Discovery and characterization of BH-501284: A non-covalent, pan-KRAS inhibitor for treatment of diverse *KRAS*-mutant tumors

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Disclosure Information

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Jean Cui, Ph.D.

I have the following relevant financial relationships to disclose:

- Co-founder and Employee of BlossomHill Therapeutics, Inc.
- Stockholder in BlossomHill Therapeutics, Inc.

Targeting oncogenic *KRAS* mutations

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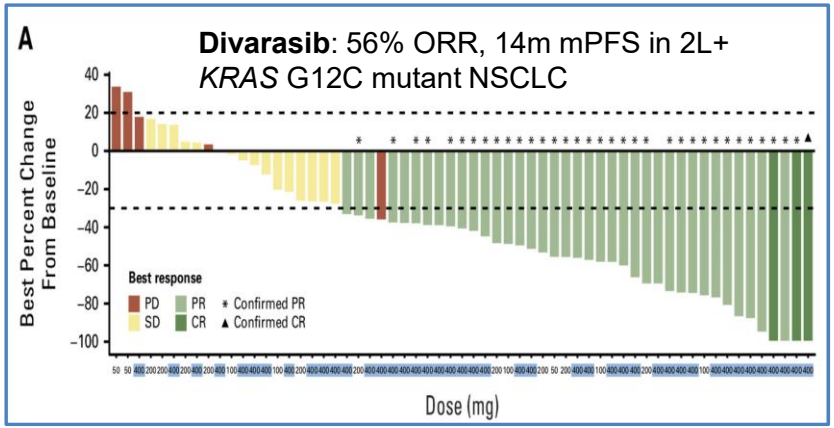
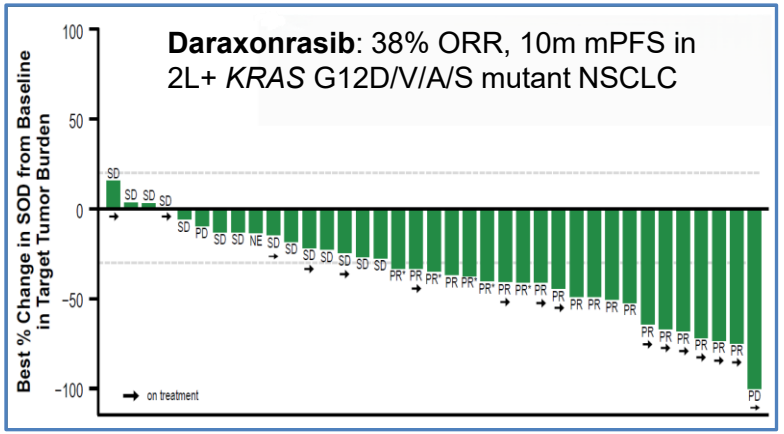
- *KRAS* mutations are the most frequent oncogenic driver alterations found in cancer
- Covalent KRAS G12C inhibitors are now FDA approved to treat *KRAS* G12C mutant NSCLC & CRC
- Investigational KRAS inhibitors leverage several emergent design approaches, including non-covalent Switch-II pocket inhibitors, tricomplex inhibitors, and degraders

Covalent Switch-II KRAS G12Ci set the bar for what could be possible with KRAS inhibition



Sacher et al, JCO, 2025

Tricomplex pan-RAS inhibitor offers broad activity but greater AE burden in clinic



Punekar et al, ELCC, 2025

Challenges beyond KRAS G12C inhibitors

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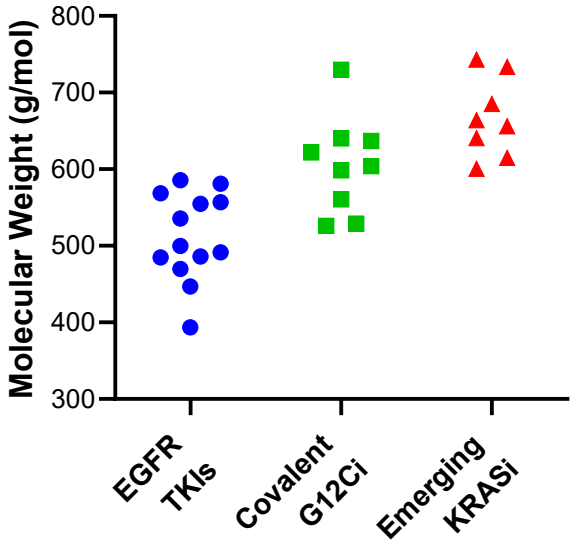
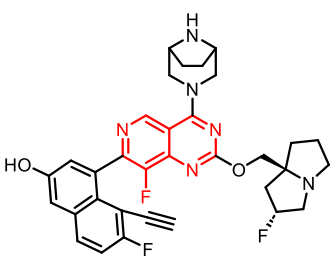
- The Switch-II pocket is shallow such that non-covalent inhibitors often require high molecular weight, resulting in unfavorable drug-like properties which can impair oral bioavailability
- **A fresh chemical scaffold will be needed to deliver a pan-KRAS Switch-II inhibitor which can achieve <u>both</u> high cell potency and marked oral efficacy in in vivo studies**

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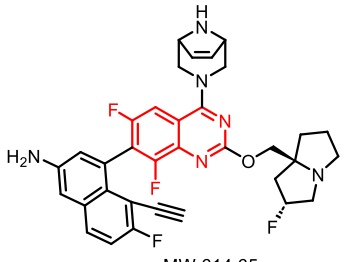
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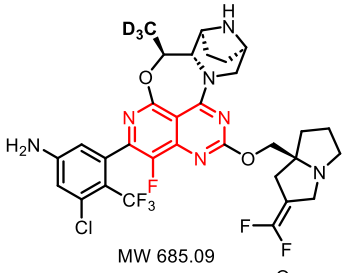
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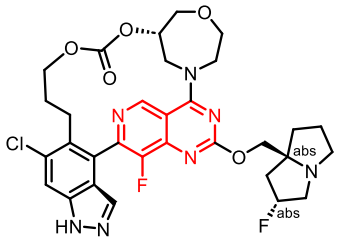
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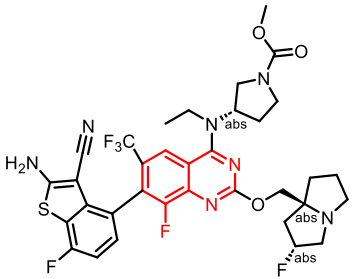
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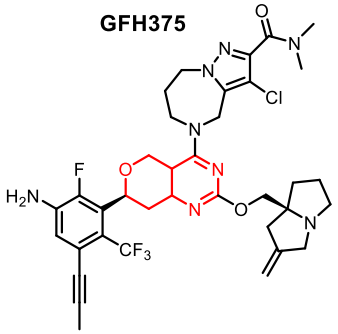
MW 745.22
ERAS-4001

KRAS Switch-II inhibitors rigidify KRAS conformation to disable binding with effectors

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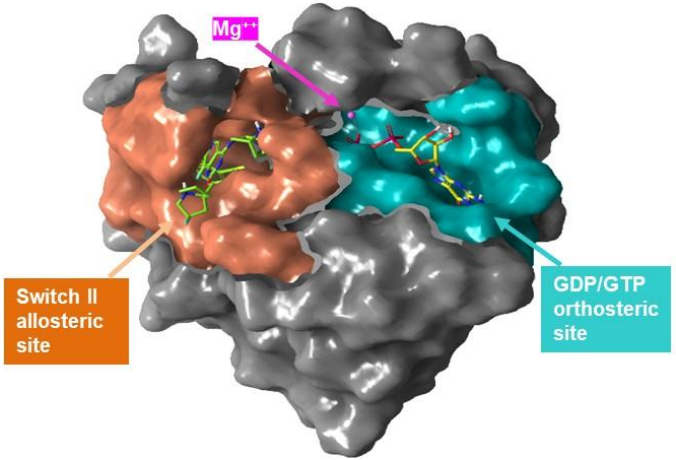
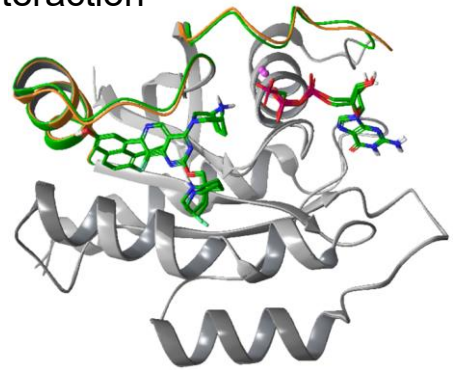
The induced Switch II allosteric pocket is available in both GTP-bound (on) and GDP-bound (off) KRAS



A potent Switch-II inhibitor can achieve dual state binding ("On" / "Off") through an induced and rigidified KRAS conformation that disables effector interaction



Overlap of MRTX1133 bound KRAS G12D in GDP "off" state (PDB:7RPZ) with GTP "on" state (PDB:7T47)

Our design approach

A novel Switch-II chemical scaffold that can induce strong conformational change leading to high binding affinity and long residence time (pseudo-irreversible) to effectively blocks KRAS interactions with effectors

BH-501284: A pseudo-irreversible pan-KRAS inhibitor with long residence and tight binding

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Nucleotide Exchange Assay (NEA)

- Potent inhibition of the SOS1-mediated KRAS bound GDP to GTP exchange with selectivity over HRAS and NRAS

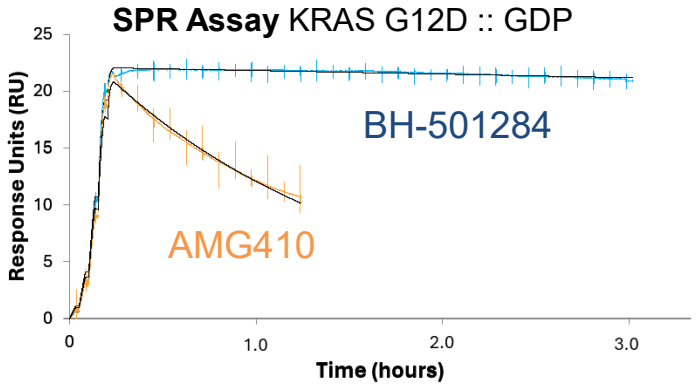
RAS Allele	NEA Assay (by SOS1) IC_{50} (nM)
KRAS G12V	0.81
KRAS G12D	0.86
KRAS G12C	0.87
KRAS G12S	0.50
KRAS G12R	0.50
KRAS G12D/T35S	0.50
KRAS WT	0.79
HRAS WT	3.37
NRAS WT	7.26

Note: Both assays (NEA and SPR) were performed at Reaction Biology

Surface Plasmon Resonance(SPR) Assay

- Picomolar binding affinity, significantly tighter than AMG410 to GDP-bound KRAS G12D
- Long residence time observed both for GDP- and GTP-bound KRAS

SPR Assay KRAS G12D :: GDP	BH-501284	AMG410
K_D (nM)	<0.0148	0.119
T_residence (hr)	>54.2	1.40



BH-501284 fast and deeply modulated active KRAS::RAF interaction and sustained blocking of KRAS Signaling

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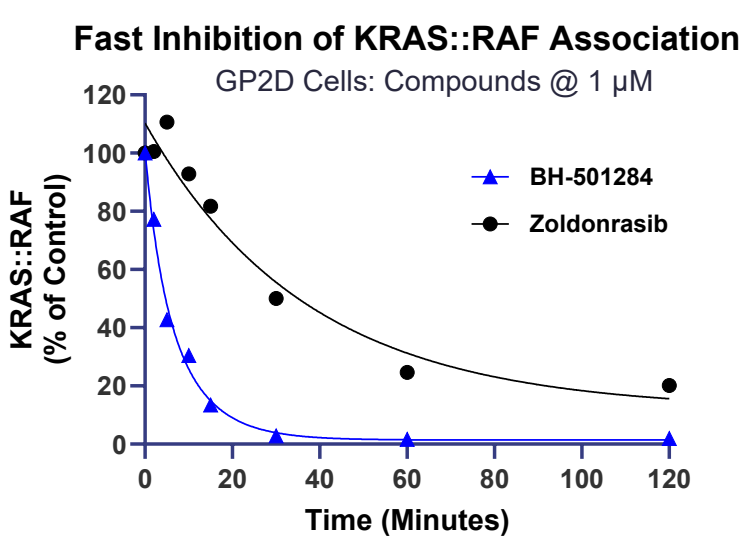

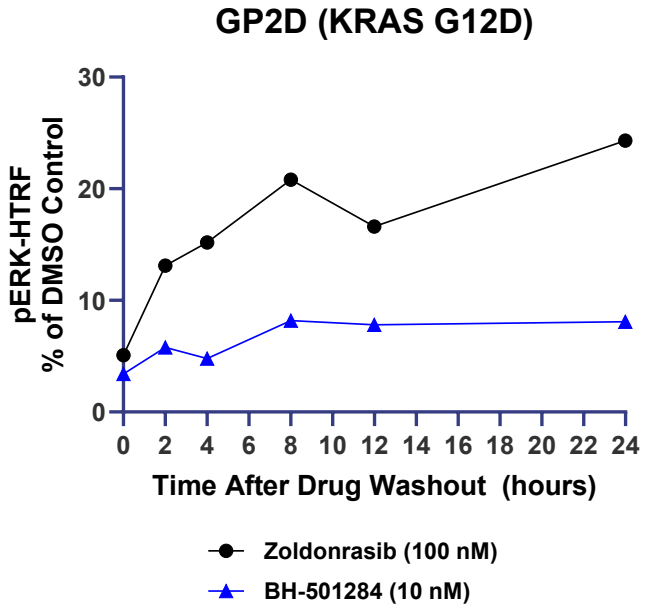

- BH-501284 showed fast and complete inhibition of active KRAS::RAF interaction
- In washout experiment in KRAS G12D mutant GP2D cells, BH-501284 effectively sustained inhibition of phosphorylation of ERK

BH-501284 demonstrated high potency in KRAS sparing HRAS and NRAS

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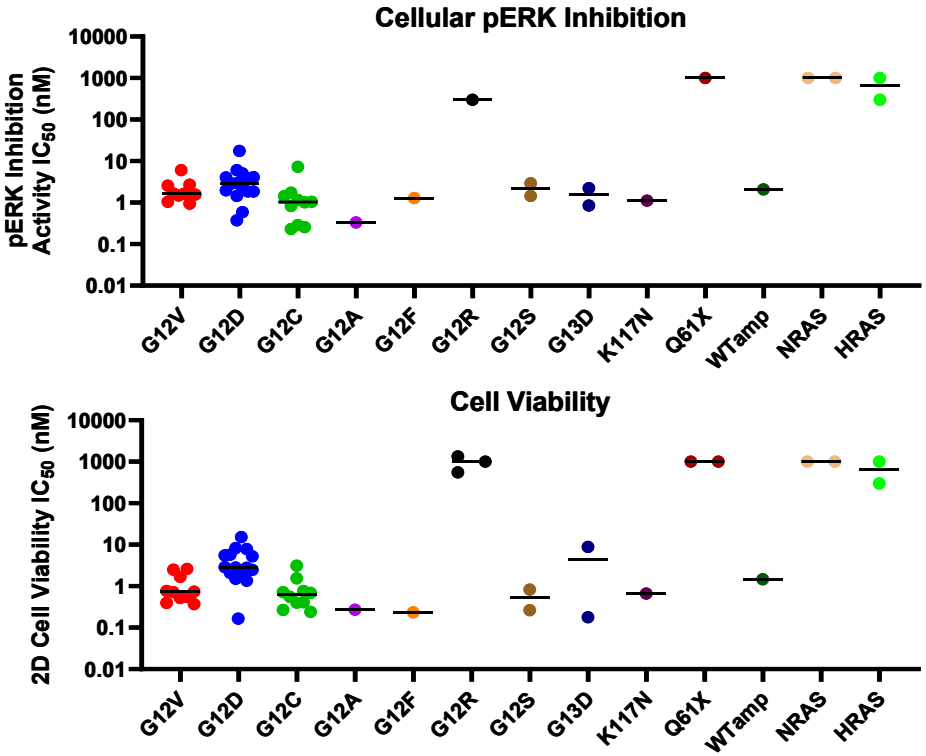

Note: Any IC_{50} value >300 nM, or >1000 nM was plotted as 300 nM, or 1000 nM, respectively.

Median cell viability IC_{50} 0.81 nM in 41 *KRAS* G12/G13 mutant cells excluding KRAS G12R

	Median IC_{50} (nM)	
RAS Mutation	pERK (N)	Cell Viability (N)
KRAS G12V	1.66 (9)	0.73 (10)
KRAS G12D	2.91 (15)	2.80 (15)
KRAS G12C	1.03 (10)	0.62 (10)
KRAS G12A	0.33 (1)	0.27 (1)
KRAS G12F	1.30 (1)	0.23 (1)
KRAS G12R	>300 (1)	>1000 (3)
KRAS G12S	2.20 (2)	0.55 (2)
KRAS G13D	1.54 (2)	4.49 (2)
KRAS K117N	1.12 (1)	0.66 (1)
KRAS Q61X	>1000 (1)	>1000 (2)
KRAS WT^{amp}	2.09 (1)	1.48 (1)
$NRAS^{Mut}$	>1000 (2)	>1000 (2)
$HRAS^{Mut}$	>650 (2)	> 650 (2)

N: Number of KRAS mutant cell lines evaluated

BH-501284 demonstrated marked efficacy in *KRAS* mutant mouse tumor models

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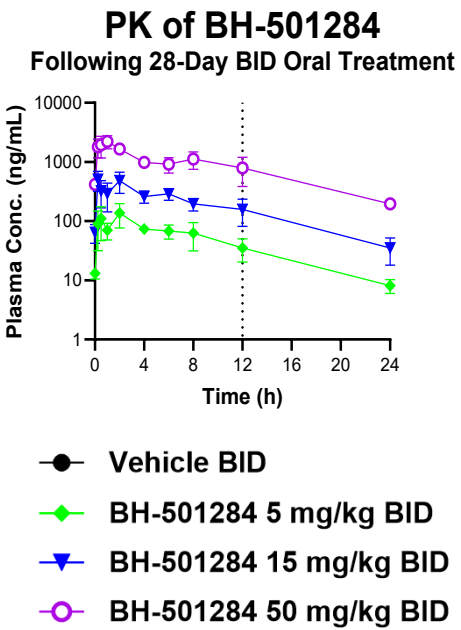
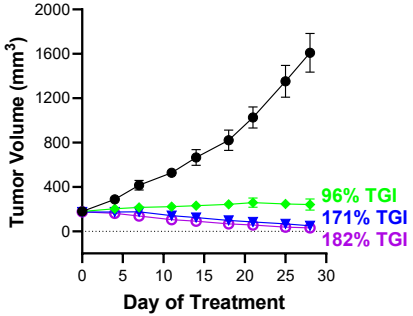
BH-501284 showed dose dependently increased exposures in mice

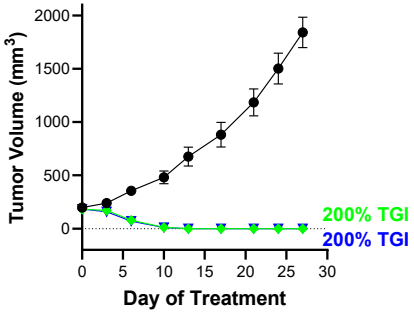


BH-501284 achieved deep tumor regression at low dose levels (5-15 mg/kg BID)

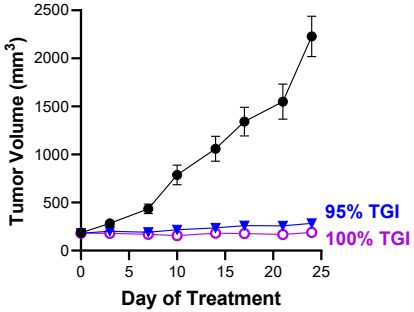
H441 (NSCLC: KRAS G12V)



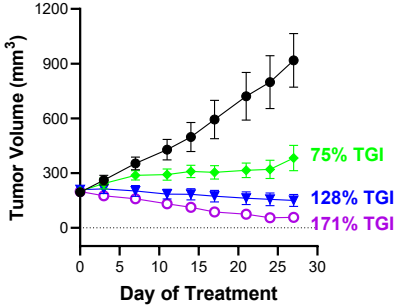
RKN (LMS: KRAS G12V)



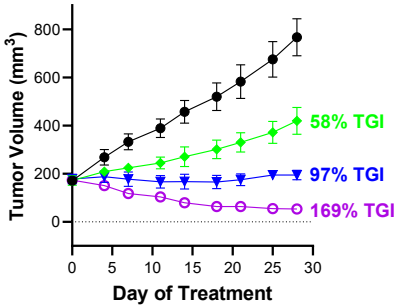
SW620 (CRC: KRAS G12V)



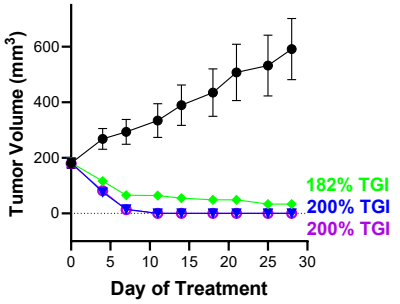
HPAC (PDAC: KRAS G12D)



AsPC1 (PDAC: KRAS G12D)



MiaPaca2 (PDAC: KRAS G12C)



BH-501284 achieved marked efficacy comparable to covalent KRAS G12Ci divarasib

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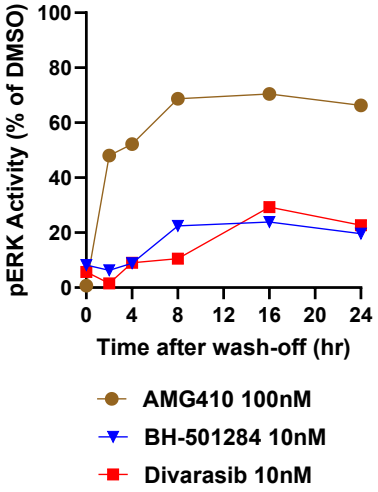
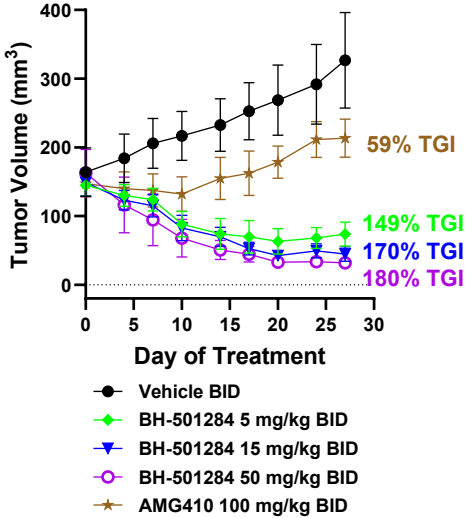
- In wash-off experiment, BH-501284 sustained pERK inhibition as effectively as divarasib, a covalent KRAS G12Ci, while AMG410 lost pERK inhibition
- In a KRAS G12C tumor model, BH-501284 induced tumor regression at a low dose level (5 mg/kg BID 149% TGI), comparable to divarasib, while AMG410 showed limited TGI at high dose

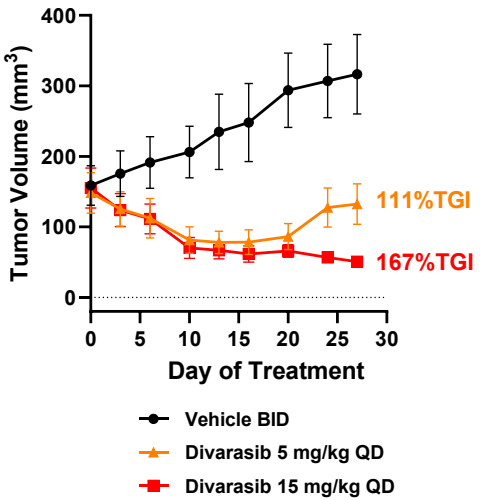
H358 (KRAS G12C)



H358 (NSCLC: KRAS G12C)



H358 (NSCLC: KRAS G12C)



BH-501284 achieved tumor regression at low dose levels compared with clinical compounds

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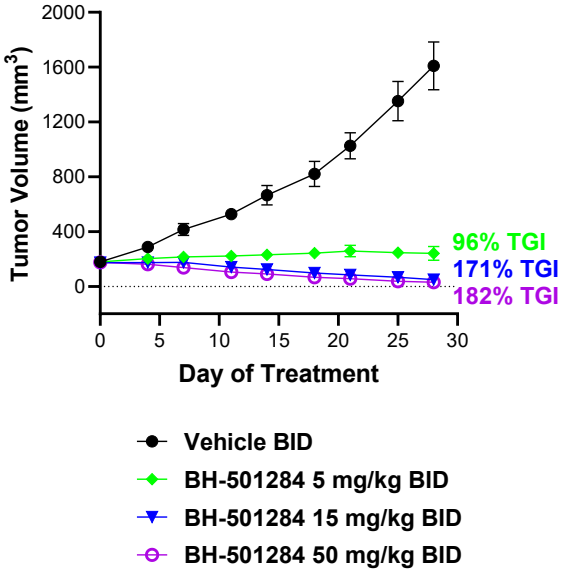
- BH-501284 achieved deep tumor regression in H441 KRAS G12V tumor model at significantly lower dose levels than reported Switch-II Inhibitors

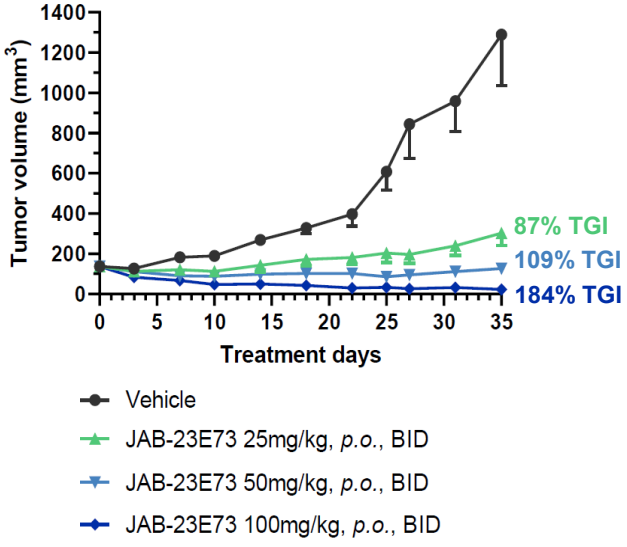
BH-501284

NCI-H441 ($KRAS^{G12V}$)



JAB-23E73

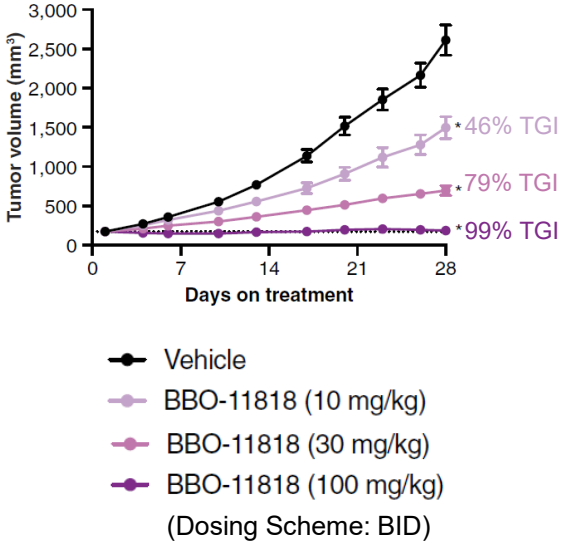
NCI-H441 ($KRAS^{G12V}$)



Wang et al., ENA 2025 Poster

BBO-11818

NCI-H441 ($KRAS^{G12V}$)



Stahlhut et al, *Cancer Disc.* 2026

Evaluation of BH-501284 in combination with cetuximab

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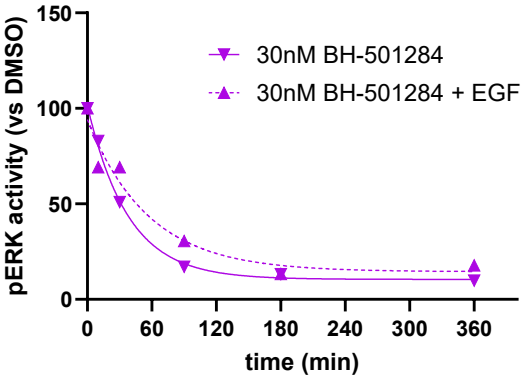
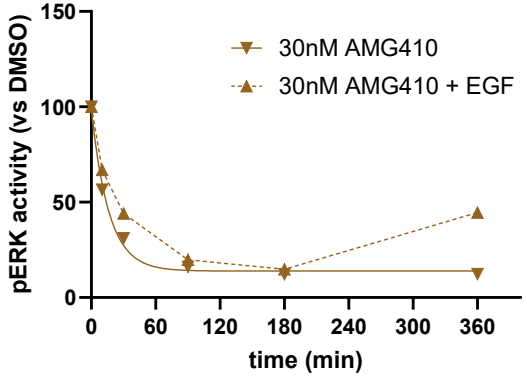
- Addition of EGF ligand (40ng/mL) reduced KRAS inhibitor potency in MiaPaca (PDAC: KRAS G12C) cell lines





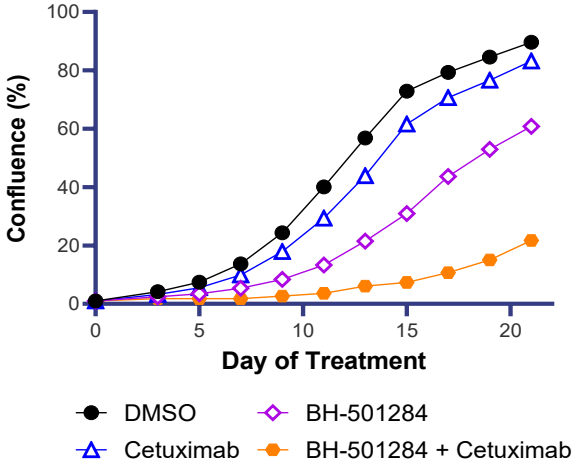
- BH-501284 sustained anti-proliferation activity with only 2-fold IC_{50} shift in H358 cells (KRAS G12C) in the presence of EGF ligand

KRAS Inhibitor	H358 Cell Proliferation IC_{50} (nM)		Fold Shift
	No EGF	+ EGF (40 ng/mL)	
BH-501284	0.38	0.77	2.02
AMG410	6.30	22.2	3.52

- Combination of BH-501284 with cetuximab prolonged the inhibitory effect on LS180 (CRC: KRAS G12D) cell growth

Long-term Cell Growth Assay
LS180 (CRC: KRAS G12D)

BH-501284: 5nM; Cetuximab: 0.5ug/mL



Summary

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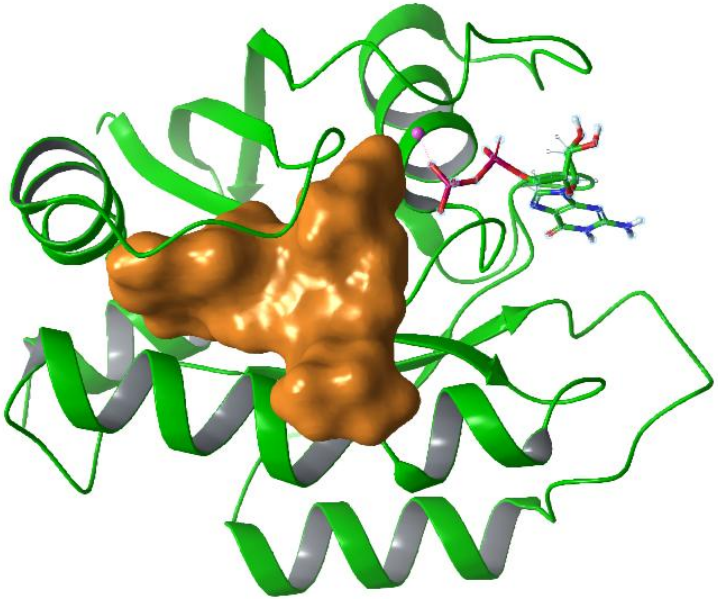
BH-501284 is a potent pseudo-irreversible dual-state pan-KRAS inhibitor, sparing H/NRAS

- High binding affinity with prolonged residence time (>54 hrs)
- Superb cell potency (low nM) with sustained inhibition against KRAS G12V/D/C, sparing H/NRAS
- Marked efficacy in multiple *KRAS* mutated mouse CDX tumor models at relatively low oral dose levels when compared with KRAS inhibitors in clinic
- Improved oral bioavailability across species (Mouse 30%; Rat 27%; Dog 13%)
- IND enabling studies ongoing



The molecular surface of BH-501284 modeled within the binding pocket of KRAS G12D in the GDP “off” state (PDB:7RPZ)