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APRIL 5-10
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BBO-8520, a first-in-class, direct inhibitor of KRAS^{G12C} (ON), locks GTP-bound KRAS^{G12C} in the state 1 conformation resulting in rapid and complete blockade of effector binding

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Disclosure Information

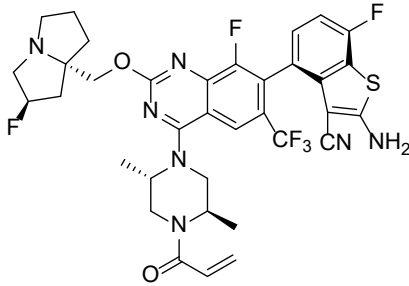
Pedro J. Beltran, Ph.D.

I have the following relevant financial relationships to disclose:

Employee of: BridgeBio Pharma Inc.

Stockholder in: BridgeBio Pharma Inc

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



- Binds to the switch II pocket (Shokat)
- Forms covalent bond with C12
- Locks GTP-bound KRAS^{G12C} (ON) in state 1 – unable to bind effectors
- Potent KRAS^{G12C} activity with 200x selectivity over WT KRAS
- Tumor regressions @ 3 mg/kg QD
- Phase 1 ONKORAS-101 (NCT06343402) trial is now open

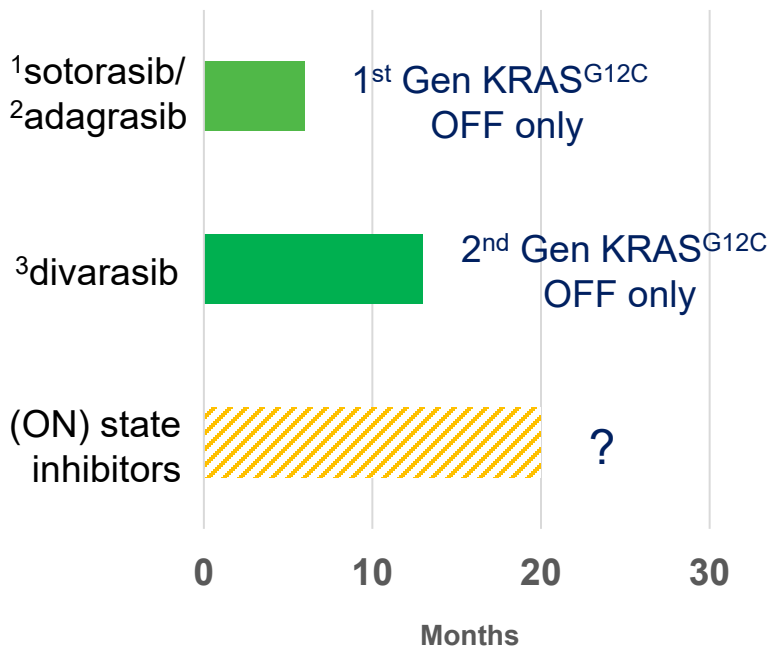
NCI-H358

Assay	BBO-8520
PPI Effector binding	33 nM
Kinact/K _i	43,000 M ⁻¹ S ⁻¹
pERK*	0.07 nM
3D viability*	0.04 nM
ED _{50/90}	0.6 / 1.6 mg/kg
>50% CR	10 mg/kg

**In vitro* IC₅₀ adjusted for free fraction in 10% FBS

Can KRAS inhibitors achieve levels of efficacy observed with other oncogene inhibitors in NSCLC?

Progression Free Survival



Best-in-class inhibitors in NSCLC

- Exquisite potency against the target
- Optimal target coverage
- Address main mechanisms of resistance/adaptation
- ORR >60%, PFS >15 month

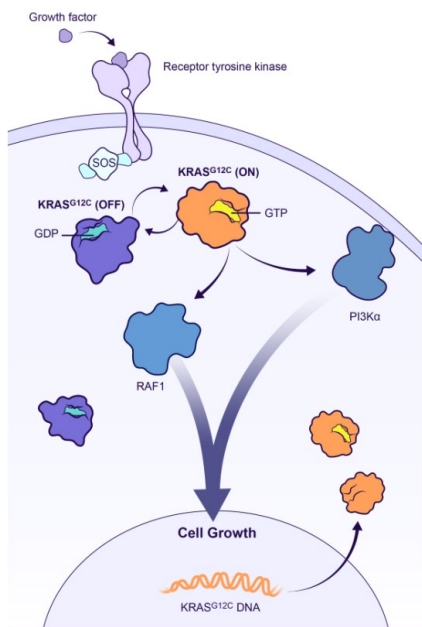
¹Skoulidis et. al NEJM 2021

³Sacher et. al NEJM 2023

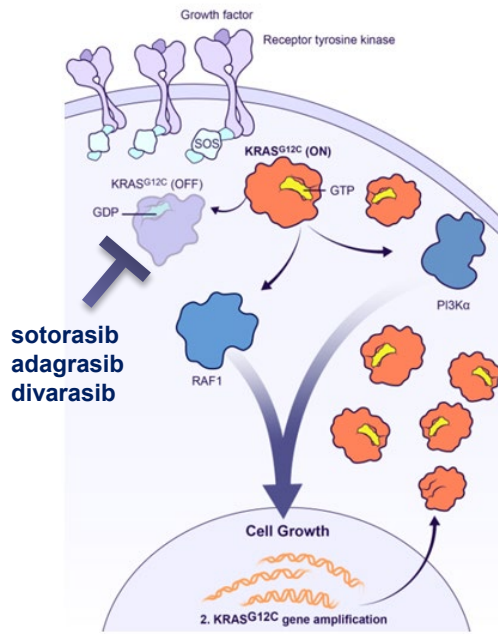
²Janne et. al NEJM 2022

Inhibition of KRAS^{G12C} (ON) is necessary for optimal target coverage and prevention of adaptive mechanisms of resistance

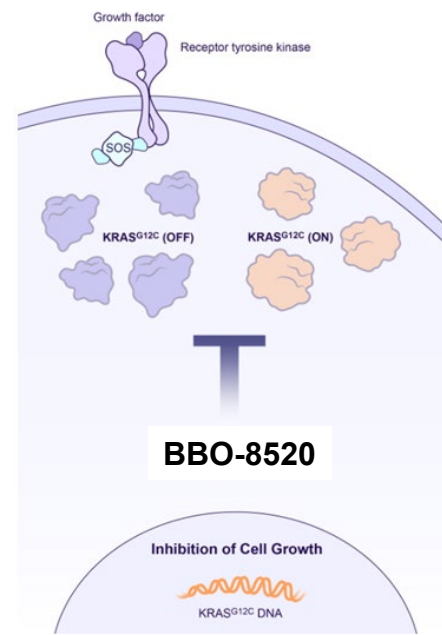
Only GTP-bound KRAS^{G12C} activates effectors



Increased GTP state is a MOA of adaptation to OFF inhibitors



BBO-8520 inhibits both the ON and OFF states of KRAS^{G12C}

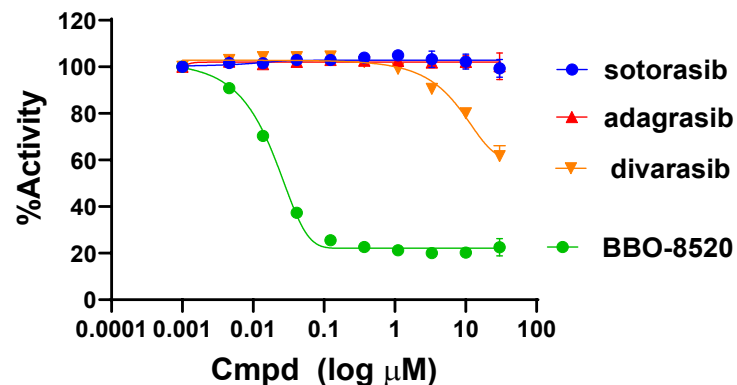
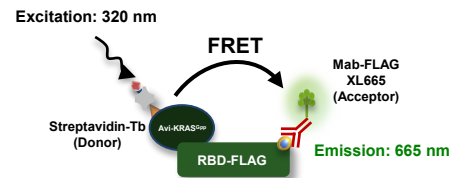


BBO-8520 modifies GTP-bound KRAS^{G12C} and inhibits effector binding

Unique ability to fully modify KRAS^{G12C} when GTP-bound

MALDI-TOF % Modified		BBO-8520	sotorasib	adagrasib	divarasib
GTP	15'	100	0	0	0
	60'	100	0	0	0
GDP	15'	91	80	73	77
	60'	100	82	84	84
Effector Binding IC ₅₀ (nM)		33	>100,000	20,000	4,200
GTP Kinact/K ₁ (M ⁻¹ S ⁻¹)		20,000	0	0	0
GDP Kinact/K ₁ (M ⁻¹ S ⁻¹)		2,743,000	11,000	180,000	1,100,000

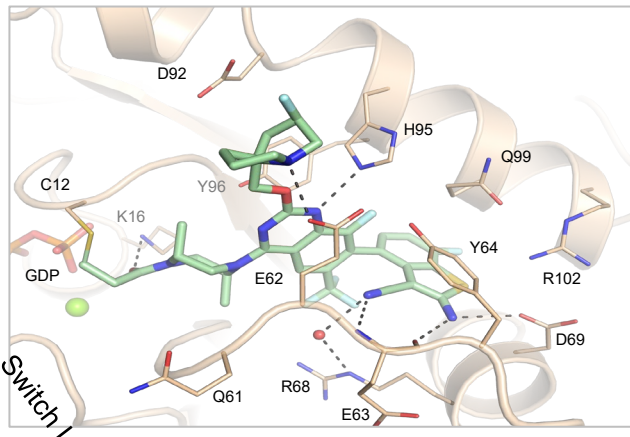
Potent inhibition of effector binding



BBO-8520: Binding mode is clinically validated

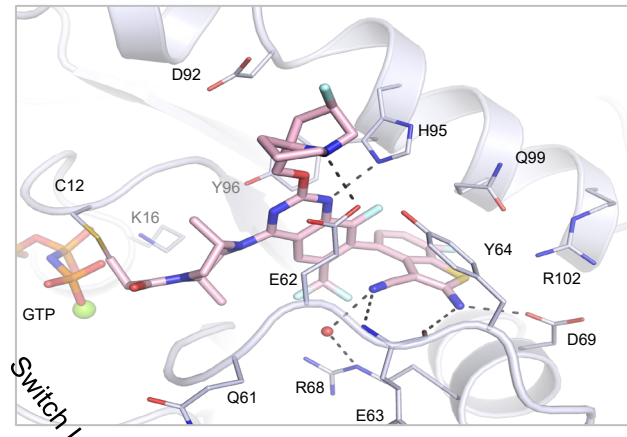
BBO-8520 binds in the pocket between Switch II and alpha Helix 3

KRAS-G12C (GDP):BBO-8520



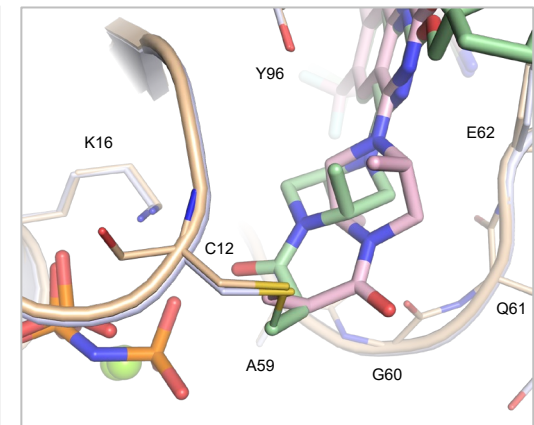
GDP

KRAS-G12C (GppNHp):BBO-8520



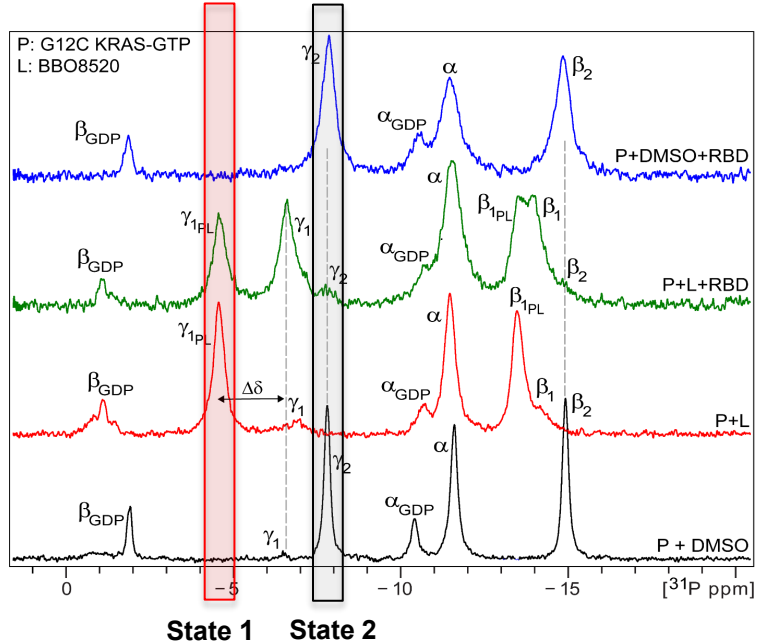
GTP

Dimethylpiperazine rotates $\sim 180^\circ$
in the presence of trinucleotide



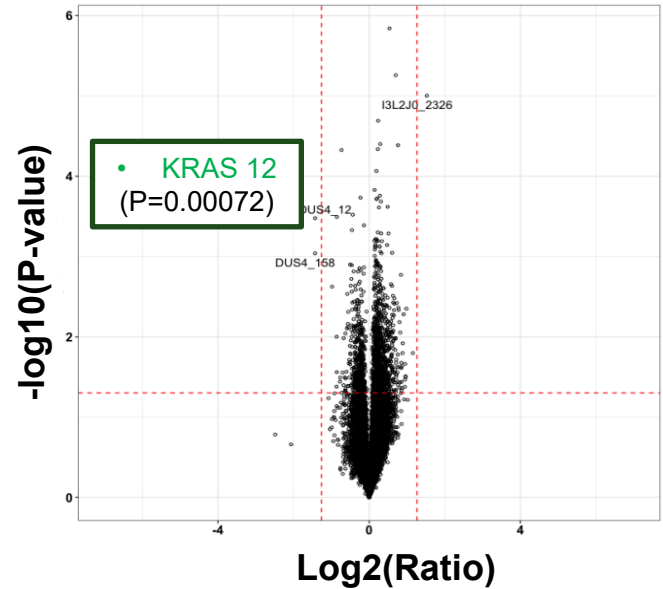
BBO-8520: Mechanism of action & selectivity

³¹P NMR spectrum: State 1 trapping



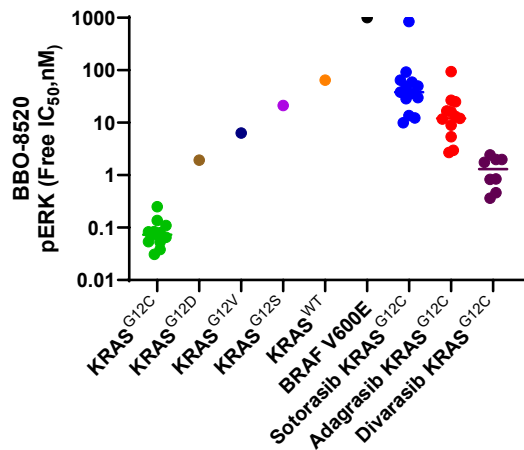
Cellular Selectivity

Global Cysteine Proteomics (20 nM)

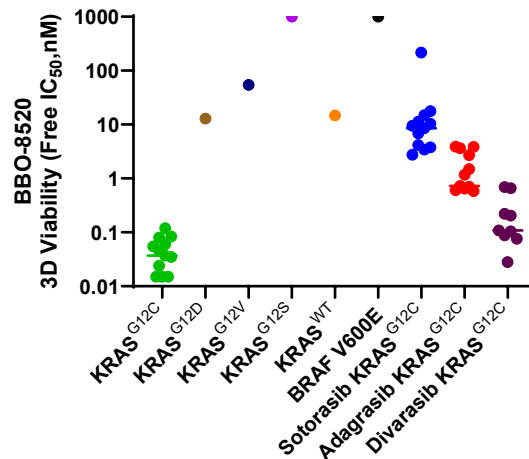


BBO-8520: Consistent, sub-nanomolar effect in multiple KRAS^{G12C} models

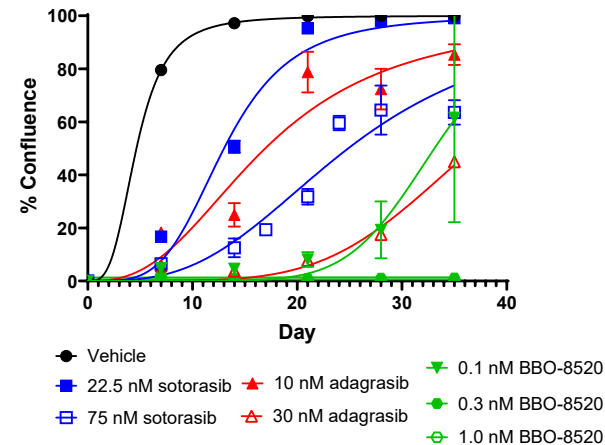
Signaling (HTRF®)



Viability (CellTiterGlo®)



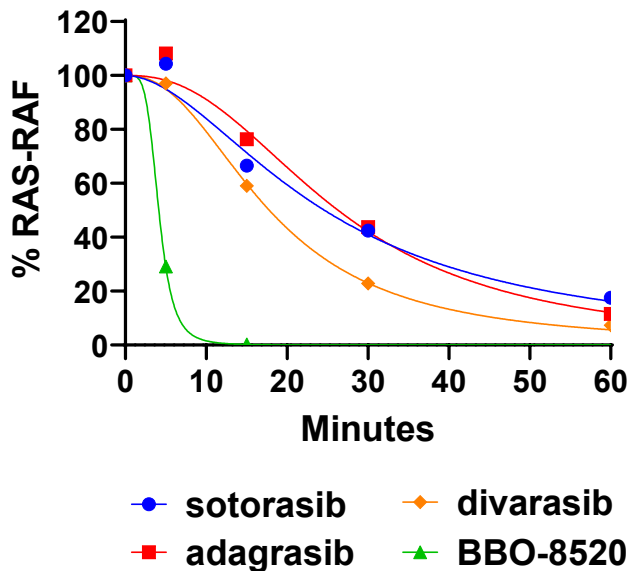
Clonogenic (Incucyte®)



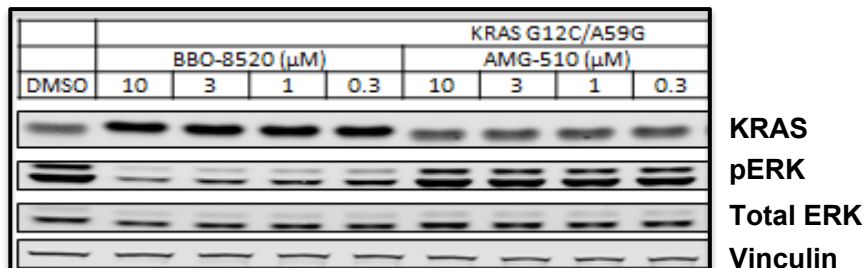
Cell Line	H358	MIA PaCa-2	Calu-1	H2030	LU99	SW837	SW1463	UM-U-C3
Viability IC ₅₀ (nM)	0.032	0.037	0.015	0.015	0.015	0.041	0.055	0.023

BBO-8520: Demonstration of differentiated cellular KRAS^{G12C} (ON) activity

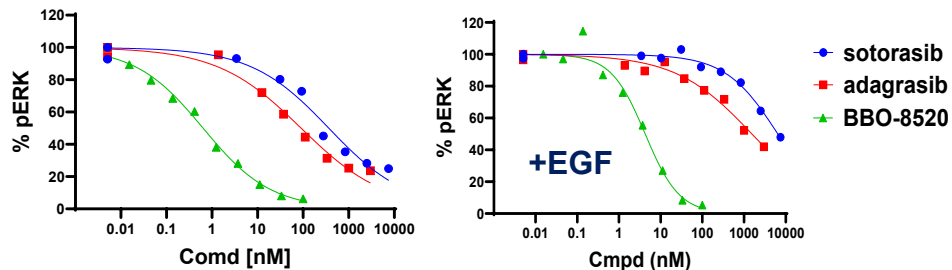
RAS:RAF1 ELISA Assay



G12C/A59G Transitional state mutant



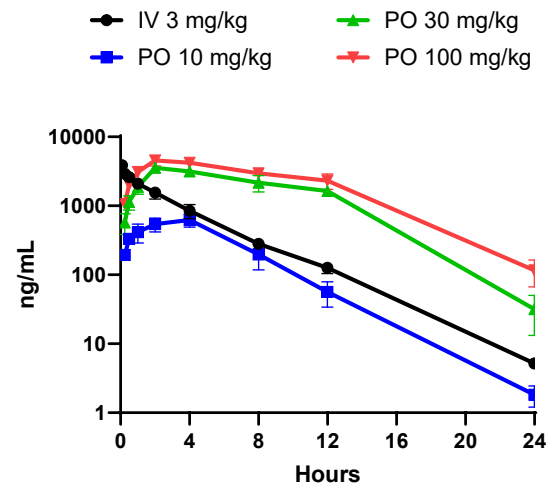
Growth factor swift assay (H358 +/- EGF)



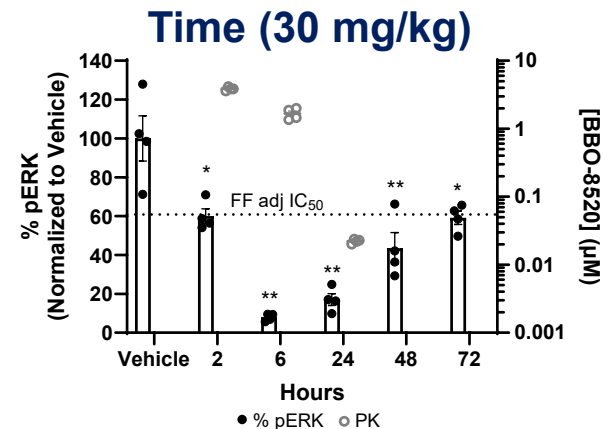
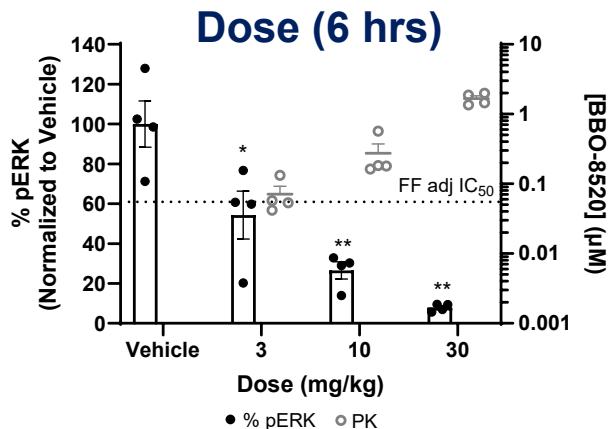
ADME properties

	BBO-8520
Microsome stability ER% H / C / D / R / M	74 / > 90 / < 30 / 68 / 37
Hepatocyte stability ER% H / C / D / R / M	40 / 53 / < 39 / 42 / < 33
MDR1-MDCK P _{app} A-B (10 ⁻⁶ cm/s)/(Efflux ratio)	3.2 / 9.1
Plasma protein binding (%) H / C / D / R / M	99.7 / 99.8 / 99.6 / 99.8 / 99.7
Whole blood stability t _{1/2} minutes H / C / D / R / M	> 371 for all species
Aqueous solubility (µg/mL): pH 1.2 / 6.8 / 7.4 / SGF / FeSSIF / FaSSIF	>2000 / 29 / 29 / >2000 / >2000 / 369
IC ₅₀ for CYP450 inhibition (µM)	3A4-M: 4.8; 3A4-T: 5.4; CYP1A2, 2B6, 2C8, 2C19, 2D6: > 15
Mouse Cl, T _{1/2} , Vss, F	5 mL/min/kg, 2.7 hr, 1.0 L/kg, 37%
Rat Cl, T _{1/2} , Vss, F	28 mL/min/kg, 3.4 hr, 7.0 L/kg, 14%
Dog Cl, T _{1/2} , Vss, F	16 mL/min/kg, 4.1 hr, 4.1 L/kg, 23%
Minipig Cl, T _{1/2} , Vss, F	64 mL/min/kg, 2.6 hr, 7.8 L/kg, 48%
Cyno Cl, T _{1/2} , Vss, F	30 mL/min/kg, 2.6 hr, 3.7 L/kg, 6%

Mouse CD-1 PK



Dose and time dependent inhibition of pERK in MIA PaCa-2 Matrigel plugs



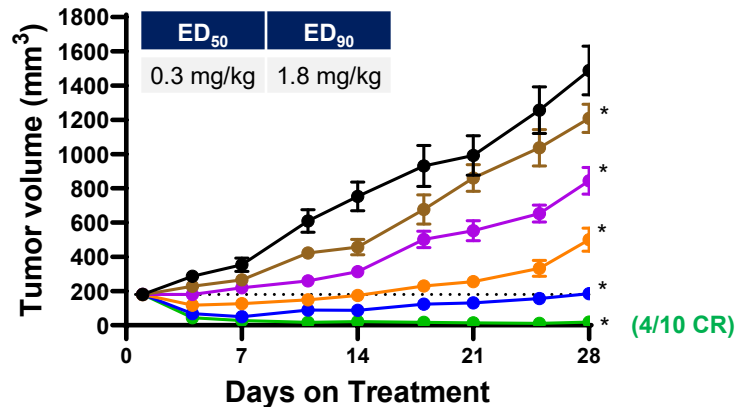
Test Article	Dose (QDx1, po)	pERK		Plasma [BBO-8520]
		Inhibition	p value vs vehicle	
BBO-8520	3 mg/kg	46%	0.0080	71 nM
BBO-8520	10 mg/kg	73%	<0.0001	274 nM
BBO-8520	30 mg/kg	92%	<0.0001	1669 nM

Test Article	Time after 30 mg/kg QD dose	pERK		Plasma [BBO-8520]
		Inhibition	p value vs vehicle	
BBO-8520	2 hrs	40%	0.0012	3868 nM
BBO-8520	6 hrs	92%	<0.0001	1669 nM
BBO-8520	24 hrs	83%	<0.0001	22 nM
BBO-8520	48 hrs	57%	<0.0001	BLQ
BBO-8520	72 hrs	41%	0.0010	BLQ

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

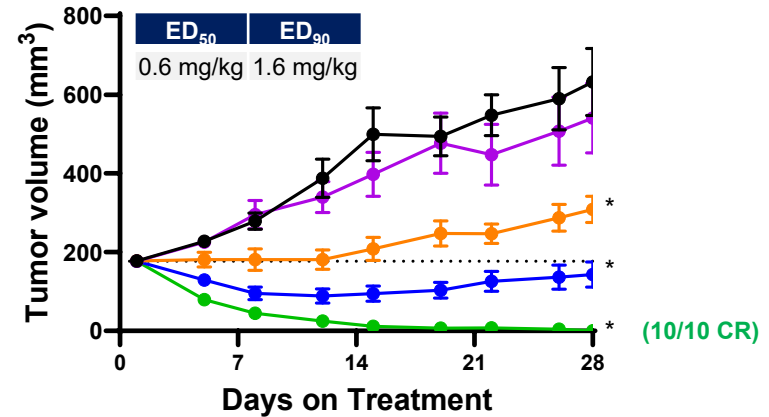
Robust tumor growth inhibition, with 10/10 regressions at 10 mg/kg observed in MIA PaCa-2 and NCI-H358 CDX models

MIA PaCa-2 KRAS^{G12C} PDAC



- Vehicle (QD, po)
- BBO-8520 (0.1 mg/kg)
- BBO-8520 (0.3 mg/kg)
- BBO-8520 (1 mg/kg)
- BBO-8520 (3 mg/kg)
- BBO-8520 (10 mg/kg)

H358 KRAS^{G12C} NSCLC

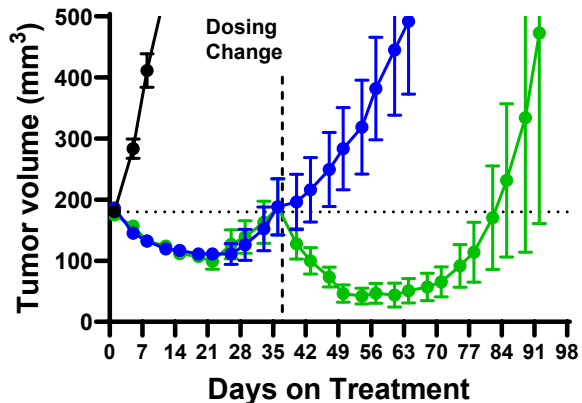


- Vehicle (QD, po)
- BBO-8520 (0.3 mg/kg)
- BBO-8520 (1 mg/kg)
- BBO-8520 (3 mg/kg)
- BBO-8520 (10 mg/kg)

Two-way RM ANOVA vs vehicle: *p<0.0001

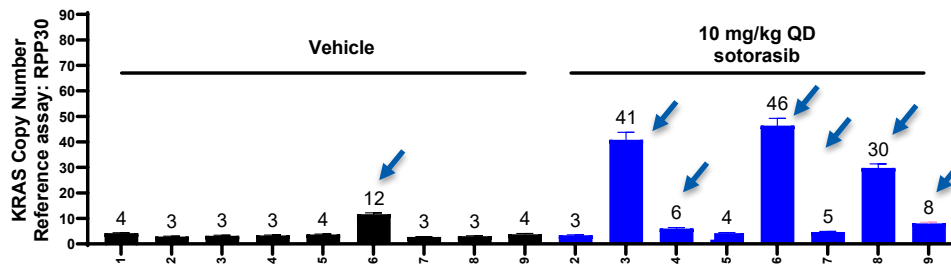
BBO-8520 can drive deep responses following the development of resistance to sotorasib

MIA PaCa-2 KRAS^{G12C} PDAC



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

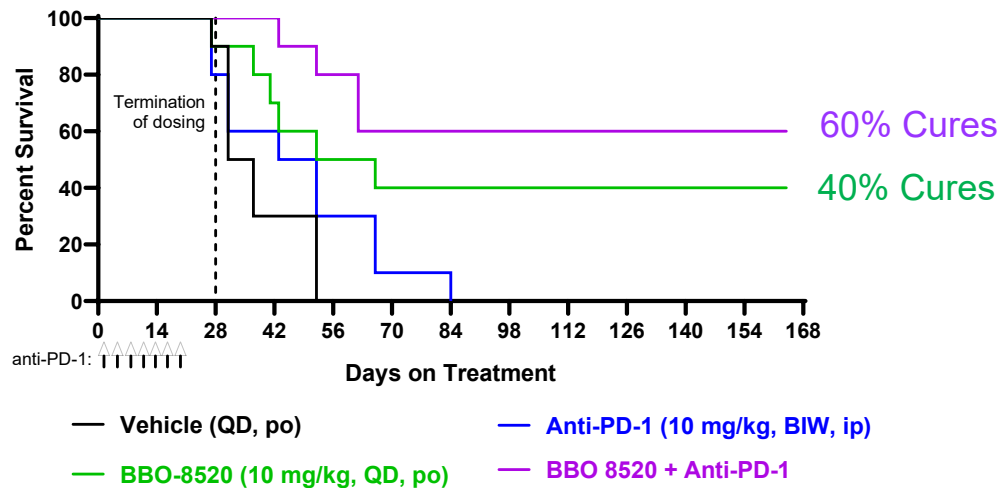
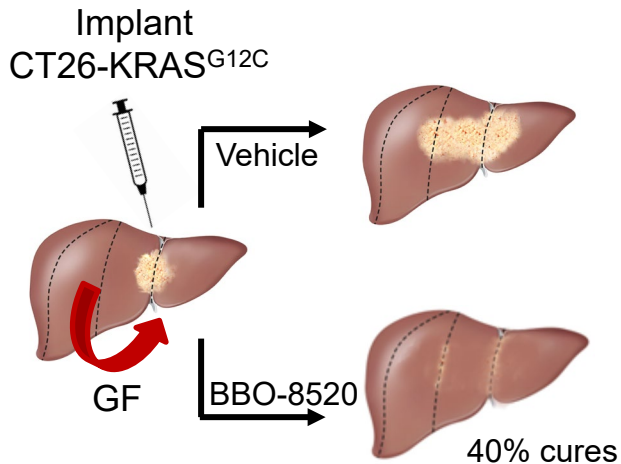
End of study ddPCR KRAS Copy Number Assay Results



Groups (n=10)	Individual Tumor volumes (day 92*)									
	ND d29	ND d33	315	323	673	732	894	1122	1281	3524
sotorasib (10 mg/kg, QD)	ND d29	ND d33	315	323	673	732	894	1122	1281	3524
sotorasib (10 mg/kg, QD×36) → BBO-8520 (30 mg/kg, QD)	ND d22	ND d33	ND d54	ND d61	ND d89	67	433	498	524	3205

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

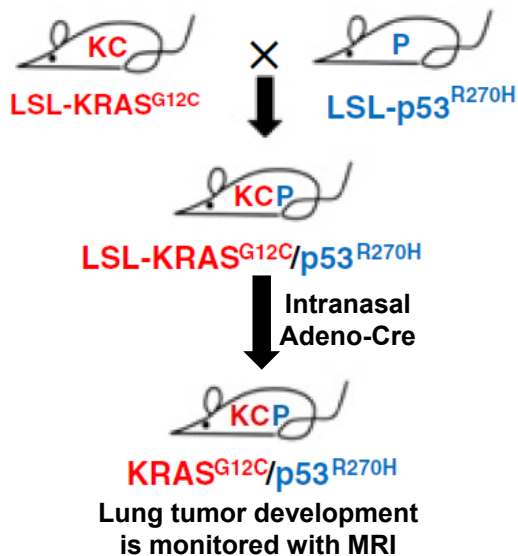
CT26-KRAS^{G12C} syngeneic liver tumors are cured by 10 mg/kg BBO-8520 and its combination with anti-PD-1 mAb



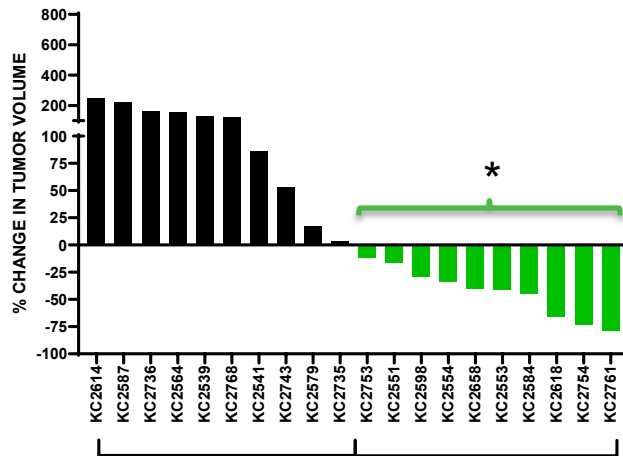
Group (n=10)	Day 164		
	p value vs vehicle	p value vs combo	Median OS (day)
Vehicle	-	-	34
Anti-PD-1 (10 mg/kg, BIW, ip)	0.3952	0.0033	48
BBO-8520 (10 mg/kg, QD, po)	0.0240	0.1932	59
BBO-8520 + Anti-PD-1	0.0001	-	Undefined

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

KCP GEMM



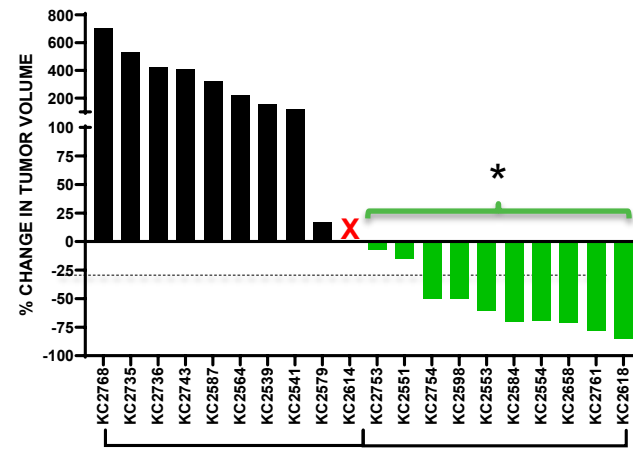
2 Weeks



Vehicle

BBO-8520

6 Weeks



Vehicle

BBO-8520

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

- Completely modifies both active GTP-bound (ON) and inactive GDP-bound (OFF) forms of KRAS^{G12C}
- Potent and selective with superior Kinact/K_i
- Binding stabilizes GTP-bound KRAS^{G12C} in state 1 which cannot bind effectors
- Strong efficacy in KRAS^{G12C} models
- Enhances target coverage and prevents adaptive resistance mechanisms to first generation KRAS^{G12C} (OFF) inhibitors
- The Phase1a/1b ONKORAS-101 trial in KRAS^{G12C} positive non-small cell lung cancer is currently open to enrollment (NCT06343402)

Team Effort



Olga Botvinnik	Sunyoung Lee	Kyle Sullivan
Howard Chang	Ken Lin	Keshi Wang
Tony Chen	Sadaf Mehdizadeh	Paul Wehn
Nathan Collett	Mike Monteith	James Winter
Robert Czerwinski	Rick Panicucci	Rui Xu
Sofia Donovan	Erin Riegler	Maggie Yandell-Zhao
Ferdie Evangelista	James Rizzi	Cathy Zhang
Cindy Feng	Saman Setoodeh	Zuhui Zhang
Siyu Feng	Jin Shu	Eli Wallace
Lijuan Fu	Devansh Singh	Bin Wang
Jennifer Gansert	Kanchan Singh	
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Victoria Hodson	Carlos Stahlhut	
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Marcin Dyba	Monalisa Swain
Dominic Esposito	David Turner
William Gillette	Jayasudhan Yerabolu
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Erik Larsen	Dwight Nissley
Tao Liao	Anna Maciag
Roger Ma	Frank McCormick

Felice Lightstone
Yue Yang

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