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Targeting RAS-Driven PI3K α Activation in Human Tumors

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Disclosure Information

San Antonio Breast Cancer Symposium®

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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

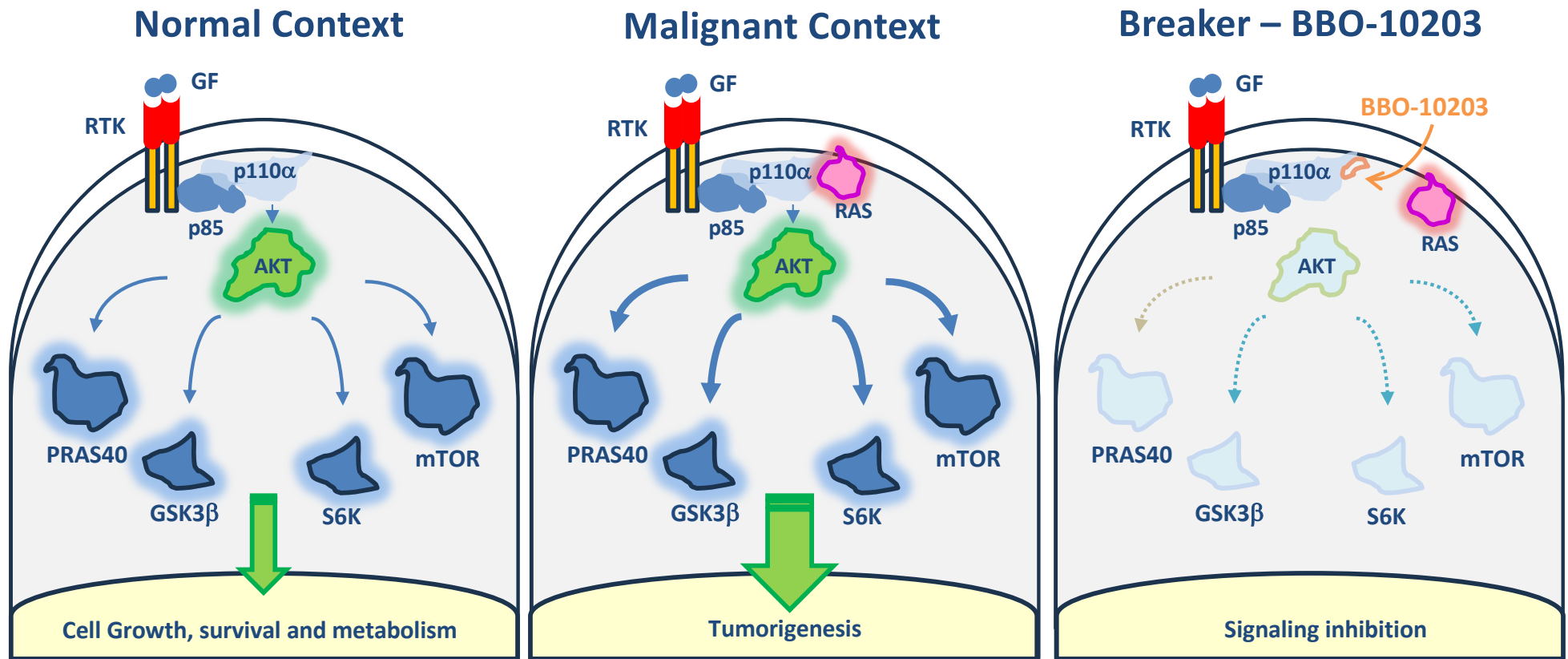
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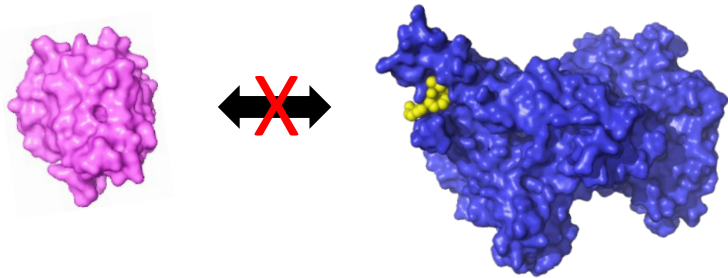
The PI3K α :RAS interaction is critical in the malignant context



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

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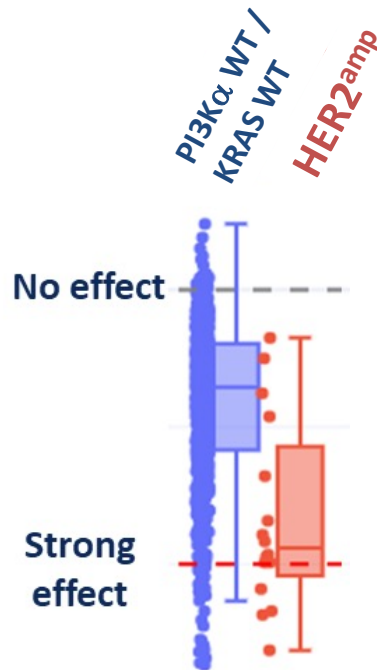
BBO-10203: a First-in-class, PI3K α :RAS Breaker to target RAS-driven PI3K α signaling in human tumors



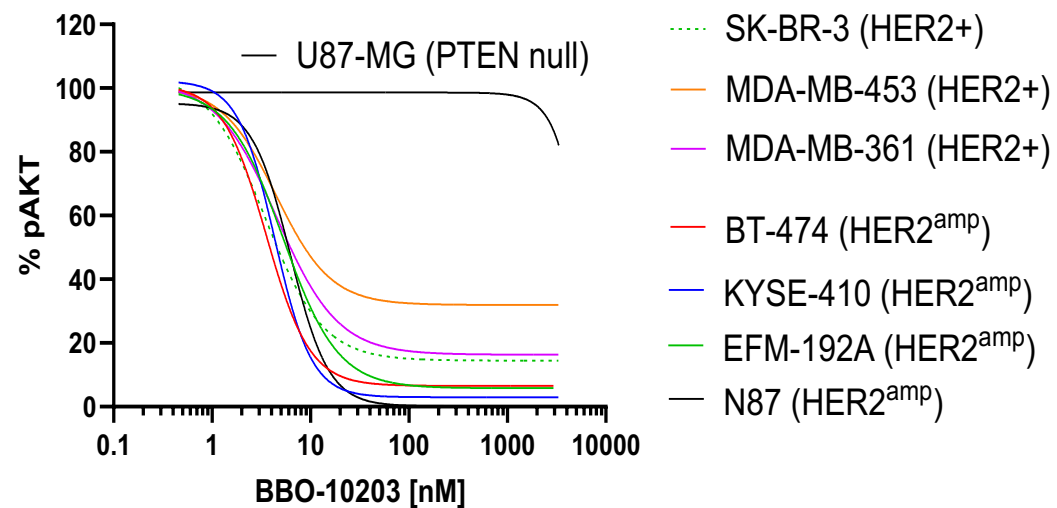
-  N-, H-, K-RAS
-  PI3K α
-  Breaker

- Selective inhibition of the physical interaction between PI3K α (not β , δ , or γ) and RAS
- No inhibition of the kinase activity of PI3K α
- Blockade of K-, H-, and N-RAS isoforms
- Dose-dependent target (PI3K α) 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



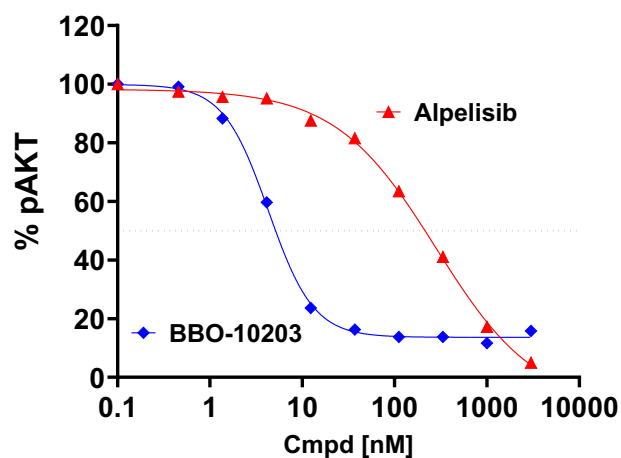
Cell Line	N87	KYSE-410	EFM-192A	BT-474	MDA-MB-361	MDA-MB-453	SK-BR-3	U87-MG
IC ₅₀ (nM)	4.0	5.0	5.0	5.0	9.0	40.3	6.0	>10000

<https://depmap.org/portal/>

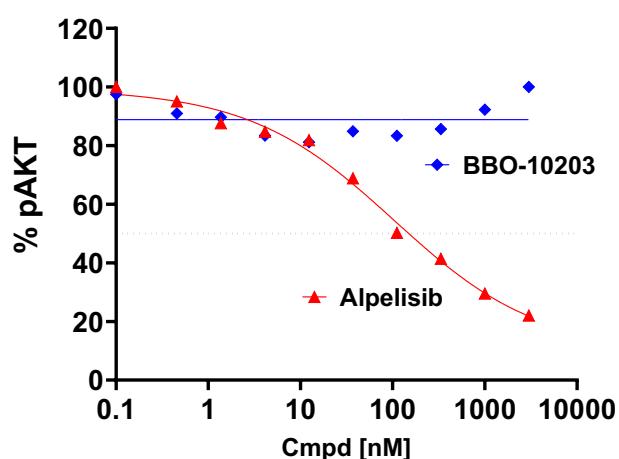
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BBO-10203 potently inhibits pAKT with no effect on PI3K α Kinase activity

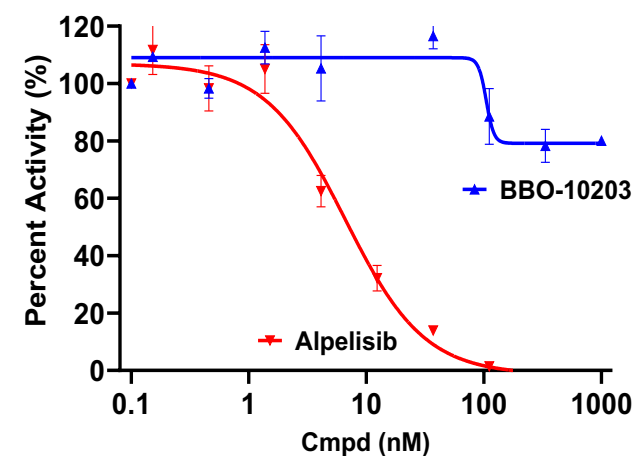
Potent pAKT inhibition in BT-474 HER2^{amp}



No pAKT inhibition in A375 BRAF mutant

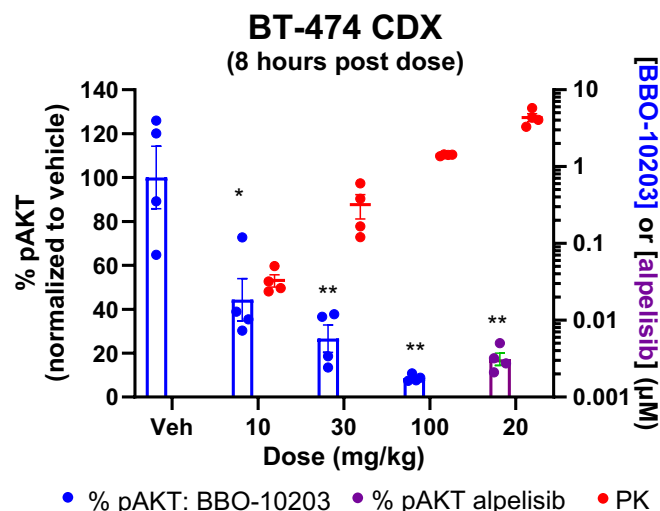


No PI3K α Kinase inhibition



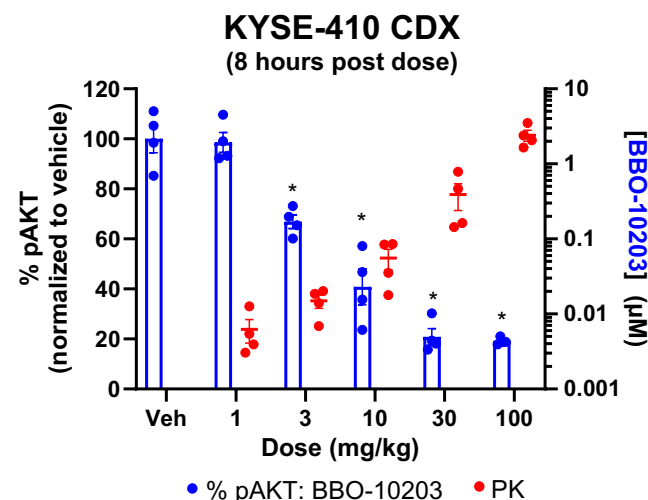
No difference in gene transcriptional regulation or AKT signaling pathway inhibition are observed between alpelisib and BBO-10203 in BT-474 cells

Dose dependent pAKT inhibition in the BT-474 (HER2^{amp}/PI3K α ^{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

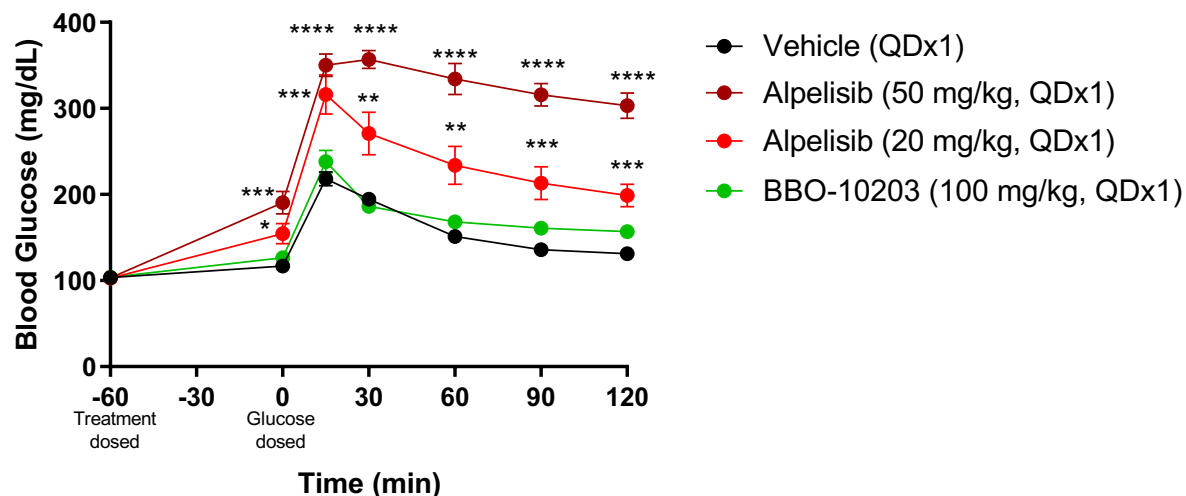


One-way ANOVA with Dunnett's test vs vehicle *p<0.001

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

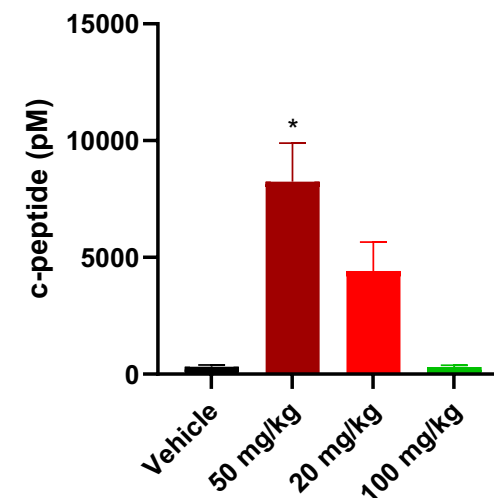
BBO-10203 does not cause hyperglycemia or hyperinsulinemia

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

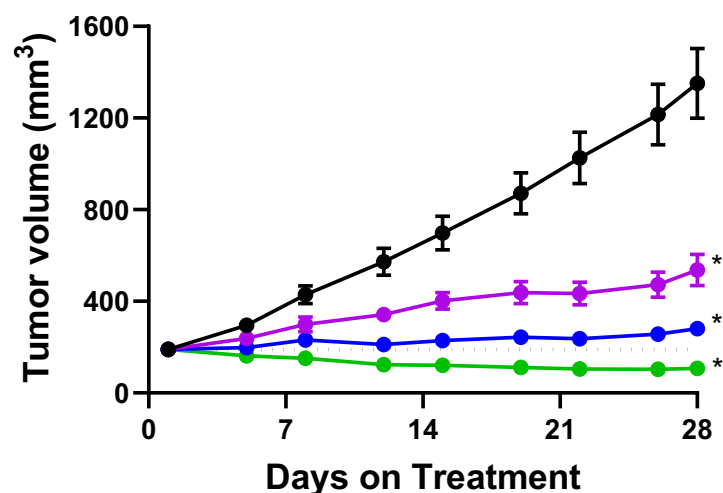


One-way ANOVA with Dunnett's test vs vehicle: *p<0.001
(Note: vehicle vs 20 mg/kg alpelisib: p=0.052)

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*

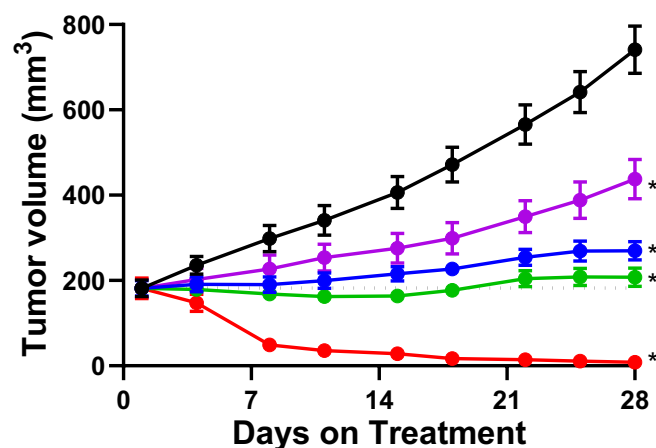
**KYSE-410 Esophageal Ca KRAS^{G12C} /
HER2^{amp} CDX model**



All treatment groups *p<0.0001 compared to vehicle group

● Vehicle (QD, po) ● 10 mg/kg, QD
 ● 3 mg/kg, QD ● 30 mg/kg, QD

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



*All treatment groups vs vehicle p<0.0001

● Vehicle (QD, po) ● 10 mg/kg, QD
 ● 3 mg/kg, QD ● 30 mg/kg, QD
 ● Kadcyla (10 mg/kg, QDx1, iv)

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

Summary

- BBO-10203 is a first-in-class PI3K α :RAS breaker
- BBO-10203 is specific for PI3K α 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



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