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Targeting RAS-Driven PI3Kα Activation in Human Tumors

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Disclosure Information

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I have the following relevant financial relationships to disclose:

Employee of: BridgeBio Pharma
Consultant for: None
Speaker's Bureau for: None
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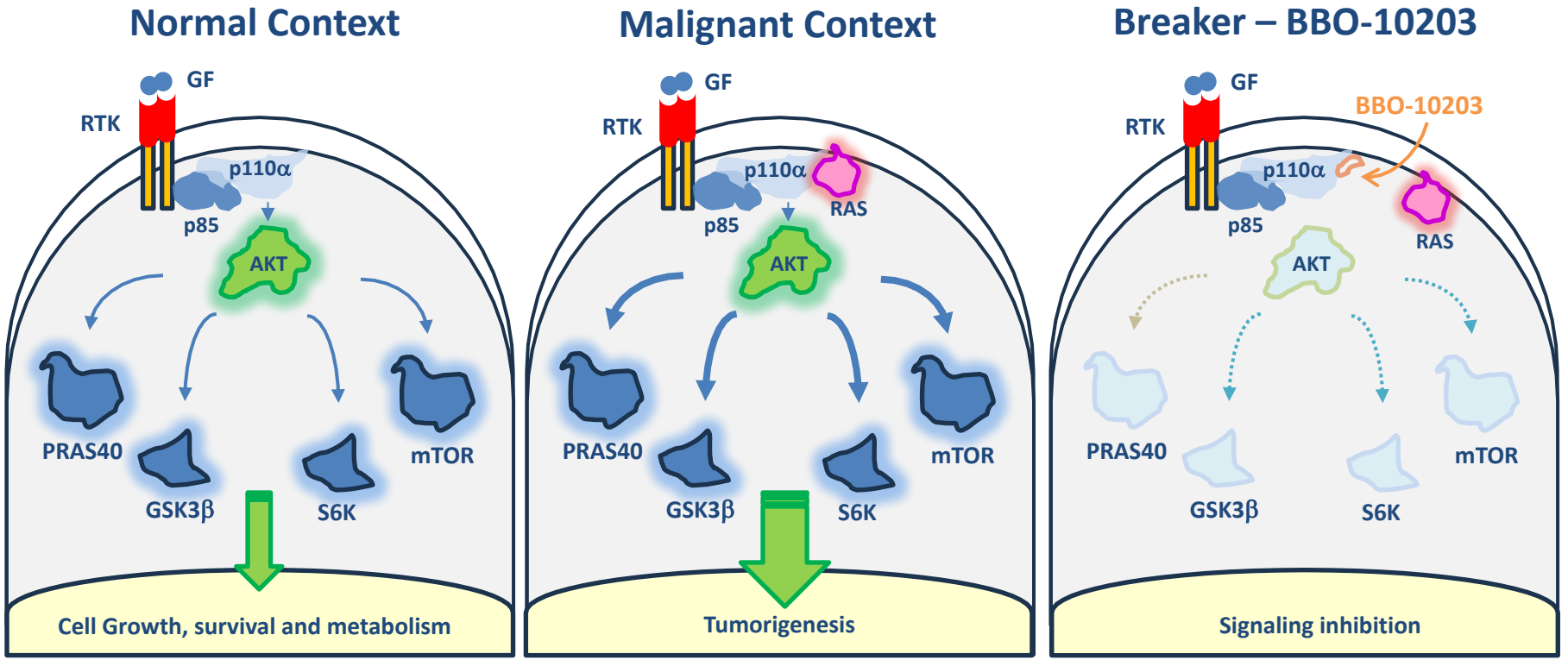
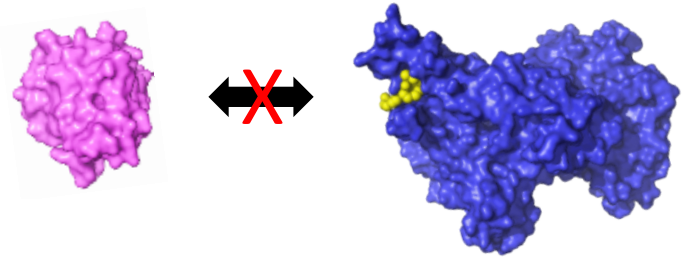
Stockholder in: BridgeBio Pharma
Honoraria from: None

The PI3Kα:RAS interaction is critical in the malignant context



GF: Growth Factor, RTK: Receptor Tyrosine Kinase, AKT: Protein Kinase B, RAS: Rat Sarcoma Virus, PI3K α: Phosphoinositide 3-kinase alpha

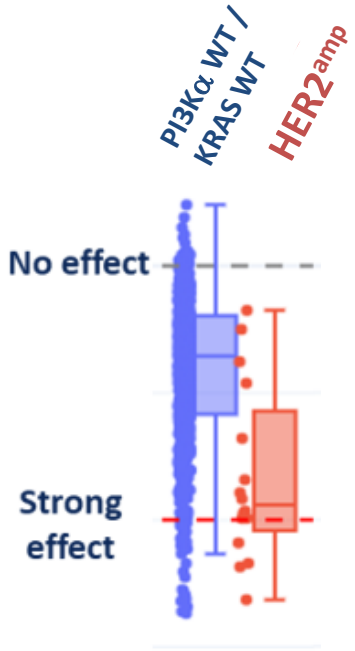
BBO-10203: a First-in-class, PI3Kα:RAS Breaker to target RAS-driven PI3Kα signaling in human tumors



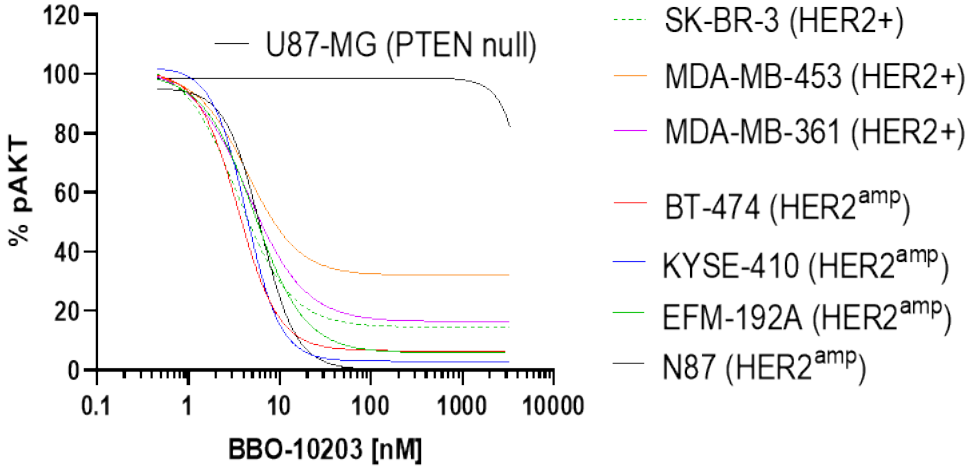
- N-, H-, K-RAS
- PI3Kα
- Breaker

- Selective inhibition of the physical interaction between PI3Kα (not β,δ,or γ) and RAS
- No inhibition of the kinase activity of PI3Kα
- Blockade of K-, H-, and N-RAS isoforms
- Dose-dependent target (PI3Kα) engagement in multiple cell types
- No pAKT inhibition in adipocytes and no hyperglycemia *in vivo*
- PK/PD and efficacy relationship in human cancer models

HER2-overexpressing lines are sensitive to PIK3CA knockout and BBO-10203 treatment



pAKT inhibition by BBO-10203

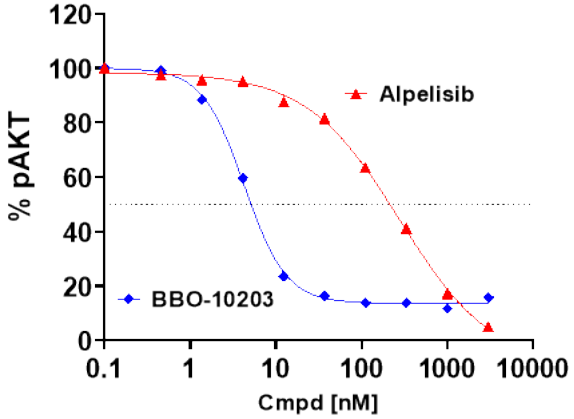


Cell Line	N87	KYSE-410	EFM-192A	BT-474	MDA-MB-361	MDA-MB-453	SK-BR-3	U87-MG
IC_{50} (nM)	4.0	5.0	5.0	5.0	9.0	40.3	6.0	>10000

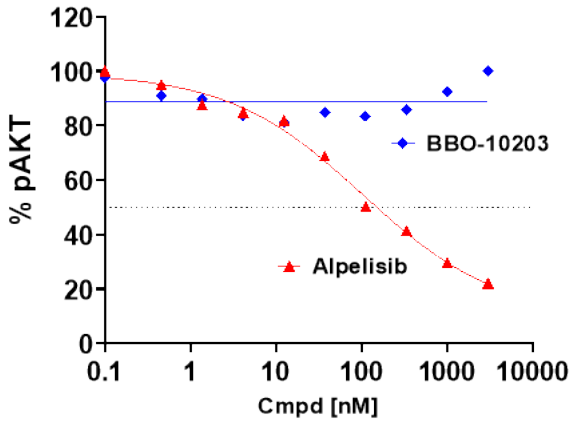
https://depmap.org/portal/

BBO-10203 potently inhibits pAKT with no effect on PI3Ka Kinase activity

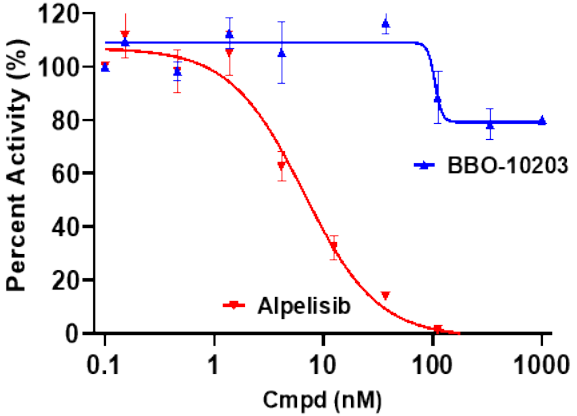
Potent pAKT inhibition in BT-474 HER2^{amp}



No pAKT inhibition in A375 BRAF mutant

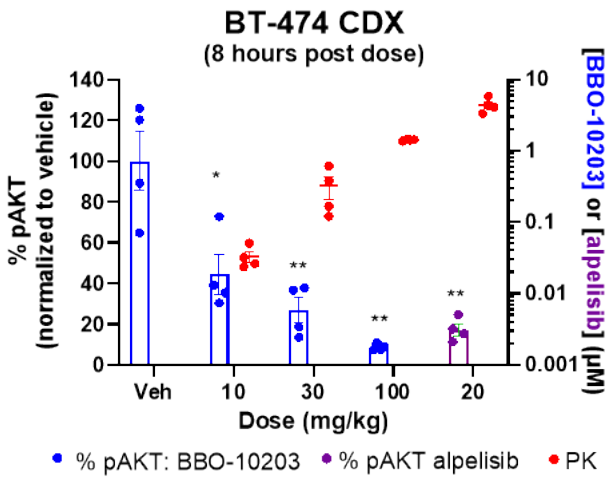


No PI3Kα Kinase inhibition



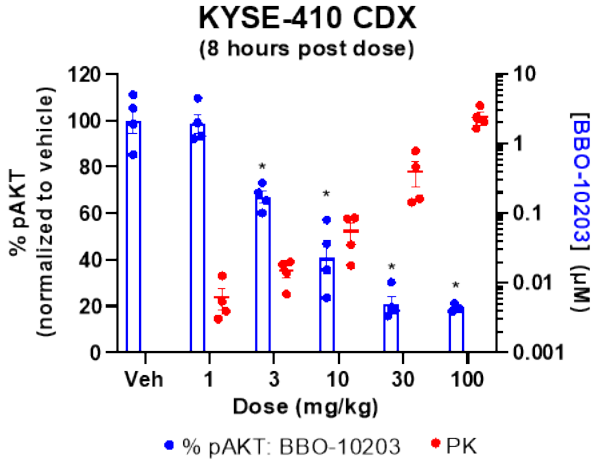
No difference in gene transcriptional regulation or AKT signaling pathway inhibition are observed between alpelisib and BBO-10203 in BT-474 cells

Dose dependent pAKT inhibition in the BT-474 (HER2^{amp}/PI3Ka^{K111N}) and KYSE-410 (HER2^{amp}/KRAS^{G12C}) CDX models



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

Test Article	Dose (QDx1, po)	pAKT		Plasma [compound]
		Inhibition	p value vs vehicle	
BBO-10203	10 mg/kg	56%	0.0003	33 nM
BBO-10203	30 mg/kg	73%	<0.0001	319 nM
BBO-10203	100 mg/kg	91%	<0.0001	1414 nM
alpelisib	20 mg/kg	83%	<0.0001	4363 nM

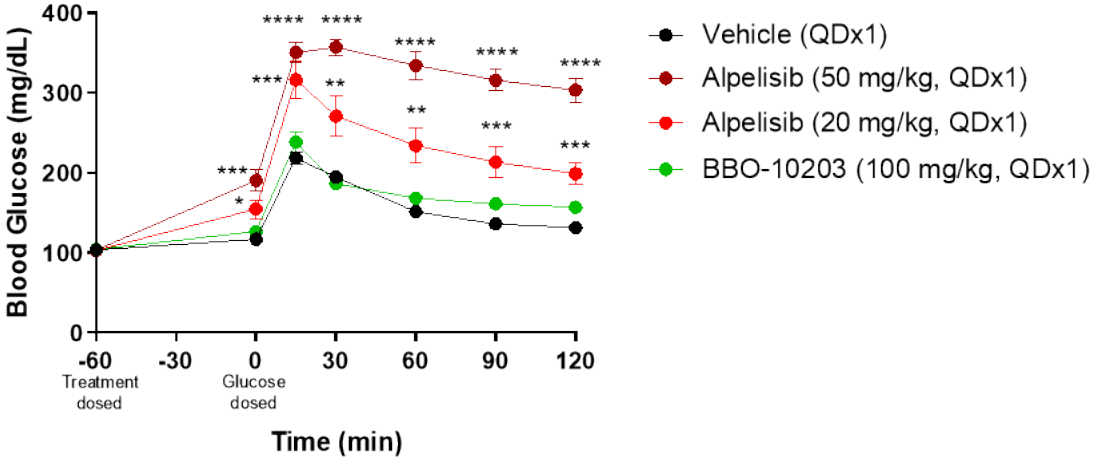


One-way ANOVA with Dunnett's test vs vehicle *p<0.001

Test Article	Dose (QDx1, po)	pAKT		Plasma [compound]
		Inhibition	p value vs vehicle	
BBO-10203	1 mg/kg	1%	0.9996	6 nM
BBO-10203	3 mg/kg	33%	p<0.0001	15 nM
BBO-10203	10 mg/kg	59%	p<0.0001	56 nM
BBO-10203	30 mg/kg	79%	p<0.0001	390 nM
BBO-10203	100 mg/kg	81%	p<0.0001	2408 nM

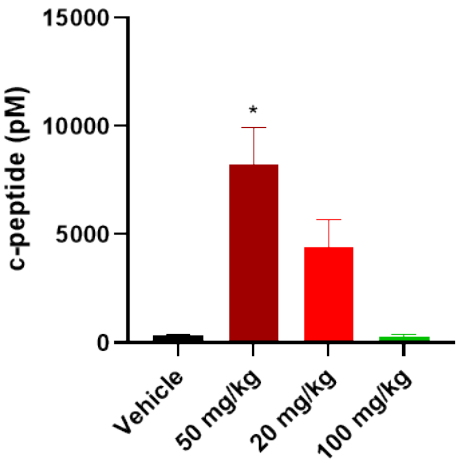
BBO-10203 does not cause hyperglycemia or hyperinsulinemia

oGTT Results: Blood Glucose Levels



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

C-peptide

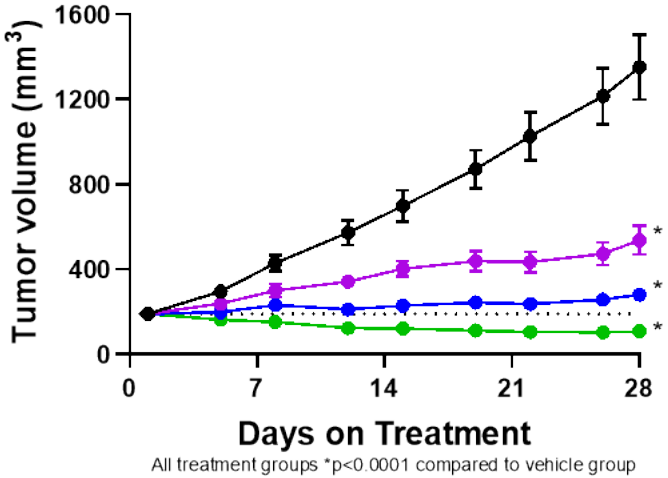


One-way ANOVA with Dunnett's test vs vehicle: *p<0.001
(Note: vehicle vs 20 mg/kg alpelisib: p=0.052)

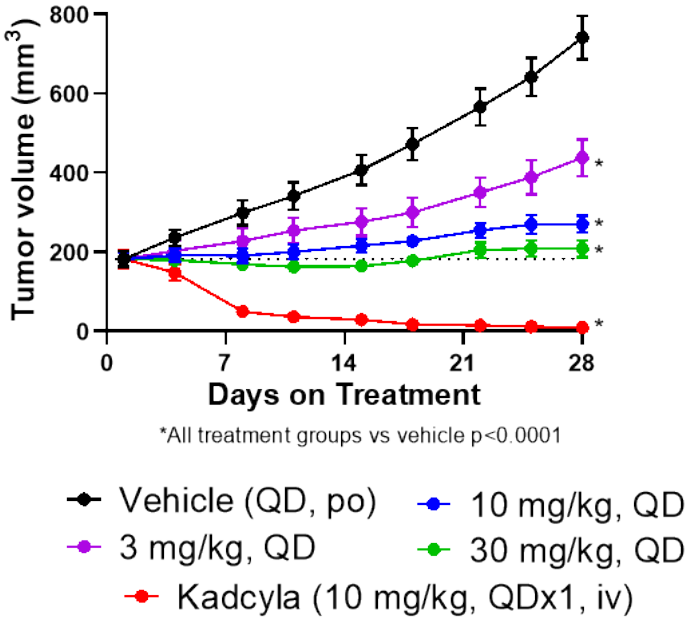
At 3x the dose needed to achieve >80% pAKT inhibition and tumor regressions, BBO-10203 does not cause hyperglycemia

BBO-10203 drives strong efficacy in HER2-expressing models *in vivo*

KYSE-410 Esophageal Ca KRAS^{G12C} / HER2^{amp} CDX model



MDA-MB-453 Breast Ca ER- PIK3CA^{H1047R} *HER2+ CDX model



*Cell-line classified as HER2^{neg} but HER2 expression has been shown by western blot

Summary

- BBO-10203 is a first-in-class PI3Kα:RAS breaker
- BBO-10203 is specific for PI3Kα and blocks N-, H-, and KRAS activation
- BBO-10203 drives potent tumor pAKT inhibition *in vivo* without causing hyperglycemia or hyperinsulinemia
- BBO-10203 inhibition of pAKT translates into potent anti-tumor activity in HER2 expressing tumor models
- BBO-10203 is currently in IND-enabling studies

Team Effort

bridgebio

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