ENA 2024
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36th Symposium

BBO-10203, an orally bioavailable small molecule that disrupts the RAS:PI3Kα interaction leading to pAKT and tumor growth inhibition in models of breast, lung and colorectal cancer

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BBOT

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NIH NATIONAL CANCER INSTITUTE

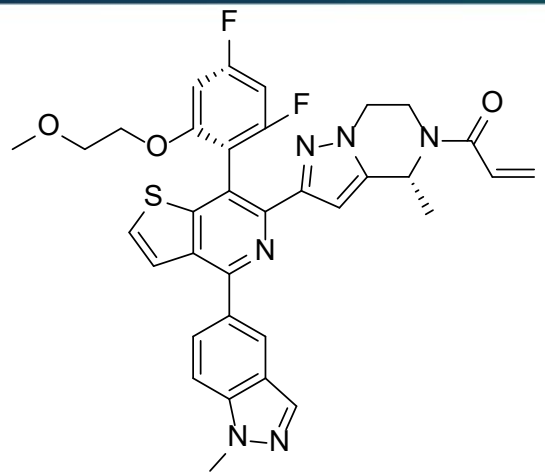
AACR American Association for Cancer Research

Conflict of Interests

Disclosures:

Current employee and stockholder of BridgeBio Oncology Therapeutics (BBOT)

BBO-10203: a first-in-class Breaker of the RAS:PI3Kα interaction

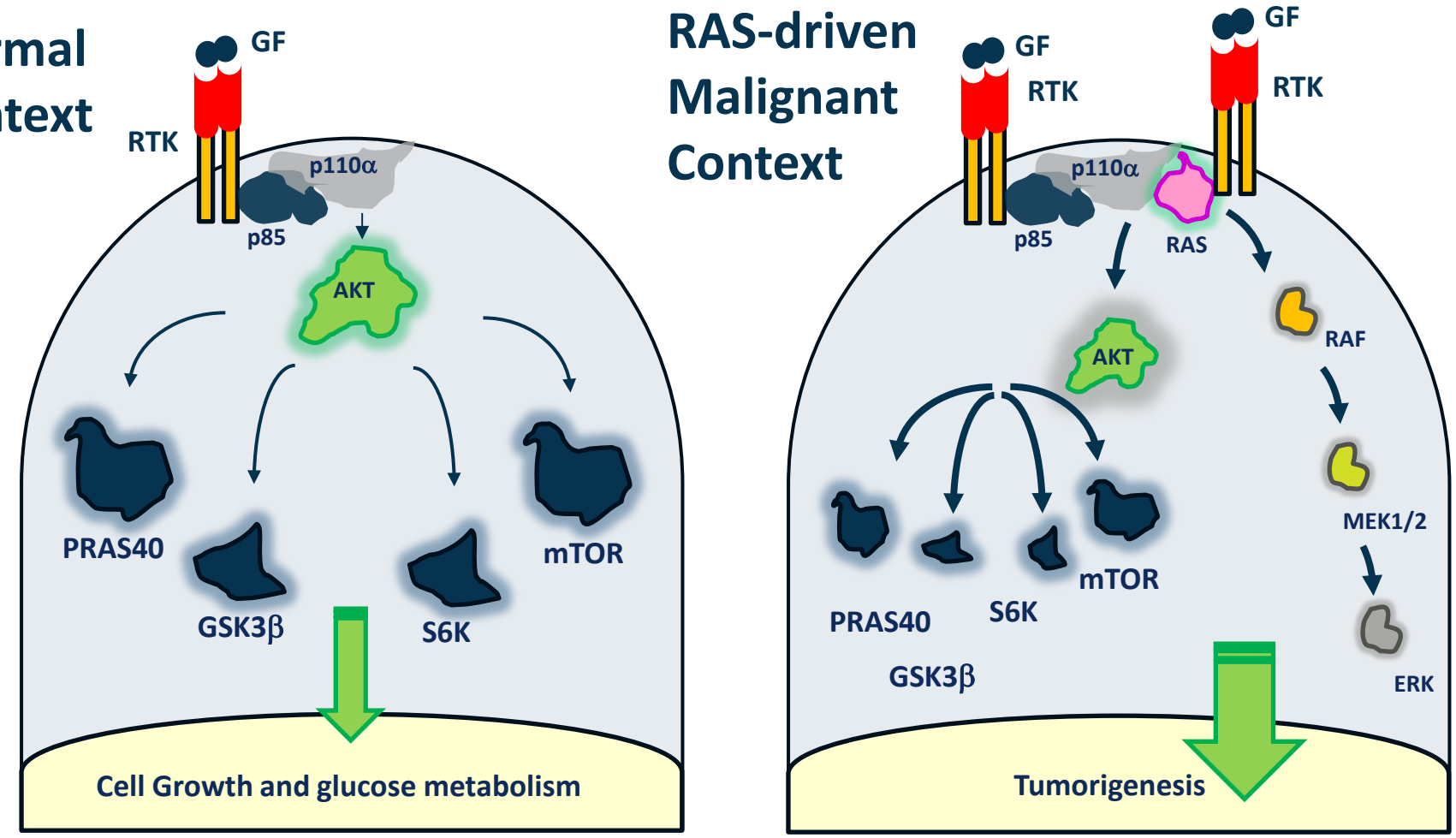


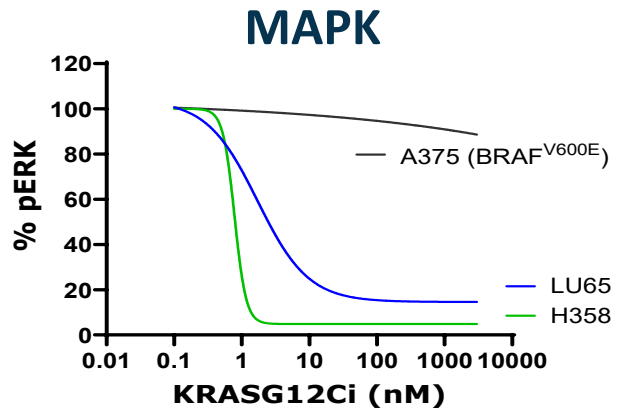
Assay	BBO-10203
MALDI-TOF	>90% at 15 min
TE PI3Kα RBD (IC_{50})	3 nM
pAKT (IC_{50})	4 nM
Kinact/K_I	7,100 $M^{-1}S^{-1}$
$ED_{50/90}$	2.5 / 4.0 mg/kg
Regressions	30 mg/kg

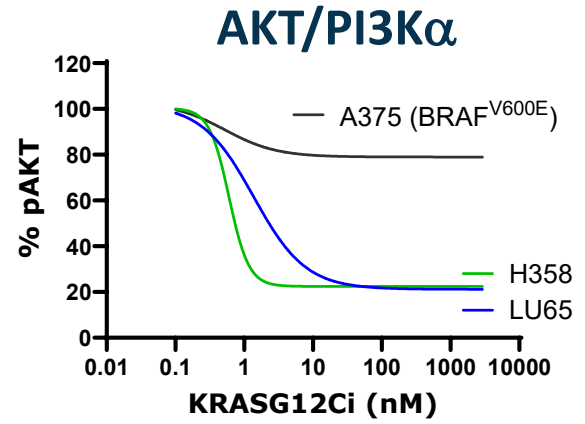
TE: Target engagement (PI3Kα RBD)
Cell and in vivo data: KYSE-410 (HER2/$KRAS^{G12C}$)

- Binds specifically to the RBD of PI3Kα
- Does not inhibit the kinase activity of PI3Kα
- Forms covalent bond with C242
- Blocks binding of K-, H-, and N-RAS to PI3Kα
- Agnostic to mutational status of either partner
- Inhibits pAKT with single digit nM potency
- No hyperglycemia *in vivo* (oGTT in C57BL/6 male mice)
- Tumor regressions @ 30 mg/kg QD
- Phase 1 BREAKER-101 (NCT06625775) trial is now open

Synchronized co-activation of MAPK and AKT pathways by RAS is important to maintain a productive malignant phenotype



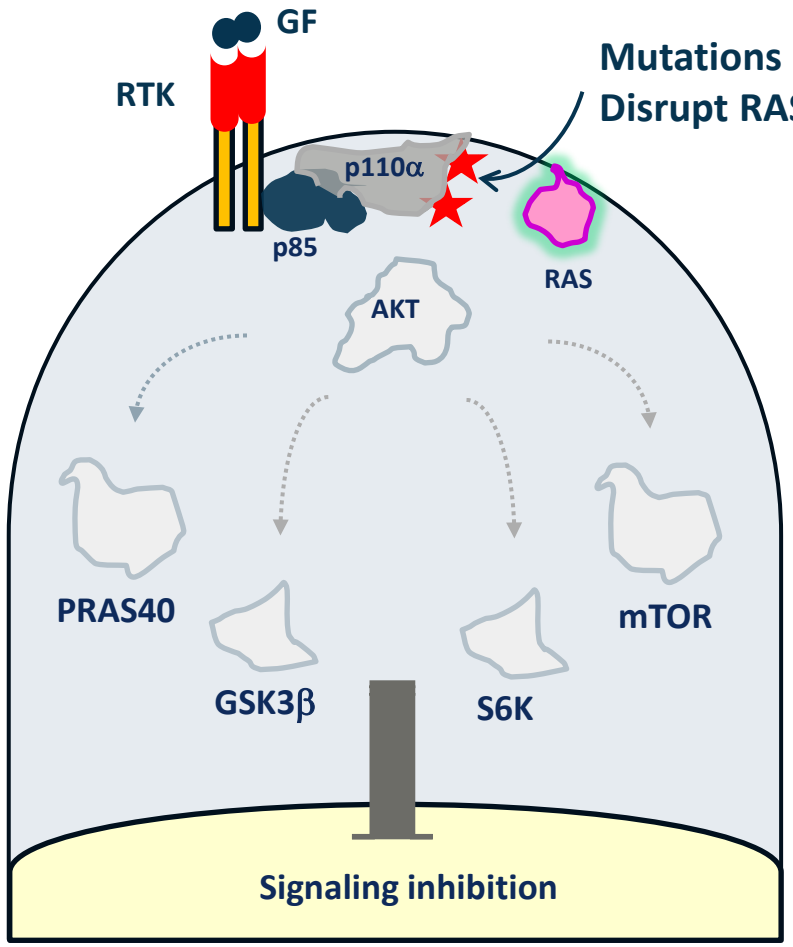




GF: Growth Factor, RTK: Receptor Tyrosine Kinase, AKT: Protein Kinase B, RAS: Rat Sarcoma Virus, PI3Ka: Phosphoinositide 3-kinase alpha

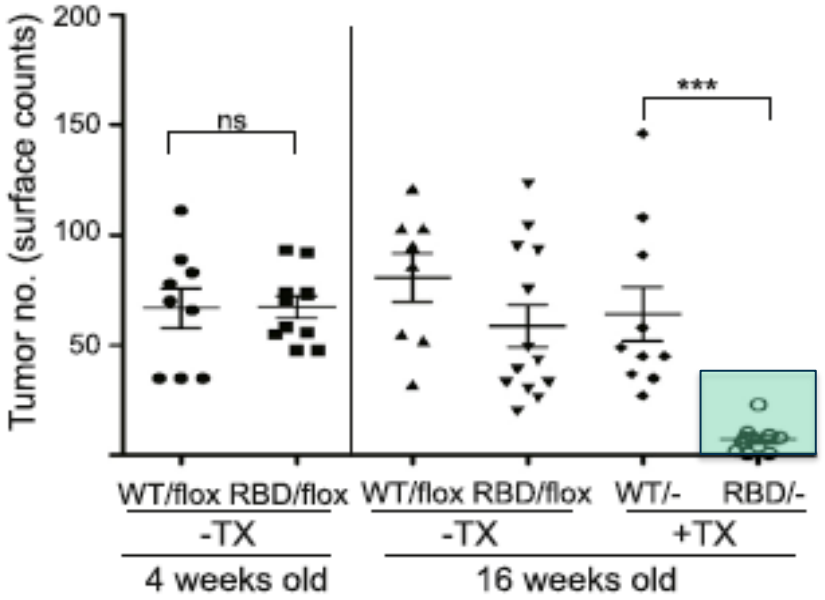
Genetic disruption of the RAS:PI3Kα interaction inhibits KRAS^{G12D} – driven tumor growth without hyperglycemia

Breaker MOA



GF: Growth Factor, RTK: Receptor Tyrosine Kinase, AKT: Protein Kinase B, RAS: Rat Sarcoma Virus, PI3Kα: Phosphoinositide 3-kinase alpha

T208D and K227A mutations in the RAS-Binding Domain (RBD) of PI3Kα slow KRAS^{G12D}-driven growth

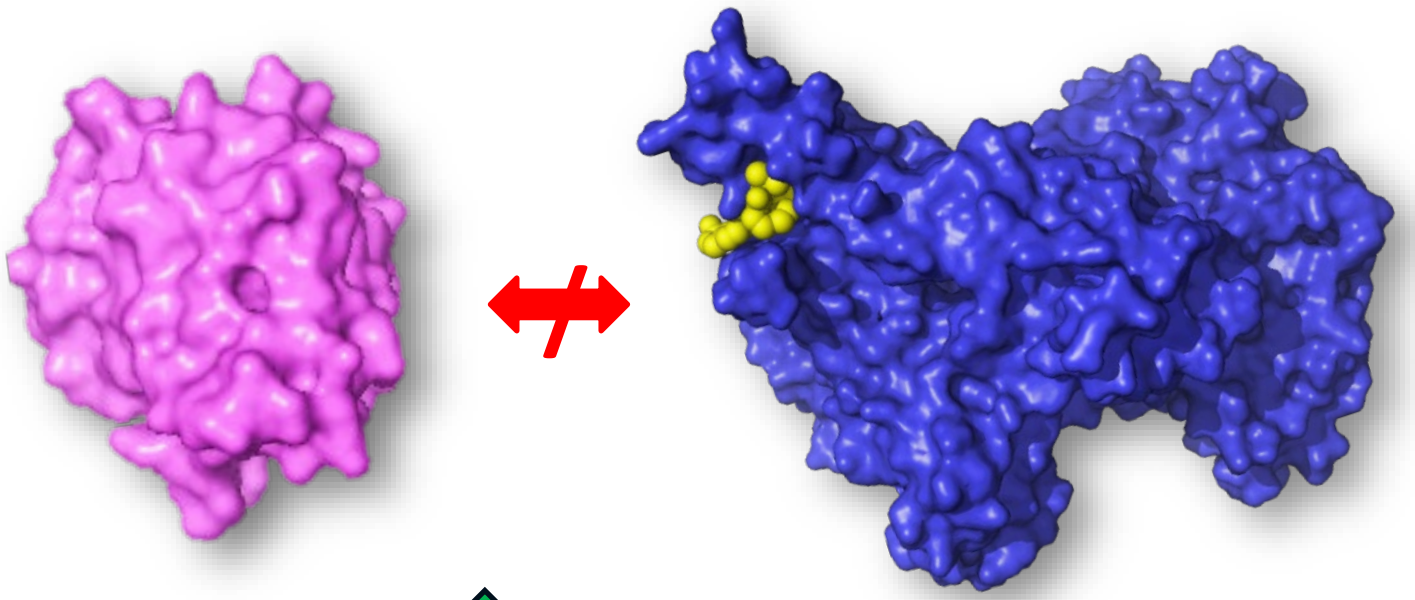


Requirement for Interaction of PI3-Kinase p110α with RAS in Lung Tumor Maintenance

Esther Castellano,[1,7] Clare Sheridan,[1,7] May Zaw Thin,[2] Emma Nye,[3] Bradley Spencer-Dene,[3] Markus E. Diefenbacher,[4] Christopher Moore,[1] Madhu S. Kumar,[1] Miguel M. Murillo,[1,6] Eva Grönroos,[5] Francois Lassailly,[2] Gordon Stamp,[3] and Julian Downward[1,6,*]

Hypothesis: a small molecule that binds the RBD domain of PI3Kα could mimic the effect of the RBD mutations

RAS



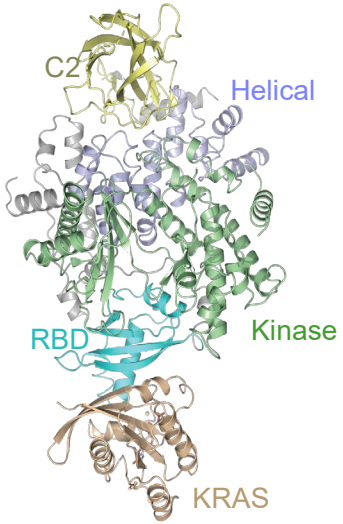
PI3Kα

Efficacy

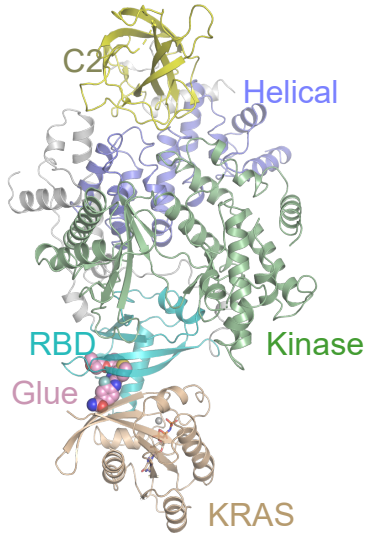
No effect on Glucose Metabolism

The pocket occupied by the RAS:PI3Kα glue inspired us to use structural information to design a Breaker

Model of KRAS-p110α complex

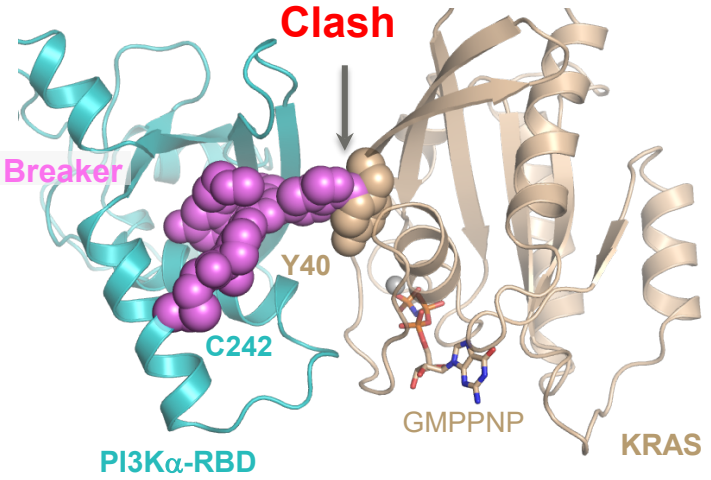


KRAS-p110α complex with glue

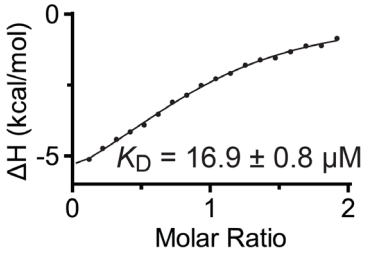


SBDD

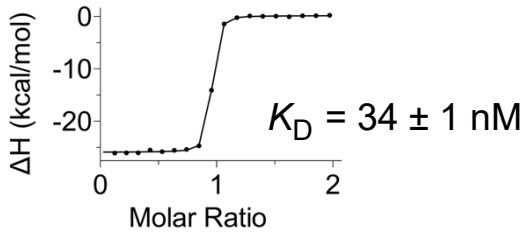
Model showing the steric clash between BBO-10203 (breaker) and the Y40 residue of KRAS



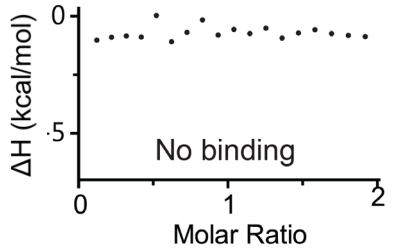
PI3Kα + KRAS



PI3Kα + KRAS + Glue



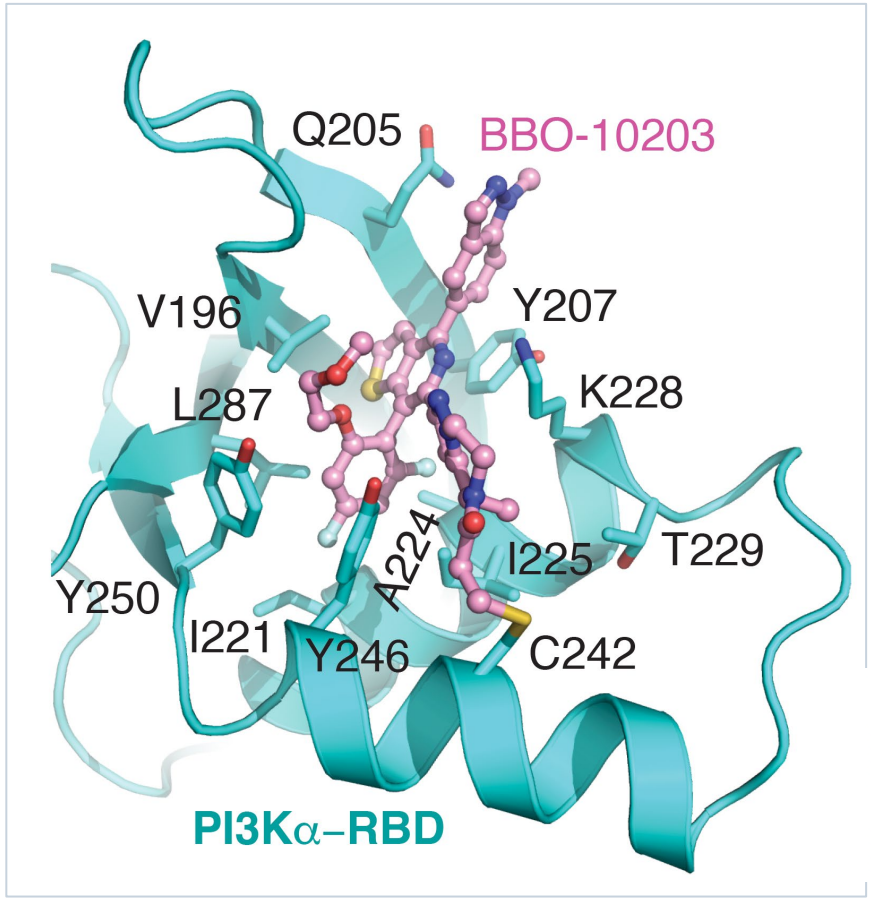
PI3Kα + KRAS + Breaker



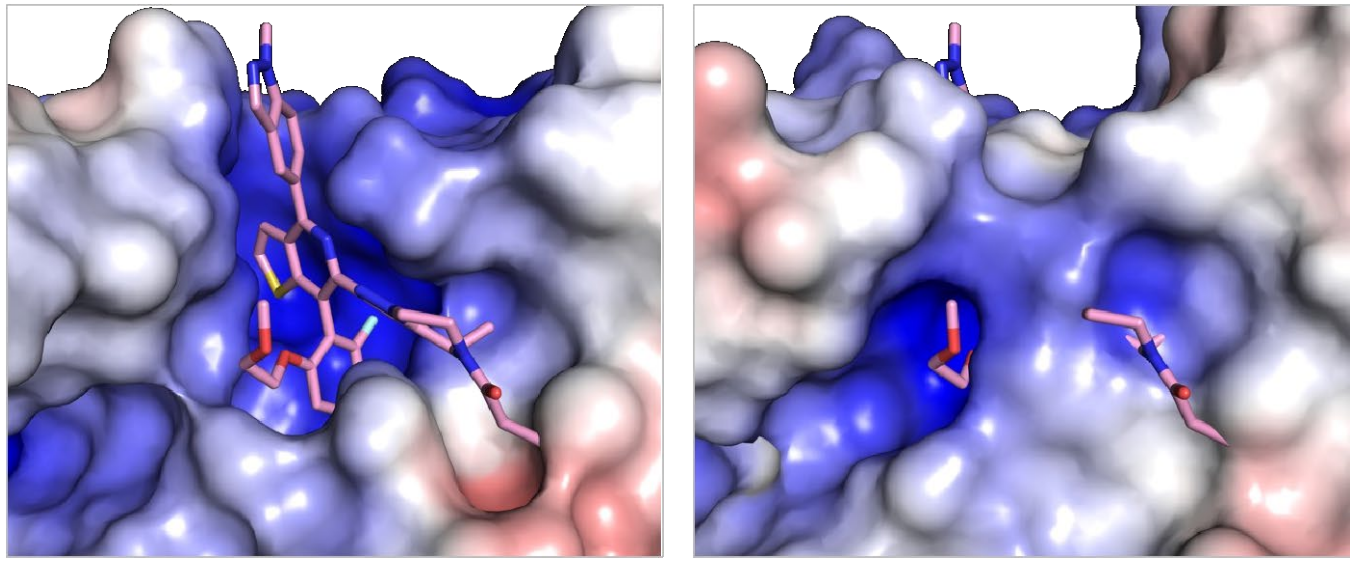
Tsuji et. Al. Bioorganic & Medicinal Chemistry Letters 29 (2019) 1785-1790

BBO-10203 covalently and selectively binds to PI3Kα RBD

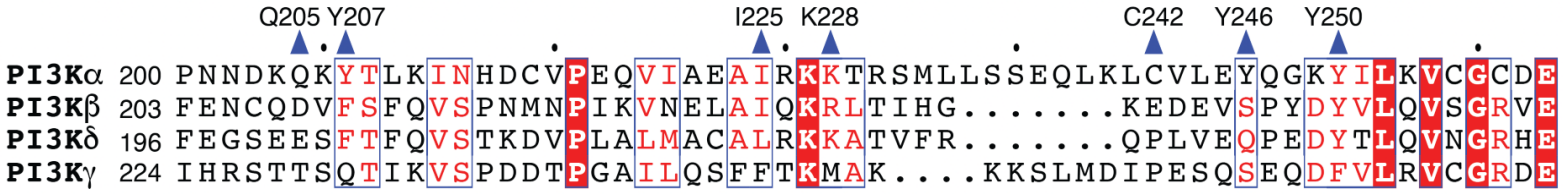
Crystal structure of PI3Kα-RBD covalently labeled with BBO-10203



Electrostatic surface representation showing the binding pocket in PI3Kα where BBO-10203 binds (left) and Apo-protein (right)

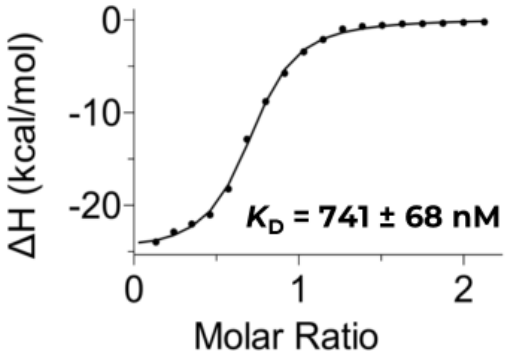


Sequence alignment of RBD of all four PI3K isoforms showing deletion and lack of conservation of key residues

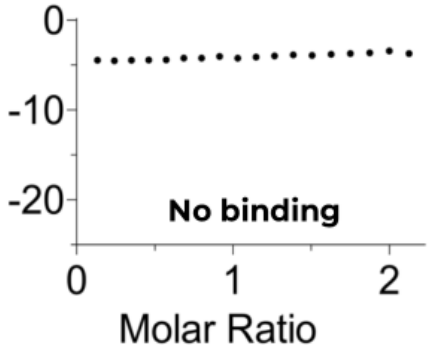


BBO-10203 binds specifically to the alpha isoform of PI3K and breaks its interaction with K-, H- and N-RAS

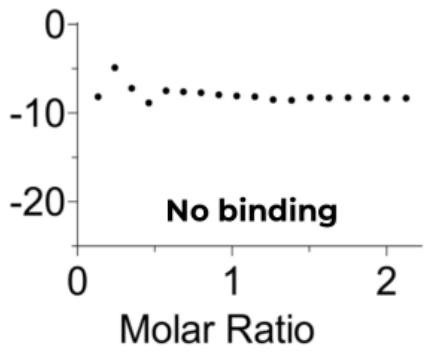
PI3Kα and BBO-10203



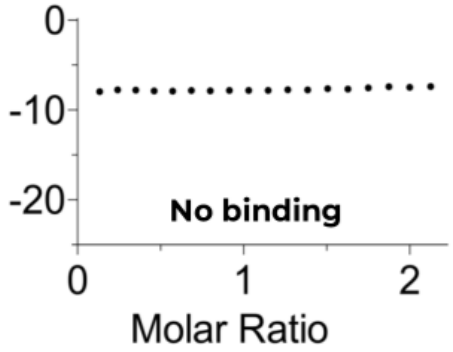
PI3Kβ and BBO-10203



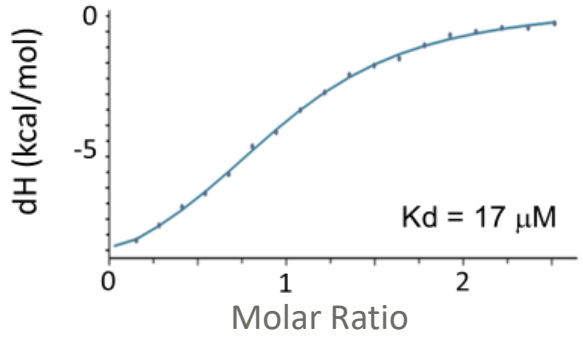
PI3Kδ and BBO-10203



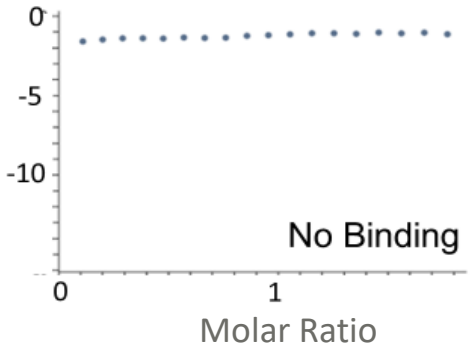
PI3Kγ and BBO-10203



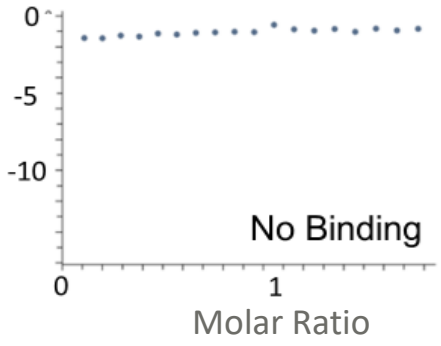
KRAS + PI3Kα (no compound)



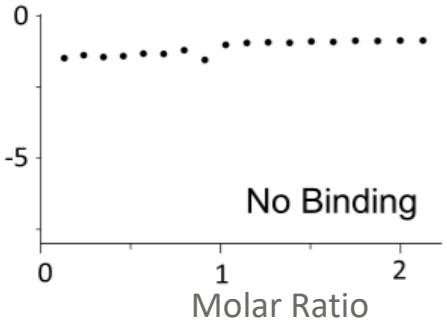
KRAS + Breaker-tethered PI3Kα



NRAS + Breaker-tethered PI3Kα

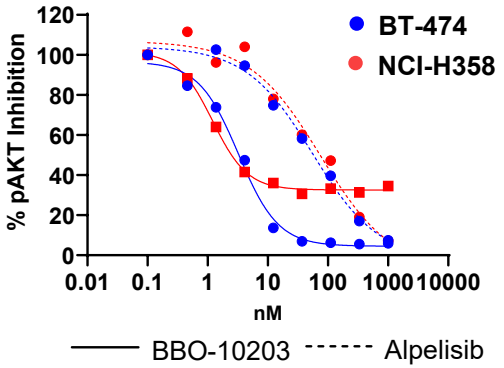


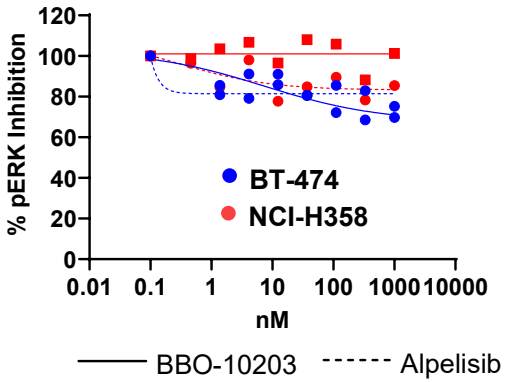
HRAS + Breaker-tethered PI3Kα



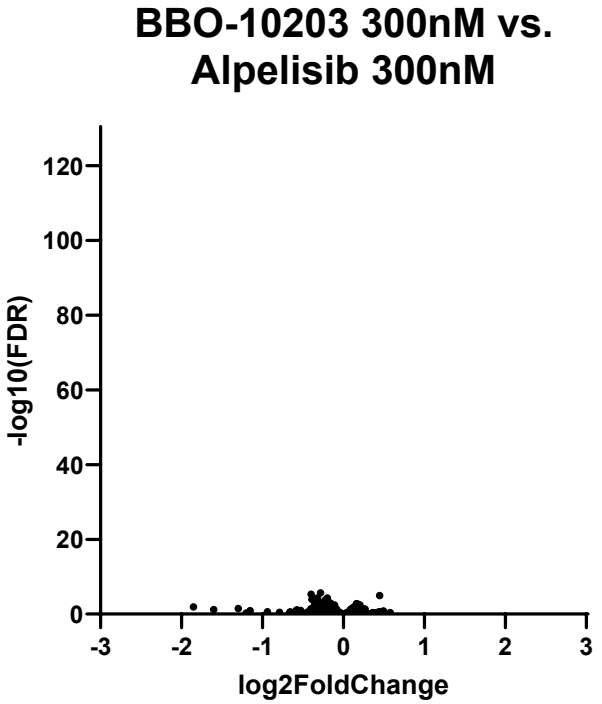
Cell potency and selectivity

AKT/ERK Signaling



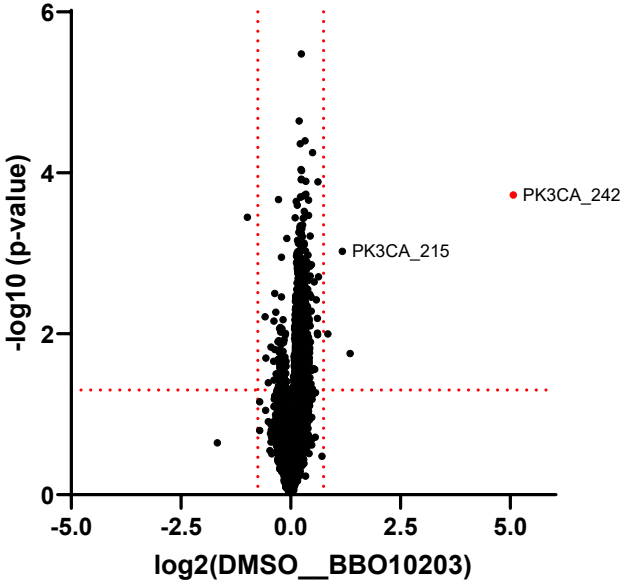


Gene Regulation



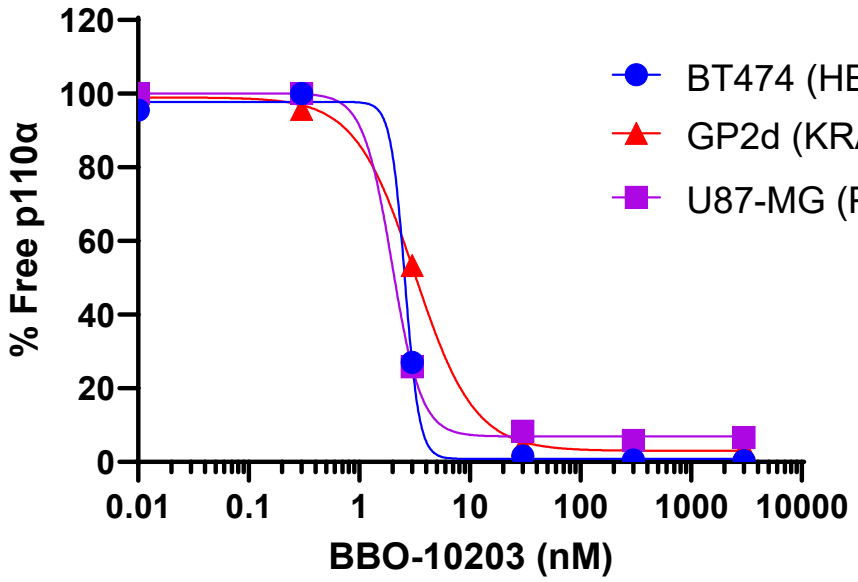
- No genes are significantly differentially regulated between BBO-10203 and alpelisib

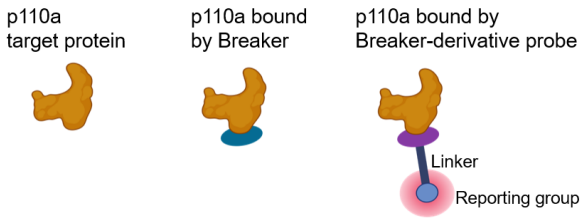
Global Cysteine Proteomics



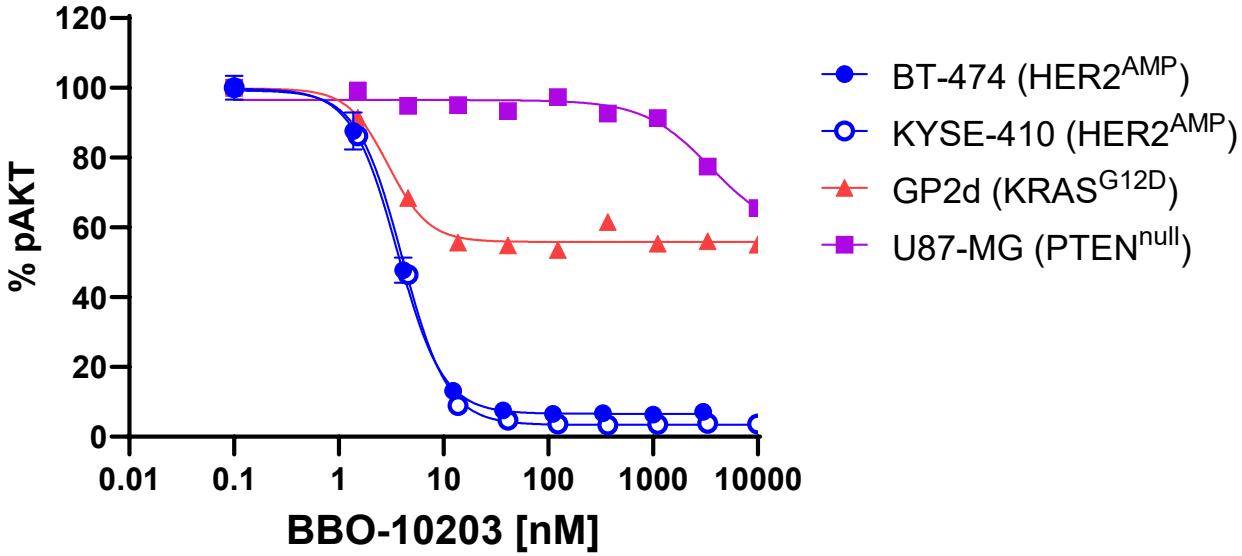
Differences in cellular pAKT inhibition are driven by RAS' ability to activate AKT

Target Engagement



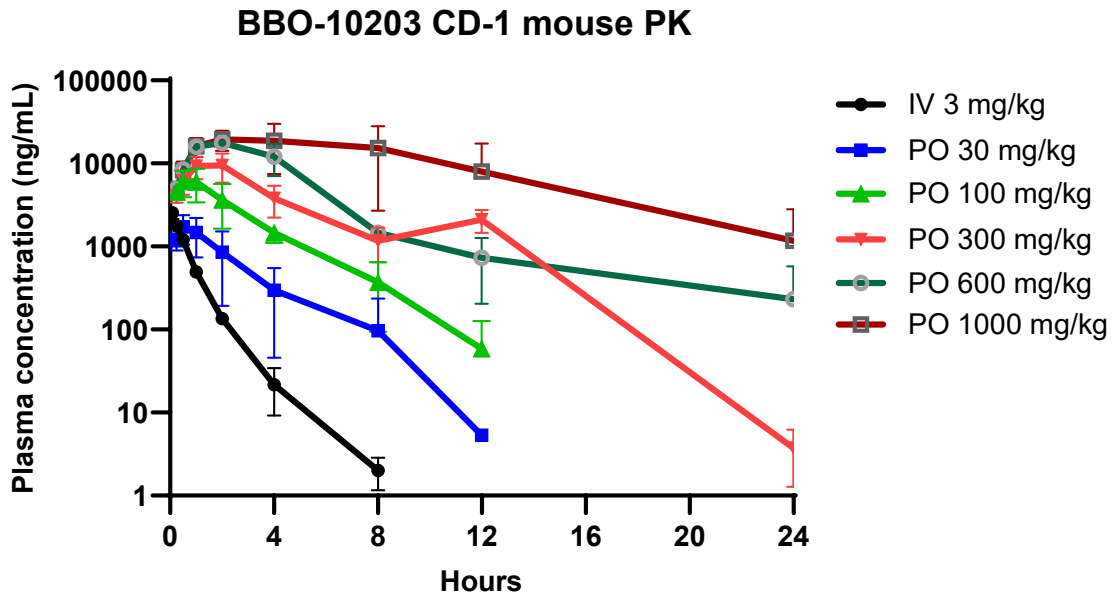


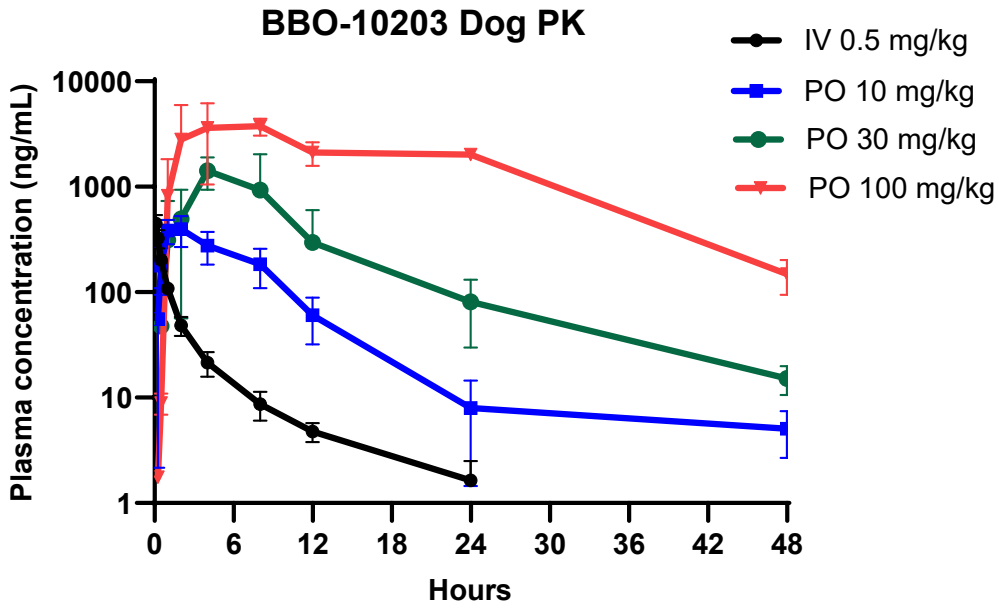
pAKT



Downstream signaling inhibition is driven by biology

BBO-10203 preclinical PK properties – good oral exposure

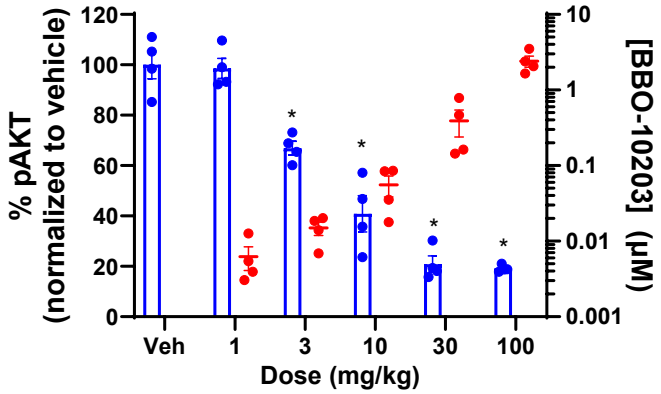




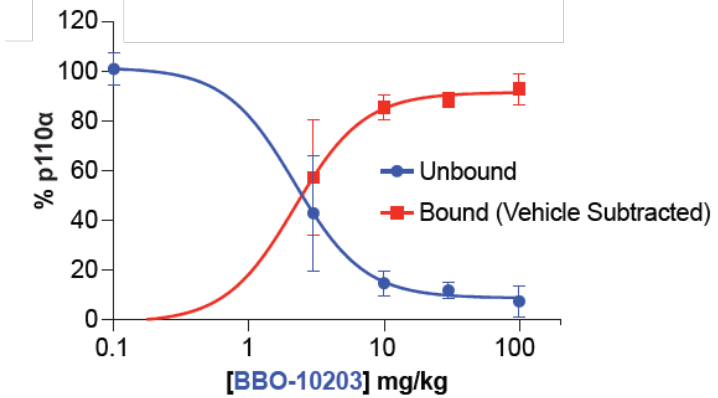
Species	Parameters	BBO-10203
Mouse	IV Cl (mL/min/kg) / $t_{1/2}$ (hr) / V_{ss} (L/kg)	26 / 0.86 / 1.2
	%F @ 30 / 100 / 300 / 600 / 1000 mg/kg PO	24 / 31 / 30 / 25 / 38
Dog	IV Cl (mL/min/kg) / $t_{1/2}$ (hr) / V_{ss} (L/kg)	16 / 6.9 / 3.7
	%F @ 10 / 30 / 100 mg/kg PO	63 / 63 / 82

BBO-10203 drives strong target engagement and efficacy in the KYSE-410 ($HER2^{amp}$/$KRAS^{G12C}$) CDX model

KYSE-410 PD Assay (8 hrs)

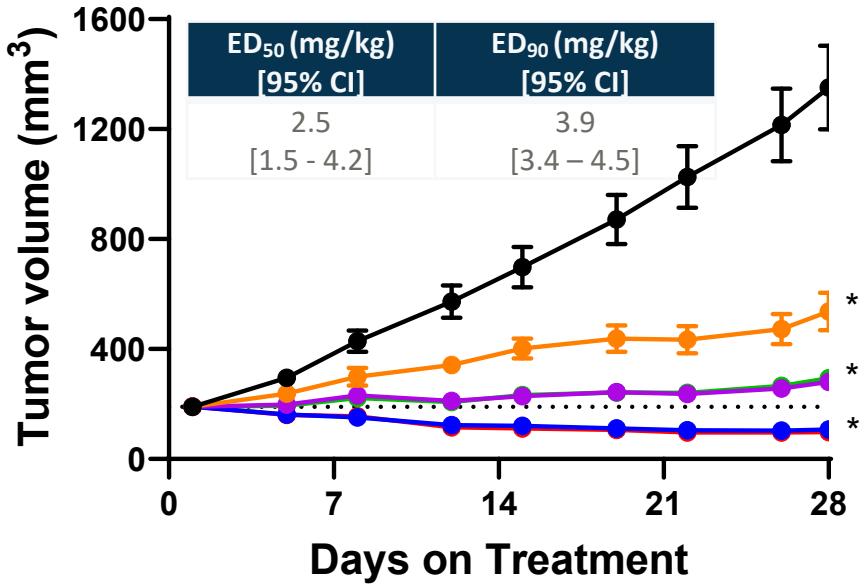


Tumor target engagement



IC_{50}	(mg/kg)
BBO-10203	1.3

KYSE-410 Efficacy



ED_{50} (mg/kg) [95% CI]	ED_{90} (mg/kg) [95% CI]
2.5 [1.5 - 4.2]	3.9 [3.4 – 4.5]

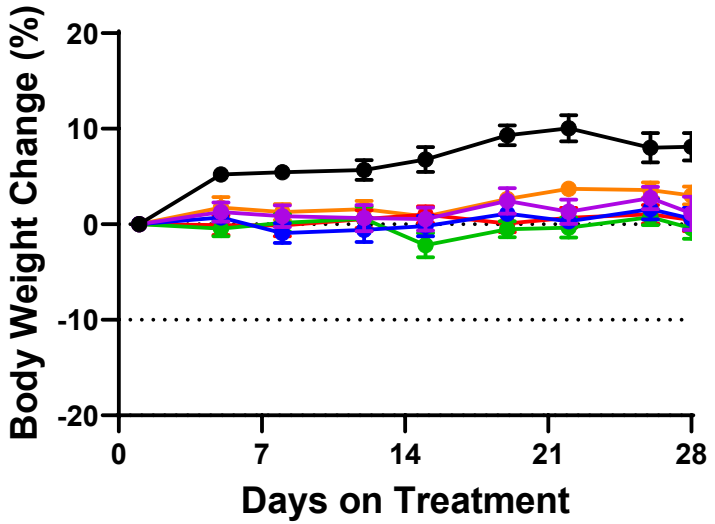
All treatment groups *p<0.0001 compared to vehicle group

- Vehicle (QD, po)
- 3 mg/kg
- 10 mg/kg
- 30 mg/kg
- 5 mg/kg, BID
- 15 mg/kg, BID

BBO-10203 dosed orally

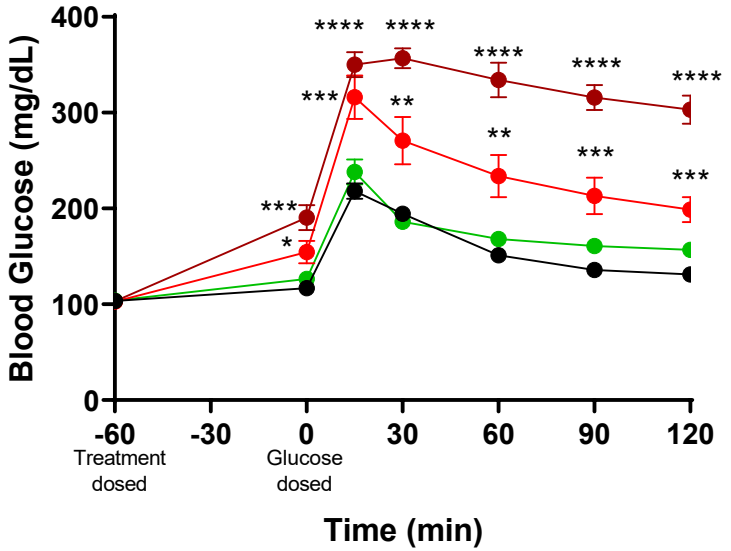
BBO-10203 does not cause hyperglycemia and is well tolerated after 28-day repeated dosing

Body Weight % Change



- Vehicle (QD, po)
- BBO-10203 (3 mg/kg, QD)
- BBO-10203 (10 mg/kg QD)
- BBO-10203 (30 mg/kg, QD)
- BBO-10203 (5 mg/kg, BID)
- BBO-10203 (15 mg/kg, BID)

oGTT Results: Blood Glucose Levels



- Vehicle (QDx1)
- Alpelisib (50 mg/kg, QDx1)
- Alpelisib (20 mg/kg, QDx1)
- BBO-10203 (100 mg/kg, QDx1)

One-way ANOVA with Dunnett's multiple comparisons test vs vehicle: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

BBO-10203 dosed orally. oGTT: oral glucose tolerance test

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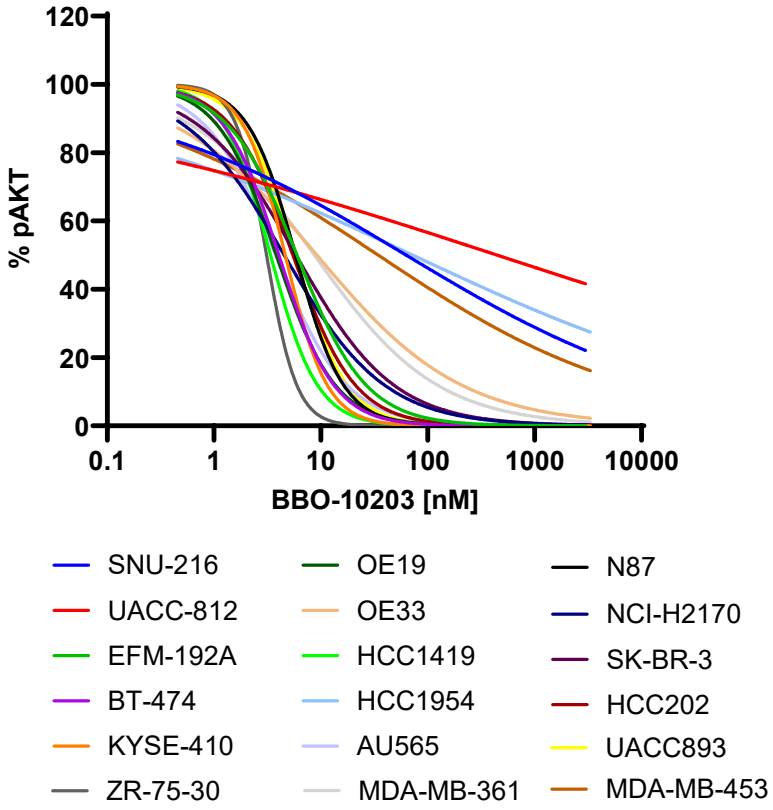
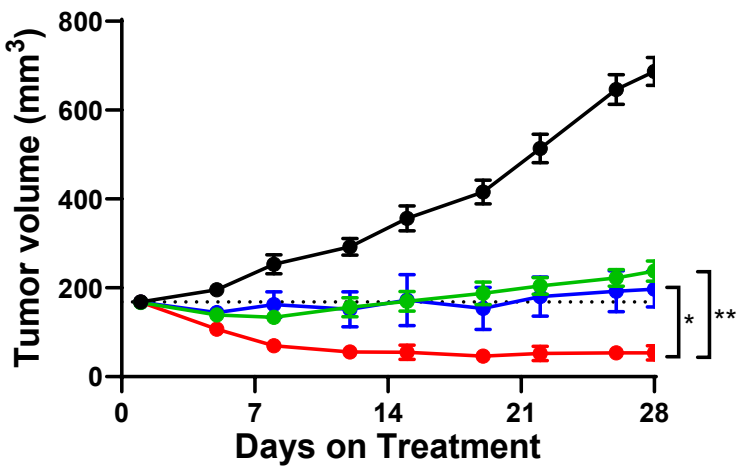
BBO-10203 inhibits pAKT leading to monotherapy and combination benefit with trastuzumab in the HER2+ BC models

HER2amp Cell Lines

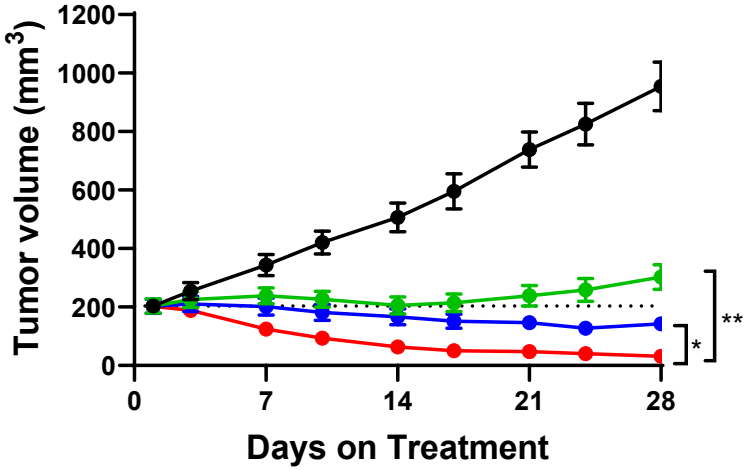


BT-474 (HER2amp / PIK3CAK111N)



- Vehicle (QD, po)
- BBO-10203 (100 mg/kg, QD, po)
- Trastuzumab (20 mg/kg, Q7D, ip)
- BBO-10203 + Trastuzumab

MDA-MB-453 (HER2++ / PIK3CAH1047R)



- Vehicle (QD, po)
- BBO-10203 (30 mg/kg, QD, po)
- Trastuzumab (4 mg/kg, Q7Dx4, ip)
- BBO-10203 + Trastuzumab

RM ANOVA, *p<0.05, **p<0.001 compared to monotherapy group

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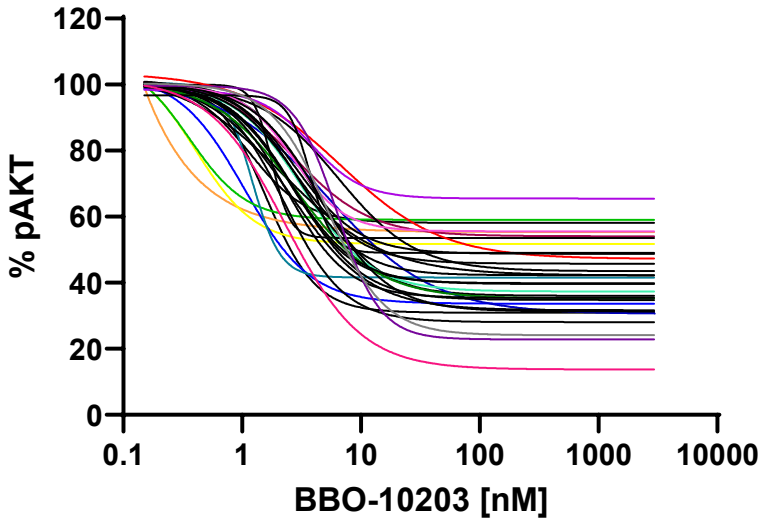
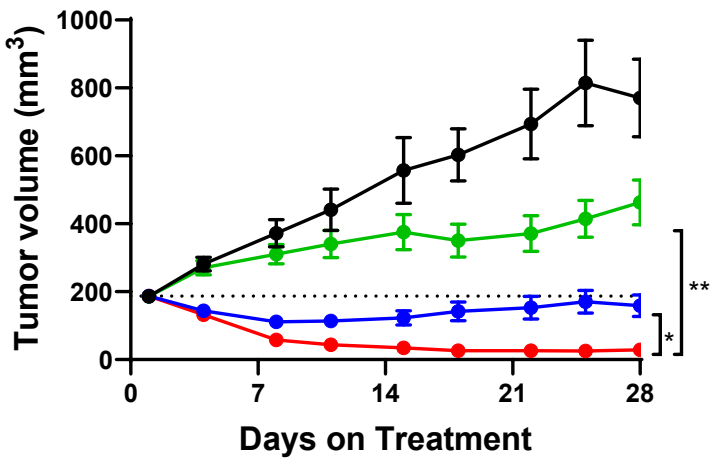
BBO-10203 inhibits pAKT leading to monotherapy and combination benefit with KRASi in KRAS mutant tumors

KRAS mutant cell Lines



SW1463
H23
LU99
H358
CAL-62
SK-CO-1
DV-90
LU65
LS 123
SW-756
Capan-1
NCI-H460
Panc 03.27
T84
143B

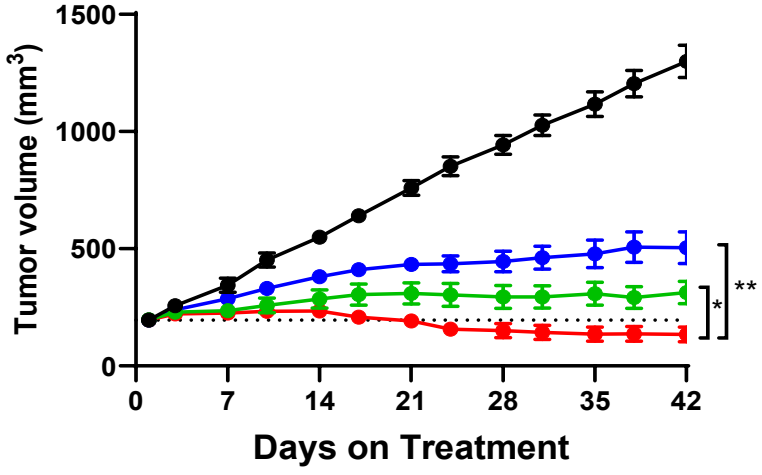
H358 ($KRAS^{G12C}$)



*p<0.01, **p<0.0001 compared to monotherapy group

Vehicle (QD, po)
BBO-10203 (100 mg/kg)
BBO-8520 (3 mg/kg)
BBO-10203 + BBO-8520

T84 ($KRAS^{G13D}$, $PIK3CA^{E542K}$)



*p<0.05, **p<0.0001 compared to monotherapy group

Vehicle (QD, po)
BBO-10203 (30 mg/kg)
5-FU (50 mg/kg, Q7D, ip)
BBO-10203 + 5-FU

BBO-8520: $KRAS^{G12C}$ ON/OFF inhibitor
5-FU: 5-fluorouracil

RM ANOVA, *p<0.05, **p<0.001 compared to monotherapy group

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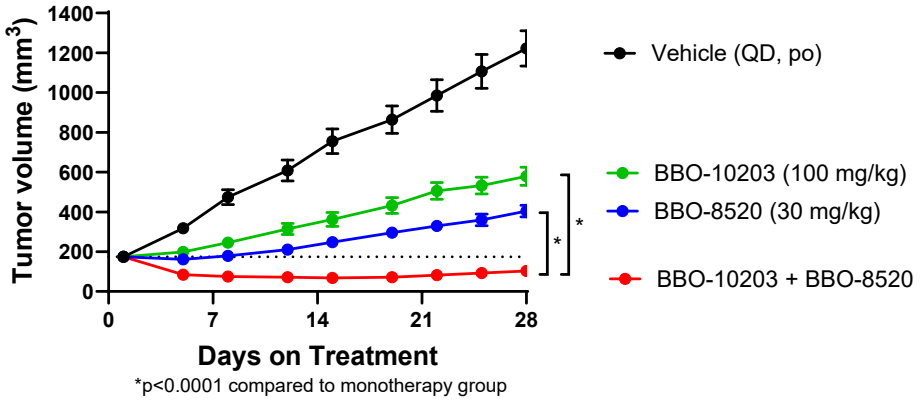
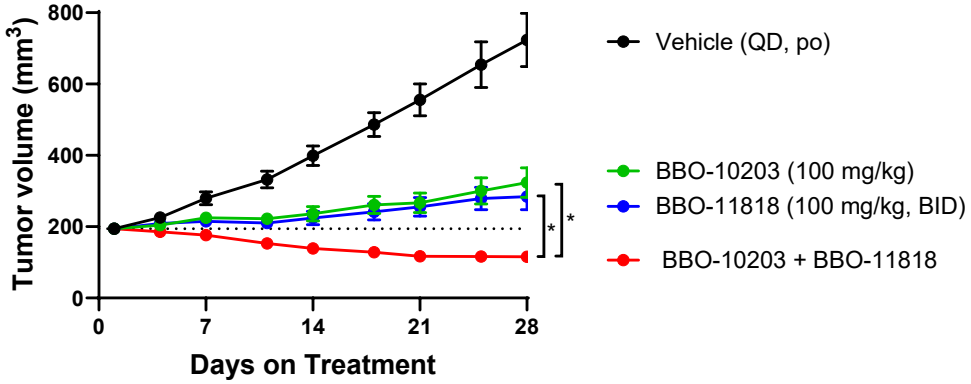
Strong G_1 arrest and apoptosis in KRAS mutant NSCLC and PDAC models in combination with KRASi

H2122 CDX ($KRAS^{G12C}$, $KEAP1_{mut}$, $STK11_{mut}$)



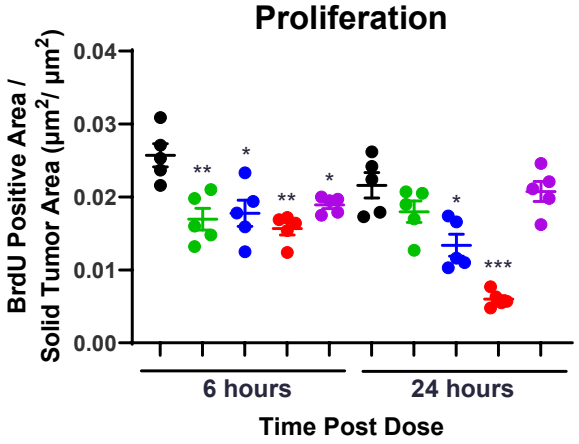
*p<0.0001 compared to monotherapy group

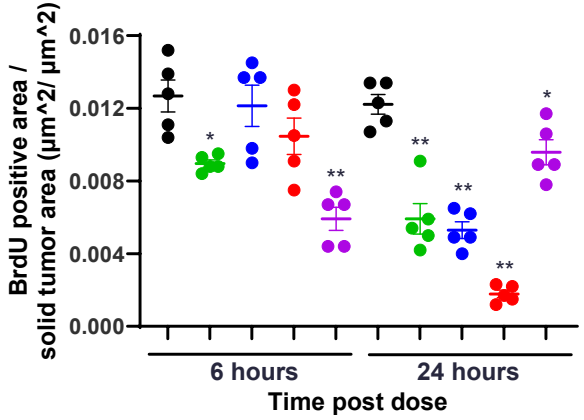
Capan-2 CDX ($KRAS^{G12V}$)



*p<0.001 combinatinon group compared to each monotherapy group

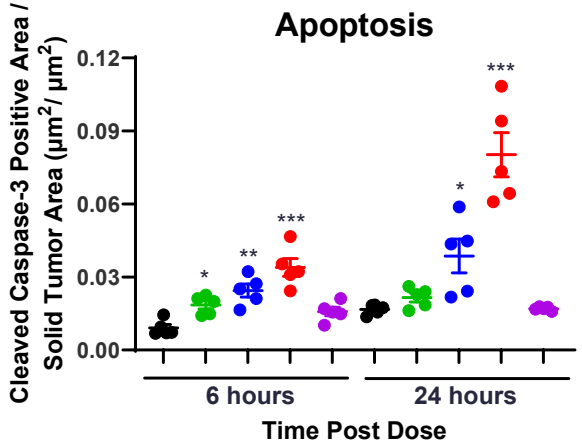
Proliferation



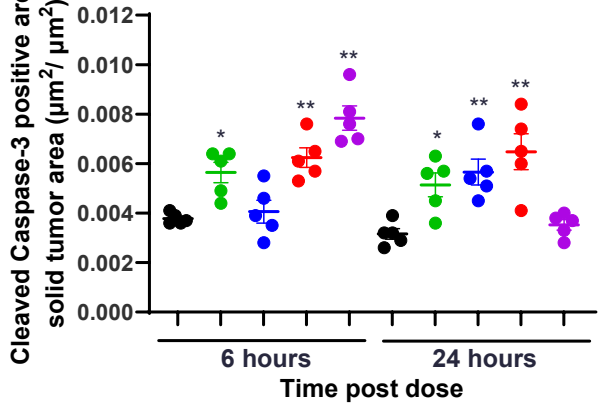


- Vehicle (QD, po)
- BBO-10203
- KRASi
- BBO-10203 + BBO-11818
- Alpelisib (20 mg/kg, QD, po)

Apoptosis



One-way ANOVA with Dunnett's test vs vehicle:
*p<0.05, **p<0.001, ***p<0.0001



One-way ANOVA with Dunnett's test vs vehicle
*p<0.05, **p<0.01

All compounds dosed orally

Note: LHS- Two-way repeated-measures ANOVA followed by Dunnett's multiple comparisons test

BBO-8520: $KRAS^{G12C}$ ON/OFF inhibitor
BBO-11818: panKRAS ON/OFF inhibitor

BBO-10203: a first-in-class Breaker of the RAS:PI3Kα interaction

- BBO-10203 provides a novel approach to inhibit the 2nd most mutated oncogene in human cancer
- Potential monotherapy and combination benefit in HER2amp, KRAS and PI3Kα mutant tumors
- BBO-10203 is agnostic to mutation status of either partner allowing targeting of KRAS mutant and PI3Kα WT tumors
- Data highlights the potential importance of RAS-coordinated activation of the MAPK and AKT signaling pathways for productive tumor cell growth and survival
- The phase 1 trial, BREAKER-101 (NCT06625775) is now open

The Team

BBOT

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