The RAS:PI3Kα Breaker BBO-10203 inhibits PI3Kα/AKT activity in HER2^{AMP} models through non-canonical RAS signaling blockade

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BridgeBio Oncology Therapeutics

Disclosure Information

AACR American Association for Cancer Research
Annual Meeting
April 17-22, 2026 SAN DIEGO
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James Stice

I have the following relevant financial relationships to disclose:

Employee of: BBOT

Stockholder in: BBOT

The interaction between RAS and PI3Kα plays a critical role in malignant cells

Normal Context

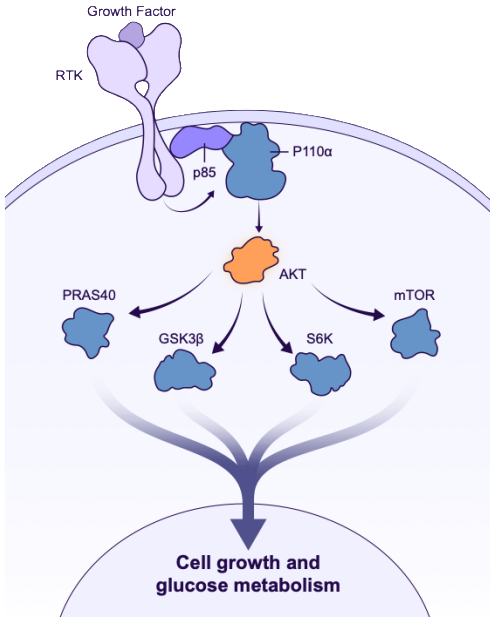


Chart derived from Hopkins et al., Nat Rev Endocrinol 16(5):276-283 (2020) .

Malignant Context

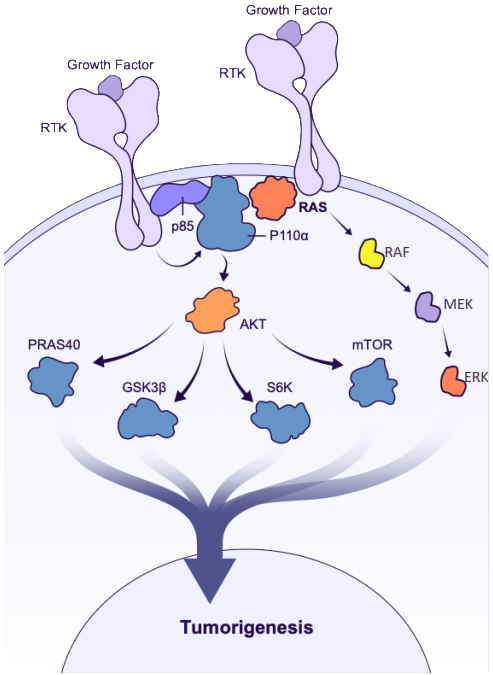
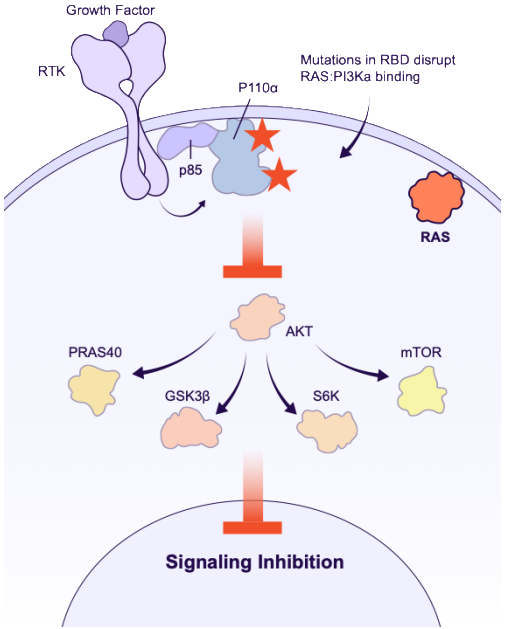


Chart derived from Cuesta et al., Genes 12(7):1094 (2021)

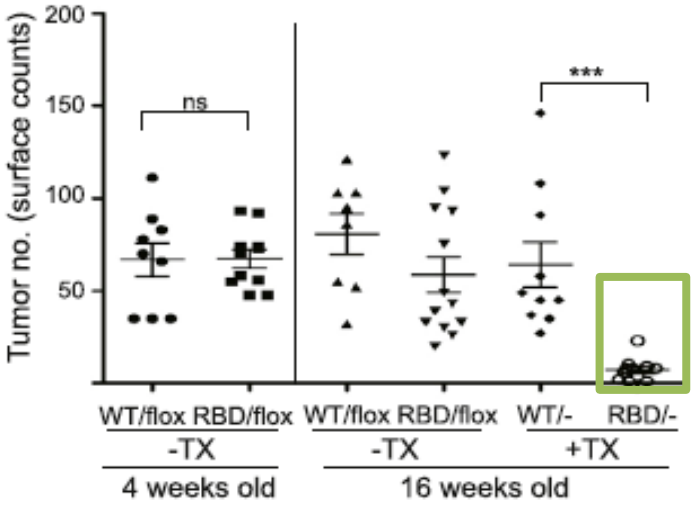
Note: GF: Growth Factor, RTK: Receptor Tyrosine Kinase, AKT: Protein Kinase B, RAS: Rat Sarcoma Virus, PI3Ka: Phosphoinositide 3-kinase alpha

Genetic disruption of the RAS:PI3Kα interaction has been shown to inhibit KRAS^{G12D}-driven tumor growth with no observed hyperglycemia

Malignant context with RBD (RAS Binding Domain) disruption



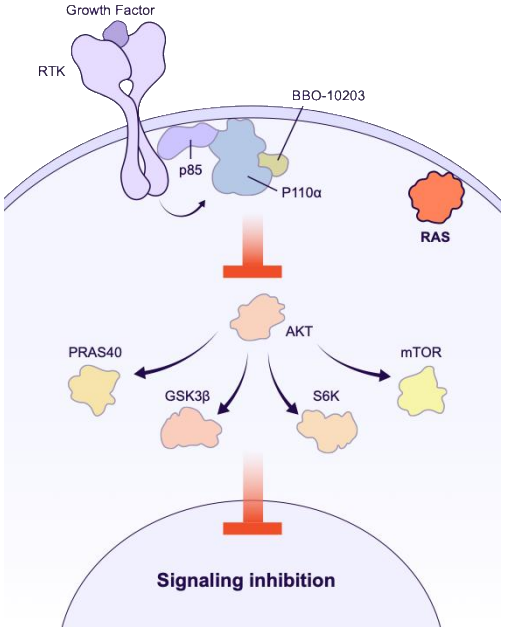
T208D and K227A mutations in the PI3Kα RBD slow KRAS^{G12D}-driven growth



Note: RBD: RAS Binding domain; GF: Growth Factor, RTK: Receptor Tyrosine Kinase, AKT: Protein Kinase B, RAS: Rat Sarcoma Virus, PI3Kα: Phosphoinositide 3-kinase alpha
Source: Gupta et. al. Cell 2007; Castellano et al., Cancer Cell. 2013; Left hand chart derived from study findings

BBO-10203 physically and allosterically disrupts the interaction between RAS and PI3Kα, leading to signaling inhibition

Malignant context with BBO-10203



BBO-10203's novel MOA leverages mutation agnostic approach

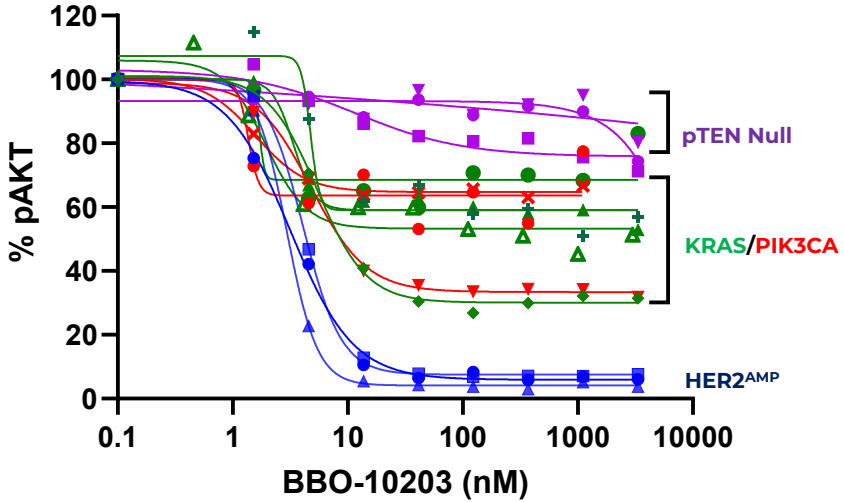
- Binds specifically to the RBD of PI3Kα
- Does not inhibit the kinase activity of PI3Kα
- Blocks binding of K-, H-, and N-RAS to PI3Kα
- Agnostic to mutational status of either partner
- Tumor regressions at 30 mg/kg QD and **no hyperglycemia at observed at 100 mg/kg QD**

Assay*	BBO-10203
MALDI-TOF	>90% at 15 min
TE PI3Kα RBD (IC_{50})	3 nM
pAKT (IC_{50})	4 nM
$ED_{50/90}$	2.5 / 4.0 mg/kg

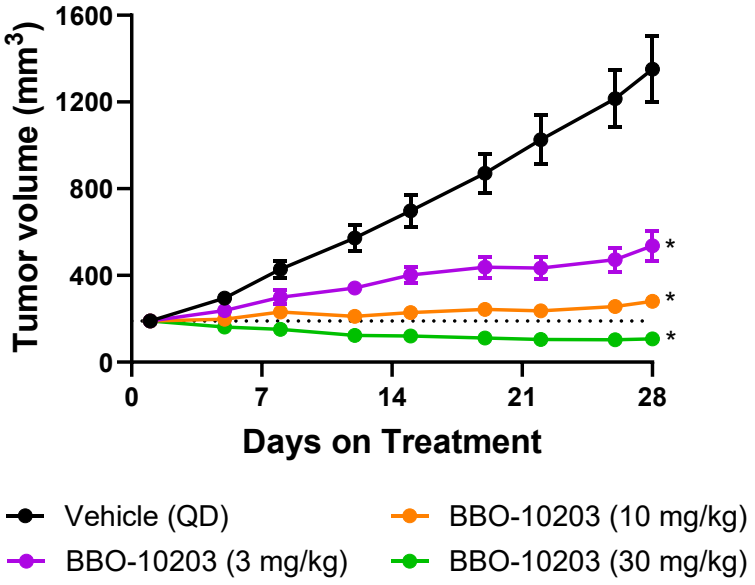
Notes: TE: Target engagement (PI3Kα RBD); BBOT cell and in vivo data: KYSE-410 (HER2/$KRAS^{G12C}$);
MOA – mechanism of action
Source: Simanshu et al., Science. 2025

BBO-10203 shows that PI3Kα activity in HER2^{AMP} cells is RAS-dependent

Cell Line Panel pAKT HTRF



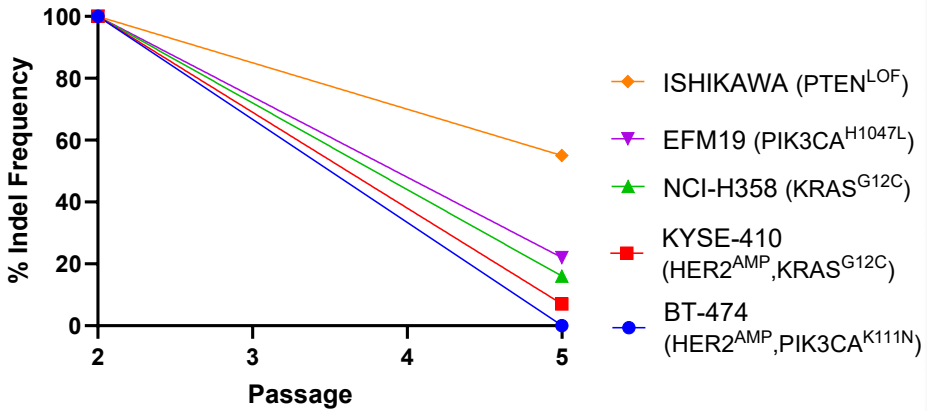
KYSE-410 (HER2^{AMP}, KRAS^{G12C}) Esophageal SCC CDX



KYSE-410 efficacy study statistical analysis: Two-way repeated measures ANOVA with Dunnett's multiple comparison test vs vehicle: *p<0.0001
Source: Simanshu et al., Science. 2025

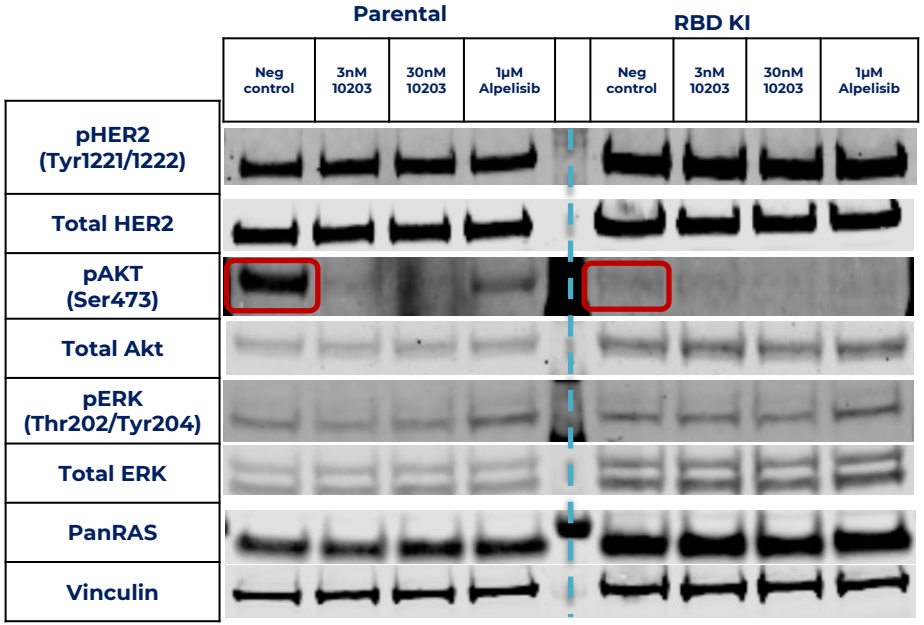
Knock-In of Ras Binding Domain mutations in p110α strongly affect pAKT and viability in HER2^{AMP} cell line models

Survival of PI3K RBD KI (viability effect)



Loss in RBD Indel (PIK3CARBDmut) Frequency Over Time

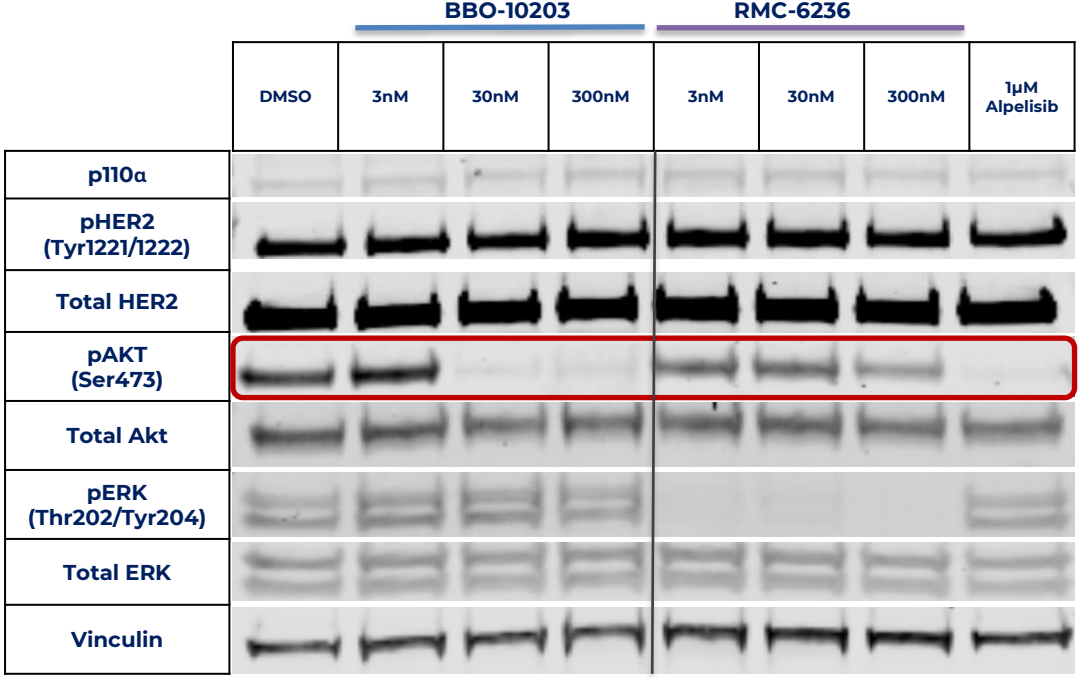
Signaling



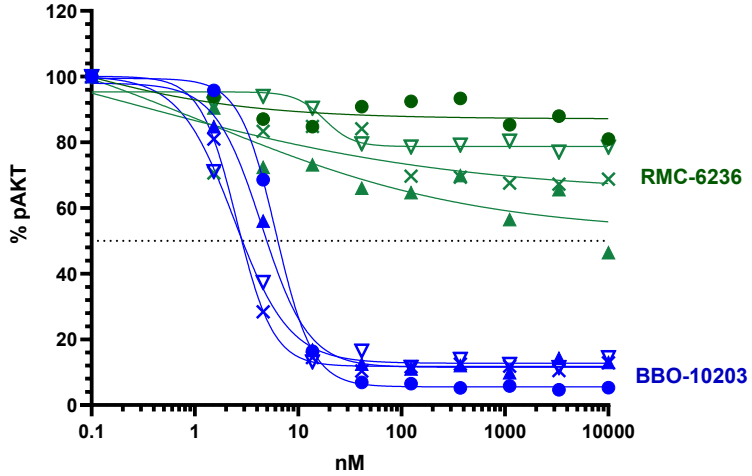
KYSE-410

Comparison with the panRAS inhibitor RMC-6236 shows the dependency is likely not K-,H-, or N-RAS driven

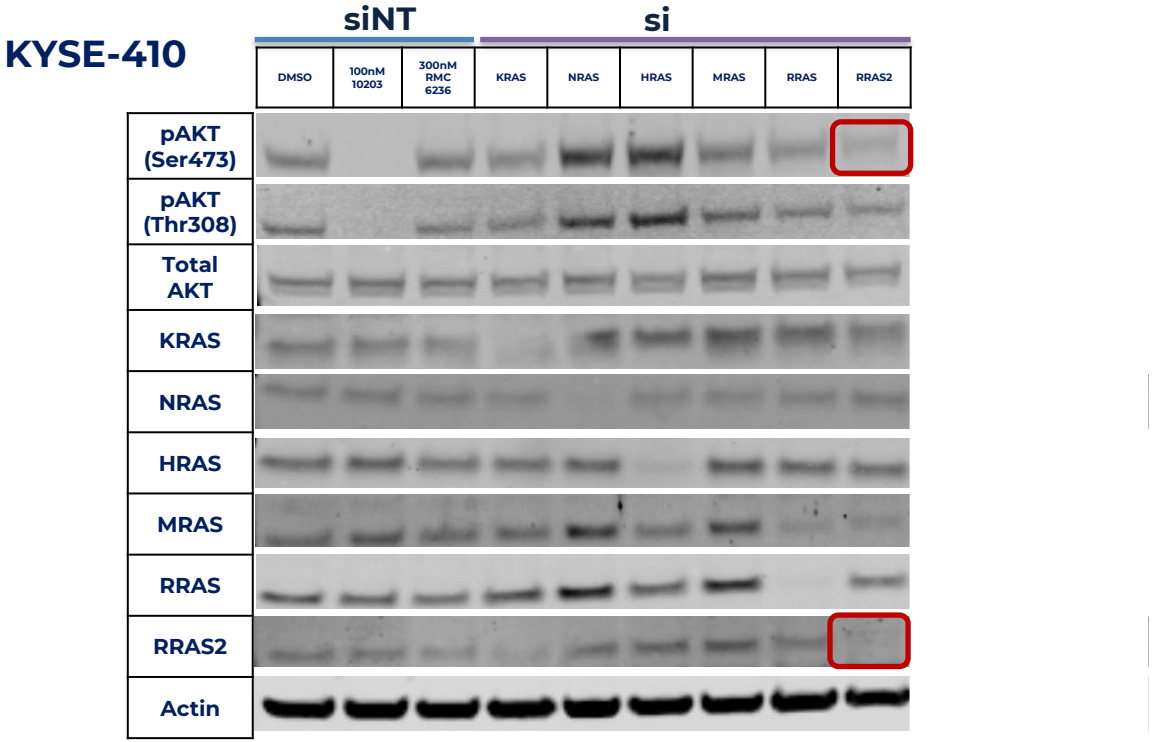
KYSE-410



HER2^{AMP} Cell Lines

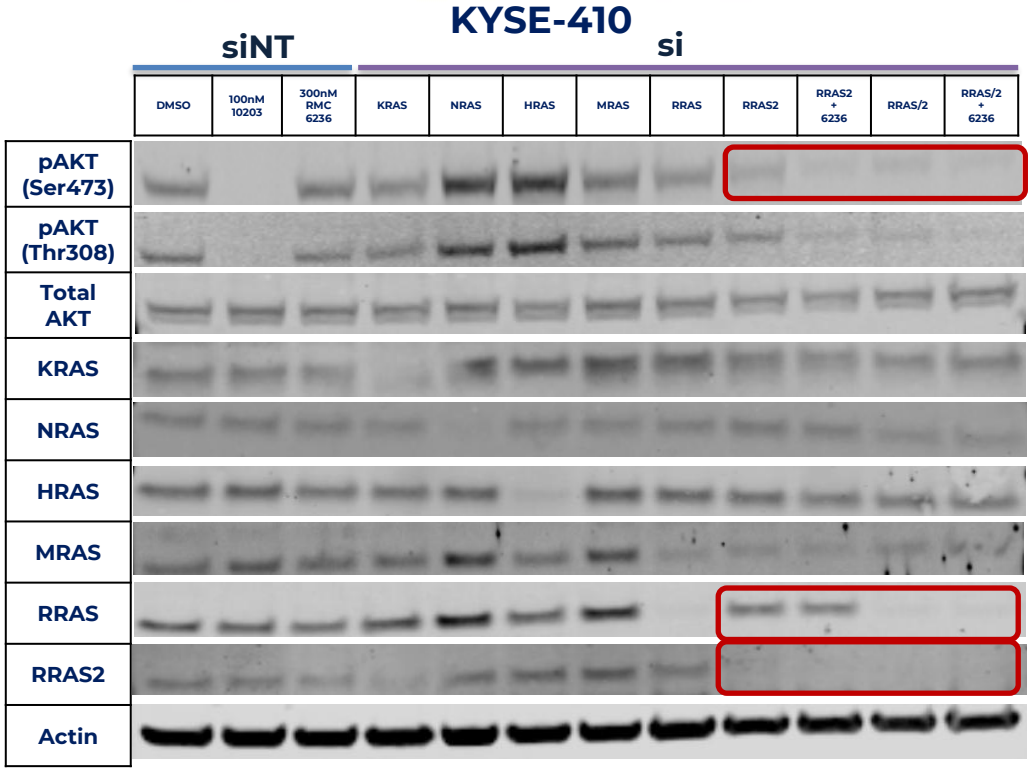


Non-canonical RAS inhibition needed to inhibit pAKT signaling in HER2^{AMP} cell lines



- RRAS2 siRNA produces ~50% decrease in pAKT

Combined R/RRAS2 siRNA and RMC-6236 needed for comparable pAKT suppression to BBO-10203



Combined effect on pAKT also observed in the BT-474 cell line

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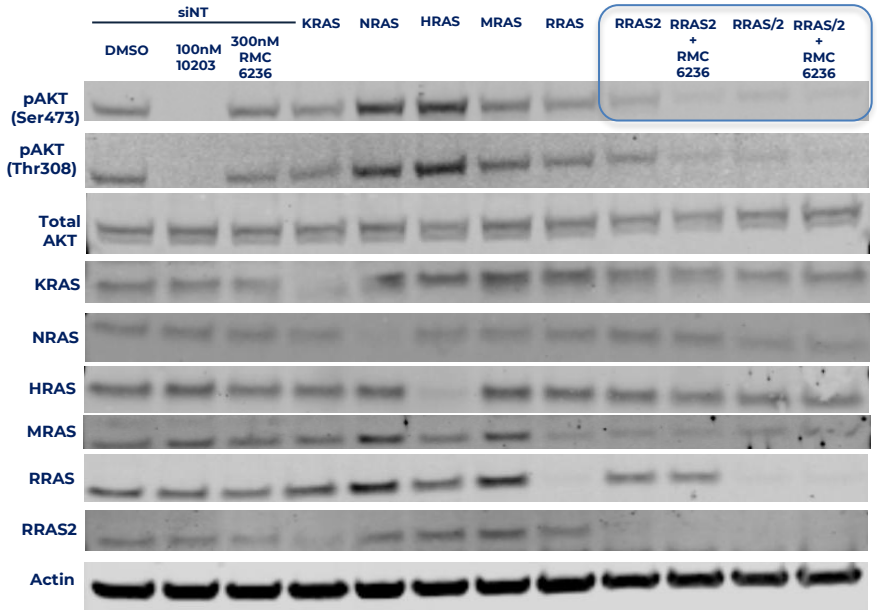
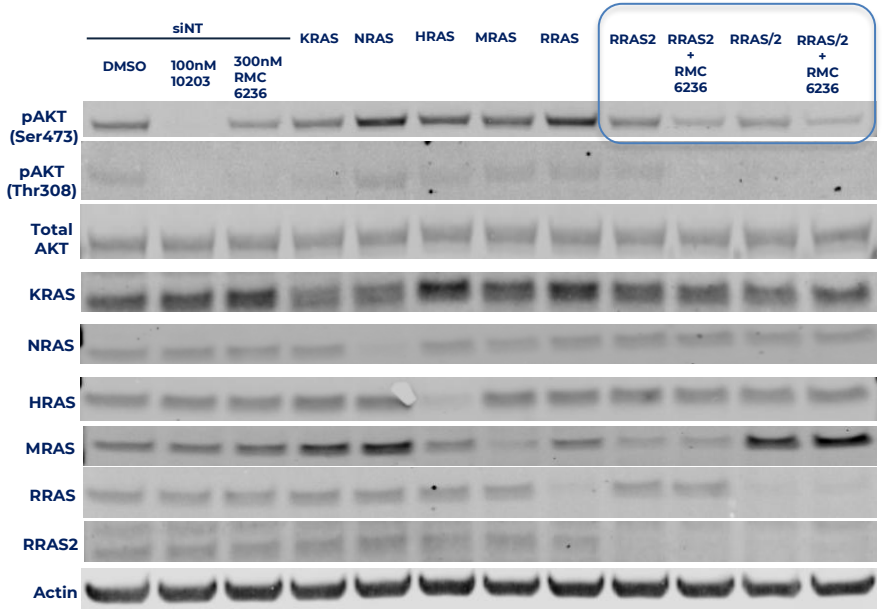
KYSE-410

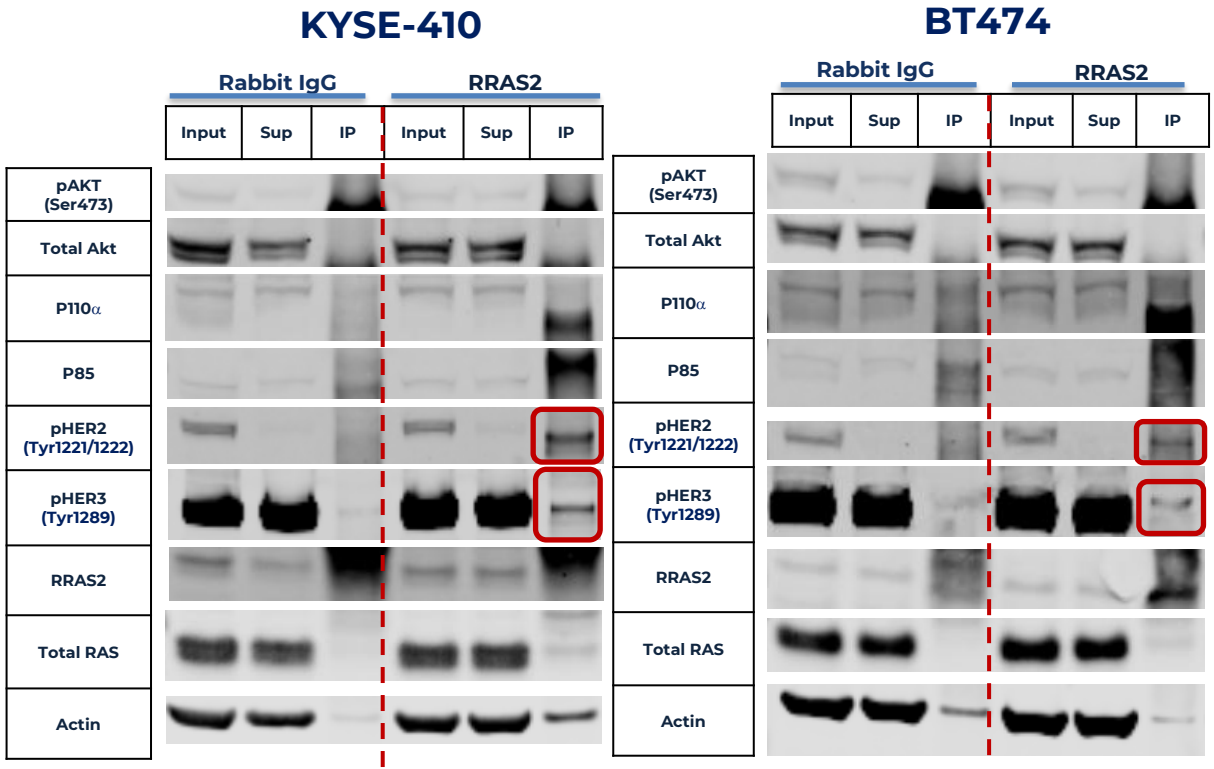


BT474



DO NOT POST

RRAS2 interacts with phosphorylated HER2 and HER3



- **We continue to study the effect of different breaker and glue molecules on the Her2/Her3 complex in HER2^{AMP} cell lines**

RRAS2 interacts with phosphorylated HER2 and HER3

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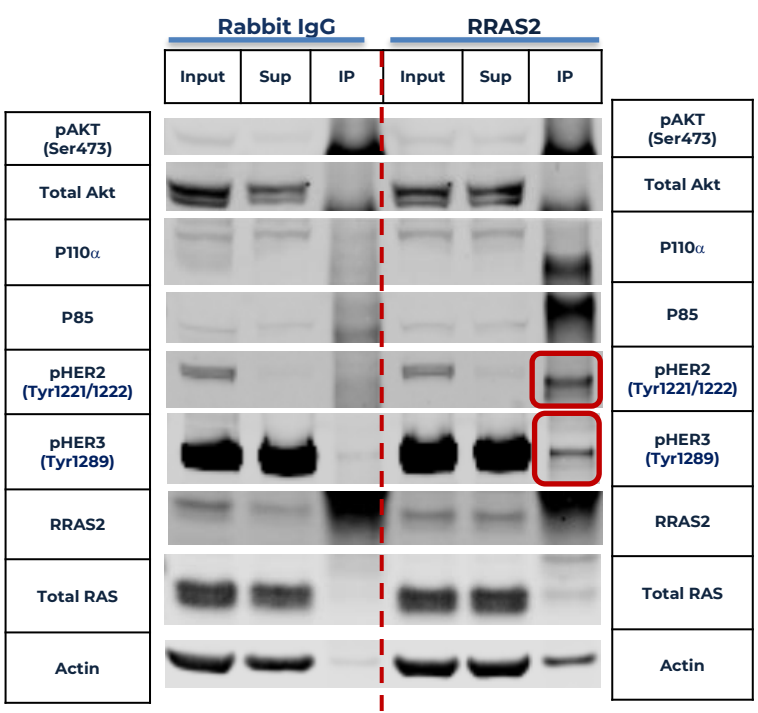
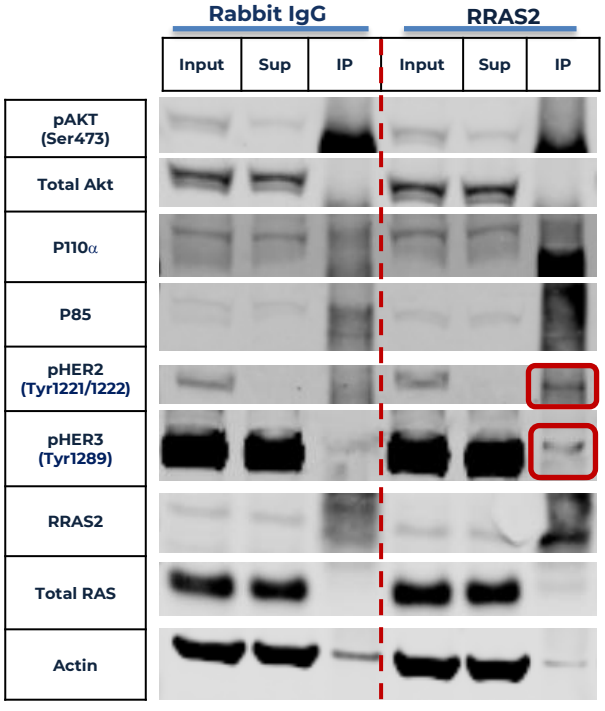
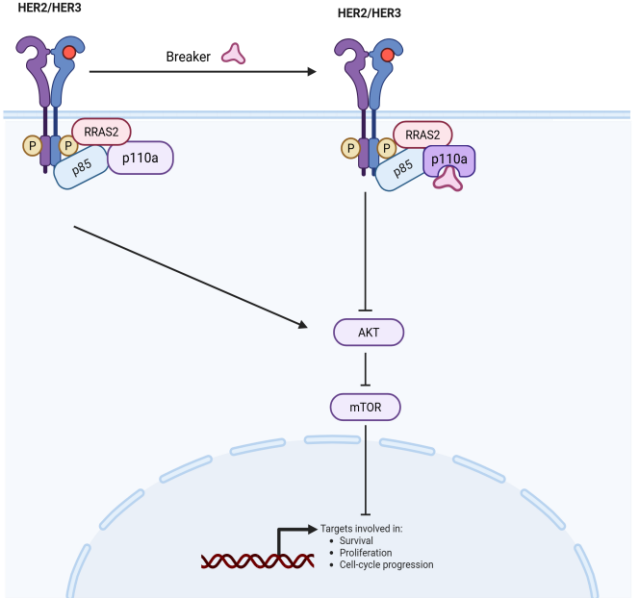


BT474



Treatment with Breaker



Created in Biorender

BBO-10203 displays strong in vivo combination effects with tucatinib or trastuzumab in HER2^{AMP} models

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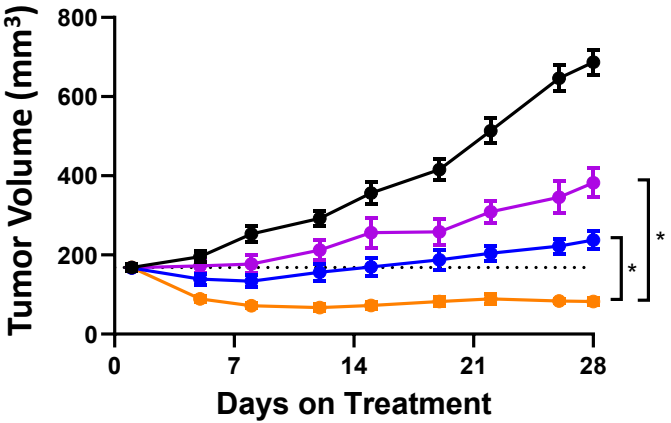
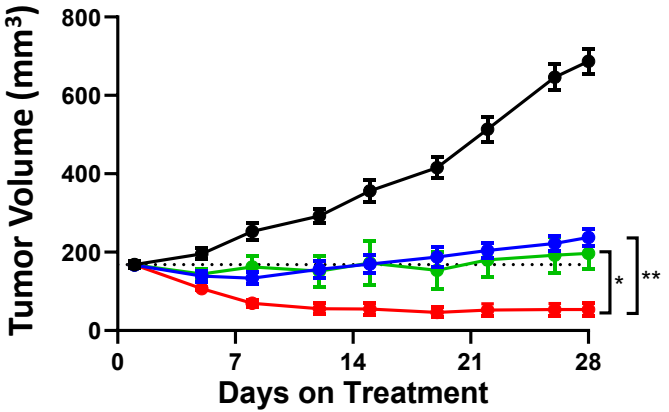
BT474 (HER2^{AMP},PIK3CA^{K111N}) Tumor Volume

BBO-10203 + Tucatinib



Vehicle (QD)
Tucatinib (50 mg/kg, QD)
BBO-10203 (100 mg/kg, QD)
BBO-10203 + Tucatinib

BBO-12003 + Trastuzumab



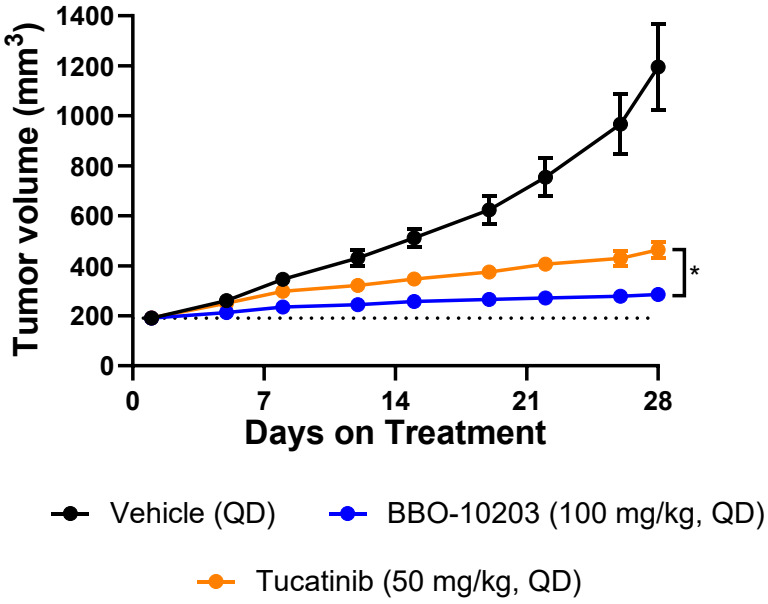
Vehicle (QD)
Trastuzumab (20 mg/kg, Q7D)
BBO-10203 (100 mg/kg, QD)
BBO-10203 + Trastuzumab

BBO-10203 + tucatinib efficacy study statistical analysis: Two-way repeated measures ANOVA combination group vs each monotherapy group *p<0.0001
BBO-10203 + trastuzumab efficacy study statistical analysis: Two-way repeated measures ANOVA combination group vs each monotherapy group *p<0.05, **p<0.0001

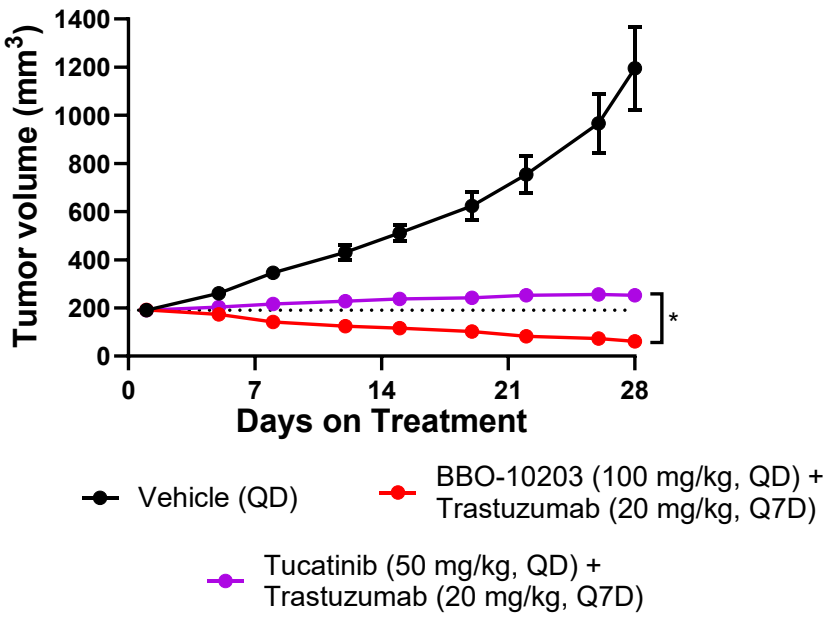
BBO-10203 is more efficacious than tucatinib as both a monotherapy and in combination with trastuzumab in HER2^{AMP} models

N87 CDX (HER2^{AMP}) Tumor Volume

Monotherapy Comparison: BBO-10203 vs tucatinib



Combination Comparison: BBO-10203 + trastuzumab vs tucatinib + trastuzumab



Monotherapy comparison efficacy study statistical analysis: Two-way repeated measures ANOVA of the indicated groups *p<0.01
Combination comparison efficacy study statistical analysis: Two-way repeated measures ANOVA of the indicated groups *p<0.0001

Summary

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- RAS RBD mutations recapitulate breaker activity in HER2^{AMP} cell lines
- RRAS2 accounts for more than 50% of pAKT activation in HER2^{AMP} cell lines
- Combined inhibition of R/RRAS2 plus RMC-6236 leads to pAKT suppression equivalent to BBO-10203, suggesting important contribution from canonical and non-canonical RAS signaling
- RRAS2 is in a complex with p85, p110α and active HER2/HER3
- BBO-10203 shows combination activity with the HER2 inhibitors tucatinib or trastuzumab in HER2^{AMP} tumor models
- BBO-10203 is currently enrolling in the BREAKER-101 trial (NCT06625775).

Team Effort

BBOT BridgeBio Oncology Therapeutics

Discovery Research Group	
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Lijuan Fu	Cathy Zhang
Jin Ju	Paul Wehn
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Saman Setoodeh	Pedro Beltran
Jin Shu	
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Carlos Stahlhut	
Eli Wallace	
Rui Xu	

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Daniel Czyzyk	Alok Sharma
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