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BBO-8520, a first-in-class direct dual inhibitor of GTP-bound (ON) and GDP-bound (OFF) KRAS^{G12C}, exhibits robust efficacy in non-small cell lung cancer preclinical models

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BBOTi BridgeBio Oncology Therapeutics

Disclosure Information

James Stice

I have the following relevant financial relationships to disclose:

Employee of: BBOT (BridgeBio Oncology Therapeutics)

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

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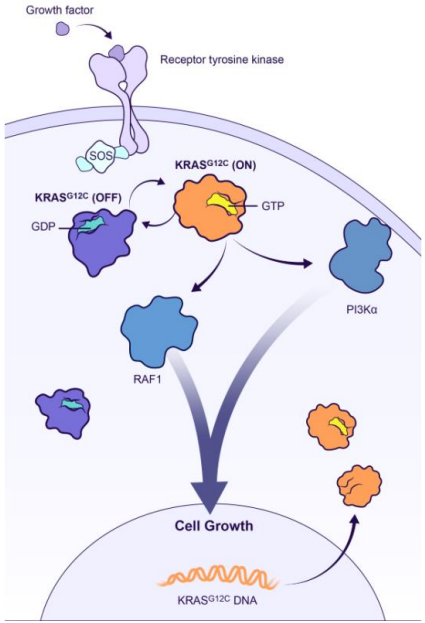
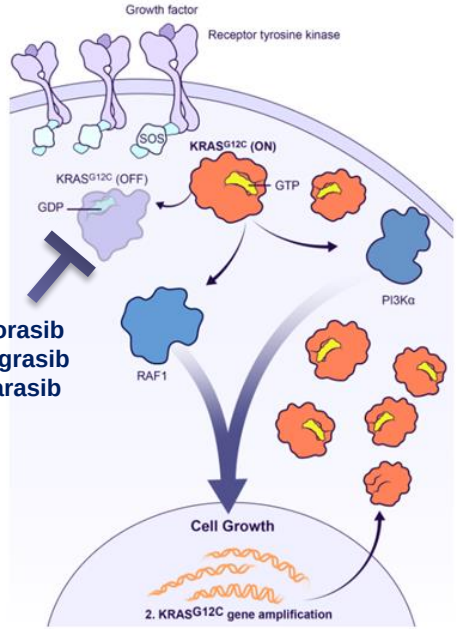
Only GTP-bound KRAS^{G12C} activates effectors

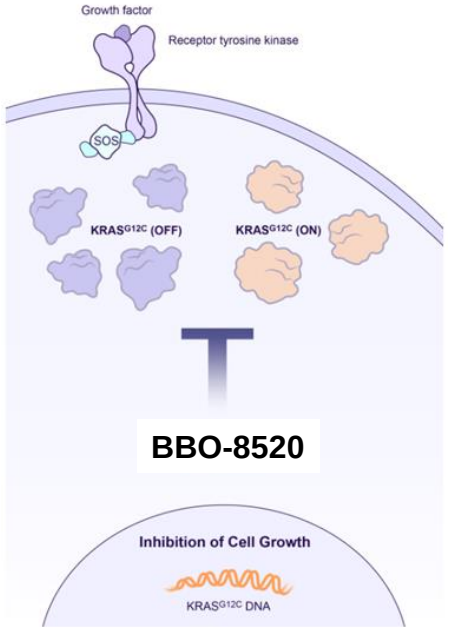


Increased GTP state is a MOA of adaptation to OFF inhibitors

sotorasib
adagrasib
divarasib



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



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

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

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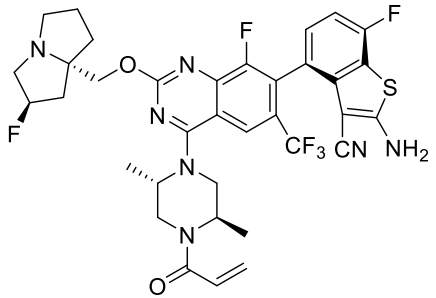
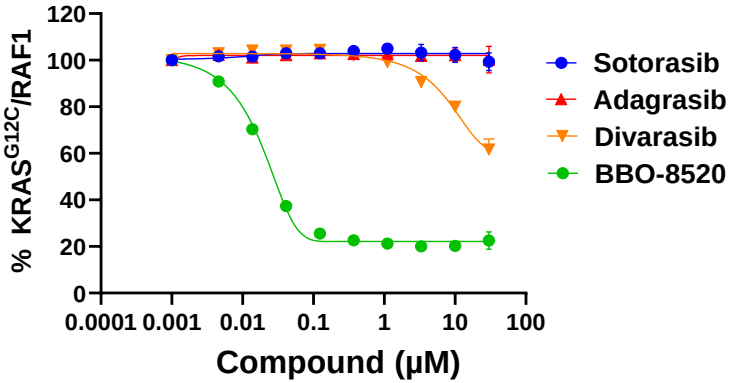
Unique ability to fully modify KRAS^{G12C} when GTP-bound

MALDI-TOF % Modified		BBO-8520	Sotorasib	Adagrasib	Divarasib
GDP	15’	95	80	73	77
	60’	100	82	84	84
GTP	15’	84	0	0	0
	60’	97	0	0	0
Effector Binding IC_{50} (nM)		25	>100,000	20,000	4,200
GTP k_{inact}/K_i ($M^{-1}S^{-1}$)		20,000	0	0	0
GDP k_{inact}/K_i ($M^{-1}S^{-1}$)		2,743,000	11,000	180,000	1,100,000





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

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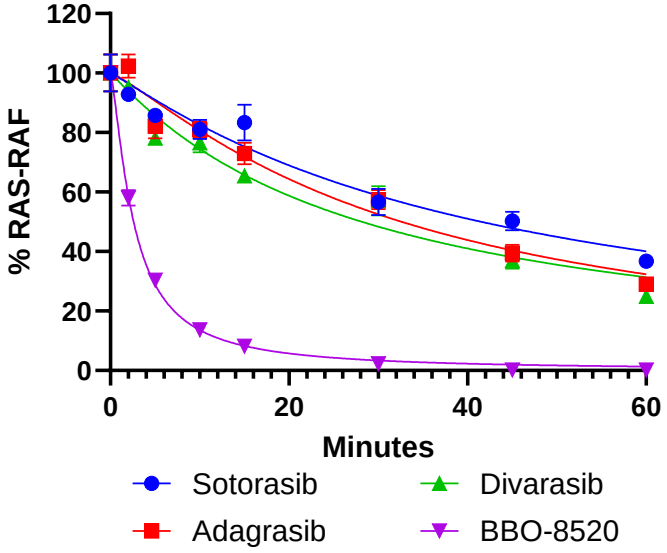
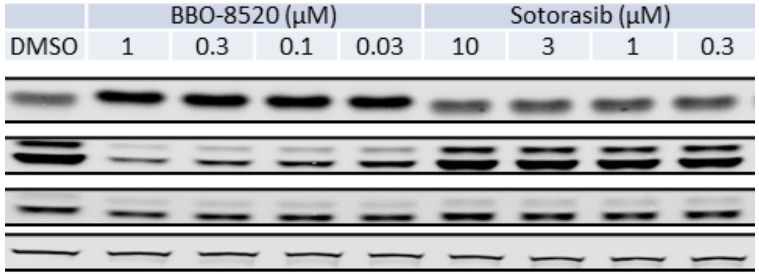
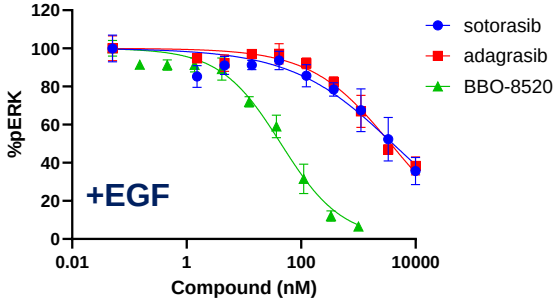
RAS:RAF1 ELISA Assay

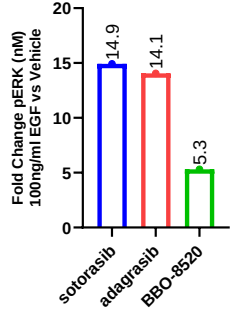


G12C/A59G Transitional state mutant



Growth factor shift assay (NCI-H358 +/- EGF)





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

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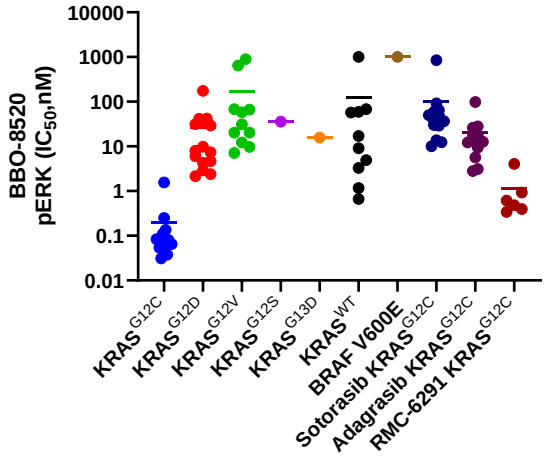
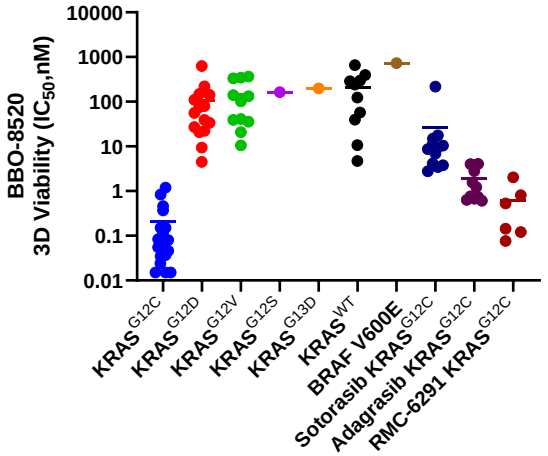
NSCLC Cell Lines

	Calu-1	LU65	LU99	NCI-H2030	NCI-H2122	NCI-H23	NCI-H358
pERK IC_{50} (nM)	0.031	0.25	0.08	0.053	1.565	0.11	0.065
3D Viability IC_{50} (nM)	0.015	0.046	0.015	0.015	0.06	0.119	0.035

Signaling (pERK)



Viability (CTG)



**In vitro* IC_{50} adjusted for free fraction in 10% FBS (Sotorasib=75%, Adagrasib=31%, RMC-6291=76%, BBO-8520=10%)

BBO-8520 shows improved potency over (OFF)-only inhibitors in a panel of cell lines derived from NSCLC KRAS^{G12C} PDX models

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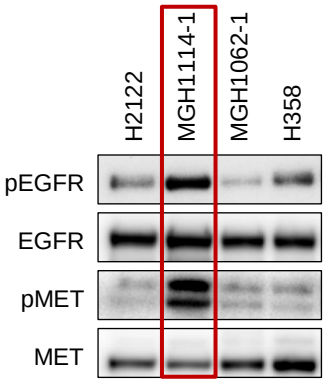
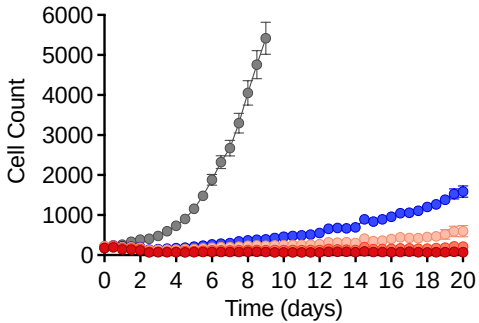
2D Viability (4 Day Tx)	EC_{50} (nM)							
	H358	LU65	MGH1112	MGH1114	MGH1088	MGH1062	MGH1138	MGH1143
	KRAS$^{G12C/WT}$	*KRAS^{G12C}*	*KRAS^{G12C}*	*KRAS^{G12C}*	*KRAS^{G12C}*	*KRAS^{G12C}*	*KRAS^{G12C}*	*KRAS^{G12C}*
BBO-8520	0.02	0.05	0.04	0.01	0.02	0.02	0.02	0.01
Sotorasib	13.67	21.13	21.31	49.12	16.70	12.75	10.86	10.07
Sotorasib/BBO-8520	622	406	507	5458	726	607	604	775

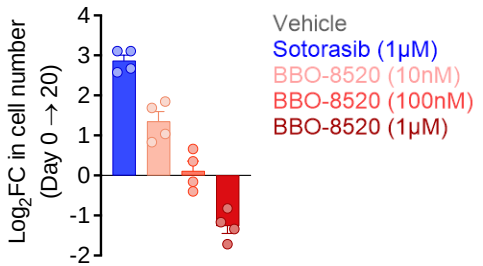
**In vitro EC_{50}* adjusted for free fraction in 10% FBS (Sotorasib=75%, BBO-8520=10%)



Clonogenic assay

MGH-1114





Vehicle
Sotorasib (1μM)
BBO-8520 (10nM)
BBO-8520 (100nM)
BBO-8520 (1μM)

Mass General Brigham
Mass General Cancer Center

Source: Data generated in Aaron Hata's Lab at MGH

BBO-8520 shows activity in NSCLC GEMMs and in models with intrinsic or acquired resistance to $KRAS^{G12C}$ (OFF) inhibitors

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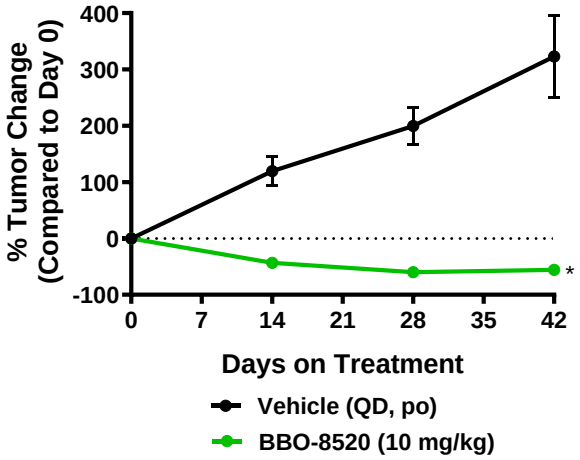
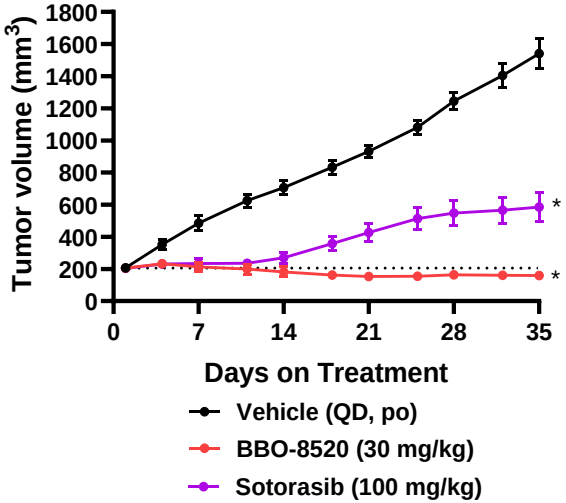
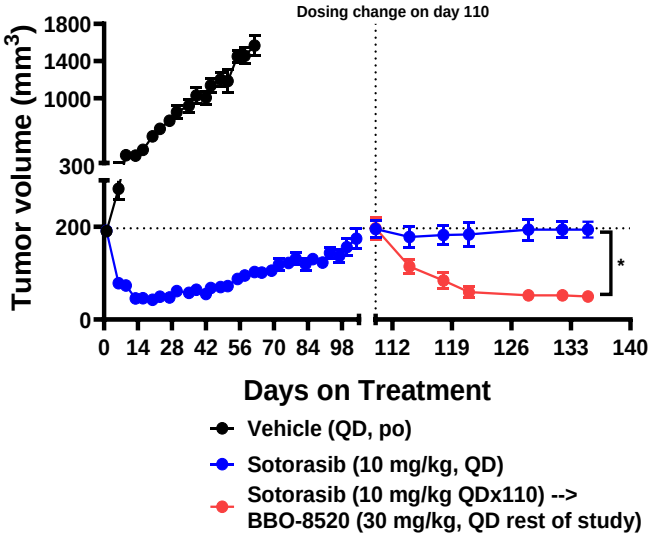
$KRAS^{G12C}$; $Trp53^{R270H}$ (KCP) NSCLC GEMM Model



LUN055 PDX ($KRAS^{G12C}$,RET^{OE})



NCI-H358 Sotorasib-Resistant CDX Model ($KRAS^{G12C}$)



Perlmutter Cancer Center

KCP, LUN055 PDX efficacy study statistical analysis: Two-way repeated measures ANOVA with Dunnett's multiple comparison test vs vehicle: *p<0.0001
NCI-H358 sotorasib-resistant CDX model statistical analysis: Two-way repeated measures ANOVA between indicated groups: *p<0.0001
Abbreviations: CDX-=Cell line-derived xenograft, GEMM=Genetically engineered mouse model, PDX=Patient-derived xenograft, RET=Rearranged during transfection

BBO-8520 offers superior in vivo potency to KRAS G12C (OFF) inhibitors

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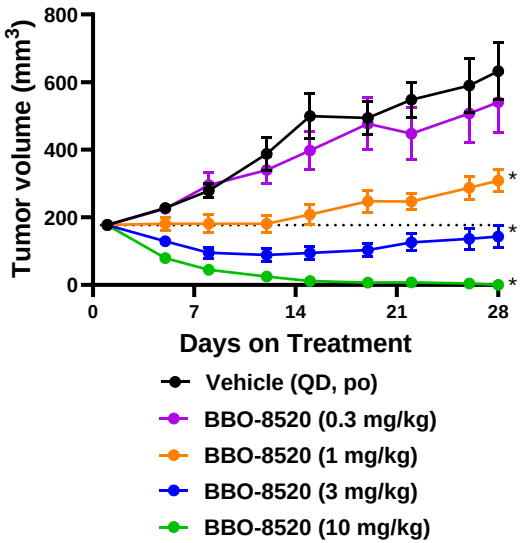
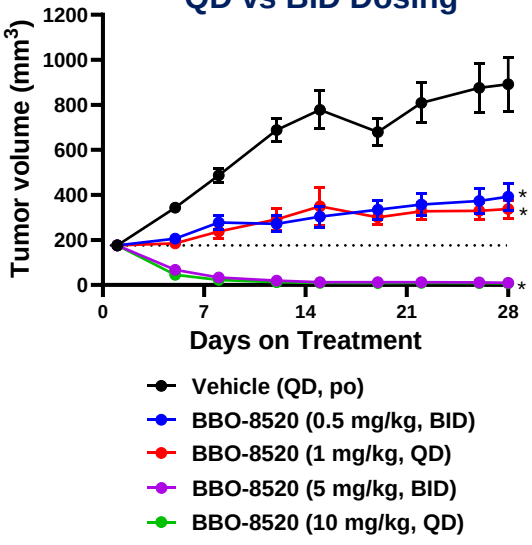
NCI-H358 CDX ($KRAS^{G12C}$)

QD Dose Response



AUC drives activity QD vs BID Dosing



Free Drug AUC_{0-24}

	Compound	Free AUC_{0-24} (h*ng/mL)	Efficacy
BBO-8520	0.3 mg/kg	0.12	20% TGI
	1 mg/kg	0.45	71% TGI
	3 mg/kg	1.4	19% REG
	10 mg/kg	4.8	100% REG
	100 mg/kg Sotorasib	2090	96% REG
	100 mg/kg Adagrasib	630*	79% REG
	15 mg/kg Divarasib	67.2*	61% REG

* published

- BBO-8520 achieves deeper regressions in the NCI-H358 model than OFF inhibitors at a fraction of the free drug concentration.

- Enrollment of patients with $KRAS^{G12C}$ mutant non-small cell lung cancer in the ONKORAS-101 trial ongoing (NCT06343402)

NCI-H358 CDX efficacy study statistical analysis: Two-way repeated measures ANOVA with Dunnett's multiple comparison test vs vehicle: *p<0.0001
Abbreviations: AUC=Area Under Curve, BID=Twice a day, QD=Once a day, REG=Regression, TGI=Tumor Growth Inhibition

BBO-8520 demonstrates positive preclinical activity in combination with anti-PD-1 therapy

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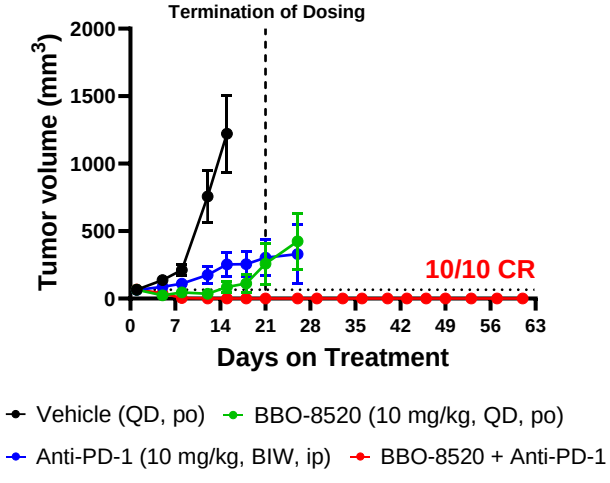
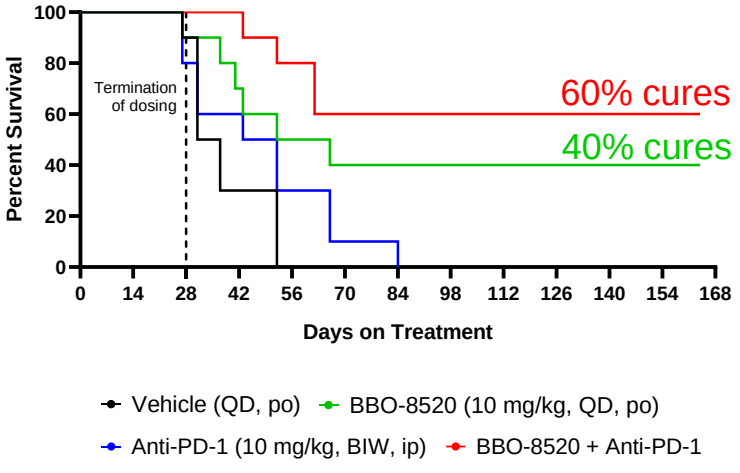
CT26-KRAS^{G12C}
Syngeneic Subcutaneous Model



CT26-KRAS$^{G12C\text{-}luc}$
Syngeneic Liver Model



- Potency and ON state inhibition designed to enable monotherapy and combination activity at low drug concentration in preclinical models
- May lead to better clinical activity and improved tolerability profile with pembrolizumab in NSCLC patients

Co-Inhibition of ERK and AKT drives deeper responses in NSCLC KRAS^{G12C} cell line models

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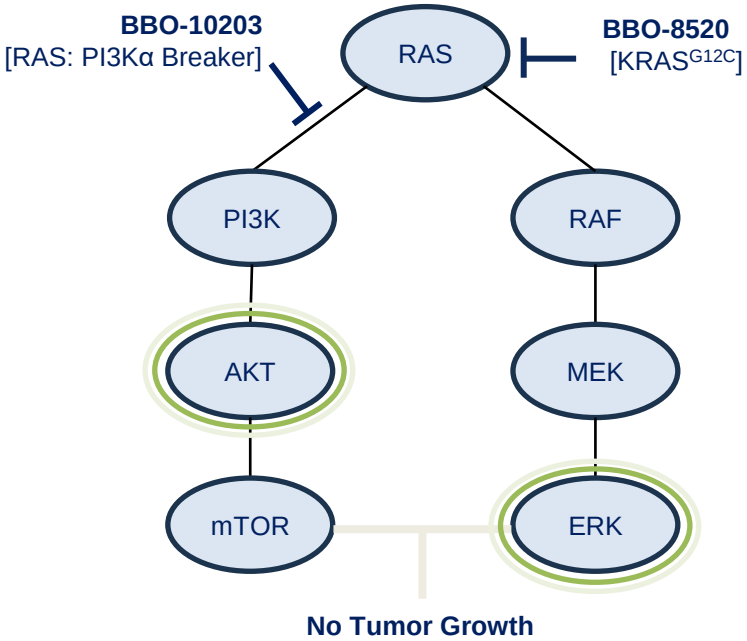
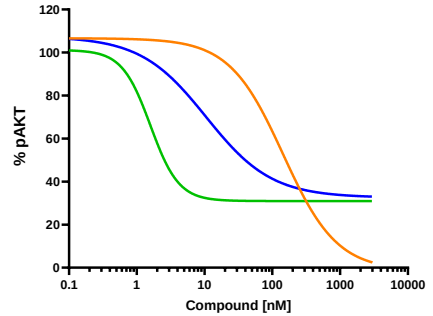
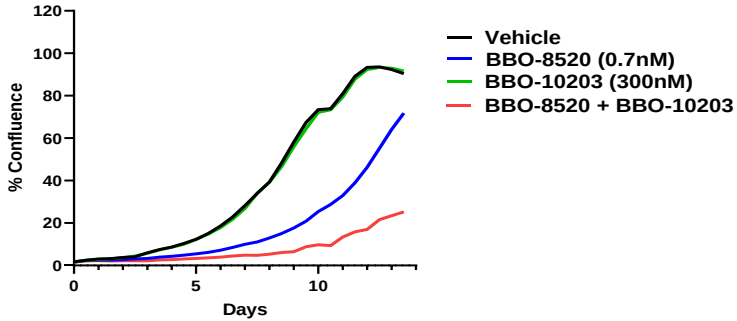


In Vitro

NCI-H2122 (KRAS^{G12C}, KEAP1^{del}, STK11^{del})





Combined treatment with BBO-8520 and BBO-10203 leads to tumor regression in the NCI-H2122 CDX model by inducing G1 arrest and apoptosis

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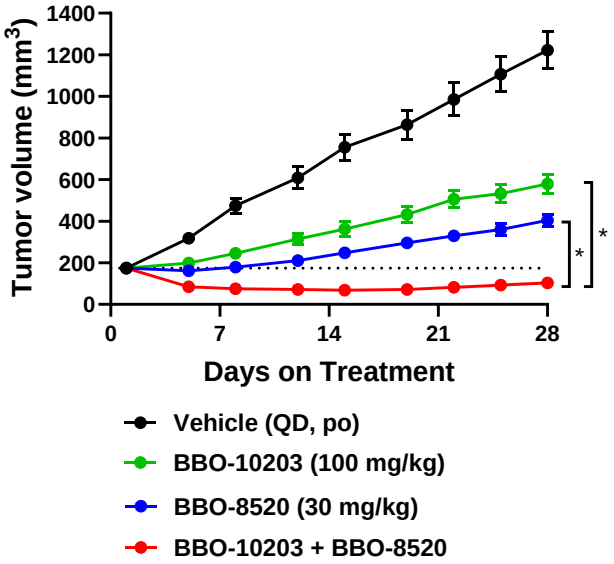
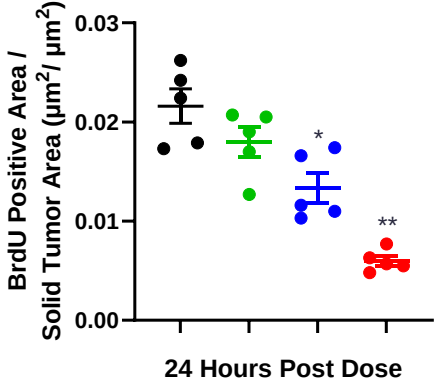
NCI-H2122 ($KRAS^{G12C}$, $KEAP1^{del}$, $STK11^{del}$)

Tumor Volume

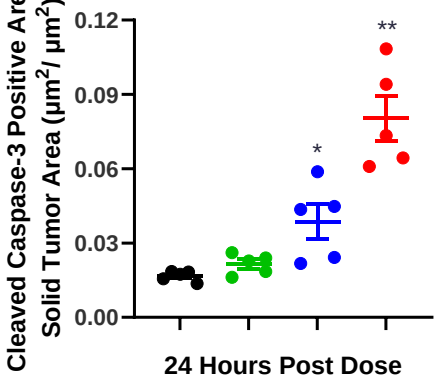


Single Dose

Decreased proliferation



Increased apoptosis



- BBO-10203 currently enrolling KRAS mutant advanced CRC or NSCLC in the BREAKER-101 trial (NCT06625775)

Efficacy study statistical analysis: Two-way repeated measures ANOVA combination group vs each monotherapy group *p<0.0001
BrdU IHC statistical analysis: One-way ANOVA with Dunnett's test vs vehicle *p<0.01, **p<0.0001
Cleaved caspase-3 IHC statistical analysis: One-way ANOVA with Dunnett's test vs vehicle *p<0.05, **p<0.0001

BBO-8520, a first-in-class direct dual inhibitor of GTP-bound (ON) and GDP-bound (OFF) $KRAS^{G12C}$

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- Completely modifies both the GTP (active) and GDP (inactive) forms of $KRAS^{G12C}$
- Demonstrates rapid inhibition of effector binding and maintains activity in the GTP bound state
- Exhibits sub-nM *in vitro* potency on pERK and viability
- Shows strong *in vivo* activity at low free drug concentrations across NSCLC $KRAS^{G12C}$ models both sensitive and resistant to GDP (OFF) inhibitors
- Displays combination activity with anti-PD-1 and the RAS:PI3Kα breaker BBO-10203
- Enrollment of patients with $KRAS^{G12C}$ mutant non-small cell lung cancer in the ONKORAS-101 trial ongoing (NCT06343402)

Team Effort

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Pedro Beltran	Jin Ju	Kyle Sullivan
Olga Botvinnik	Sunyoung Lee	Kalyan Vasudevan
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Tony Chen	Sadaf Mehdizadeh	Keshi Wang
Nathan Collett	Mike Monteith	Paul Wehn
Robert Czerwinski	Rick Panicucci	James Winter
Sofia Donovan	Erin Riegler	Rui Xu
Ferdie Evangelista	James Rizzi	Maggie Yandell-Zhao
Cindy Feng	Saman Setoodeh	Yue Yang
Siyu Feng	Jin Shu	Cathy Zhang
Lijuan Fu	Devansh Singh	Zuhui Zhang
Jennifer Gansert	Kanchan Singh	Eli Wallace
Foster Gonsalves	Kerstin Sinkevicius	Bin Wang
Victoria Hodson	Carlos Stahlhut	
Chunmei Ji	James Stice	

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Bill Bocik	Megan Rigby
Albert Chan	Alok Sharma
Daniel Czyzyk	Dhirendra Simanshu
Caroline DeHart	Swapnil Singh
John-Paul Denson	Brian Smith
Sathiya Dharmaiah	Thomas Sova
Robert D'Ippolito	Andy Stephen
Marcin Dyba	Monalisa Swain
Dominic Esposito	David Turner
William Gillette	Jayasudhan Yerabolu
Claudia Haywood	RAS Reagent Research Team
Erik Larsen	Dwight Nissley
Tao Liao	Anna Maciag
Roger Ma	Frank McCormick

Lawrence Livermore National Laboratory

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Aaron Hata

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