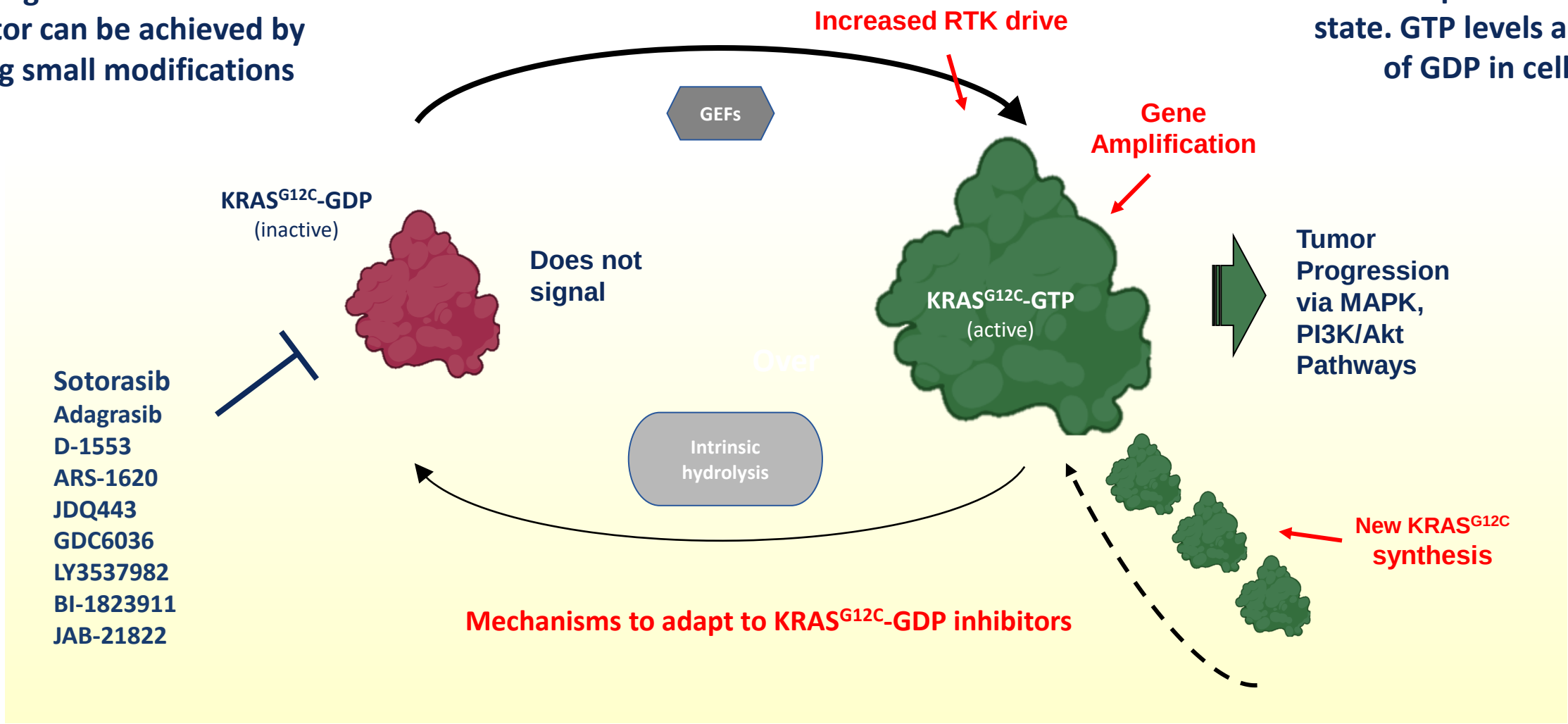
KRAS^{G12C} mutant found in ~15% of all NSCLC (and ~3% of CRC)

Moore et.al. Nat Rev Drug Discov. 2020 August ; 19(8): 533–552

KRAS^{G12C}-GDP Inhibitors target a “dead” protein with no signaling or transforming potential

Adapting to a KRAS^{G12C}-GDP inhibitor can be achieved by making small modifications

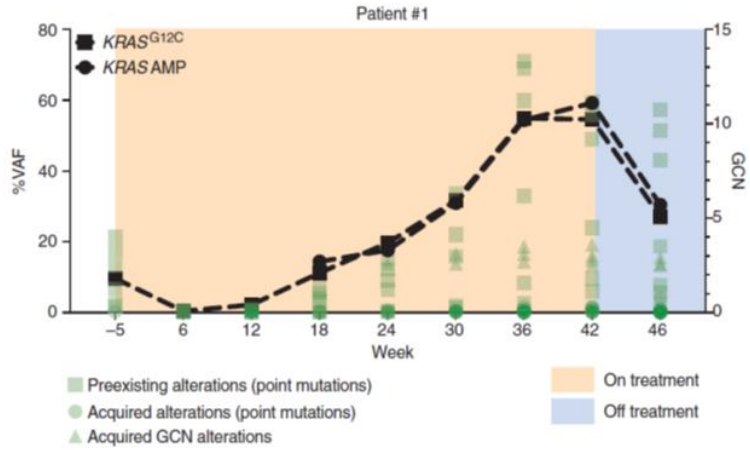
KRAS^{G12C} prefers the GTP state. GTP levels are 10x of GDP in cells



$KRAS^{G12C}$ amplification and RTK-drive ensure that enough $KRAS^{G12C}$ is found in the (ON) state rendering GDP inhibitors inactive

$KRAS^{G12C}$ amplification is associated with clinical progression

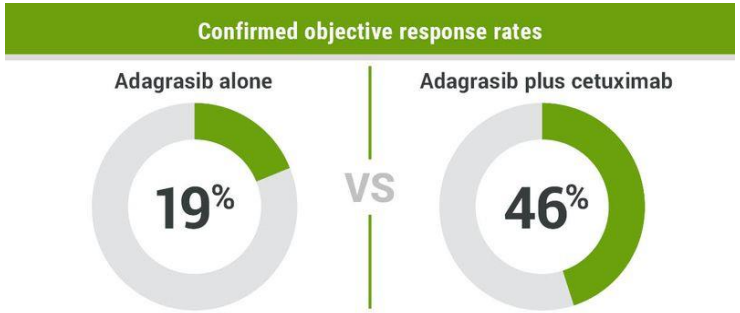
- Rapid loss of G12C amplification with change in treatment suggest that it is a likely “adaptive mechanism” of resistance to GDP inhibitors

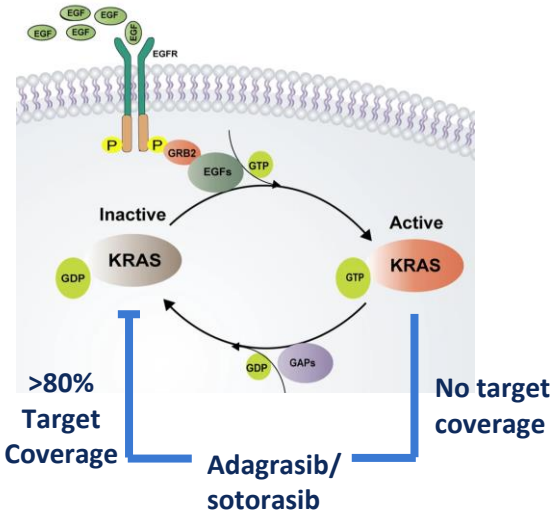


Newly synthesized KRASG12C is GTP-bound

Cetuximab doubled the objective response rate to adagrasib in CRC

- EGFR and other RTKs identified in 30% of resistant NSCLC
- EGFR and Her2 activation often observed as quick response to GDP inhibitors





Ref: Yaeger et al Cancer Discovery 2023 Xue, et. al. Nature | Vol 577 | 16 January 2020

Efficacy of KRAS^{G12C}-GDP inhibitors in the clinic is clearly suboptimal when compared to other driver-targeted therapies in the pathway

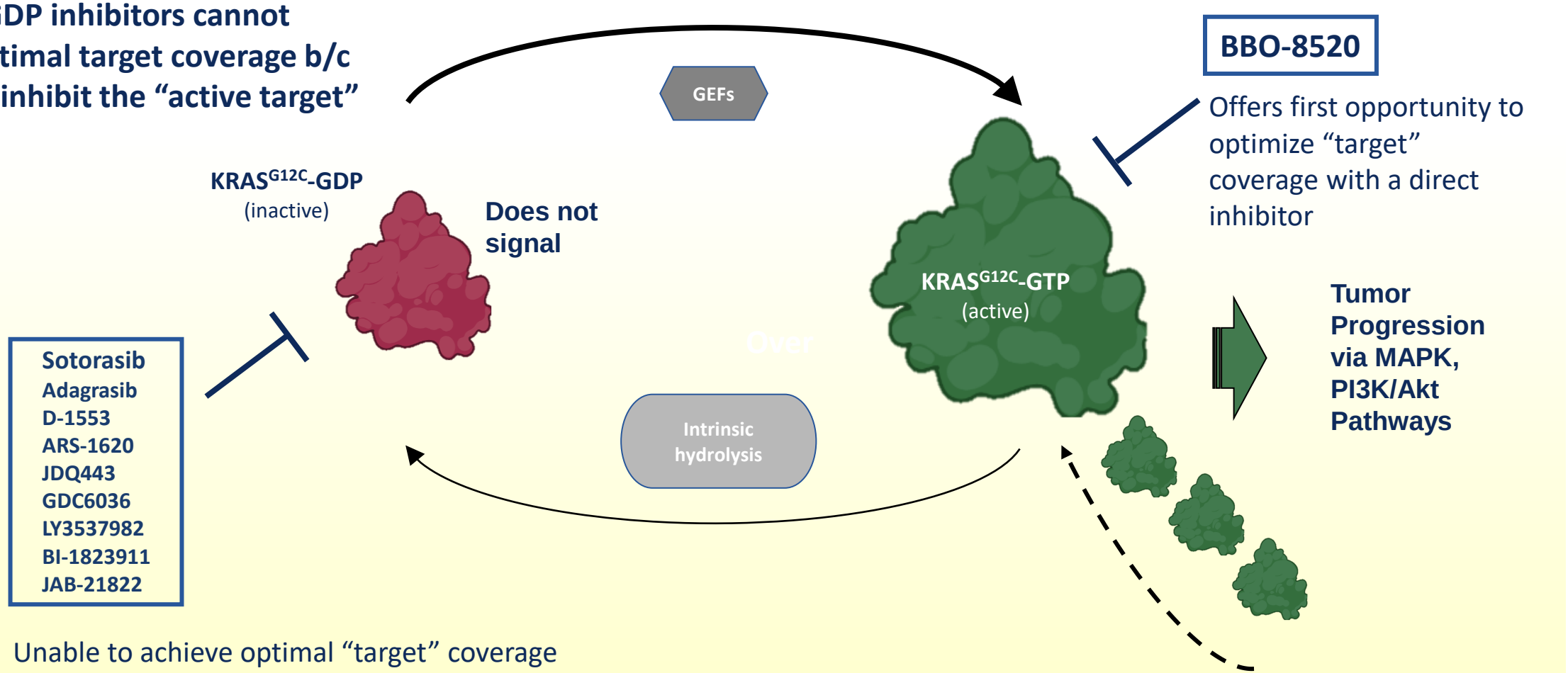
	KRAS^{G12C}-GDP inhibitors			RTK targeted agents			
	Sotorasib	Adagrasib	GDC-6036	Selpercatinib	Alectinib	Osimertinib	Capmatinib
	2L+ KRAS G12C NSCLC			2L+ RET Fusion+ NSCLC	1L ALK+ NSCLC	1L EGFR mutant NSCLC	1L cMET exon14 NSCLC
ORR	41%	43%	53%	64%	79%	77%	68%
mPFS (mo.)	6.3	6.5	13.1	*tbd*	25.7	18.9	12.4

Phase 3 CODEBREAK 200 – PFS 5.6 months; ORR 28%

ORR, overall response rate PFS, progression-free survival; Sources: Sotorasib data from registrational Ph2 CODEBREAK 100 & Ph3 CODEBREAK 200 results presented at 2022 EMSO meeting; Adagrasib data from KRYSTAL-1 results presented at 2022 ASCO Meeting; GDC-6036 data from 2022 WCLC meeting; Analog data taken from product labels

Optimal "target" coverage of mutant $KRAS^{G12C}$ requires activity against $KRAS^{G12C}$ (ON)

No matter the drug exposure, $KRAS^{G12C}$-GDP inhibitors cannot provide optimal target coverage b/c they don't inhibit the "active target"



BBO-8520 is the only direct KRAS^{G12C} inhibitor that can show potent activity against KRAS^{G12C} (ON)

First-In-Class KRAS^{G12C} dual inhibitor

			BBO-8520	Sotorasib	Adagrasib	GDC-6036
% modified	KRAS^{G12C} GTP (ON)	15’	100	0	0	0
		60’	100	0	0	0
	KRAS^{G12C} GDP (inactive)	15’	91	80	73	77
		60’	100	82	84	84
KRAS^{G12C} : RAF1 Effector Binding IC_{50} (nM)			33	>100,000	20,000	4,200
H358 pERK IC_{50} @ 30’ (nM)			4	50	310	8
kinact/Ki (M*s)-1	Cellular H358		43,000	776	1064	27,000
	KRAS^{G12C} GTP (ON)		17,900	0	0	0
	KRAS^{G12C} GDP (inactive)		>1,500,000	NA	180,000	1,100,000

KRAS^{G12C}-GDP inhibitors show no detectable activity against KRAS^{G12C} (ON) protein

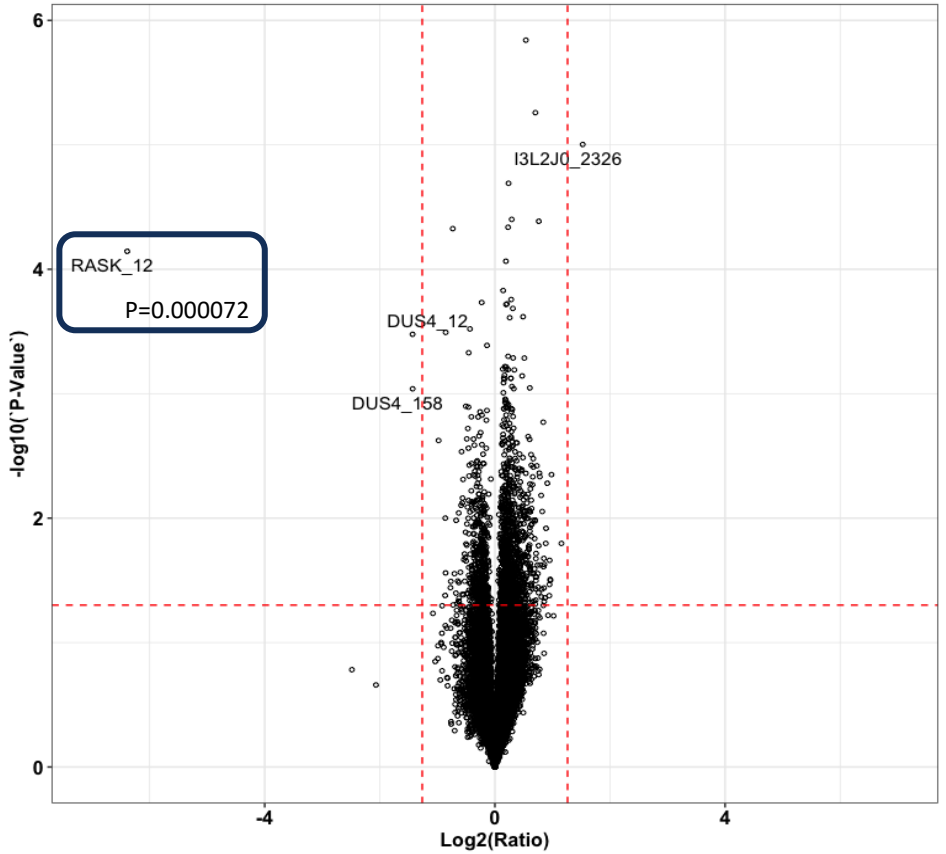
Biochemical selectivity and global cysteine proteomics

Biochemical Selectivity

		Avi-KRAS-GppNHp	Avi-KRAS-GDP
KRAS SPR* Kd (µM)	WT	5.2	0.002
	G12D	7.3	ND
	G12V	19	ND

KRAS:RAF1 PPI** IC_{50} (µM)	G12C	0.033
	WT	1.95
	G12D	1.07
	G12V	3.2
	G12R	4.3

Global Cysteine Proteomics

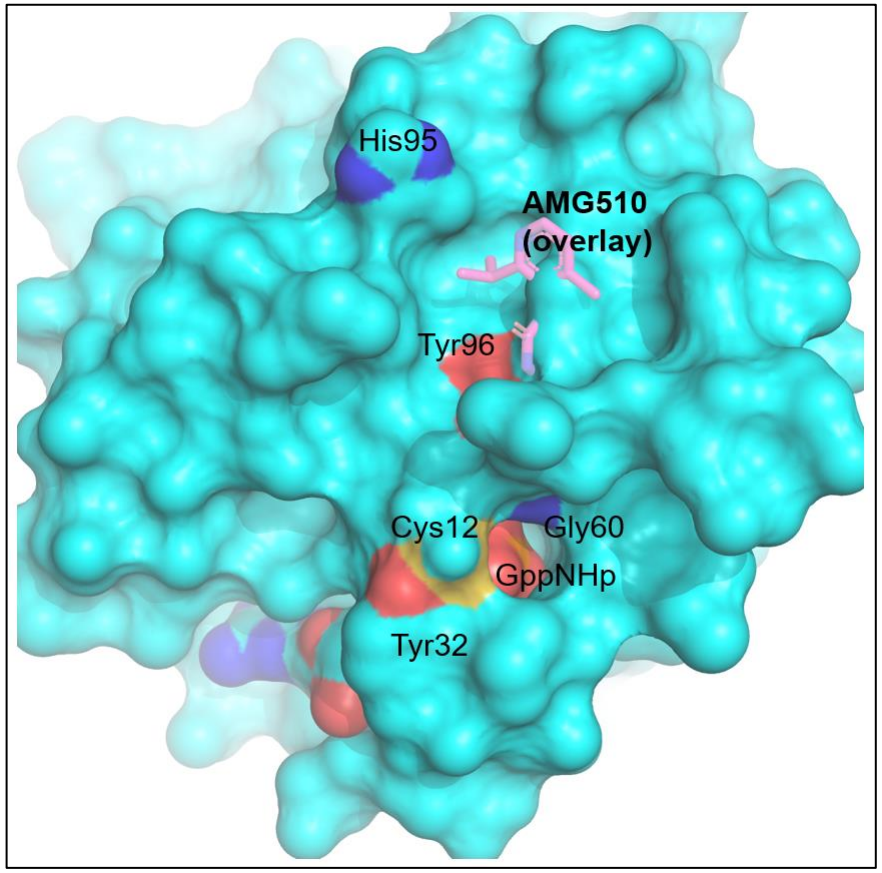


BBO-8520 shows high selectivity for $KRAS^{G12C}$

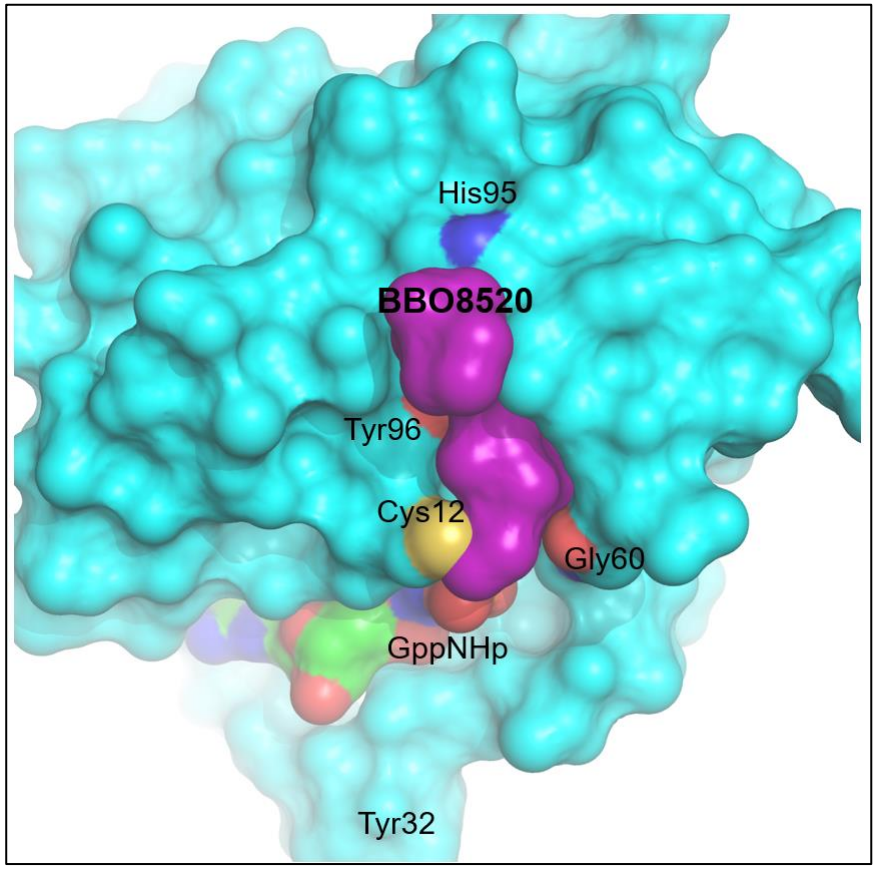
*Unable to determine a Kd for G12C due to extremely tight binding and covalent modification
**PPI assay is HTRF-based, using 50nM of KRAS protein and RAF1

BBO-8520 drives an optimal SW-II interaction allowing modification of G12C in the active state

Apo KRAS G12C GppNHp crystal structure overlay with AMG510

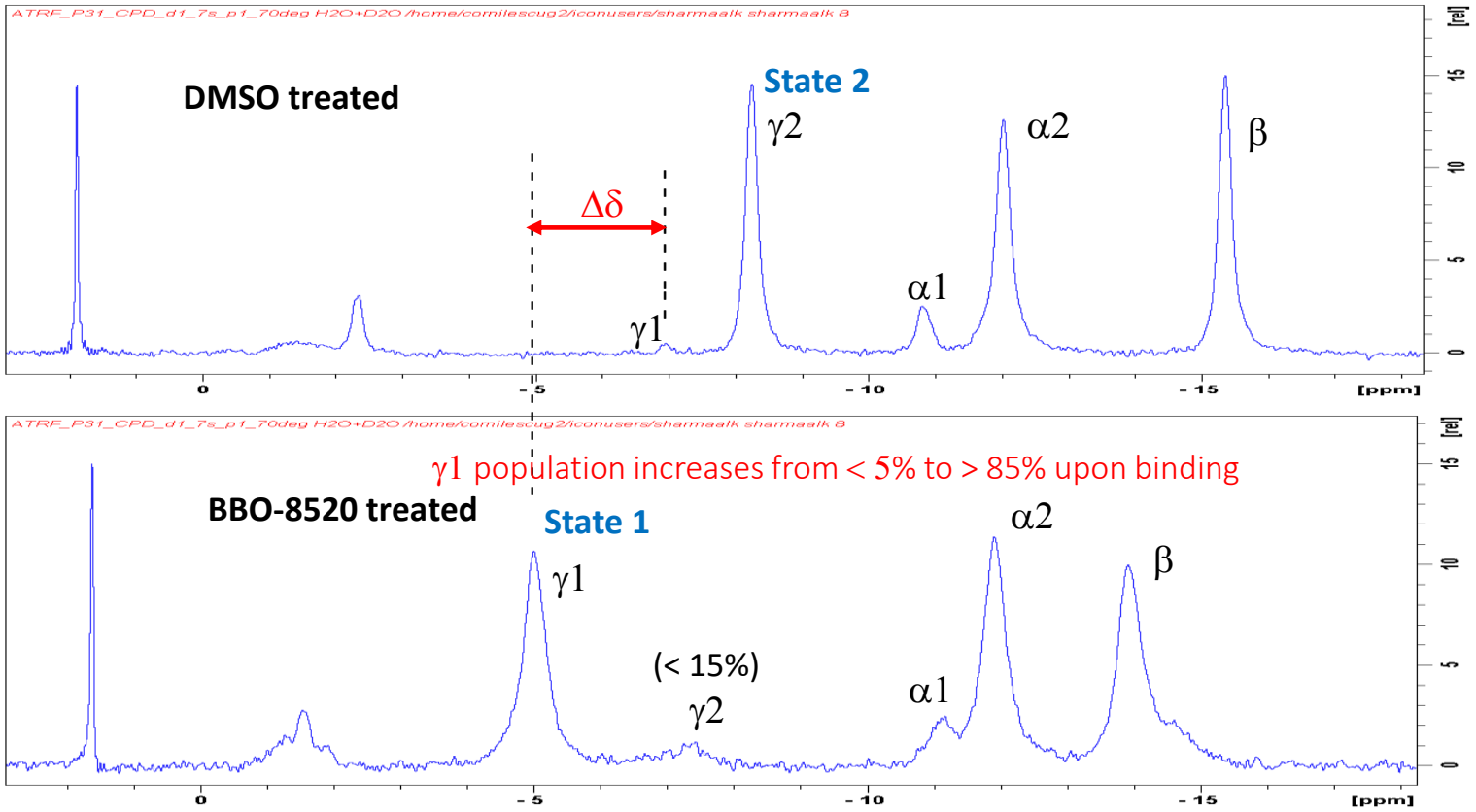


Crystal structure of BBO-8520 in KRAS G12C GppNHp protein



^{31}P NMR peak shifts suggest that BBO-8520 stabilizes State 1 of active GTP-bound KRAS, which disrupts effector protein binding

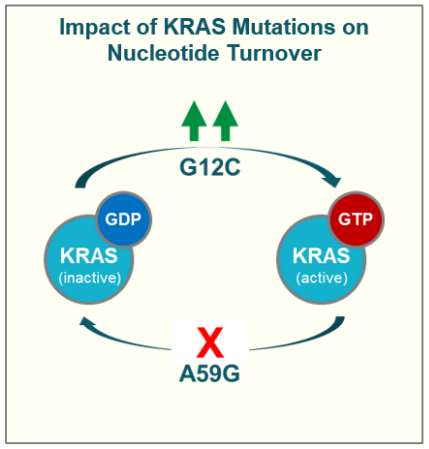
1D ^{31}P NMR spectrum @ 5 ^{o}C



BBO-8520 disrupts effector protein binding by shifting conformational equilibrium of active GTP-bound KRAS^{G12C} to State 1

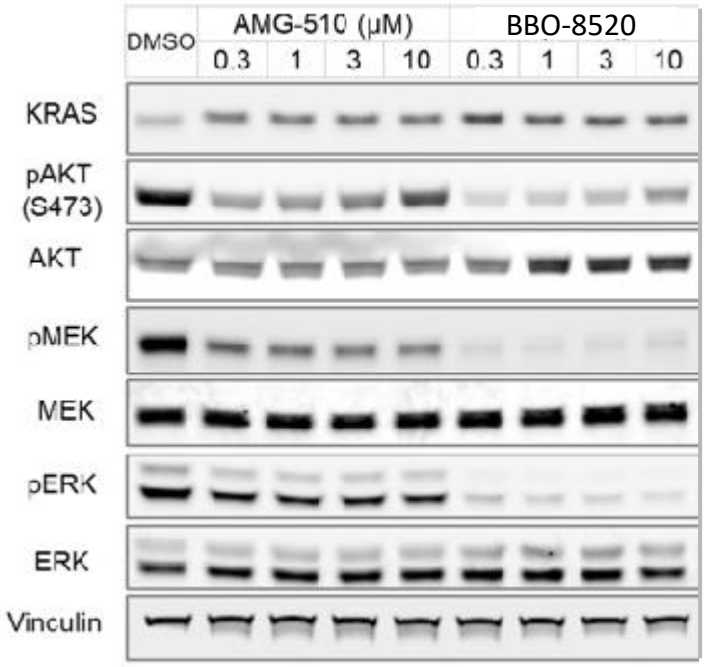
Experiments conducted on KRAS-G12C-C118S without inhibitor pre-incubation / modification

MAPK and PI3Kα signaling suppression in KRAS$^{G12C/A59G}$ double mutant that is locked in the active, GTP bound conformation

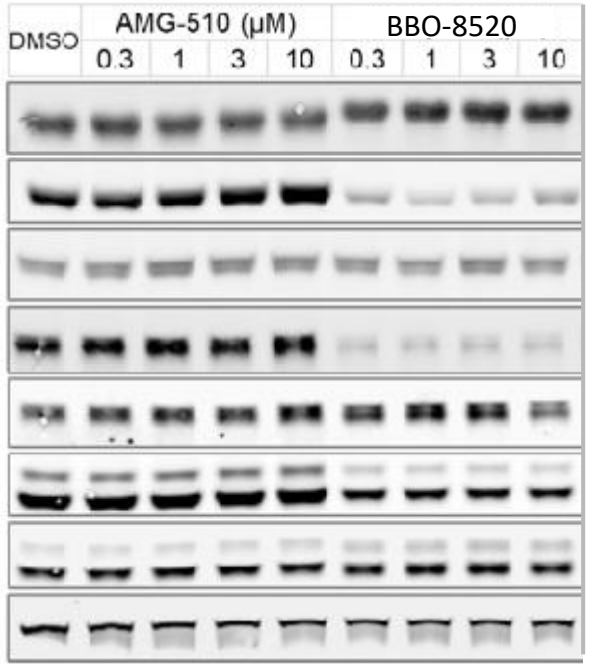


A59G is a 'transition state' **mutant** that abrogates GTPase activity

HELA G12C



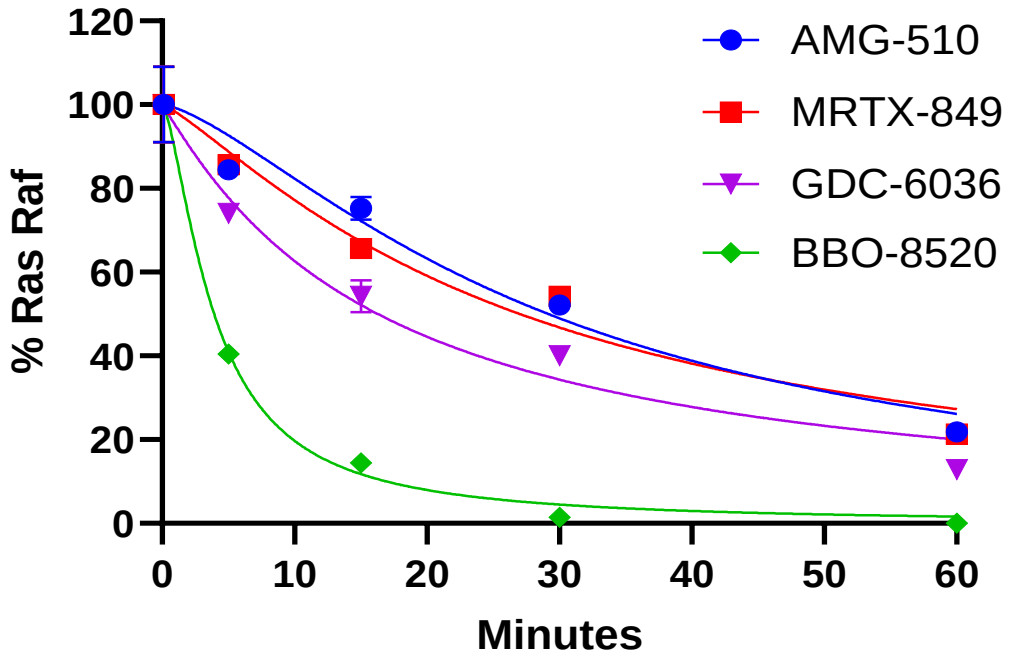
HELA G12C / A59G



Only inhibitors with the ability to inhibit KRAS^{G12C} (ON), like BBO-8520, display potency against G12C/A59G mutants

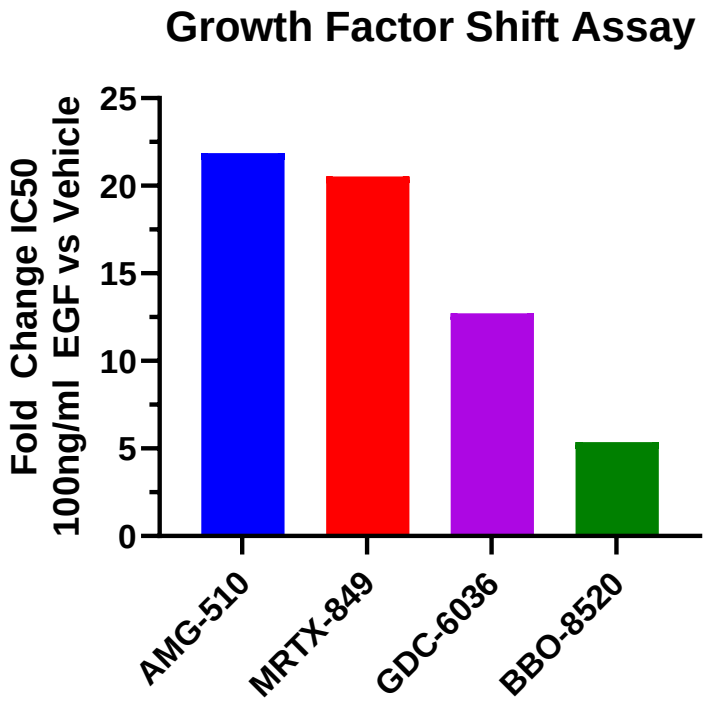
Targeting KRAS^{G12C} (ON) activity allows for rapid and complete signal inhibition

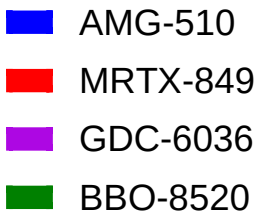
Rapid and total inhibition of KRAS^{G12C} (ON)



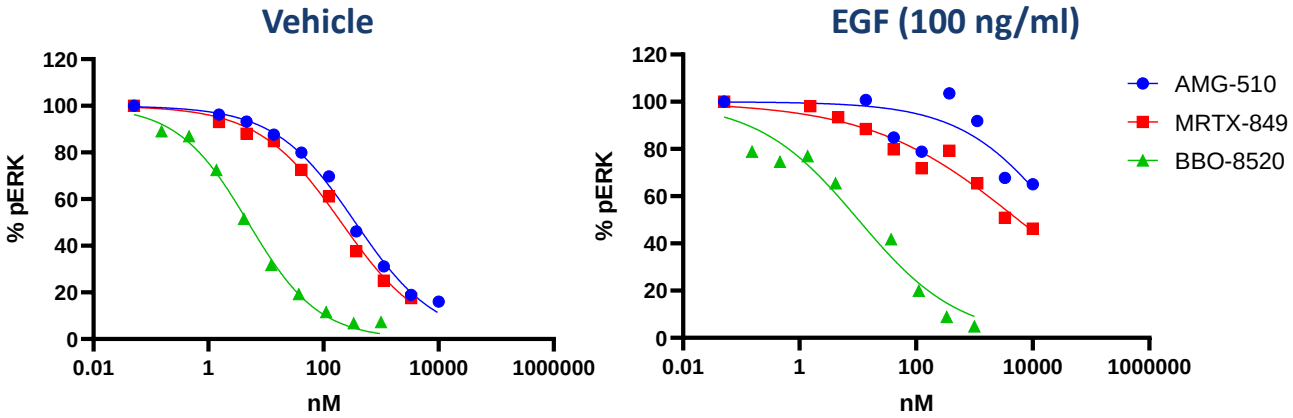
Compound	Maldi-TOF% GTP, 5min	Time (min) to IC_{50}	% of AMG510 Time to IC_{50}
AMG510	0	21.9	100
MRTX849	0	20.5	100
GDC-6036	0	12.7	55.8
BBO-8520	94	5.4	13.5

Targeting KRAS^{G12C}-GTP activity allows for rapid signal inhibition and overcomes RTK drive





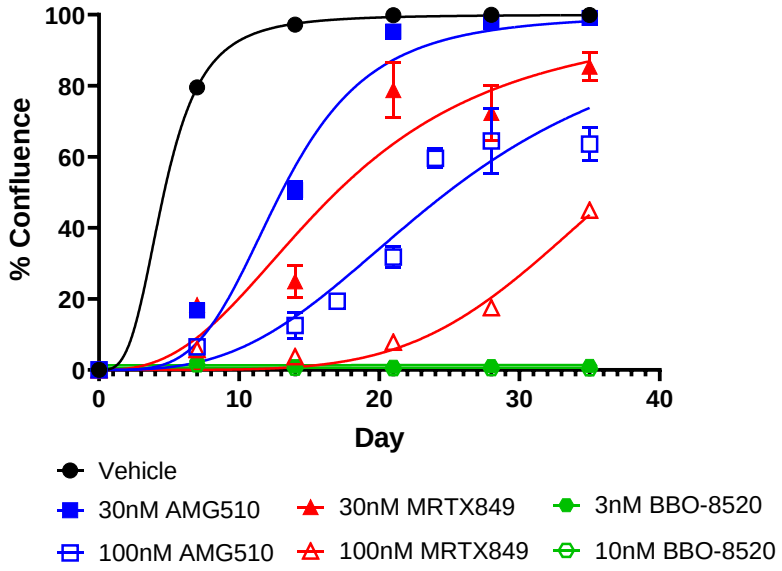
GFs abundantly present in human tissues render GDP inhibitors inactive (H358)



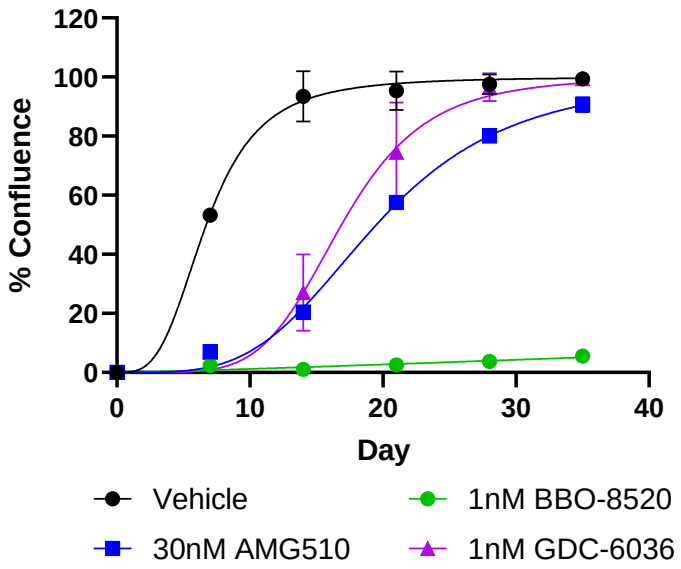
% pERK (IC_{50},nM)		
Treatment	Vehicle	EGF (100ng/ml)
AMG-510	355.4	>10000
MRTX-849	203.1	5650
BBO-8520	4.8	10.19

Potency alone is not enough to maintain efficacy in the long-term clonogenic assay in H358 cells. Data suggests KRAS^{G12C}-GTP inhibition prevents fast adaptation

H358 Clonogenic Assay

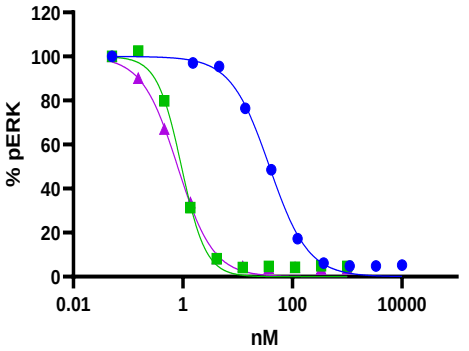


H358 Clonogenic Assay

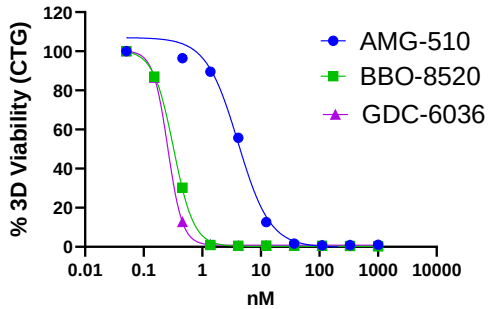


Potency comparison of GDC-0636 KRAS^{G12C}-GDP inhibitor

2 hr pERK



4-d 3D viability



- Clonogenic assay suggests inhibition of GTP-bound KRAS^{G12C} may reduce development of resistance
- GDC-6036 shows similar loss of potency as other GDP inhibitors in EGF assays (data not shown)

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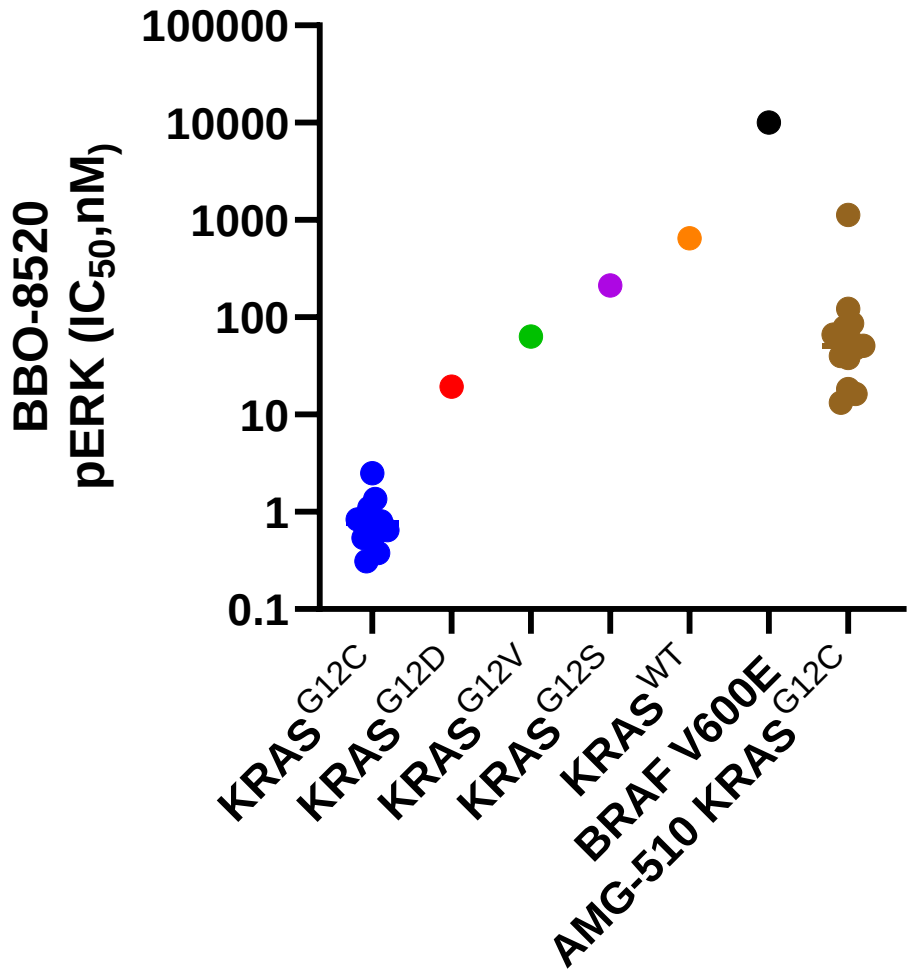
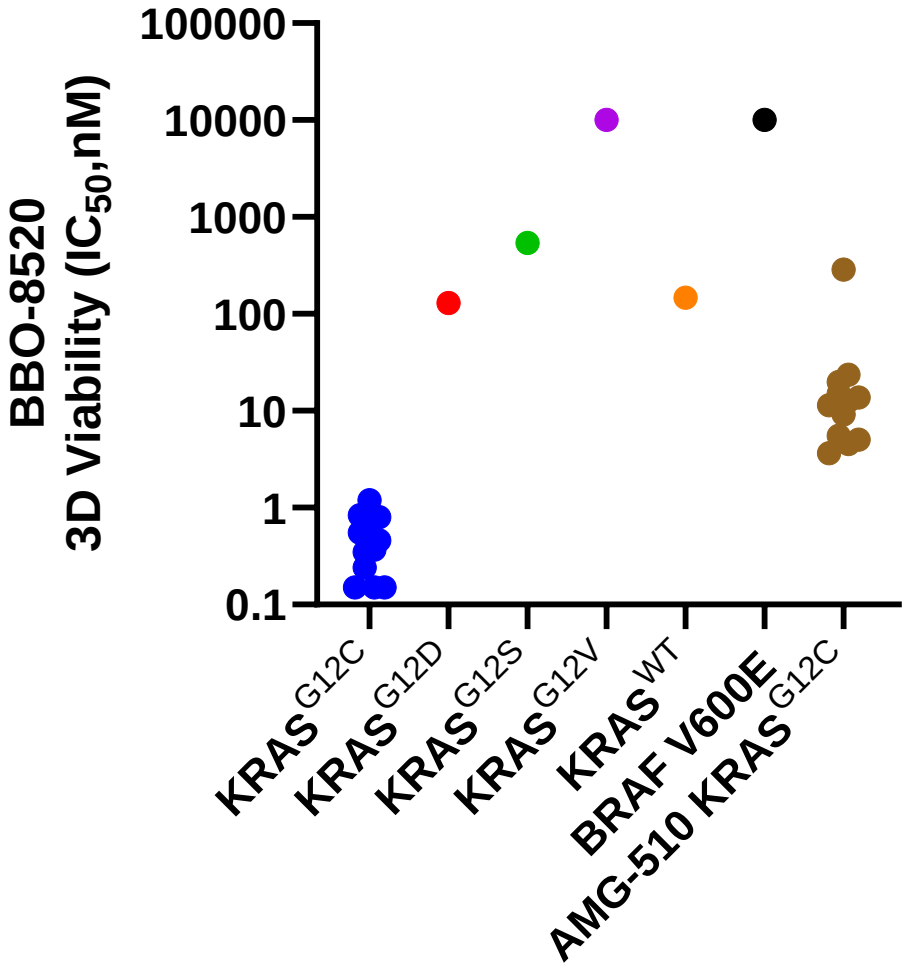
BBO-9866: Back-up compound with similar properties to BBO-8520

BBO-8520's potency and selectivity in KRAS^{G12C} cell lines



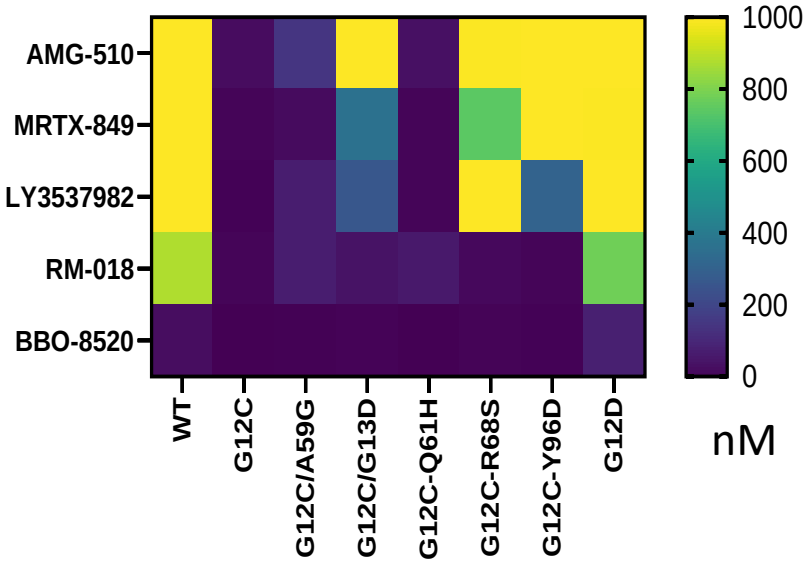
	BBO-8520 pERK (IC_{50},nM)		AMG-510 (IC_{50},nM)
$KRAS^{G12C}$	Calu-1	0.3	16.4
	KYSE-410	0.8	1126.4
	LU-65	2.5	86.6
	LU-99	0.8	122.4
	MiaPaca-2	0.7	48.2
	NCI-H23	1.1	78.7
	NCI-H2030	0.5	18.3
	NCI-358	0.7	40.0
	SW1463	1.4	51.0
	SW1573	0.8	66.3
	SW837	0.5	66.0
	UM-UC-3	0.4	13.3
$KRAS^{G12D}$	GP2d	19.3	-
$KRAS^{G12S}$	A549	63.2	-
$KRAS^{G12V}$	SW480	212.9	-
$KRAS^{WT}$	NCI-H1993	646.3	-
$BRAF^{V600E}$	A375	10000	10000

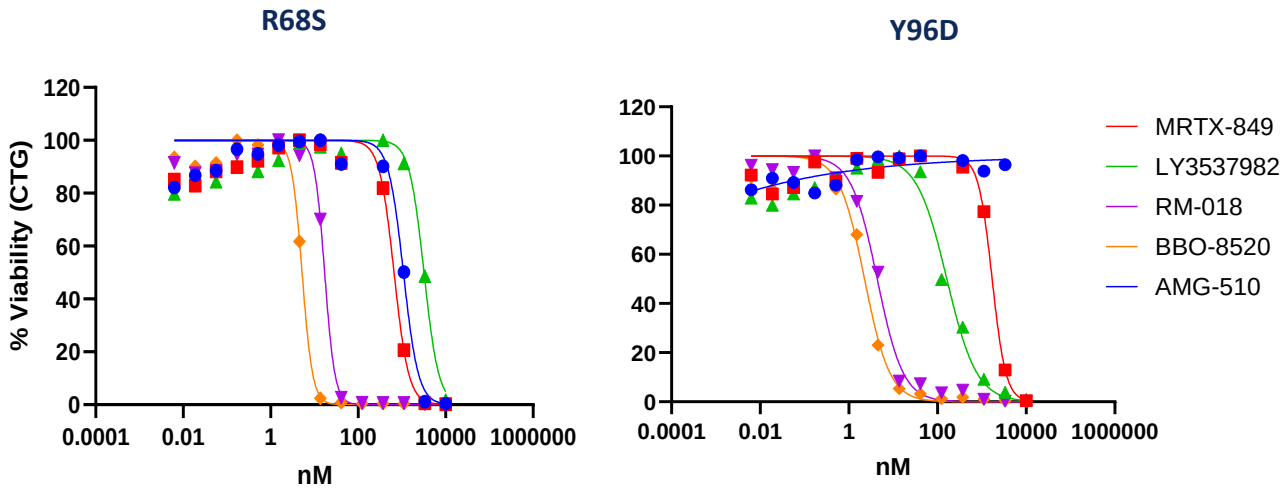
BBO-8520 shows superior potency and selectivity on viability in KRAS^{G12C} Cell Lines



	BBO-8520 3D Viability (IC_{50},nM)		AMG-510 (IC_{50},nM)
KRAS^{G12C}	Calu-1	0.2	11.4
	KYSE-410	0.8	287.5
	LU-65	0.5	4.6
	LU-99	0.2	13.8
	MiaPaca-2	0.4	5.5
	NCI-H23	1.2	23.5
	NCI-H2030	0.2	5.0
	NCI-H2122	0.6	12.7
	NCI-358	0.4	3.7
	SW1463	0.6	19.8
	SW837	0.8	9.1
	UM-UC-3	0.2	15.0
KRAS^{G12D}	GP2d	129.5	-
KRAS^{G12S}	A549	641.4	-
KRAS^{G12V}	SW480	10000	-
KRAS^{WT}	NCI-H1993	147.3	-
BRAF^{V600E}	A375	10000	10000

Single digit nM potency across multiple KRAS^{G12C} resistant mutations

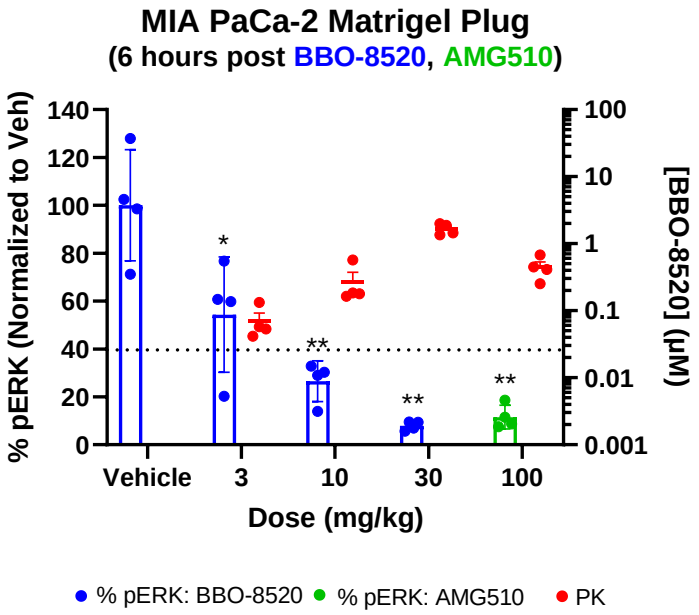




	IC$_{50}$ % Viability CTG							
	WT	G12C	G12C/A59G	G12C/G13D	G12C/Q61H	G12C/R68S	G12C/Y96D	G12D
AMG-510	1000.0	27.8	152.4	1000.0	39.1	995.6	1000.0	1000.0
MRTX-849	1000.0	8.7	26.0	371.1	8.9	745.6	1000.0	994.9
RM-018	880.3	7.8	75.8	46.5	63.8	17.7	7.8	780.6
BBO-8520	**29.9**	**0.2**	**1.0**	**5.3**	**0.2**	**5.6**	**3.5**	**83.4**

Dose- and time-dependent inhibition of pERK correlates well with target engagement in the MIA PaCa-2 model

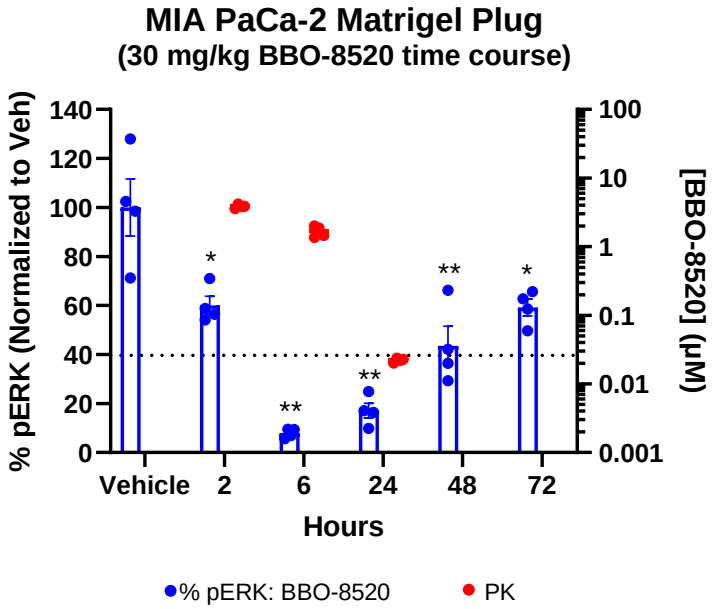
Dose Response



One-way ANOVA with Dunnett's test vs vehicle *p<0.01, **p<0.0001

..... **pERK FF adj IC50 (assume bound to 10% FBS)**

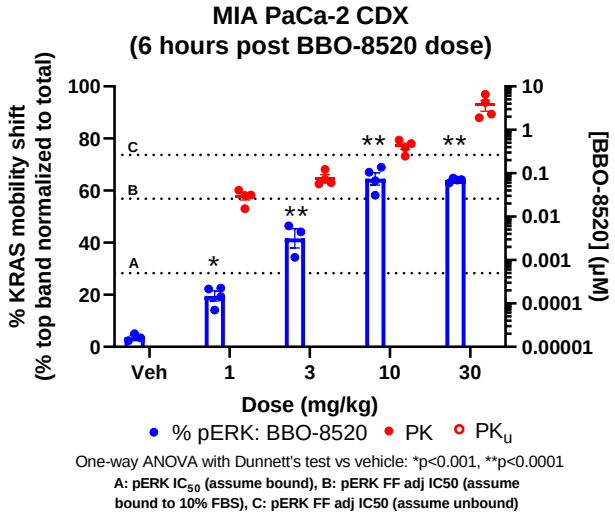
Time Response



One-way ANOVA with Dunnett's test vs vehicle: *p<0.01, **p<0.0001

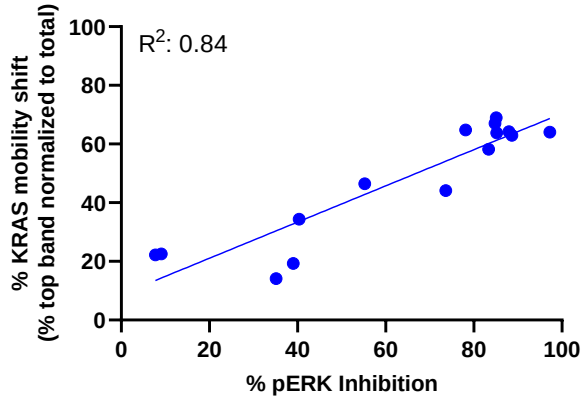
..... **pERK FF adj IC50 (assume bound to 10% FBS)**

TE and pERK strongly correlated



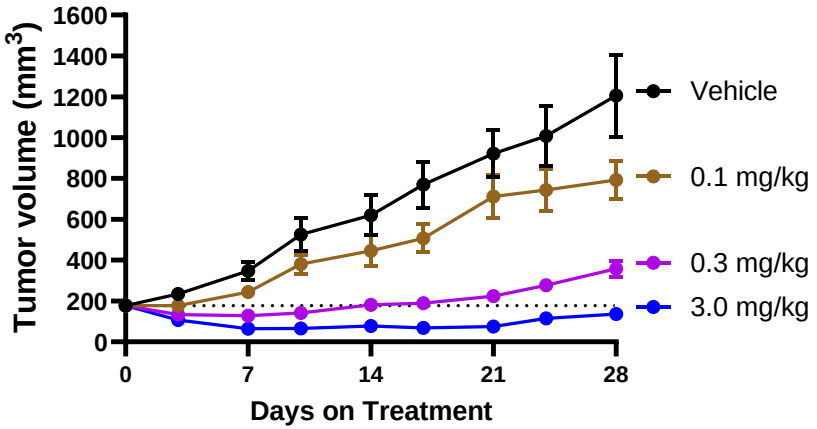
One-way ANOVA with Dunnett's test vs vehicle: *p<0.001, **p<0.0001

A: pERK IC_{50} (assume bound), B: pERK FF adj IC50 (assume bound to 10% FBS), C: pERK FF adj IC50 (assume unbound)



BBO-8520 exhibits strong efficacy in KRAS^{G12C} models

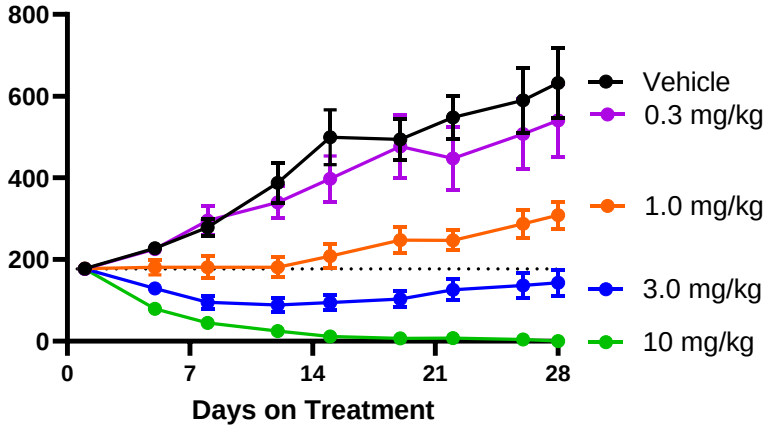
Potency
MIA PaCa-2 – Pancreatic Cancer



ED_{50}	ED_{90}
0.13 mg/kg	0.4 mg/kg
EC_{50}	EC_{90}
4.6 nM	9.9 nM

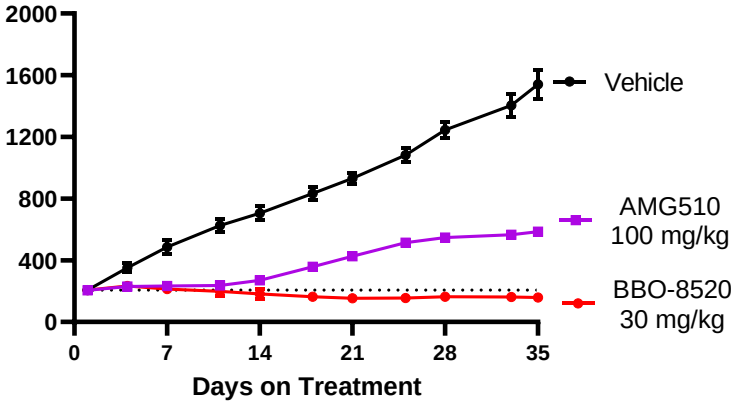
Deeper Efficacy
H358 - NSCLC

10/10 complete regressions at 10 mg/kg QD



ED_{50}	ED_{90}
0.61 mg/kg	1.6 mg/kg
EC_{50}	EC_{90}
14.1 nM	33.6 nM

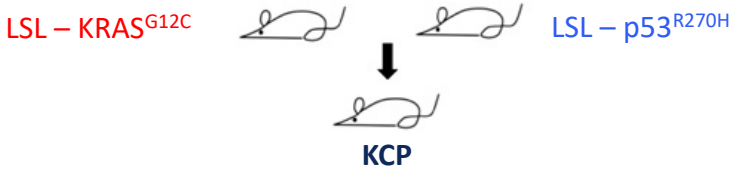
Differentiated
LUN055 (PDX) - NSCLC



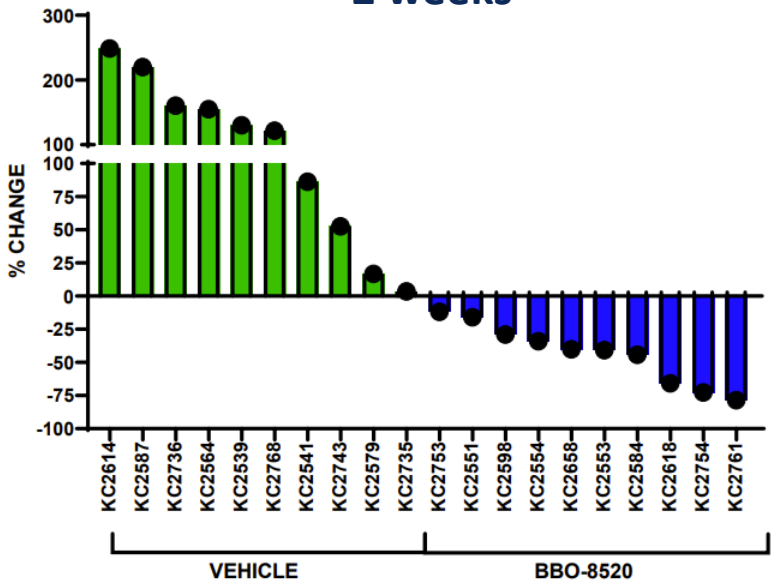
Group (n=10)	Day 35		
	TGI	Regression	FF AUC_{0-24} (ng*hr/ml)
BBO-8520	100%	23% (7/10)	59
AMG510	71%	- (1/10)	1563

BBO-8520 is efficacious in cell line and PDX models with greater potency, efficacy and differentiated activity

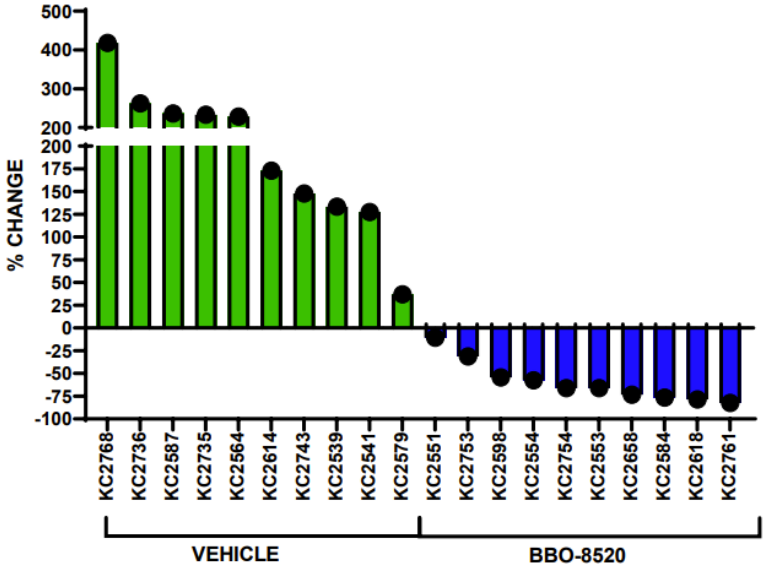
BBO-8520 shows ~60% tumor regression in the KCP GEMM at 10 mg/kg QD



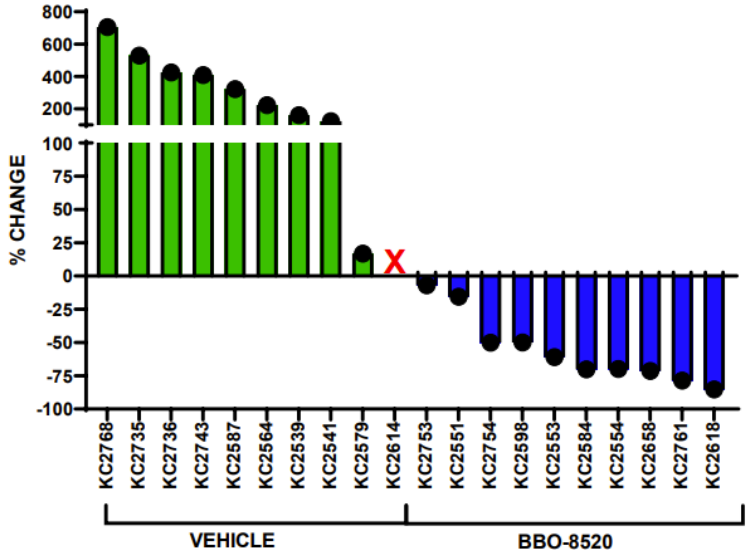
Tumor Volume - % Change 2 weeks



Tumor Volume - % Change 4 weeks



Tumor Volume - % Change 6 weeks



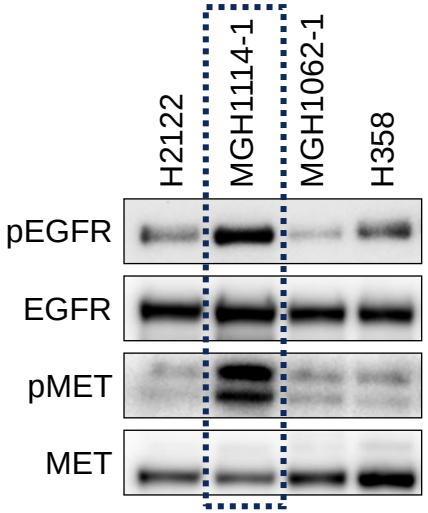
NYU Langone Health

NOTE: Mouse KC2614 (Vehicle) died the day before of 6 weeks MRI scan

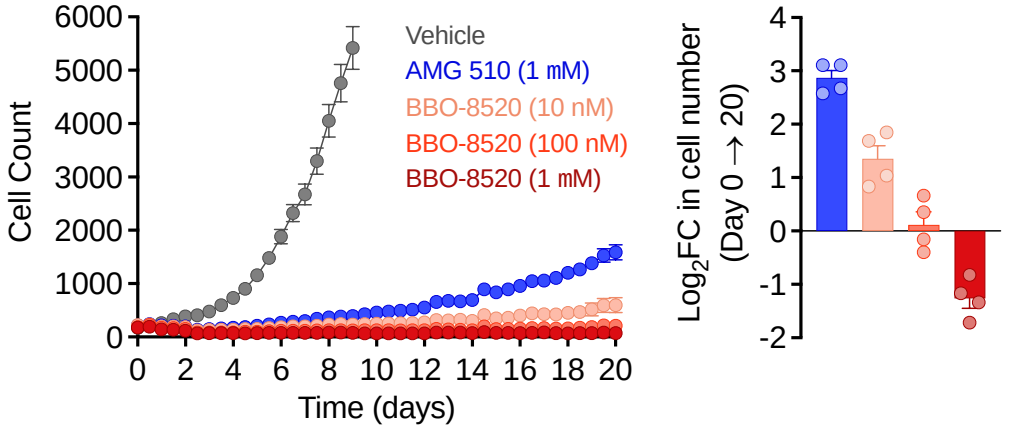
In collaboration with Kwok Wong's lab

BBO-8520 demonstrates >50x more potency than AMG 510 (and MRTX849) in the MGH series of *KRAS^{G12C}* mutant NSCLC cell lines

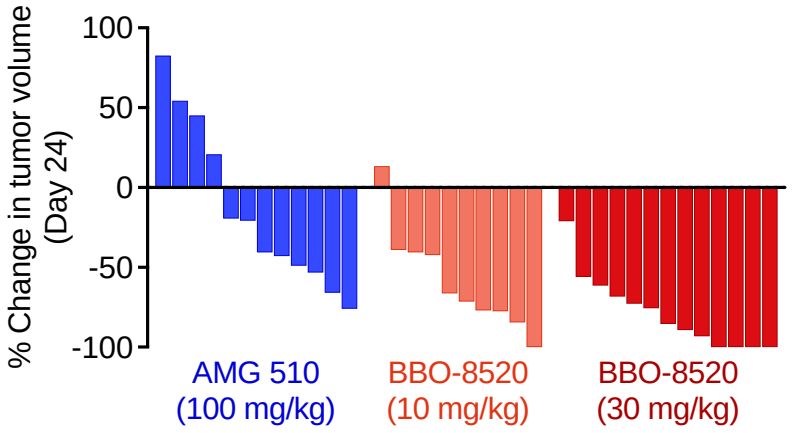
2D Viability (4 Day Tx)	EC_{50} (nM)							
	H358	LU65	MGH1112	MGH1114	MGH1088	MGH1062	MGH1138	MGH1143
	KRAS$^{G12C/WT}$	*KRAS^{G12C}*	*KRAS^{G12C}*	*KRAS^{G12C}*	*KRAS^{G12C}*	*KRAS^{G12C}*	*KRAS^{G12C}*	*KRAS^{G12C}*
BBO-8520	0.22	0.52	0.42	0.09	0.23	0.21	0.18	0.13
AMG 510	18.15	28.04	28.29	65.20	22.16	16.92	14.42	13.37
AMG 510/BBO-8520	83	53	67	725	95	81	78	86



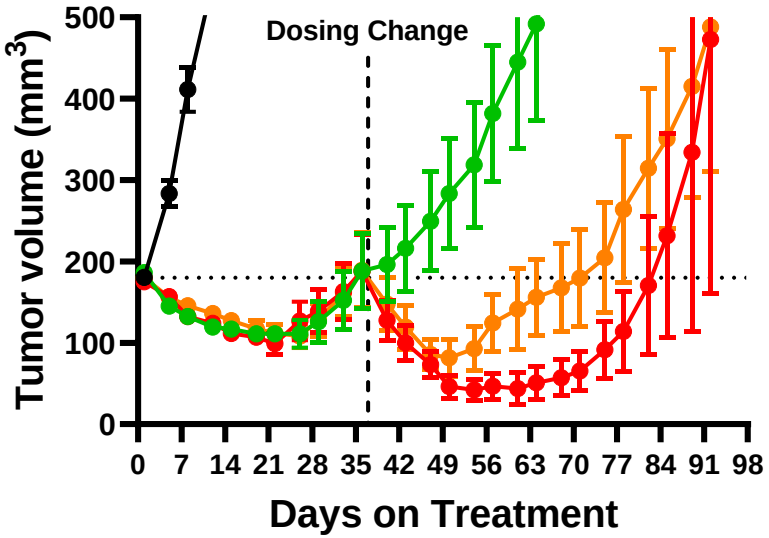
Clonogenic assay



In vivo Efficacy



BBO-8520 can drive deep responses in sotorasib-resistant MiaPaCa-2 tumors

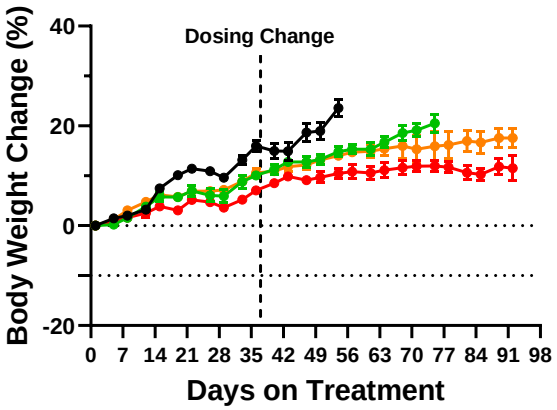


- Vehicle (QD for whole study)
- AMG510 (10 mg/kg, QD for whole study)
- AMG510 (10 mg/kg, QD×36), BBO-8520 (30 mg/kg, QD rest of study)
- AMG510 (10 mg/kg, QD×36), AMG510 (100 mg/kg, QD rest of study)

Treatment of sotorasib resistant MiaPaPa-2 tumors with BBO-8520 led to 50% cures

Groups (n=10)	Individual Tumor volumes (day 92*)									
AMG510 (10 mg/kg, QD)	**ND** d29	**ND** d33	315	323	673	731	893	1122	1280	3520
AMG510 (10 mg/kg, QDx36) → AMG510 (100 mg/kg, QD)	**ND** d33	**ND** d43	60	201	357	358	451	666	952	1833
AMG510 (10 mg/kg, QDx36) → BBO-8520 (30 mg/kg, QD)	**ND** d22	**ND** d33	**ND** d50	**ND** d54	**ND** d61	**ND** d89	432	497	523	3200

*Day 75 for AMG-510 alone group, ND: not detectable, d: first day of non-detectable tumor

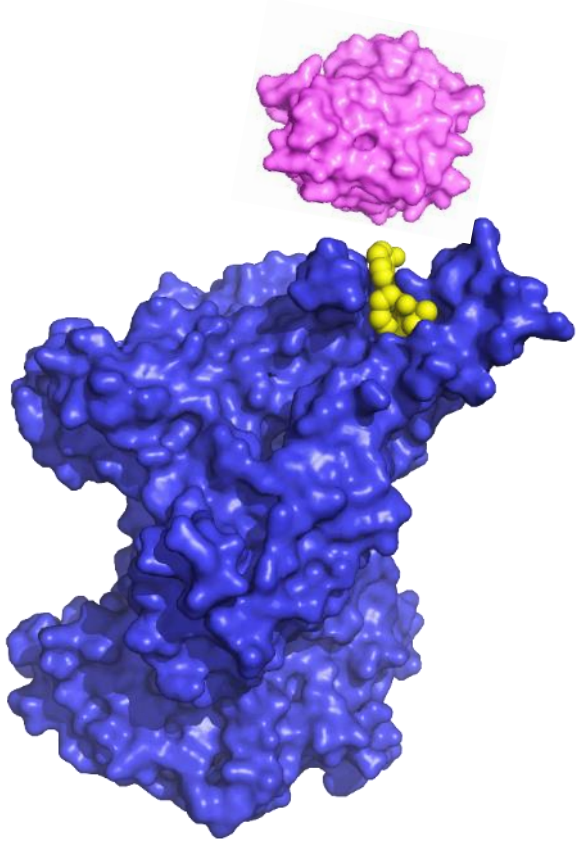


BridgeBio has designed first-in-class, potent and selective PI3Kα:RAS breakers

RAS

PI3Kα

Breaker

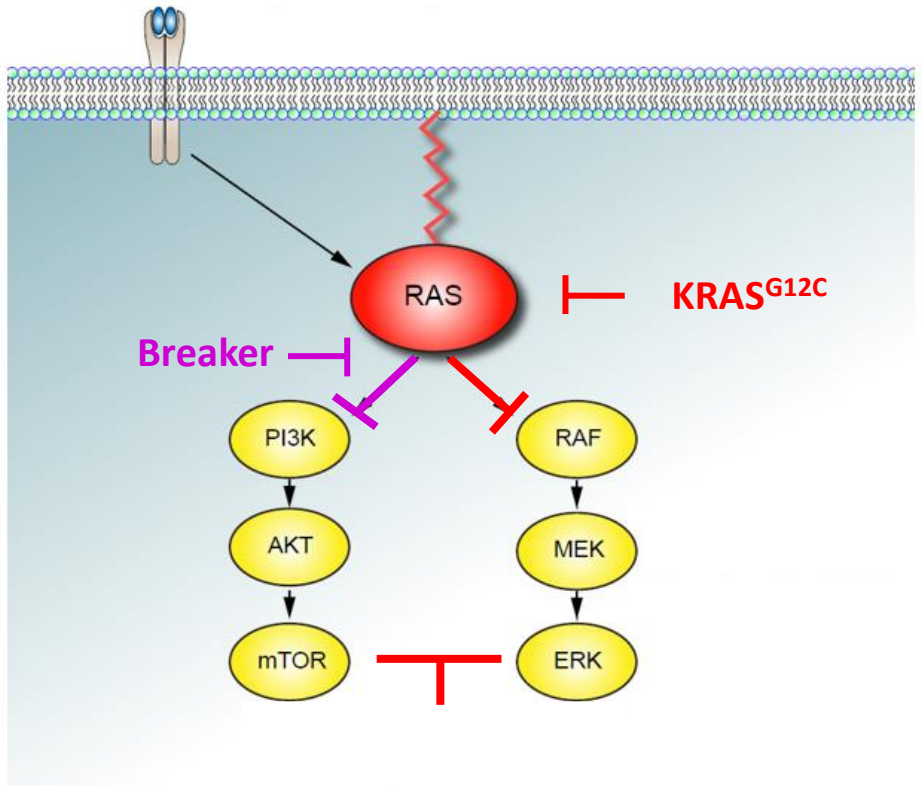


- Structural insights provide a novel approach to develop PI3Kα:RAS breakers
- Small molecules covalently bind to a new induced pocket in PI3Kα
- PI3Kα:RAS breakers selectively bind to PI3Kα
  - PI3Kα amino acid sequence in the region of the binding pocket is unique amongst all the isoforms
  - No binding affinity to KRAS
- PI3Kα:RAS breakers do not affect kinase activity

Multiple series of potent PI3Kα:RAS covalent inhibitors have been identified

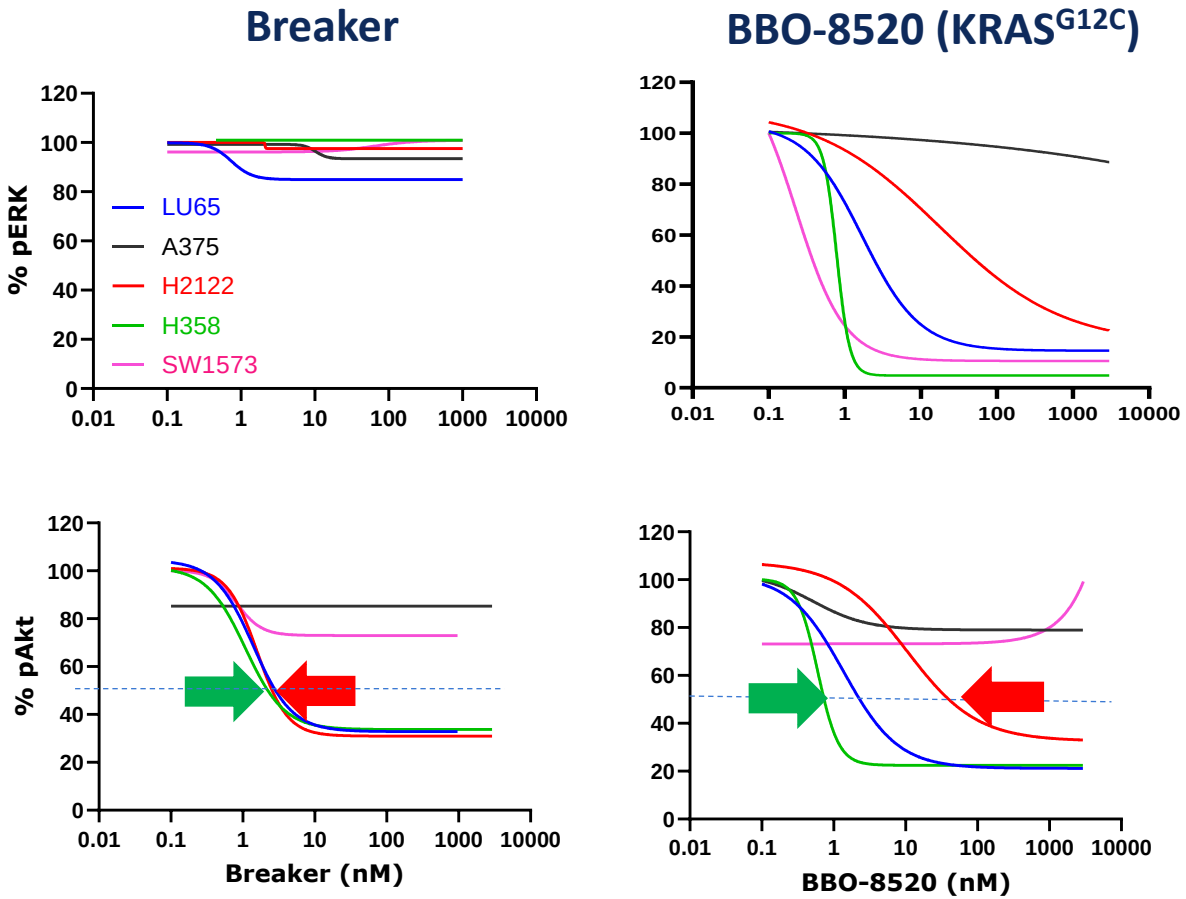
Breaker activity can optimize target (pAKT) coverage of KRAS inhibitors

Combination of Breaker and RASi should optimize target coverage for AKT pathway



No Tumor Growth ?

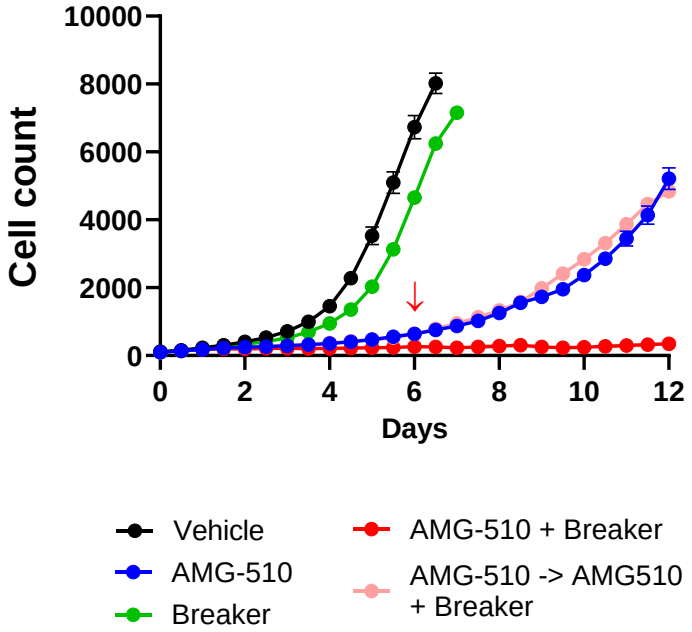
Homogenous inhibition of pAKT amongst NSCLC KRAS^{G12C} cell lines



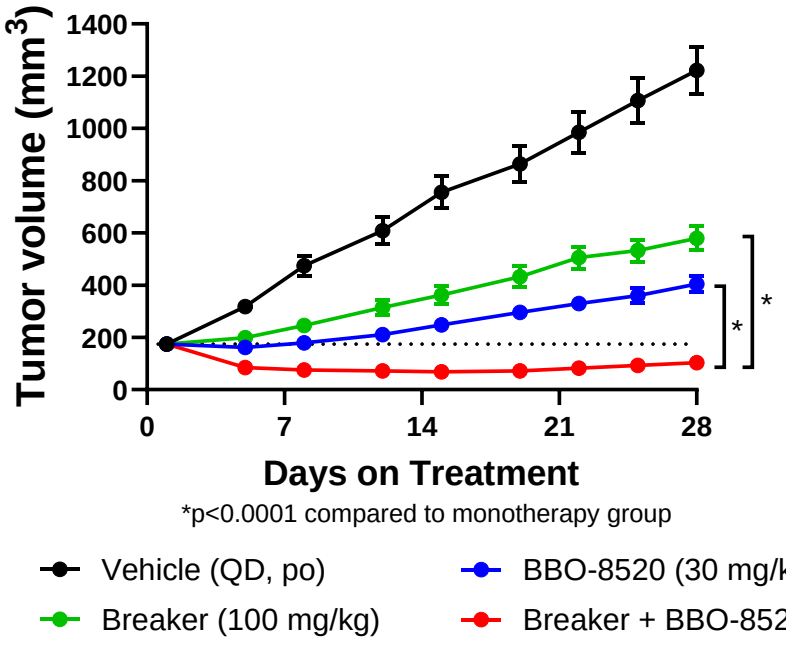
Modified from: National Cancer Institute/Marielle Yohe, M.D., Ph.D.

Strong combination benefit is also observed in the KRAS^{G12Ci} resistant H2122 NSCLC model

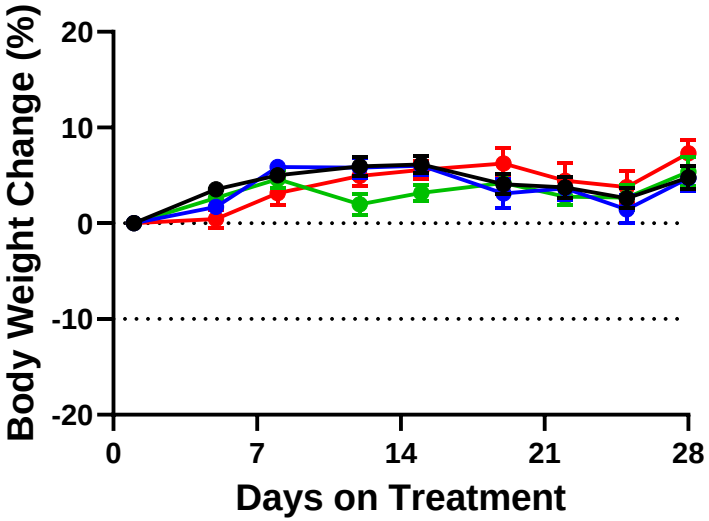
Clonogenic Assay (*in vitro*)



Efficacy model (*in vivo*)



Body Weight (*in vivo*)



Combination is very well tolerated

H2122 **KRASG12C / KEAP1mut / STK11mut**

BBO-8520: Direct KRAS^{G12C} (ON) inhibitor, *RMANOVA

BridgeBio has designed a first-in-class, direct inhibitor of $KRAS^{G12C}$ (ON)

- BBO-8520 is a first-in-class direct inhibitor of $KRAS^{G12C}$ (ON) and inactive (GDP-bound) forms
  - Inhibition of the (ON) GTP-state is necessary to realize the full potential of KRAS inhibition
  - Inhibition of the (ON) state results in rapid and complete inhibition of KRAS activity independent of growth factor stimulation or KRAS amplification
  - BBO-8520 drives strong tumor growth inhibition in multiple models of $KRAS^{G12C}$ even after resistance to sotorasib
- Multiple opportunities for combination in the clinic, including with BBOT's internal pipeline assets

Team Effort

bridgebio

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Ferdie Evangelista	Rick Panicucci	Maggie Yandell-Zhao
Cindy Feng	Erin Riegler	Cathy Zhang
Siyu Feng	Saman Setoodeh	Zuhui Zhang
Lijuan Fu	Jin Shu	James Rizzi
Jennifer Gansert	Devansh Singh	Dana Minnick
Foster Gonsalves	Kanchan Singh	Robert Czerwinski
Victoria Hodson	Kerstin Sinkevicius	Eli Wallace
Jin Ju	Carlos Stahlhut	Pedro Beltran
Sunyoung Lee	James Stice	Rui Xu

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Albert Chan	Megan Rigby
Daniel Czyzyk	Alok Sharma
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William Gillette	Jayasudhan Yerabolu
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