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Novel Approaches to Target RAS

October 2022

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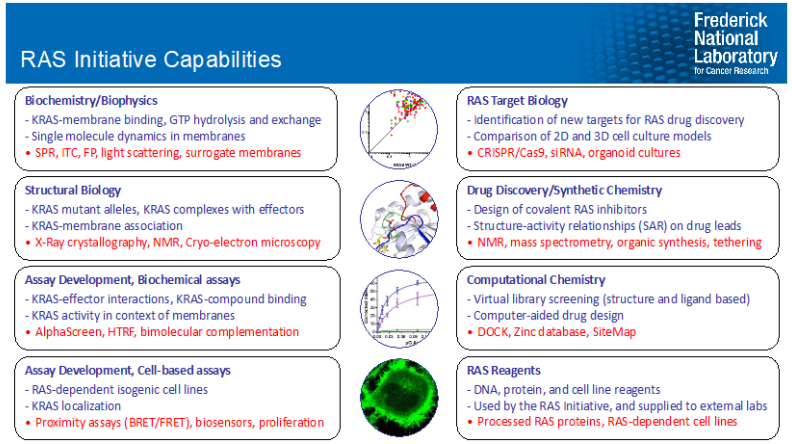
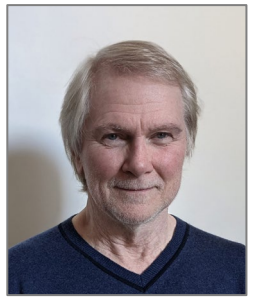
Our effort includes partnerships with leading experts to drive the science and our programs forward

Frederick National Laboratory for Cancer Research



- Partnership with the National RAS Initiative, including **60 of the world's foremost RAS researchers**

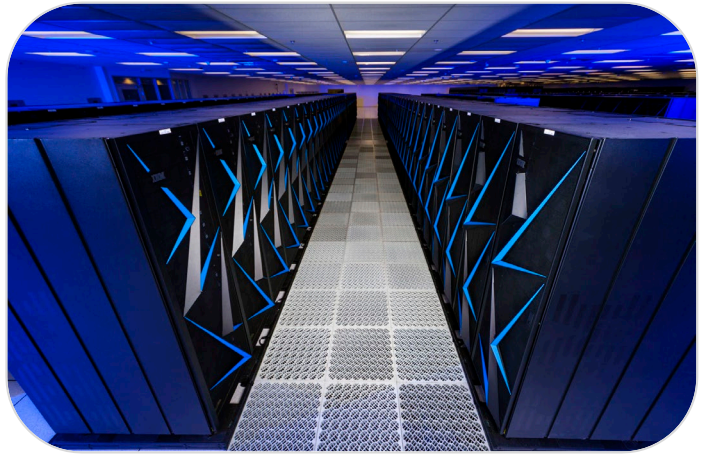

Frank McCormick


Dwight Nissley


Anna Maciag

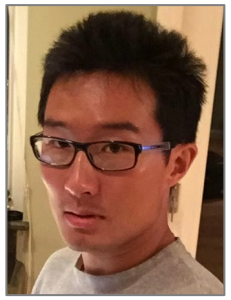

Dhirendra Simanshu

Lawrence Livermore National Laboratory

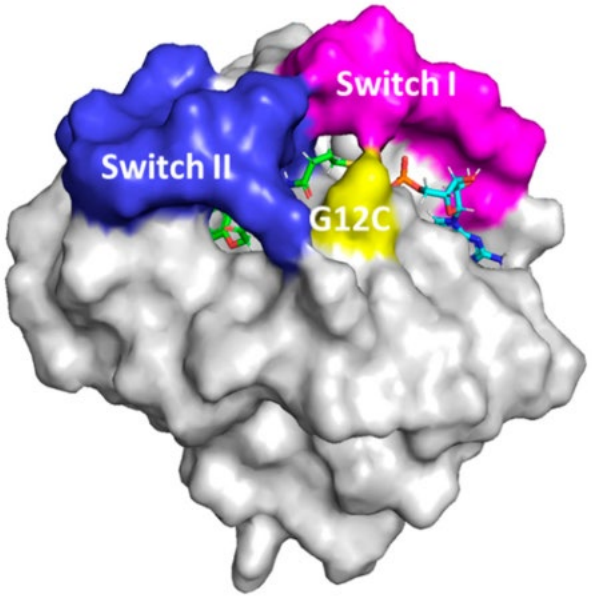


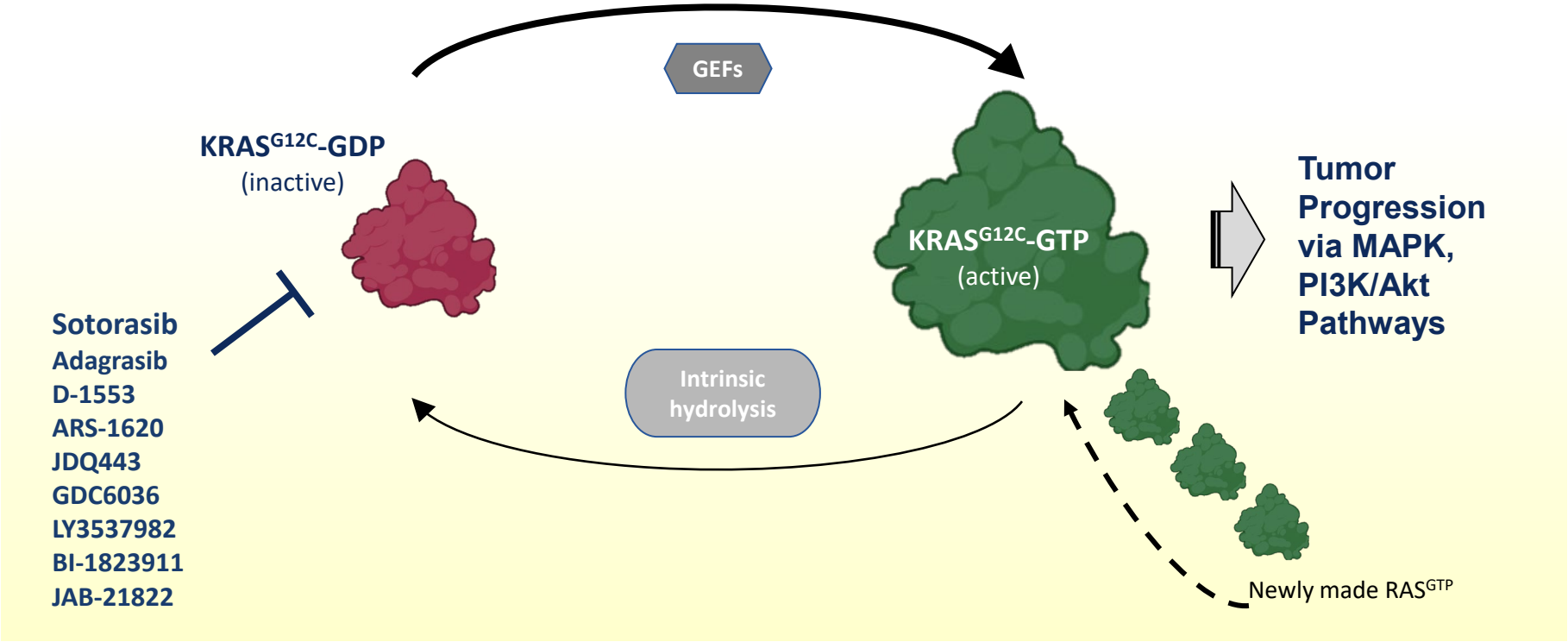
- Partnership with the computational chemistry team at LLNL enabling **high-throughput molecular dynamics and free energy simulations** of protein-ligand complexes, and highly efficient in silico modeling


Felice Lightstone


Yue Yang

$KRAS^{G12C}$-GDP Inhibitors have changed our understanding of RAS biology, as well as cancer treatment





Shokat's discovery led to an explosion of $KRAS^{G12C}$-GDP inhibitors; led by sotorasib, these will change the treatment paradigm for people with $KRAS^{G12C}$-driven cancers

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%	46%	64%	79%	77%	68%
mPFS (mo.)	6.3	6.5	*tbd*	*tbd*	25.7	18.9	12.4

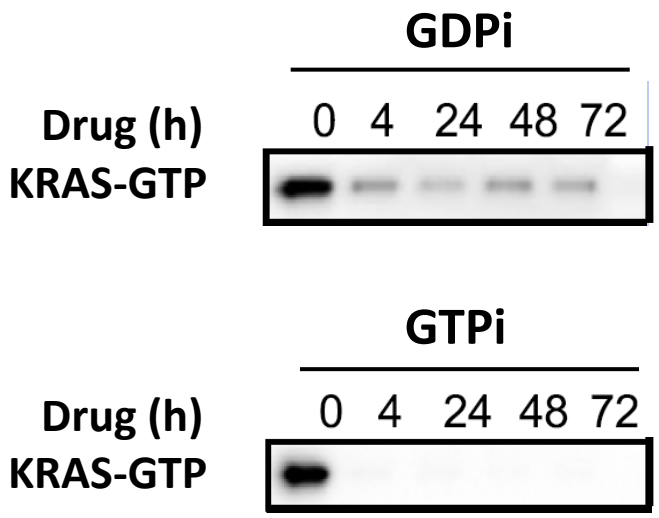
- Only 41% of patients had confirmed ORR after 70% showed significant (>30%) tumor shrinkage at their first scan suggesting a rapid onset of resistance to sotorasib
- Phase 3 CODEBREAK 200 – PFS 5.6 months; ORR 28%

mPFS, median progression-free survival; ORR, overall response rate; NSCLC, non small-cell lung cancer

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; RTK targeted agent data taken from product labels

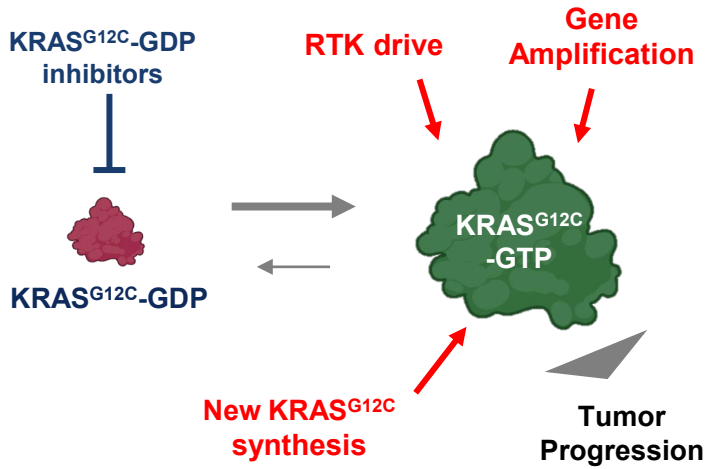
A compound that inhibits both GTP (active) and GDP (inactive) forms of KRAS^{G12C} will be superior to one that only inhibits the latter

GDPi does not achieve complete inhibition of "active" KRAS^{G12C}*



Growth factors render GDPi completely inactive

KRAS^{G12C} prefers the GTP state: GTP levels are 10x GDP levels



- A mechanism of resistance was not identified for most NSCLC patients that became refractory to sotorasib**
- Among patients with identified resistance mechanisms to sotorasib, the majority were driven by RTK re-activation**

We believe efficacy of targeting of KRAS^{G12C} can be improved by targeting the oncogenic active GTP form

*Ryan et al. Cell Reports 2022; **Li BT, et al. Journal of Clinical Oncology 40, no. 16_suppl (June 01, 2022) 102-102

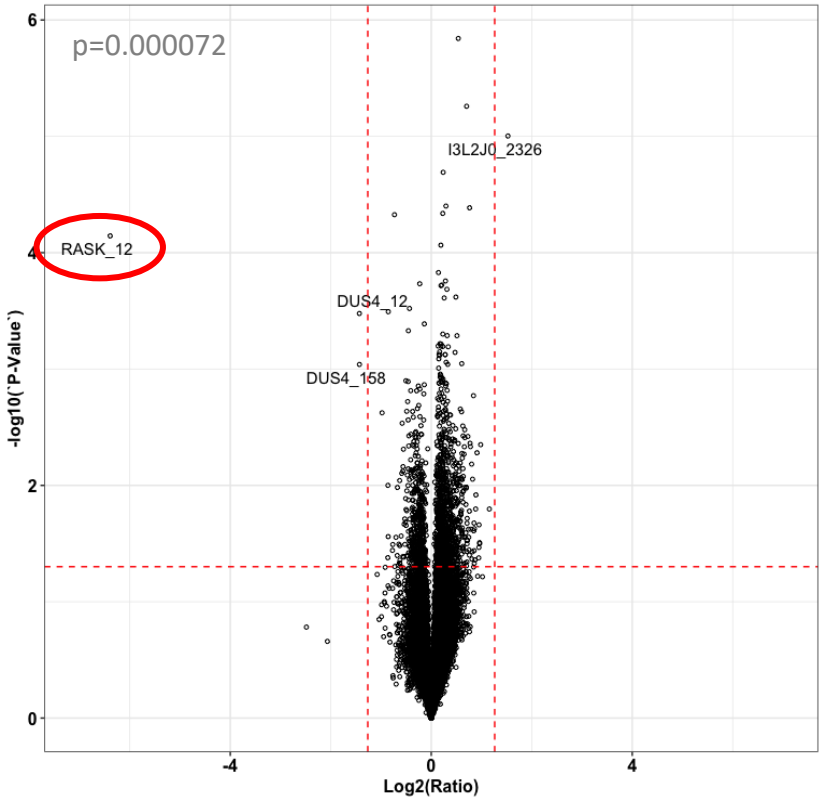
BBO-8520 completely modifies both GTP (active) and GDP (inactive) forms of $KRAS^{G12C}$ and is exceptionally potent

			BBO-8520	Sotorasib	Adagrasib	GDC-6036
% modified	$KRAS^{G12C}$ GTP (active)	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
H358 kinact/Ki (M*s)-1			43,000	776	1064	27,000

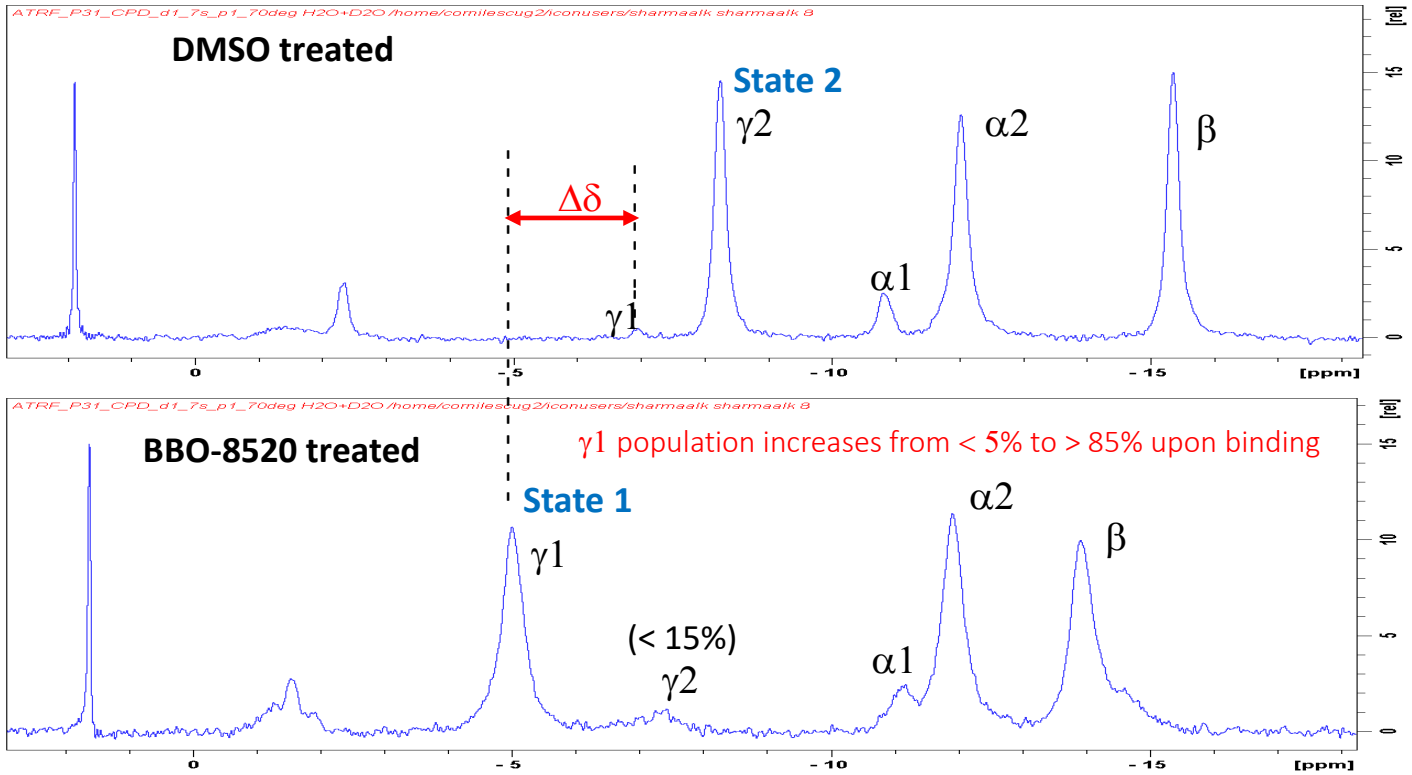
- High degree of protein modification supports high affinity binding to GTP state
- Potent inhibition of effector binding and oncogenic signaling
- Superior kinact/Ki

Cysteine proteome selectivity and mechanism of action

Global cysteine proteomics shows high degree of selectivity for G12C



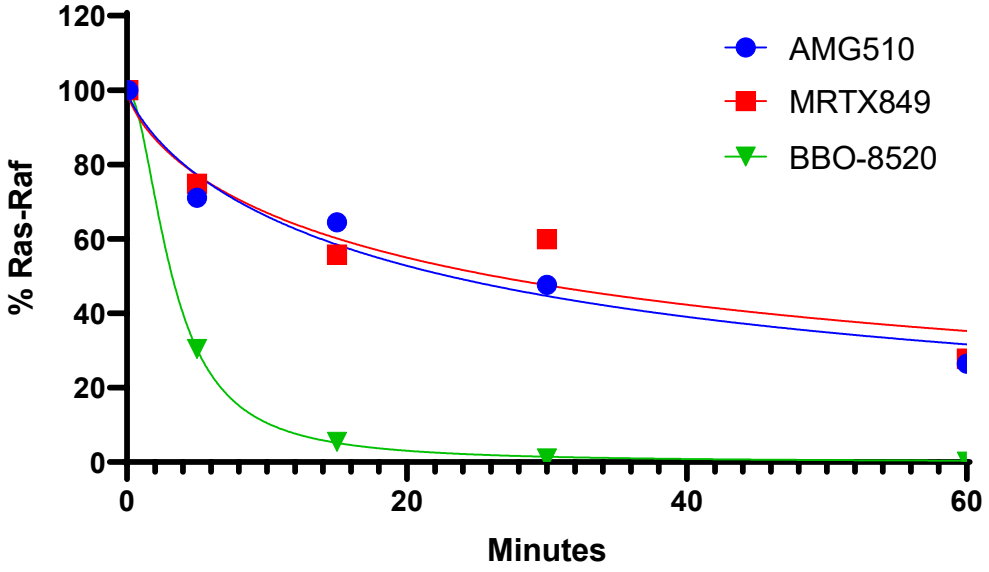
^{31}P NMR peak shifts suggest that BBO-8520 stabilizes State 1 of active GTP-bound KRAS, which disrupts effector protein binding



^{31}P NMR spectrum @ 5 °C

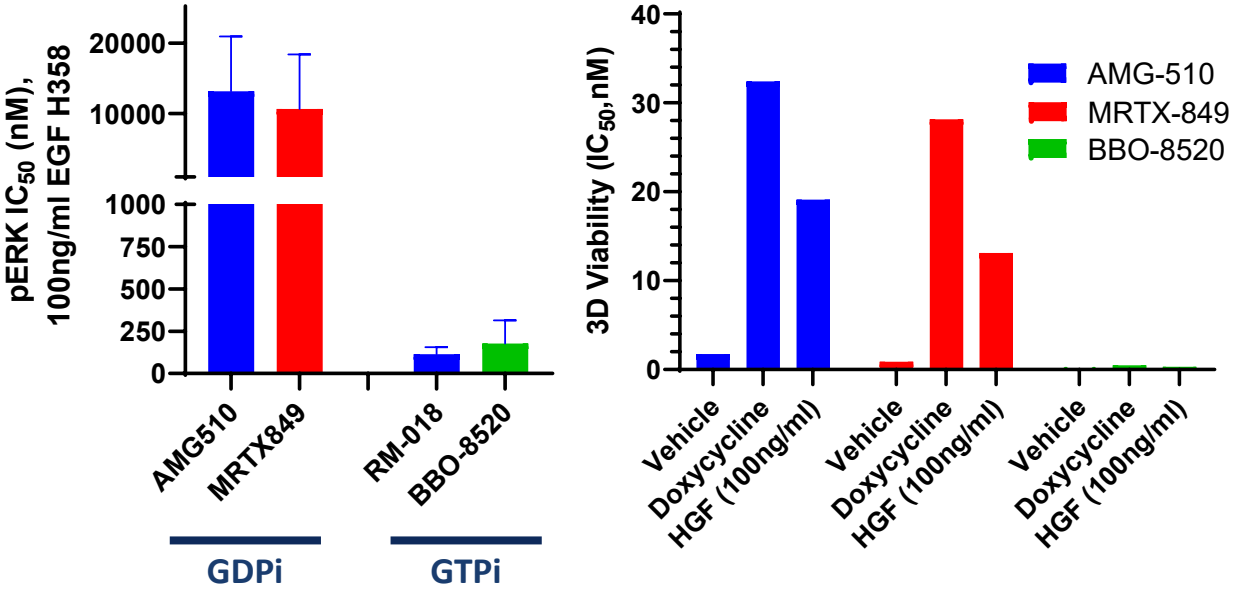
Targeting KRAS^{G12C}-GTP activity allows for rapid signal inhibition and overcomes RTK drive

Rapid and complete inhibition of KRAS^{G12C}-GTP



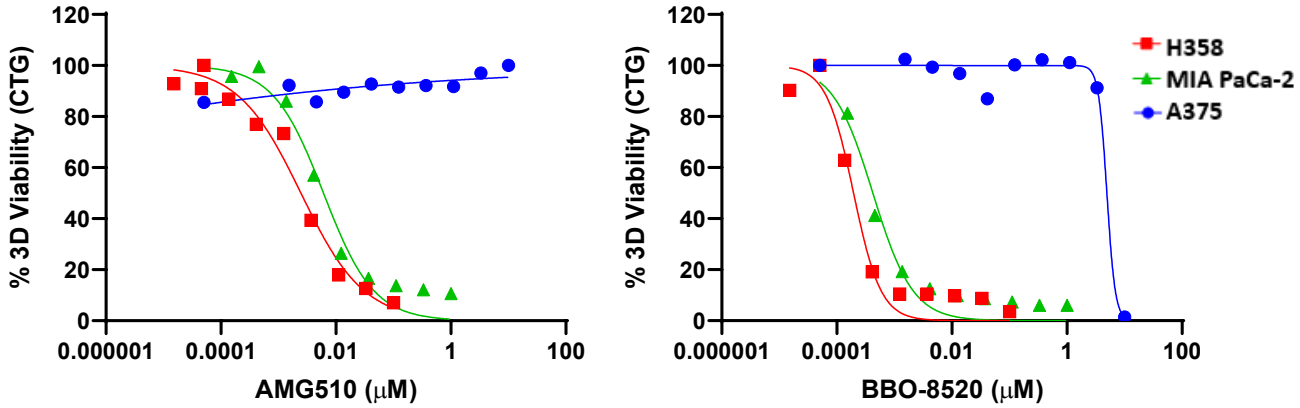
Compound	MALDI-TOF% GTP, 5min	Time (min) to IC_{50}	% of AMG510 Time to IC_{50}
AMG510	0	22	100
MRTX849	0	26	118
BBO-8520	**94**	**3.0**	**14**

GFs abundantly present in human tissues render GDP inhibitors inactive



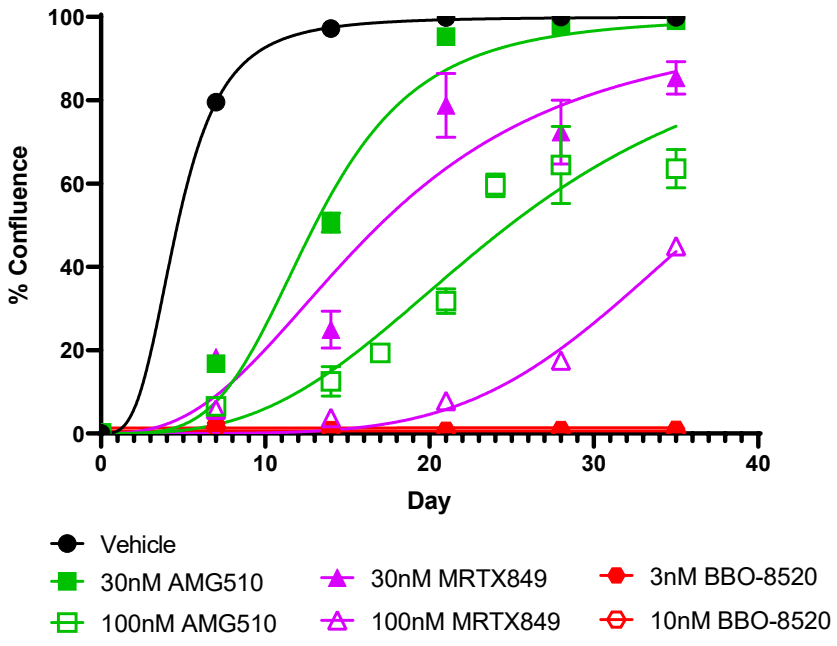
Cellular data support hypothesis that targeting the GTP form yields greater potency and deeper responses

10x increased potency is observed in viability assays



Compound	IC_{50} (nM)	
	H358	MIAPaCa-2
AMG510	2	5
BBO-8520	0.2	0.3

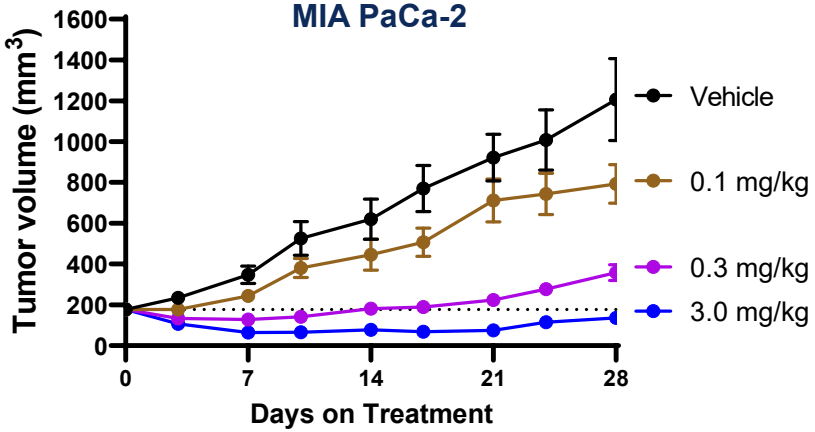
H358 Clonogenic Assay suggests GTPi may reduce development of resistance



BBO-8520 retains single-digit nM activity against reported GDP-inhibitor active-site mutants, including G12C/R68S, G12C/Y96D, G12C/G13D, G12C/Q61H, and G12C/A59G

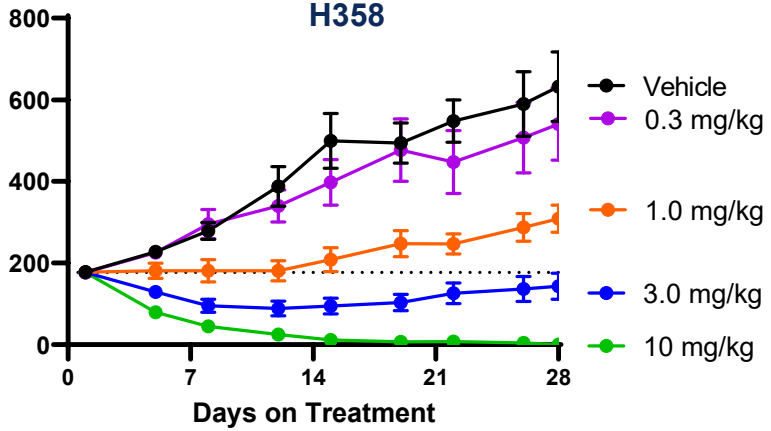
BBO-8520 exhibits strong efficacy in KRAS^{G12C} models

High Potency



ED_{50}	ED_{90}
0.13 mg/kg	0.40 mg/kg
EC_{50}	EC_{90}
4.6 nM	9.9 nM

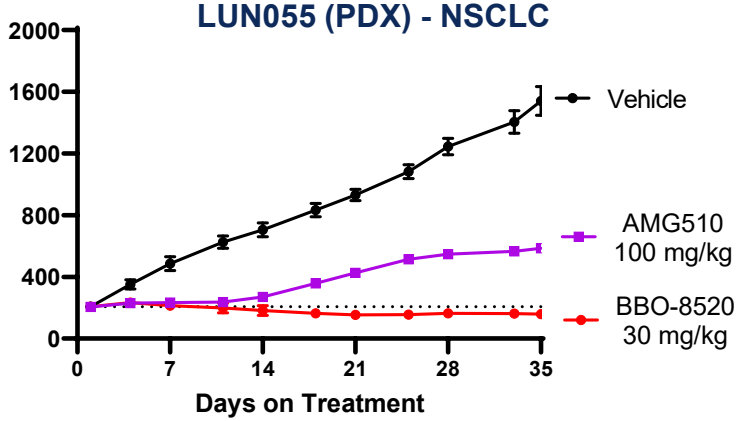
Deep Efficacy



10/10 CRs at 10 mg/kg

ED_{50}	ED_{90}
0.61 mg/kg	1.6 mg/kg
EC_{50}	EC_{90}
14 nM	34 nM

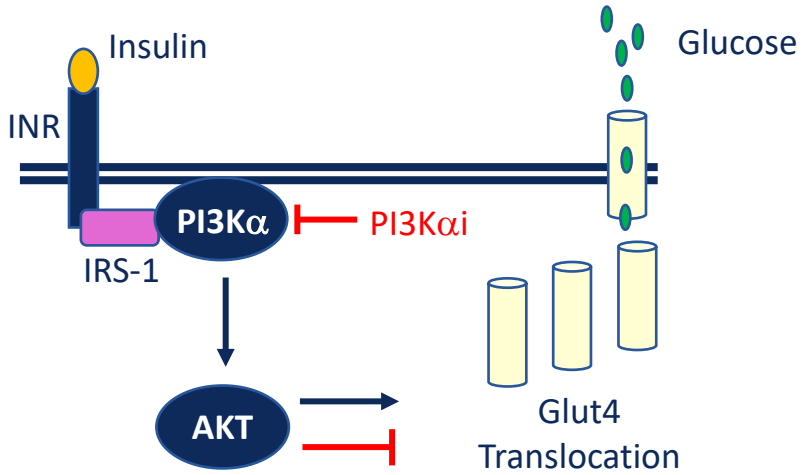
Differentiated



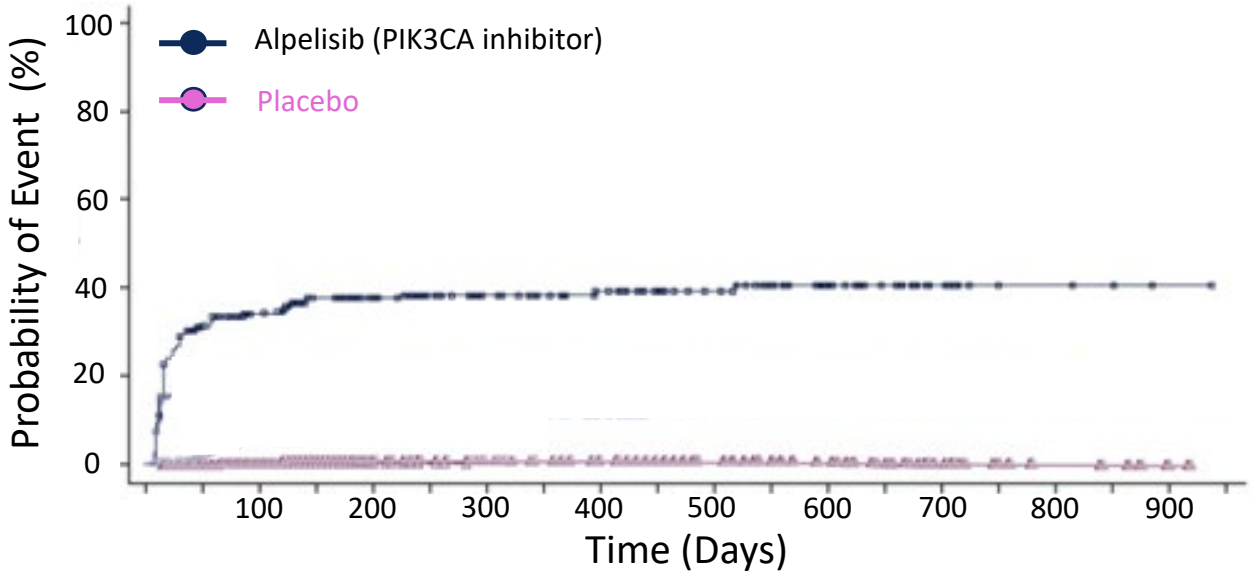
Group (n=10)	Day 35		
	TGI	Regression	FF AUC_{0-24} (ng*hr/ml)
BBO-8520	100%	23% (7/10)	59
AMG510	71%	- (1/10)	1563

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

Inhibiting the 2nd most mutated oncogene (PIK3CA) in human cancer has been limited by side effects of glucose metabolism



Solar-1 study – Hyperglycemia*



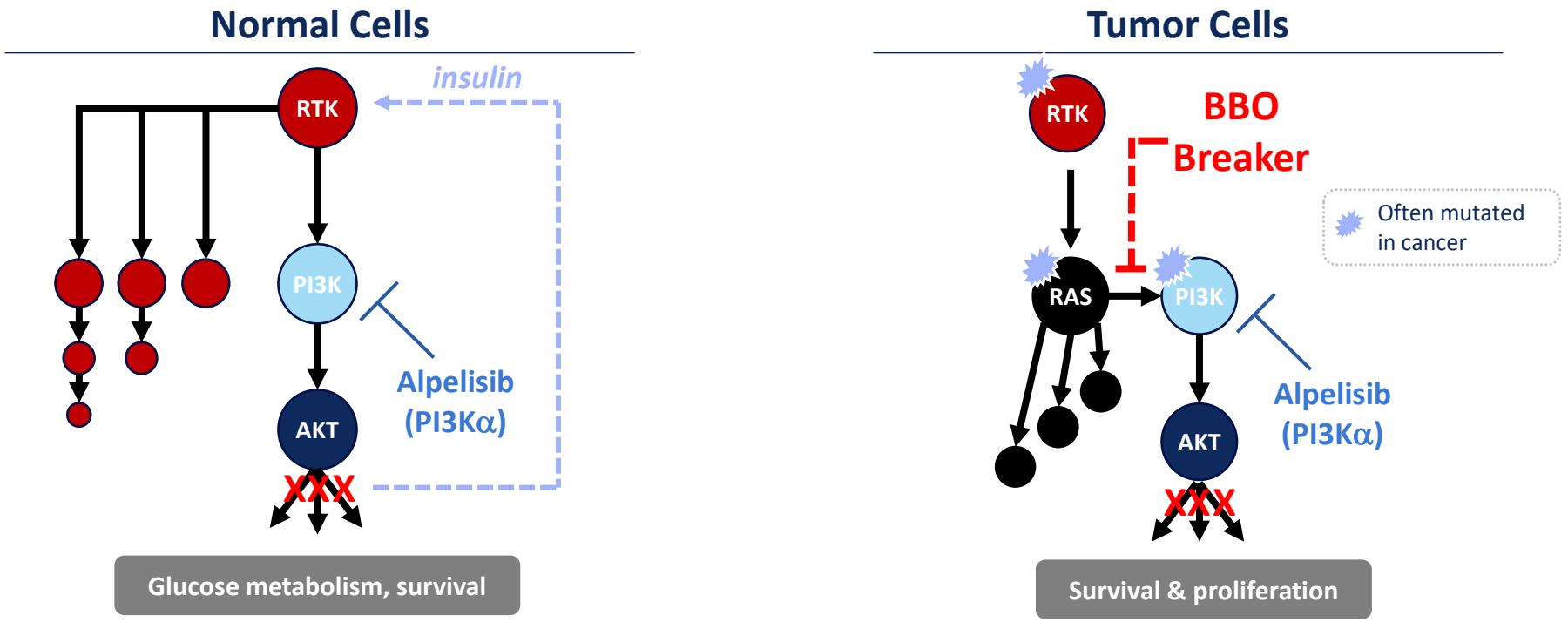
- High rate of dose modifications and interruptions (>30%) does not allow effective target coverage
- Adverse events are not conducive to combination studies
- Increased insulin secretion leads to increased pathway signaling and resistance

- Dose interruptions occurred in 66% versus 21% in placebo
- Dose reductions due to adverse events occurred in 55% versus 4.5% in placebo
- The most common adverse reactions were hyperglycemia (65%), diarrhea (58%), and rash (52%)

*Adapted from Rugo et al. Annals of Oncology 2020

Inhibiting PI3Kα activity by preventing its interaction with RAS provides a "tumor selective" mechanism that spares glucose metabolism

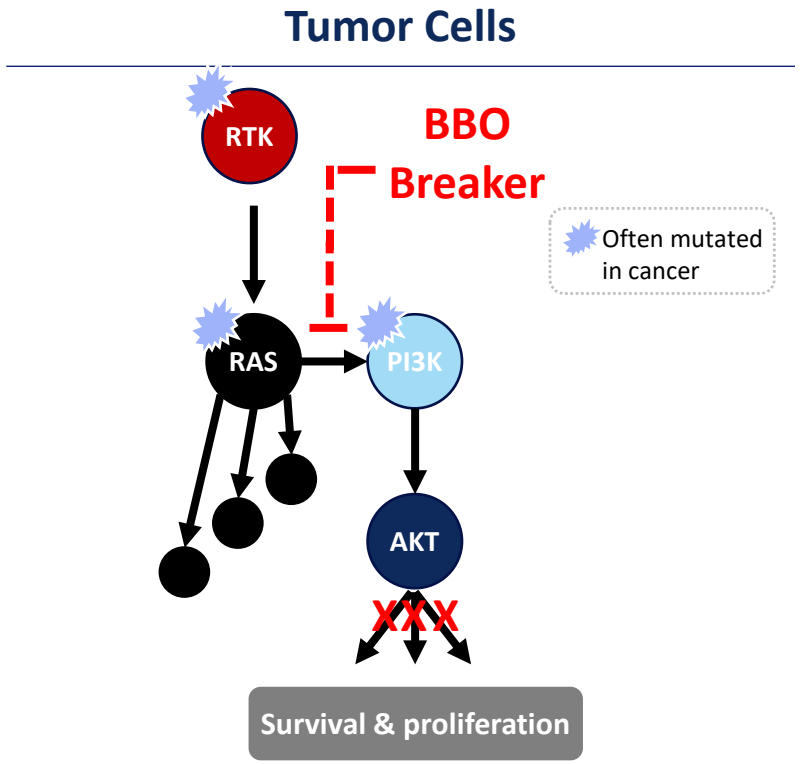
- PI3Kα kinase inhibitors ***block normal cell signaling*** resulting in ***dose-limiting hyperglycemia and insulin-driven resistance***
- Inhibiting PI3Kα:RAS PPI with a ***"PI3Kα Breaker"*** should avoid hyperglycemia and insulin-driven resistance by specifically targeting tumor cells and may provide multiple therapeutic opportunities
- Mice with mutations in the RBD that impair the PI3Kα:RAS interaction block oncogene-driven NSCLC tumor growth *in vivo* and have no effect on glucose metabolism*



PPI, protein-protein interactions; RBD, RAS-binding domain

*Gupta et al. Cell 2007; Castellano et al. Cancer Cell 2013; Murillo et al., Cell Reports 2018

BridgeBio has designed potent and selective PI3Kα:RAS breakers

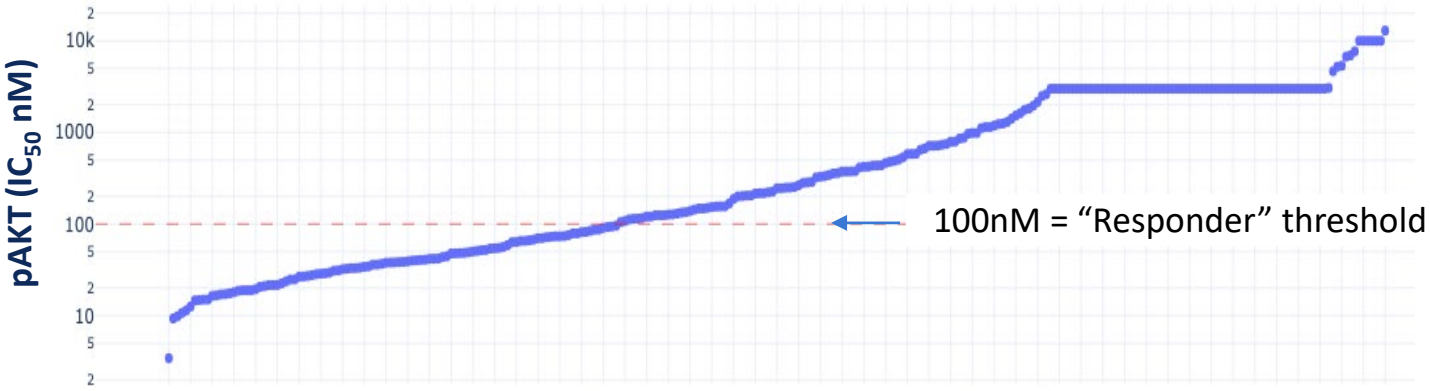


- PI3Kα:RAS breakers selectively bind to PI3Kα
- By ITC and SPR we observe
  - RAS binds to PI3Kα with ~10 μM affinity
  - Breakers binding to PI3Kα blocks its interaction with RAS
  - No binding affinity to RAS
- PI3Kα:RAS breakers do not affect kinase activity of PI3Kα

		BBO	Alpelisib
BT474	pAKT (IC_{50}, nM)	34	169
	Cell Viability (nM)	67	744

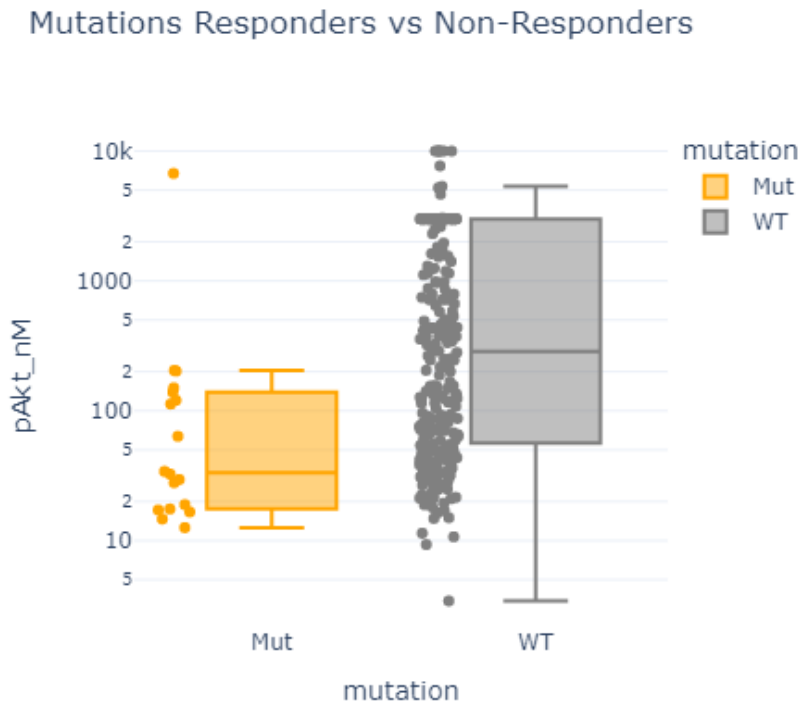
One third of all cancer cell lines depend on PI3Kα:RAS interaction for activation of AKT signaling

pAKT cell line screen



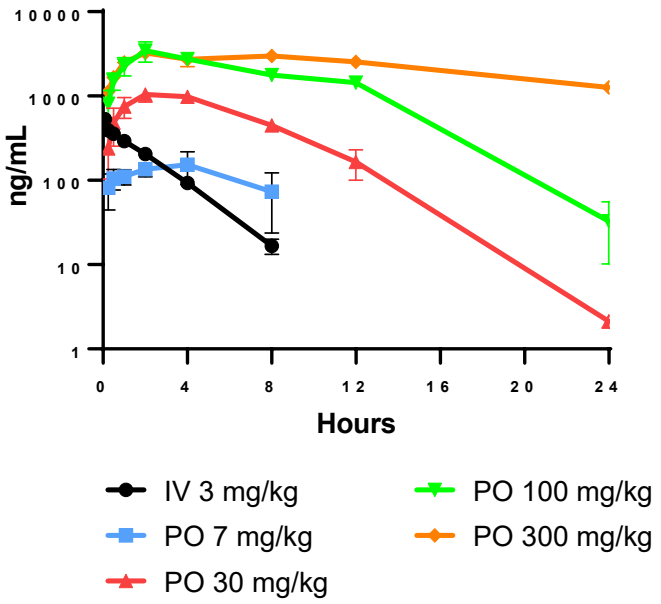
- 105/282 (37%) of screened cell lines are responders
- 29/50 (58%) of screened <u>KRAS^{G12X}</u> cell lines are responders

PIK3CA helical mutants are highly sensitive

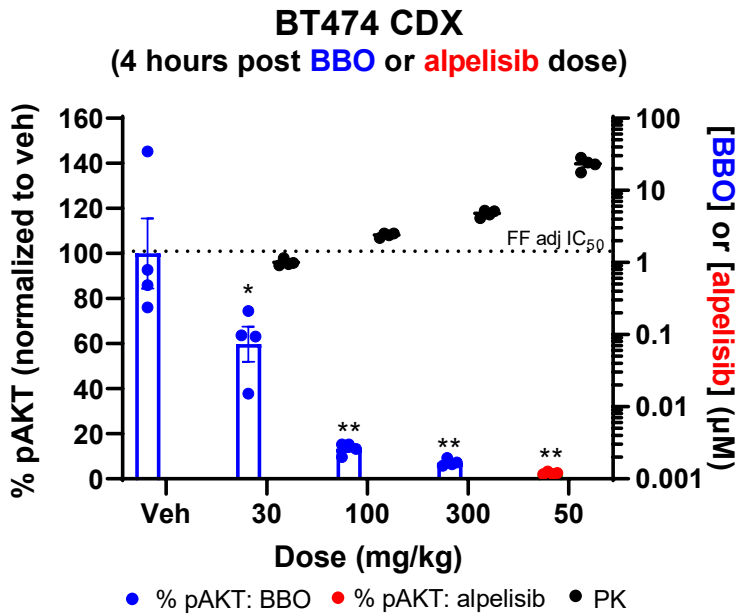


BBO is orally bioavailable and achieves near complete inhibition of signaling in tumors at 100 mg/kg without risk of hyperglycemia

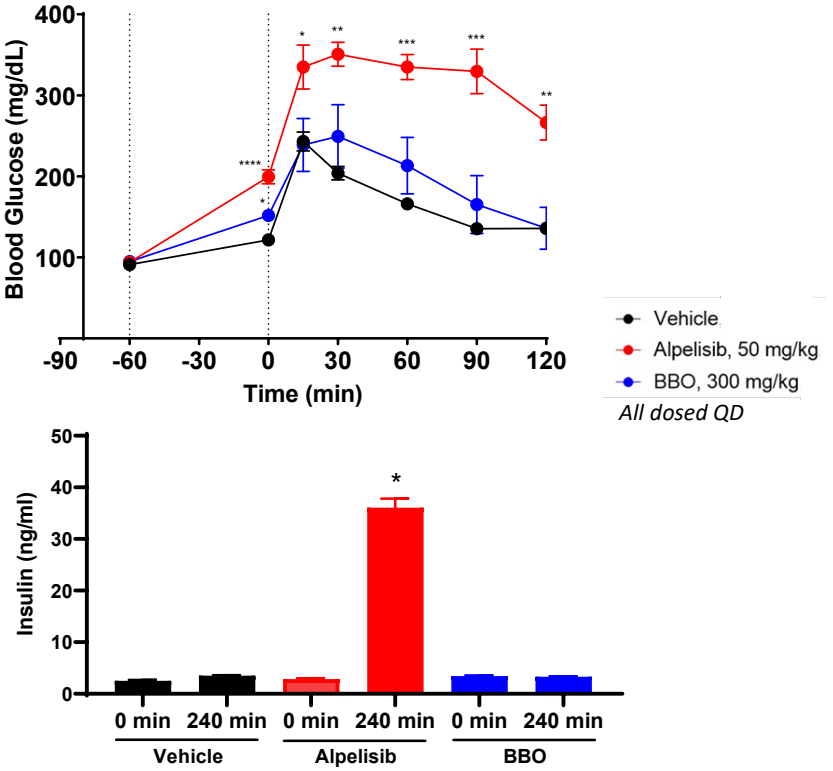
BBO Dose Ranging Mouse PK



BBO Dose Response PD[1]
Full target inhibition achieved at 100 mg/kg



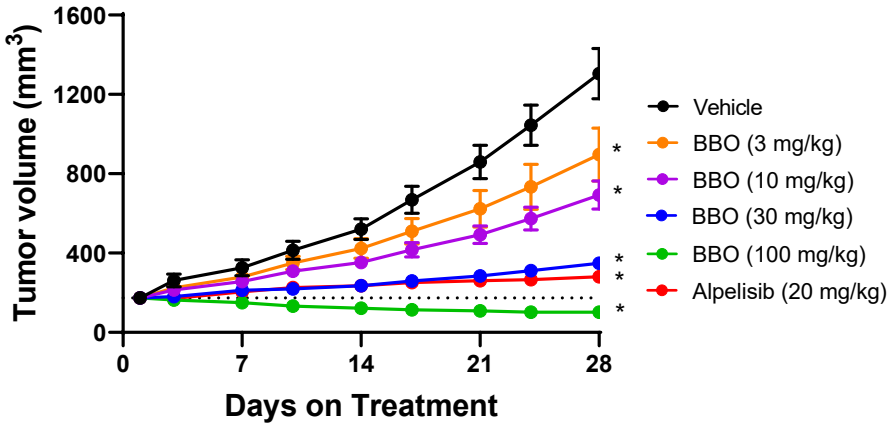
Unlike alpelisib, Breaker MOA does not affect glucose metabolism[2]



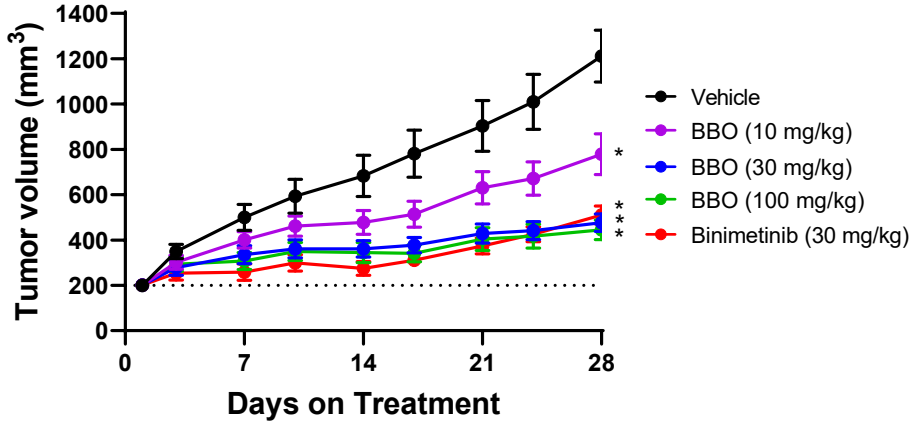
1. One-way ANOVA with Dunnett's test vs vehicle; *p<0.01, **p<0.0001
2. Top: One-way ANOVA with Dunnett's test vs vehicle, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, Bottom: One-way ANOVA with Tukey's multiple comparisons test vs all other groups : *p<0.0001

PI3Kα breakers are efficacious in xenograft models

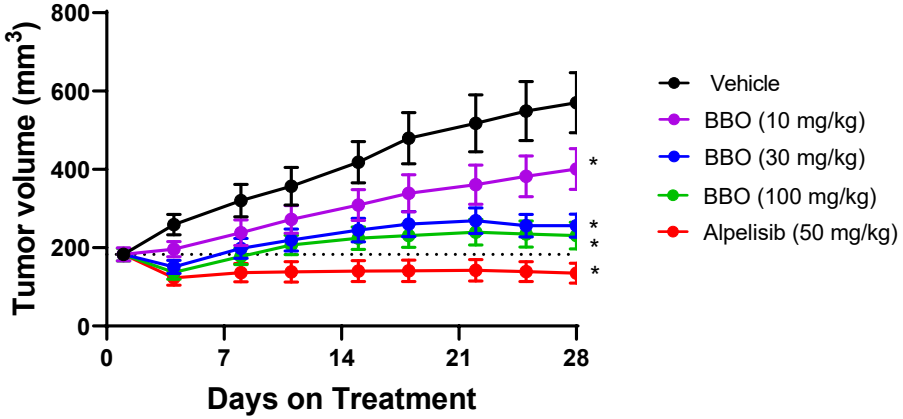
KYSE-410 CDX
- $KRAS^{G12C}$
- $HER2^{amp}$



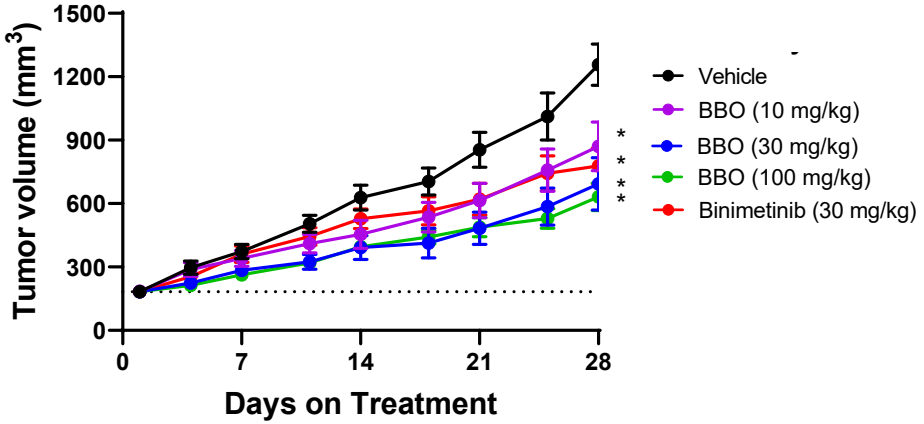
GP2d CDX
- $KRAS^{G12D}$
- $PIK3CA^{H1047L}$



SNU-601 CDX
- $KRAS^{G12D}$
- $PIK3CA^{E542K}$



SNU-16 CDX
- $KRAS^{G12D}$



Efficacy is observed in models with $KRAS^{G12X}$ mutations, with or without PIK3CA mutation

All groups dosed PO, QD, *p<0.0005 RM ANOVA vs vehicle

Conclusions

- **$KRAS^{G12C}$ GTP/GDP dual inhibitor**
  - Completely modifies both GTP (active) and GDP (inactive) forms of $KRAS^{G12C}$
  - Is exceptionally potent and selective with high kinact/Ki
  - Stabilizes GTP-bound $KRAS^{G12C}$ in state 1, which cannot bind effectors
  - Overcomes RTK drive
  - Exhibits strong efficacy in $KRAS^{G12C}$ models

- **PI3Kα:RAS Breaker**
  - Represents novel mechanism of action: PI3Kα breakers selectively block RAS activation of PI3Kα
  - Exhibits potent inhibition of AKT activation in $KRAS^{G12x}$, PIK3CA helical mutations and HER family driven populations
  - Exhibits potent efficacy in multiple models, without hyperglycemia

Team Effort

Pedro Beltran	Lijuan Fu	Kerstin Sinkevicius
Bin Wang	Foster Gonsalves	Carlos Stahlhut
Rui Xu	Jin Ju	James Stice
Afra Berger	Christina Liang	Kyle Sullivan
Olga Botvinnik	Ken Lin	Keshi Wang
Tiana Carroll	Shane McGann	Paul Wehn
Howard Chang	Sadaf Mehdizadeh	James Winter
Tony Chen	Mike Monteith	Lauren Wood
Nathan Collett	Rick Panicucci	Peter Xu
Sofia Donovan	Erin Riegler	April Yang
Ferdie Evangelista	Stephanie Santiago	Maggie Yandell-Zhao
Cindy Feng	Saman Setoodeh	Cathy Zhang
Siyu Feng	Jin Shu	Zuhui Zhang
Bert Frederich	Devansh Singh	

Frank McCormick	William Gillette
Dwight Nissley	Erik Larsen
Anna Maciag	Tao Liao
Dhirendra Simanshu	Roger Ma
Patrick Alexander	Dana Rabara
Maria Abreu Blanco	Megan Rigby
Bill Bocik	Alok Sharma
Christopher Brassard	Swapnil Singh
Allison Champagne	Brian Smith
Albert Chan	Thomas Sova
Daniel Czyzyk	Andy Stephen
Caroline DeHart	Monalisa Swain
John-Paul Denson	David Turner
Sathiya Dharmaiah	Wupeng Yan
Robert D'Ippolito	Jayasudhan Yerabolu
Marcin Dyba	Protein Expression Laboratory
Dominic Esposito	

Felice Lightstone
Yue Yang
Paola Bisignano
Jun Pei
Sergio Wong