

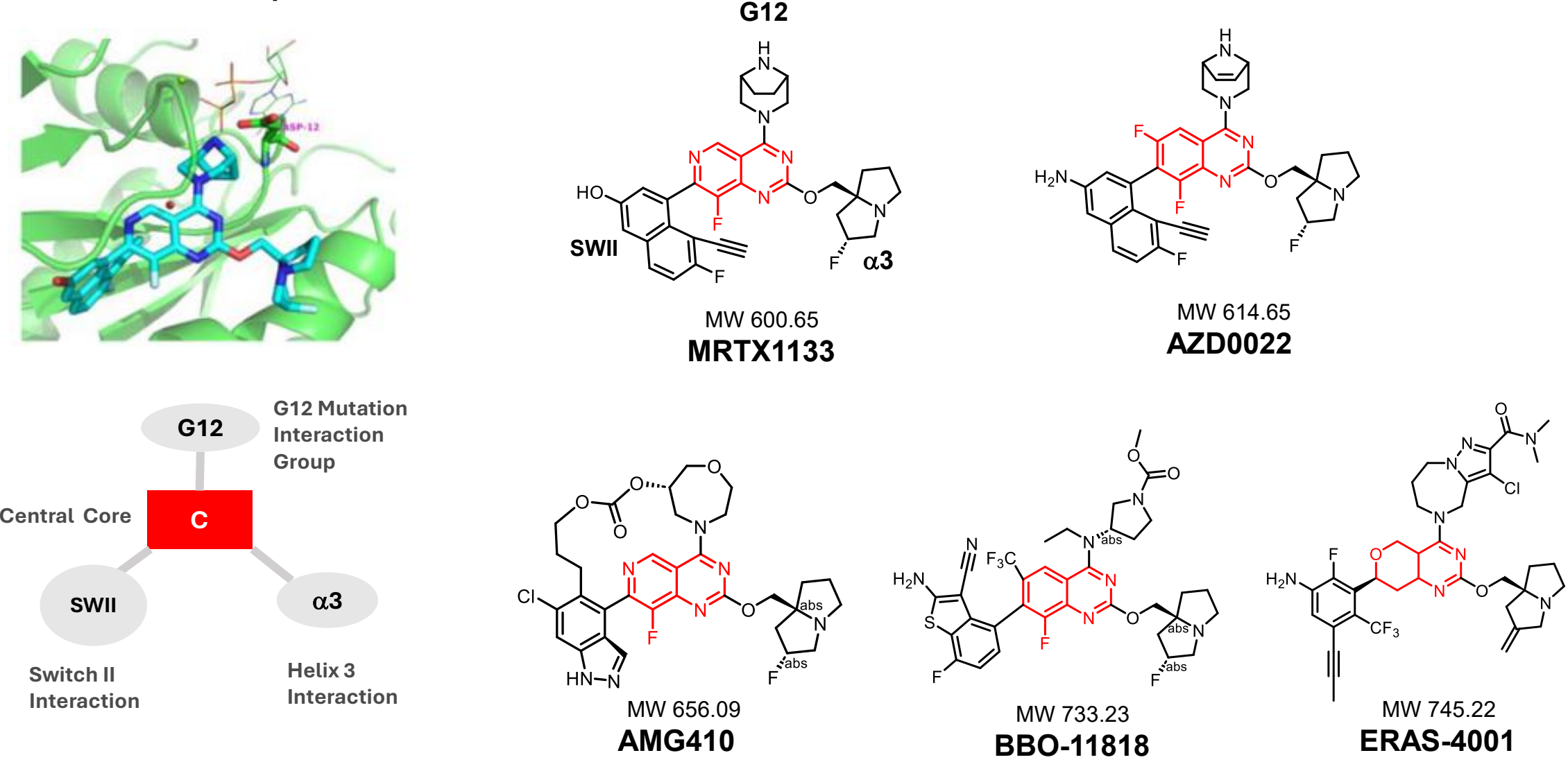
Pseudo-irreversible, Pan-KRAS Inhibitor BH-501284 Achieves Prolonged Inhibition of KRAS Signaling Leading to Deep and Durable Antitumor Efficacy in Mouse Tumor Models

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Introduction

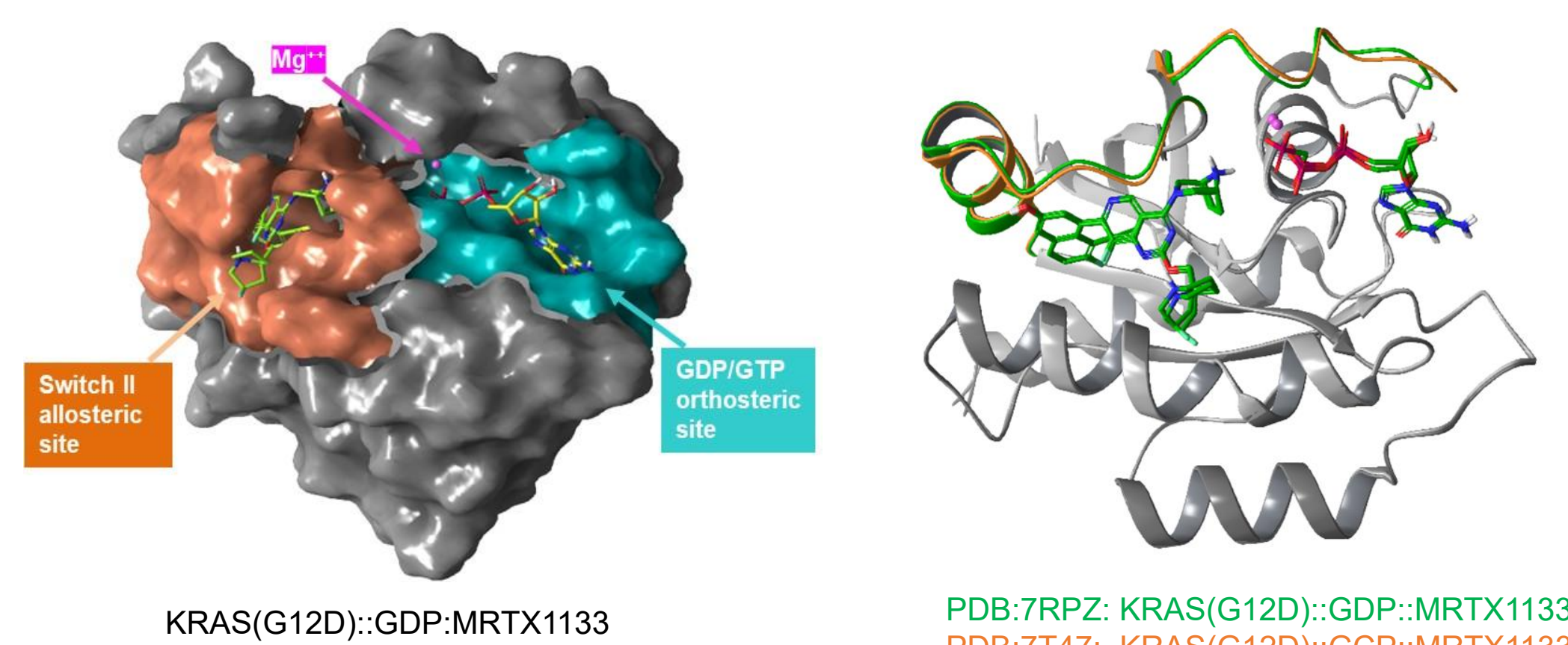
KRAS mutations are involved in approximately 25% of all tumors and occur as oncogenic drivers in lung (32%), colorectal (40%) and pancreatic cancers (85-90%). The most common KRAS driver mutations are on codon 12 and 13, including G12C, G12D, G12V, G12R, G12A, G13D etc. The G12C mutation has been effectively targeted using a covalent strategy that exploits the unique reactivity of the Cys residue to lock the KRAS G12C inhibitors in an induced Switch-II allosteric pocket. The G12D inhibitors, as exemplified by MRTX1133, form salt bridge with mutated Asp residue to achieve high binding affinity. However, the Switch-II pocket is shallow such that non-covalent inhibitors often require high molecular weight, resulting in unfavorable drug-like properties. Nevertheless, multiple Switch-II binding KRAS inhibitors targeting G12D, G12V, or pan-KRAS mutations have advanced into clinical trials.



Design of BH-501284: Principles and Approach

KRAS Switch-II Inhibitors Rigidify KRAS Conformation to Disable Binding with Effectors: A Foundation for Design Strategy

- KRAS Switch-II inhibitors act allosterically inside an induced pocket near Switch-II range, which is available in both GTP-bound (on) and GDP-bound (off) KRAS
- A Switch-II inhibitor can achieve dual state binding ("On" / "Off") through an induced and rigidified KRAS conformation that disables effector interaction
- Allosteric switch-II inhibitors rigidified KRAS conformation to disable binding with effectors and arrest the GTPase cycling



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 block KRAS interactions with effectors and arrest the GTPase cycling

Broad Activity Inhibiting Nucleotide Exchange

- BH-501284 showed potent activity inhibiting SOS1-mediated nucleotide exchange from GDP to GTP across broad spectrum of KRAS mutations

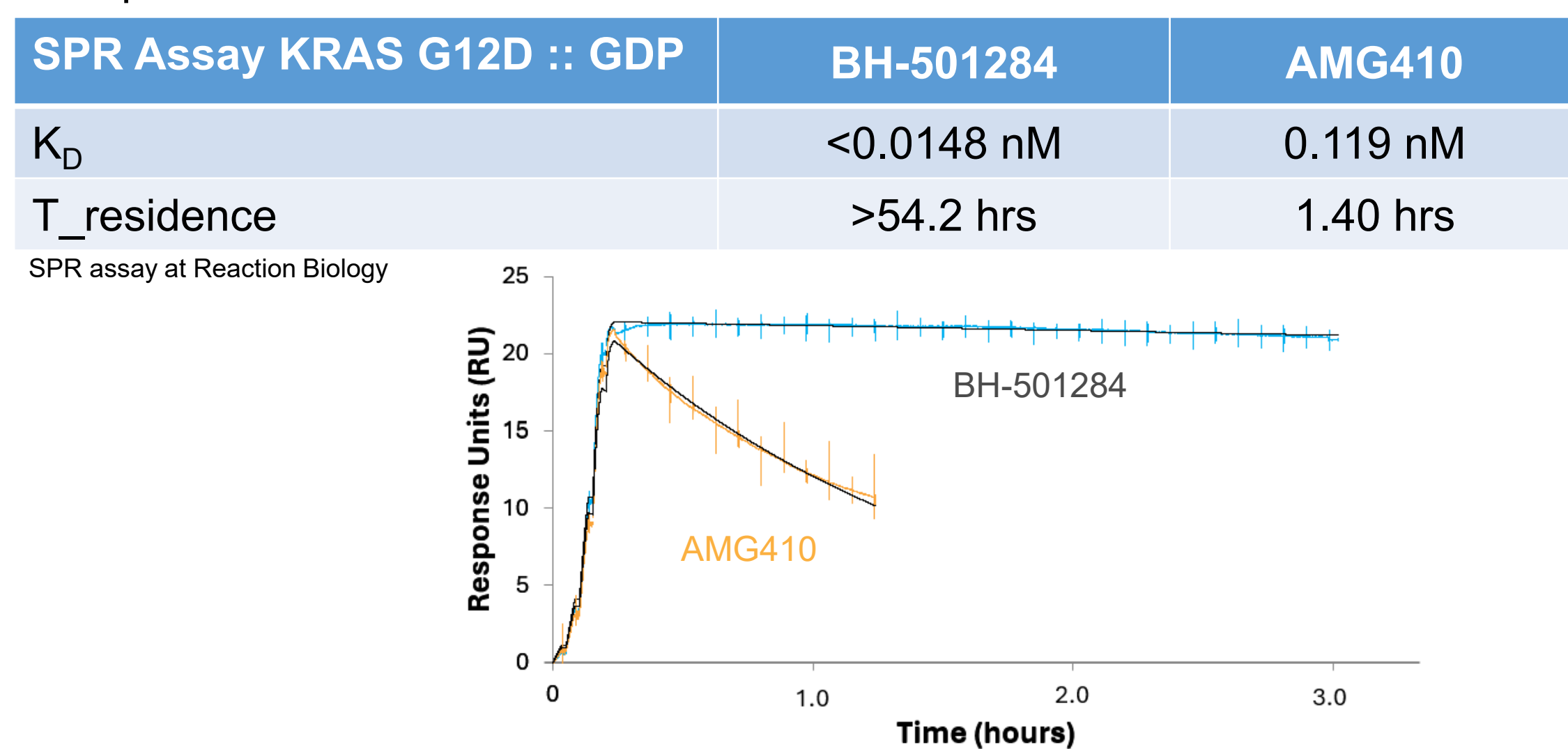
KRAS Allele	G12V	G12D	G12C	G12D/T35S	G12S	G12R	WT
BH-501284 IC ₅₀ (nM)	0.81	0.86	0.87	0.50	0.50	0.50	0.79

HTFR nucleoside exchange assay at Reaction Biology (Data cut-off 31JAN2026).

BH-501284: Pseudo-irreversible Pan-KRAS Inhibitor

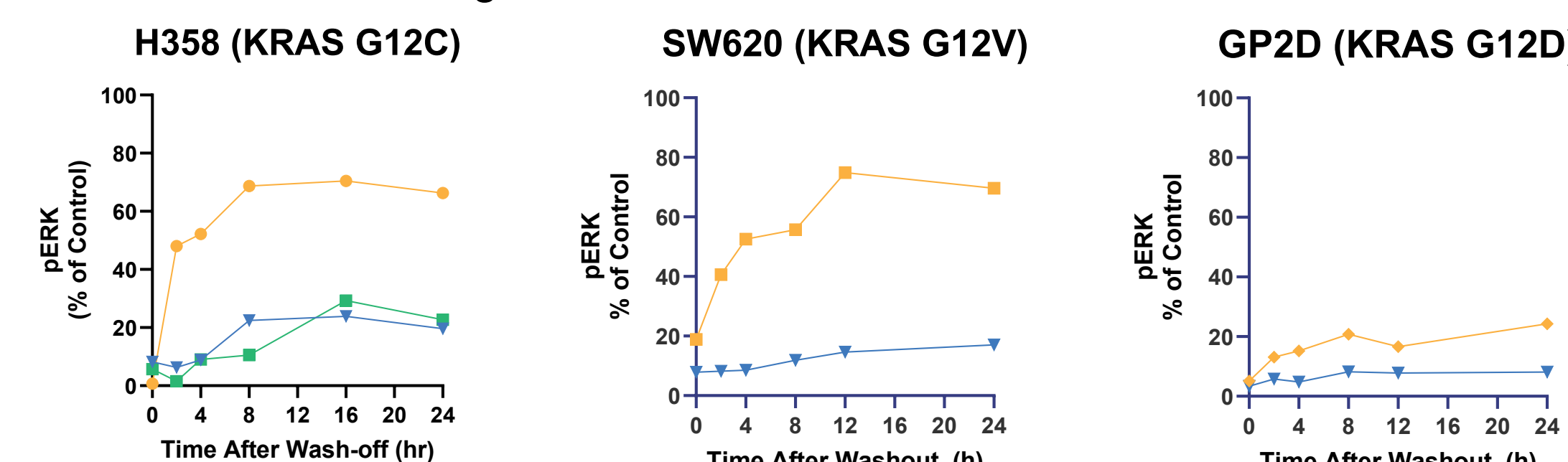
Tight Binding and Long Residence Time in SPR Assay

- BH-501284 has picomolar binding affinity, significantly tighter than AMG410 to GDP-bound KRAS G12D protein
- BH-501284 showed long residence time observed both for GDP- and GTP-bound KRAS proteins

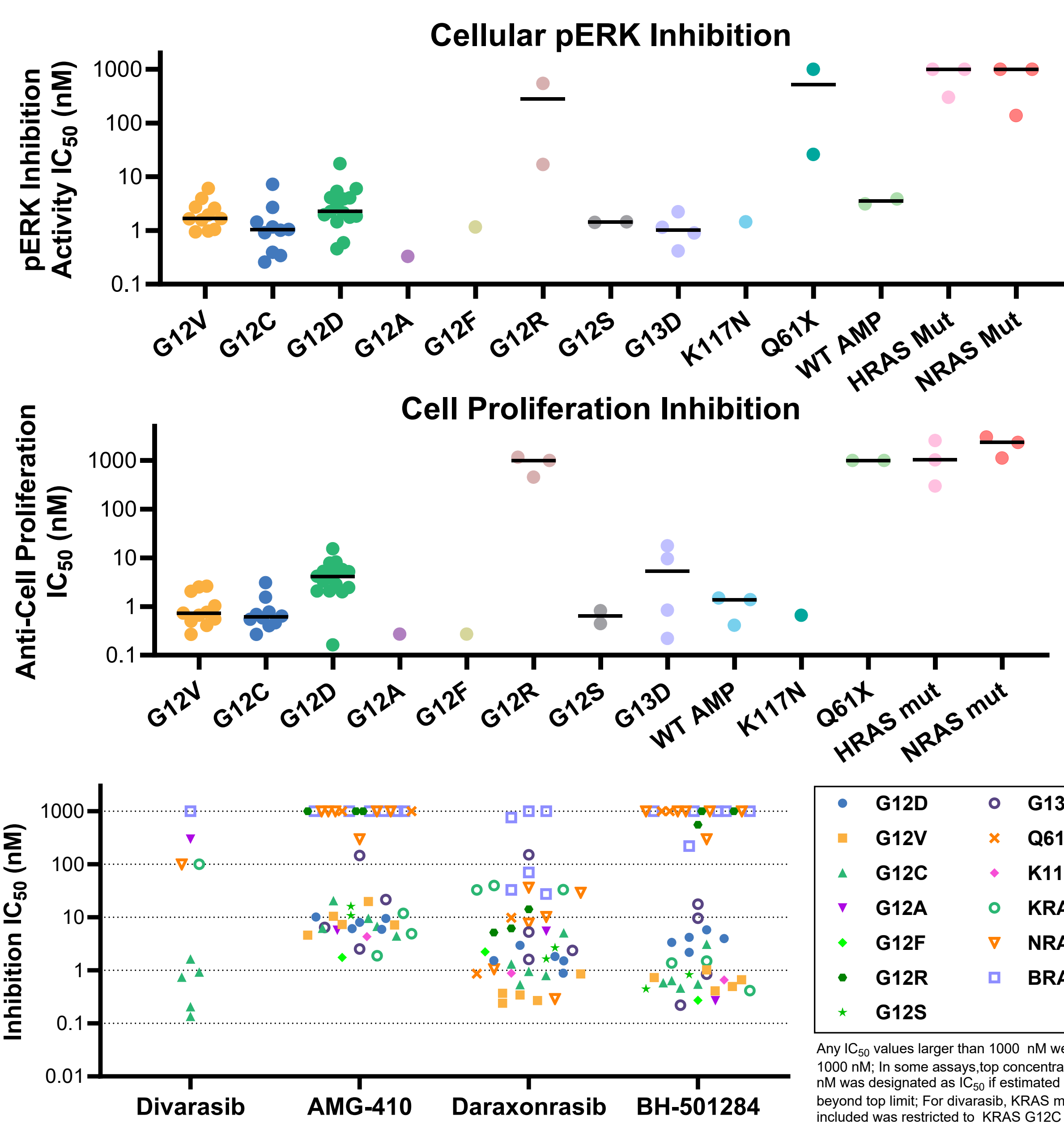


Prolonged KRAS Signaling Inhibition in Cellular Washout Assay

- In washout experiment, BH-501284 sustained pERK inhibition as effectively as irreversible inhibitors divarasil and zoldonarasib, while AMG410 or BBO-11818 lost pERK inhibition after drug removal

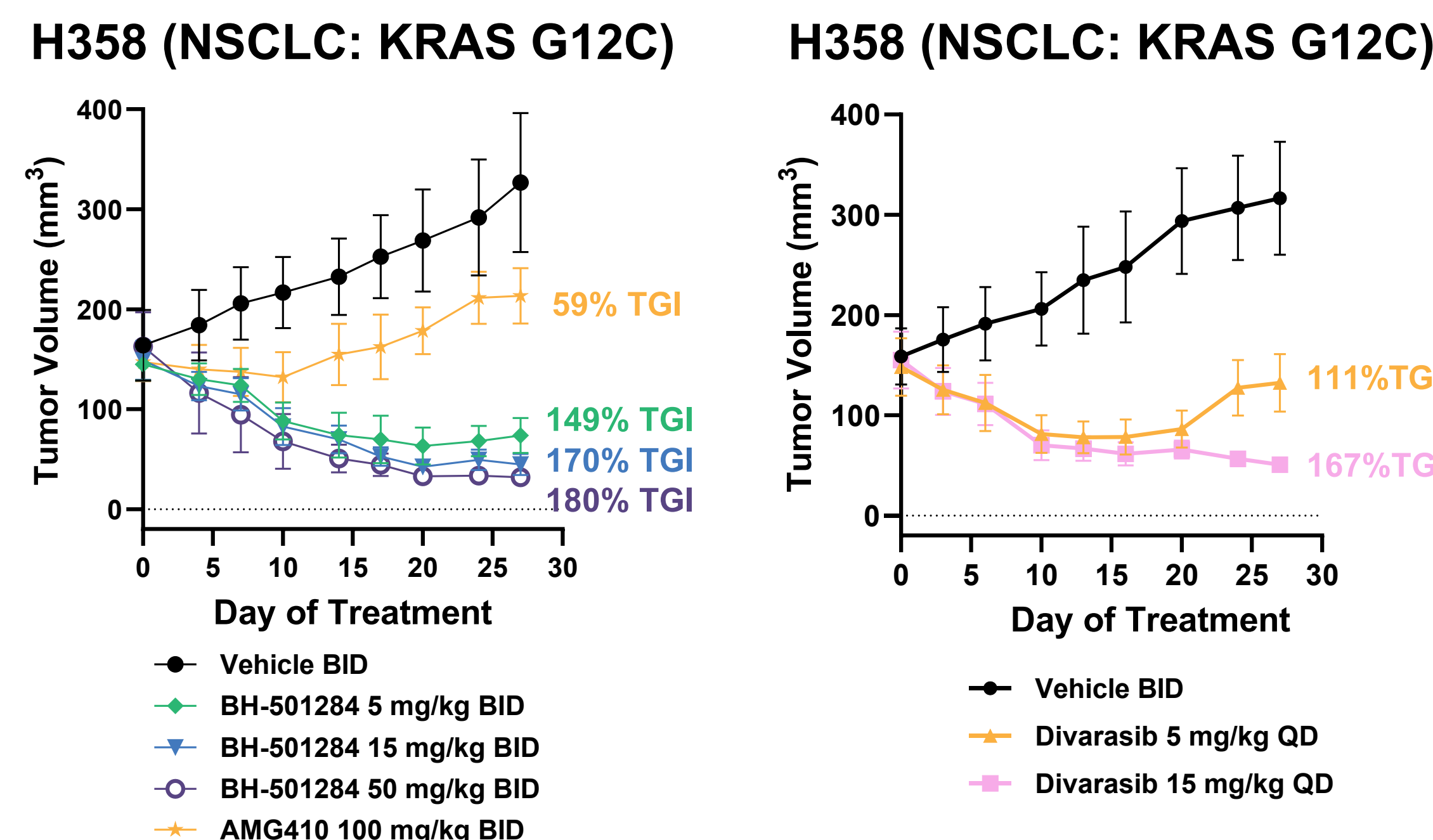


BH-501284: Potent Inhibition of pERK and Cell Proliferation



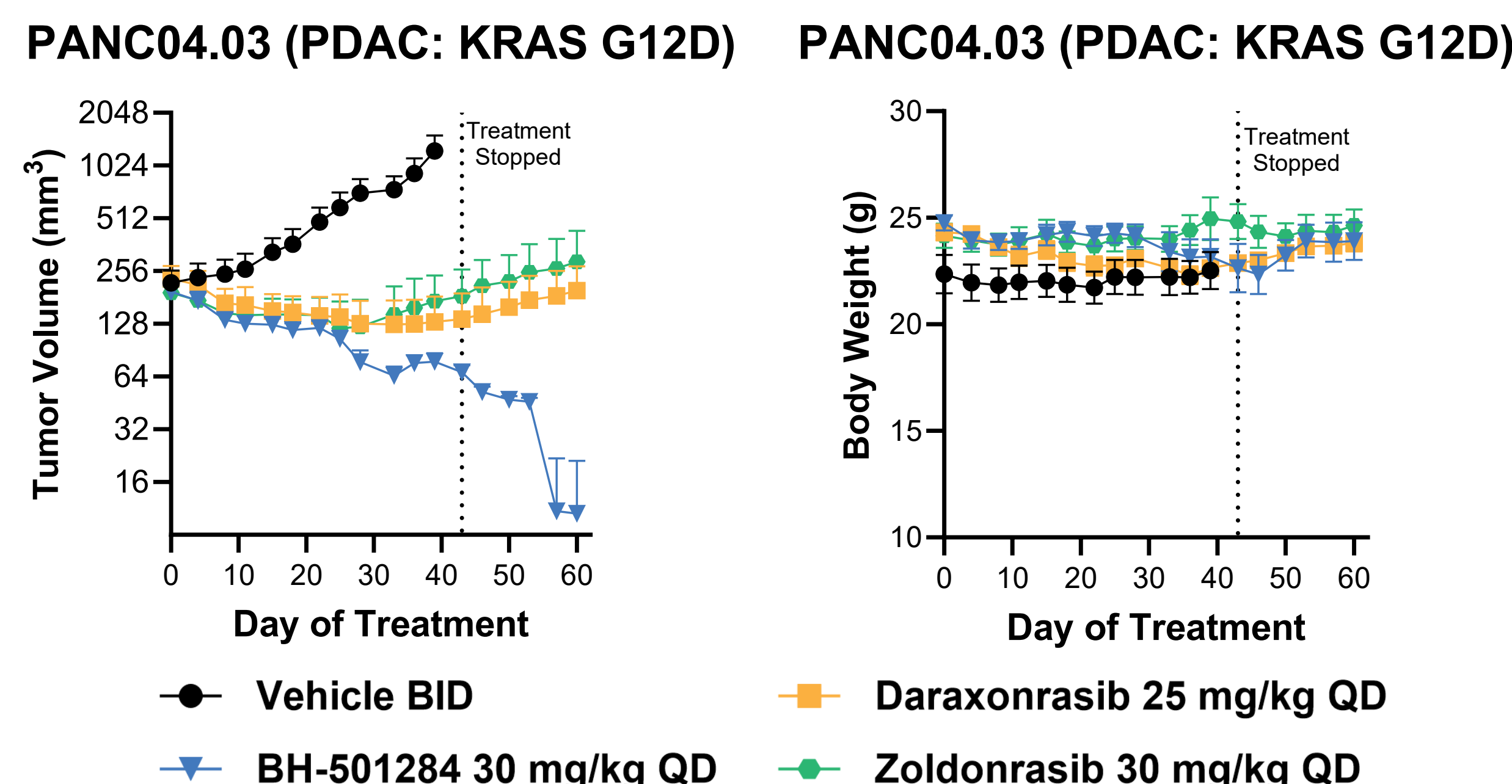
BH-501284: Comparable Efficacy to Covalent KRAS G12C Inhibitor Divarasil

- In H358 KRAS G12C tumor model, BH-501284 induced tumor regression at a low dose level (5 mg/kg BID 149% TGI), comparable to divarasil, while AMG410 showed limited TGI at high dose

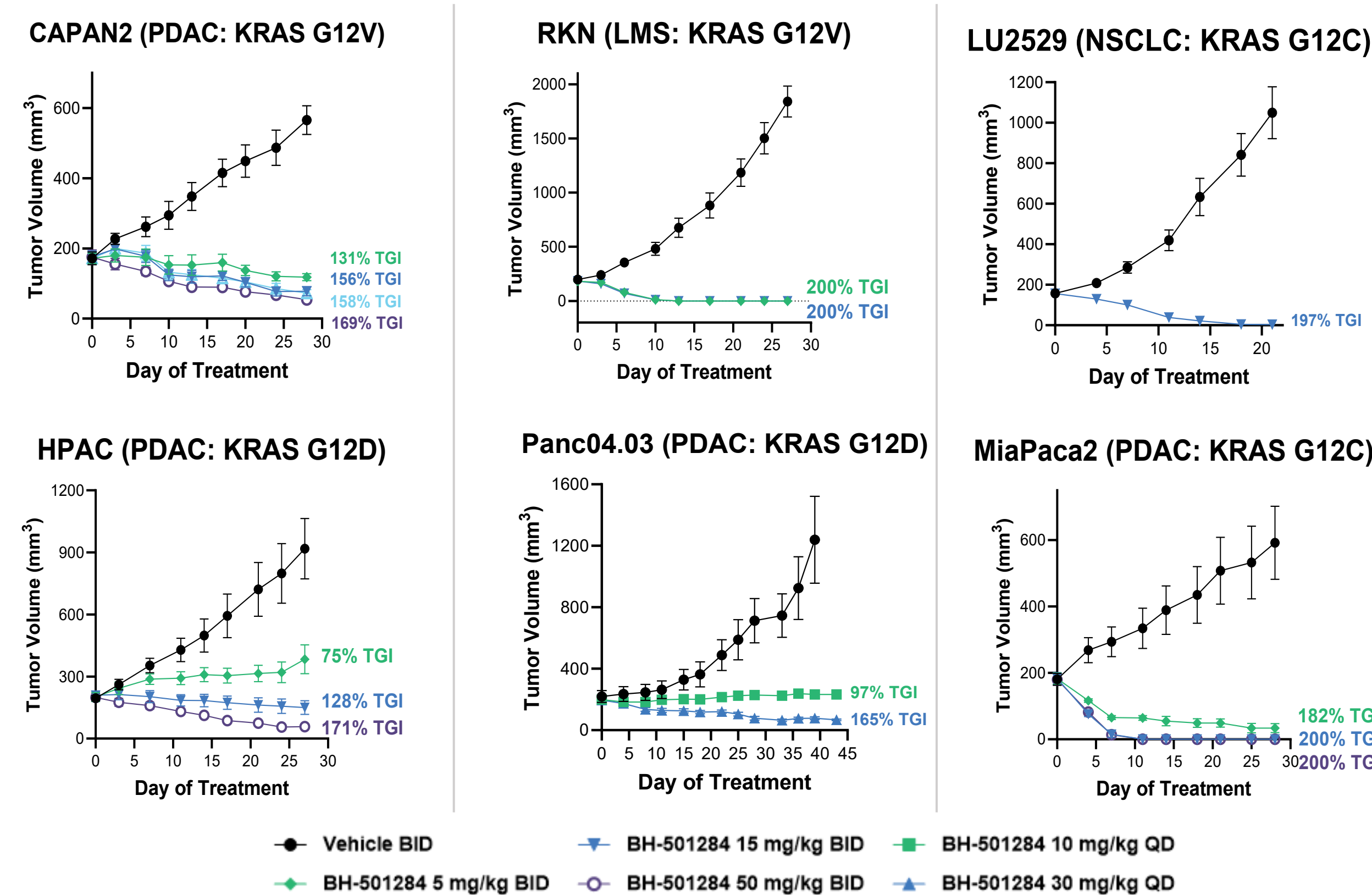


BH-501284 Induced Deeper and More Sustainable Tumor Regression than Tri-complex RASi

- Compared to tri-complex RAS-ON inhibitors daraxonarasib and zoldonarasib, BH-501284 showed deeper tumor regression and more sustained antitumor activity in the Panc 04.03 KRAS G12D tumor model, even after treatment withdrawal.

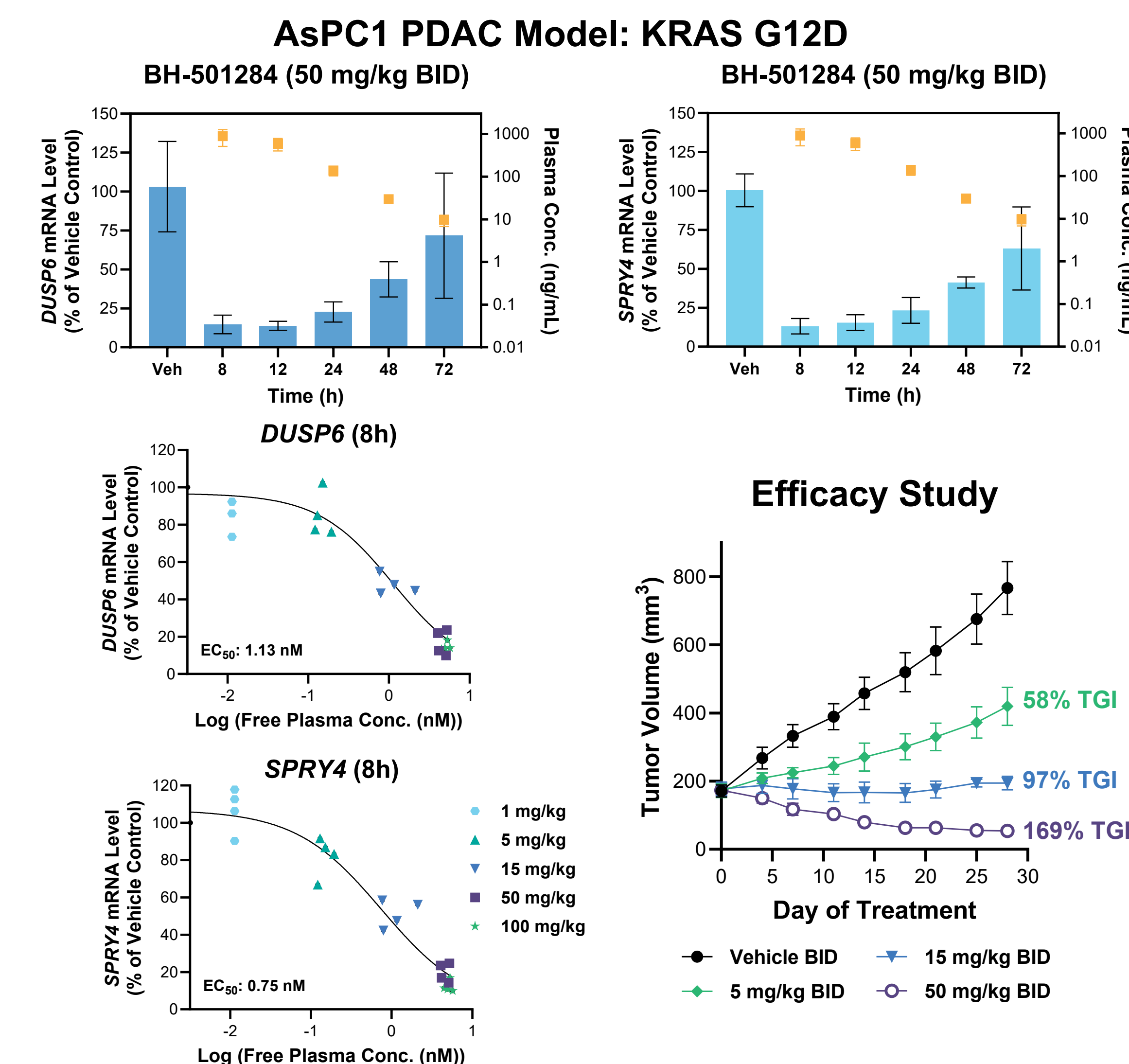


BH-501284: In Vivo Efficacy at Low Dose Levels in Multiple KRAS-Mutant Models



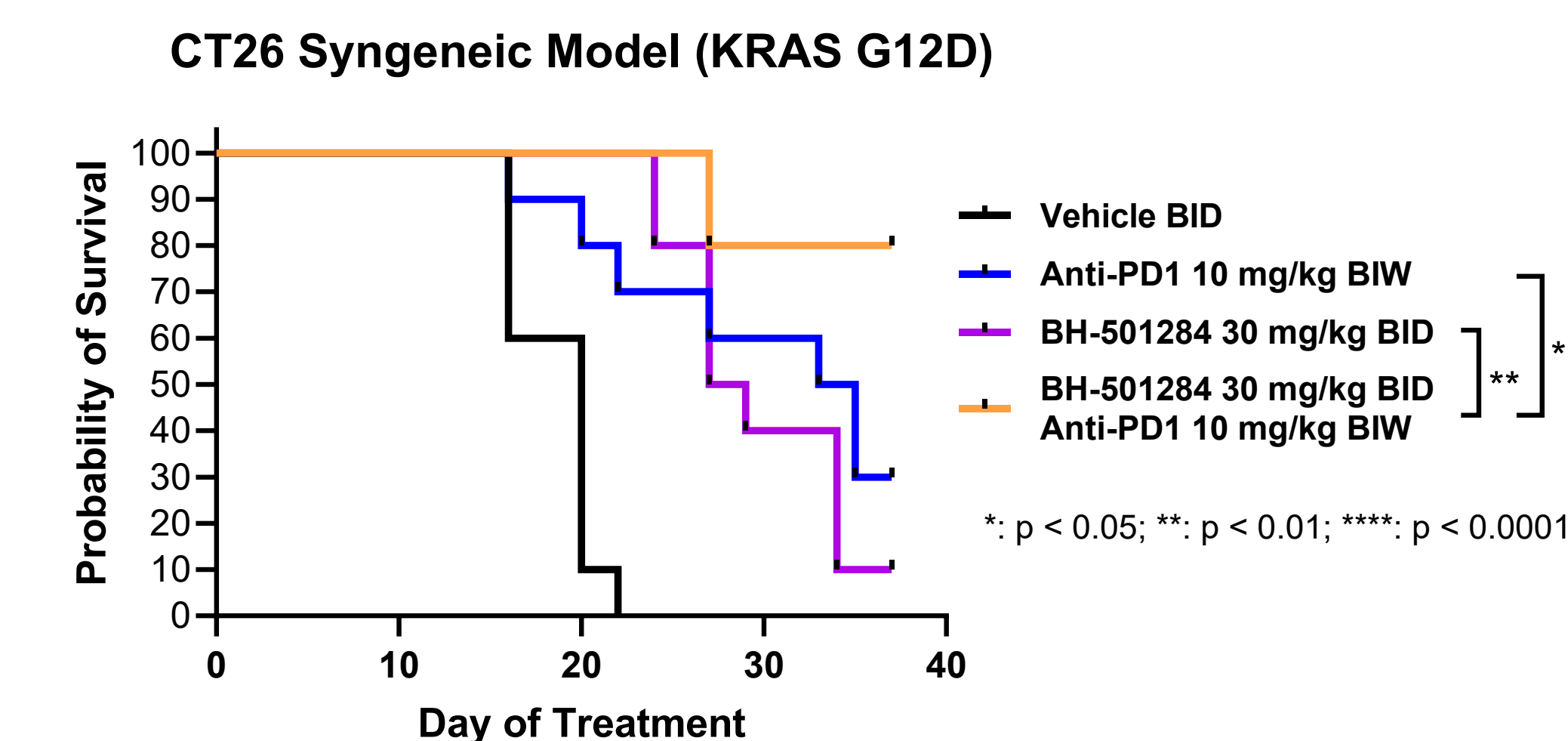
BH-501284: Extended and Potent KRAS Signaling Inhibition In Vivo

- PK/PD was studied using mRNA expression levels of *DUSP6* and *SPRY4* as biomarkers for KRAS activity in the AsPC-1 KRAS G12D CDX tumor model after the last dose following 2-day BID treatment.
- Extended inhibition of KRAS signaling biomarkers after the last dose was observed
- At 8h post the last dose at various dose levels, BH-501284 showed EC₅₀ approximately 1 nM for both biomarkers in the AsPC1 KRAS G12D model



BH-501284 in Combination with Anti-PD1 Improved OS in CT26 Syngeneic Model

- Combination of BH-501284 and anti-PD1 antibody extended median survival time in the CT26 syngeneic model harboring the KRAS G12D mutation



Conclusions

- BH-501284 is designed and discovered to be a novel non-covalent Switch-II inhibitor that exhibits high binding affinity and pseudo-irreversible characteristics
- BH-501284 exhibited extended suppression of KRAS signaling and potent antitumor activity across multiple KRAS-mutant cancer models in vitro and in vivo
- As a non-covalent pan-KRAS inhibitor, BH-501284 showed comparable efficacy to covalent KRAS inhibitor divarasil and is more efficacious than tri-complex RAS-ON inhibitors in KRAS-mutant tumor models
- These data support the potential of BH-501284 to overcome limitations of available KRAS and pan-RAS inhibitors and strongly support advancement of BH-501284 toward an IND submission in Q1 2027

Note: All reference compounds in this poster are proxy ones from commercial vendors.