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BBP-398, a potent, small molecule inhibitor of SHP2, enhances the response of established NSCLC xenografts to KRAS^{G12C} and EGFR^{mut} inhibitors

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I have the following financial relationships to disclose:

Consultant for: none

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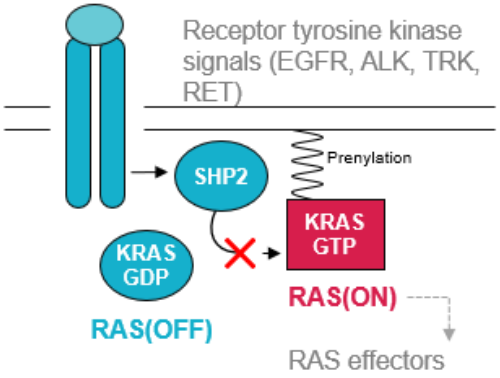
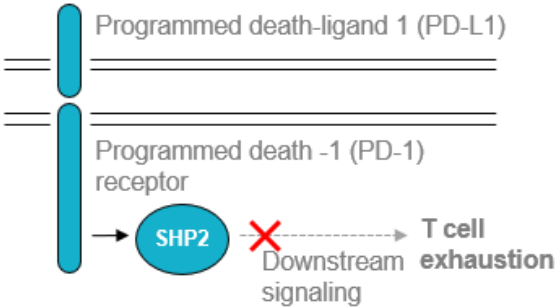
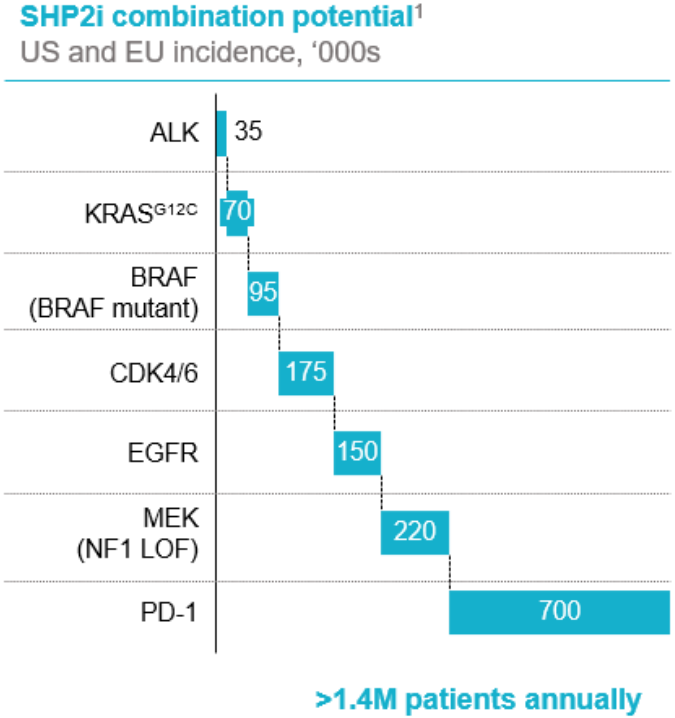
SHP2 inhibition has the potential to become a combination drug across a myriad of cancers



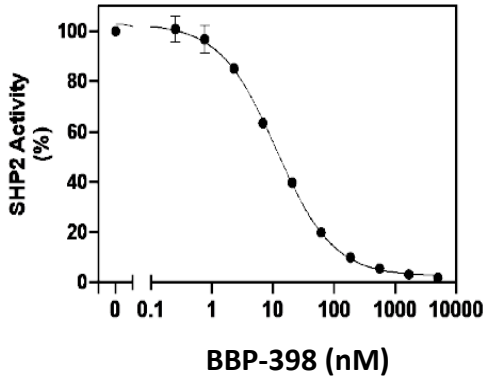




1 Preclinical data of combination efficacy with SHP2i
SOURCE: Primarily WHO Globocan 2020, SEER and AACR GENIE, with multiple supplementary literature sources

BBP-398 is a potent and selective SHP2 inhibitor with a favorable PK profile

SHP2 Enzyme Potency



Phosphatase	IC_{50} (nM)
Wild-type SHP2	13
SHP1	>10000
SHP2 E76K	>10000

SHP2 Selectivity

Class	Results
419 Kinase Ambit panel @ 1 μM	4 Kinases: PRKCH, LATS1, GCN2, HPK1
CEREP & PTPase panel @ 10 μM	No significant inhibition

BBP-398 Pharmacokinetics

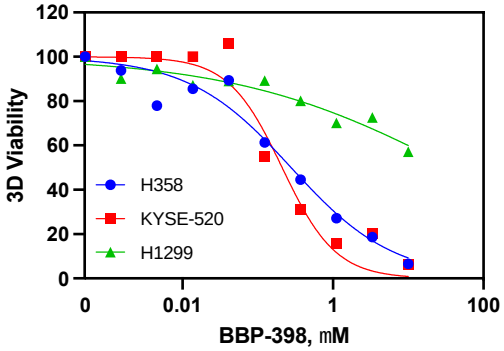
Species	Dose IV/PO (mg/kg)	CL (ml/min/kg)	Vd_{ss} (L/kg)	$T_{1/2}$ (hr) IV	C_{max} (mM) PO	F%
Rat	0.3 / 10	10.2	6.0	9.2	0.67	51
Dog	1 / 10	8.5	5.5	8.2	6.5	115
Cyno	0.3 / 1	6.0	2.7	6.4	0.43	52

BBP-398 is a selective SHP2i with no hERG inhibition at concentrations up to 30 μM*

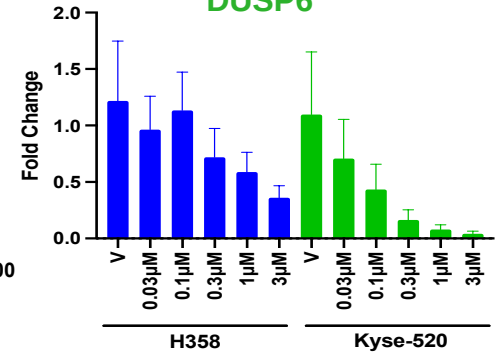
*patchclamp

BBP-398 shows potent pathway and tumor growth inhibition across a panel of cell lines with active MAPK signaling

SHP2 Cell-Based Potency

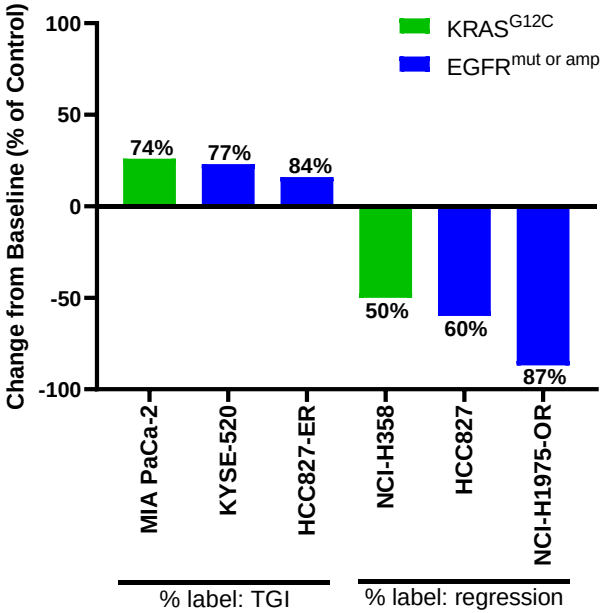


DUSP6



Cell Line	Mutation	pERK (IC_{50},nM)	3D CTG (IC_{50},nM)
KYSE-520	$EGFR^{amp}$	80	210
NCI-H1975	$EGFR^{L858R/T790M}$	400	180
HCC827	$EGFR^{Ex19del}$	460	1200
NCI-H358	$KRAS^{G12C}$	690	280
NCI-H1299	$NRAS^{Q61K}$	>25,000	>25,000

BBP-398 Preclinical In Vivo Monotherapy Efficacy

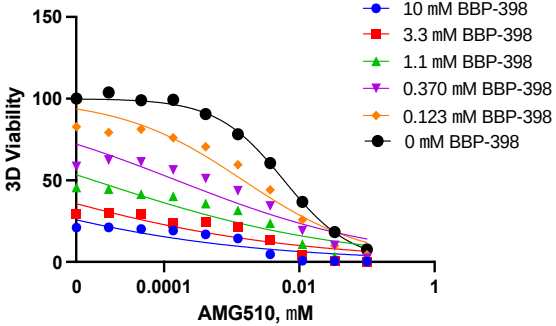


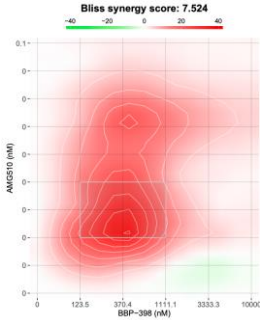
CDX models dosed QD PO with 100 mg/kg BBP-398
Two-way ANOVA for all models: p<0.0001 vs vehicle

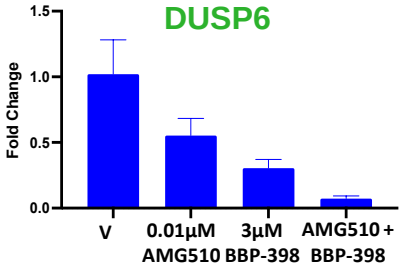
HCC827-ER: erlotinib resistant
NCI-H1975-OR: osimertinib resistant

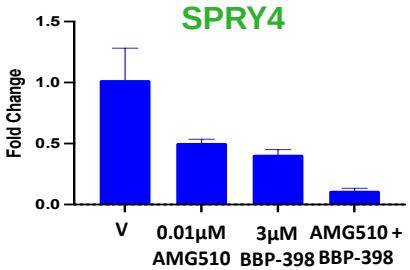
BBP-398 and sotorasib (AMG510) synergize to inhibit MAPK signaling and cell viability in NCI-H358 KRAS^{G12C} cells

NCI-H358 (KRAS^{G12C}) In Vitro Viability

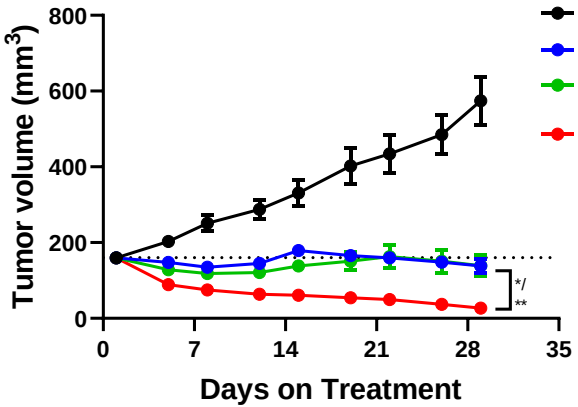








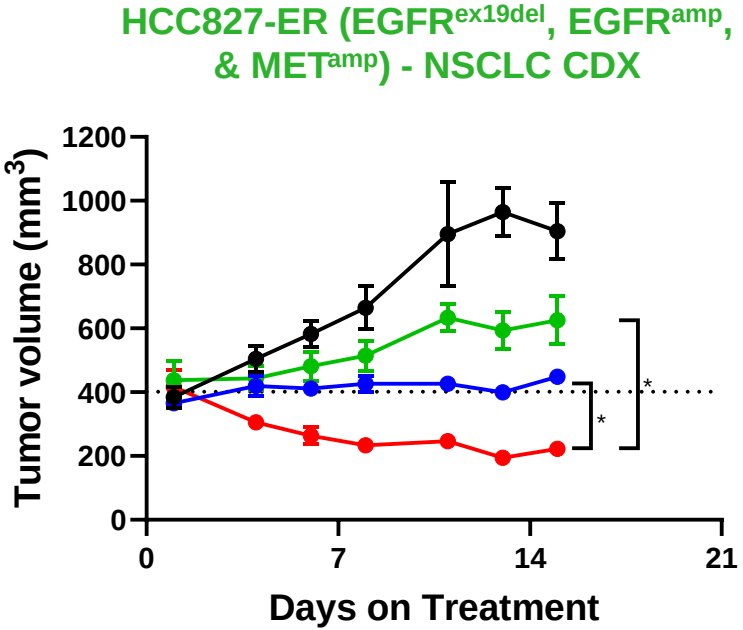
NCI-H358 (KRAS^{G12C}) - NSCLC CDX



All groups dosed QD, PO
Two-way repeated-measures ANOVA:
*p < 0.001 for sotorasib vs combo,
**p< 0.0001 for BBP-398 vs combo

Group (n=10)	Day 29		
	Mean tumor regression	Number of regressions	Mean body weight change
Vehicle	-	0/10	+5.1%
BBP-398 (100 mg/kg)	14%	8/10	-6.5%
Sotorasib (10 mg/kg)	13%	9/10	-0.3%
BBP-398 (100 mg/kg) + sotorasib (10 mg/kg)	83%	10/10	-2.4%

Combination of BBP-398 and osimertinib induces robust regressions in the osimertinib-resistant HCC827-ER xenograft model



Group (n=5)	TGI	Day 15*		
		Mean tumor regression	Number of regressions	Mean body weight change
Vehicle		-	0/2	+5.2%
BBP-398 (100 mg/kg)	84%	-	0/4	+6.3%
Osimertinib (5 mg/kg)	64%	-	0/4	+1.0%
BBP-398 (100 mg/kg) + osimertinib (5 mg/kg)	-	47%	5/5	-6.3%

*3/5 mice in the vehicle group, 1/5 mice in the BBP-398 group, and 1/5 animals in the osimertinib group were euthanized due to tumor ulcerations before day 15

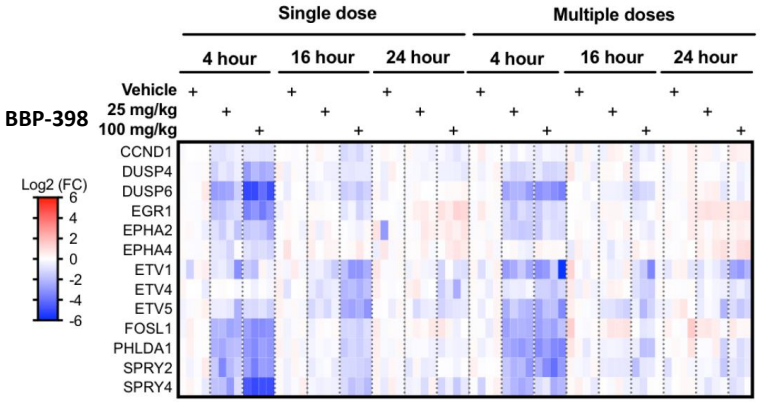
All groups dosed QD, PO
Two-way repeated-measures ANOVA: *p< 0.0001
HCC827-ER: HCC827-erlotinib resistant

KYSE-520 tumor PD analysis suggests target coverage for ~16 hrs over IC_{50} and daily recovery lead to optimal efficacy

In vivo PD in KYSE-520 Tumors (mRNA)

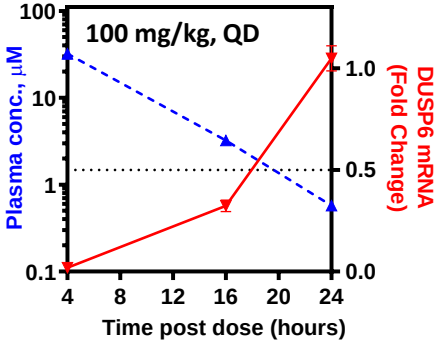
Maximum effective dose: 100 mg/kg QD

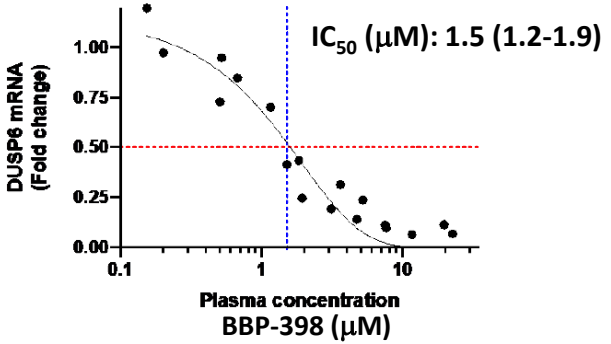
Decreased expression of MAPK pathway is observed soon after BBP-398 dosing



DUSP6 (mRNA)

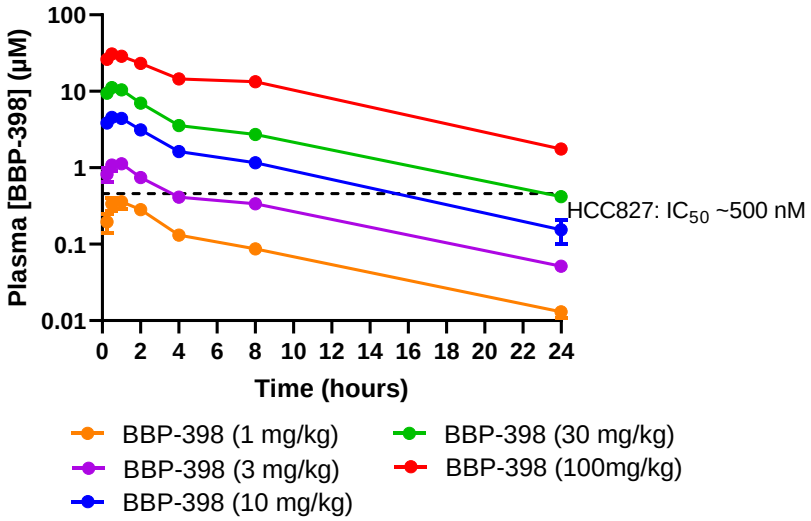
PK/PD relationship and IC_{50} determination in KYSE-520 treated with BBP-398





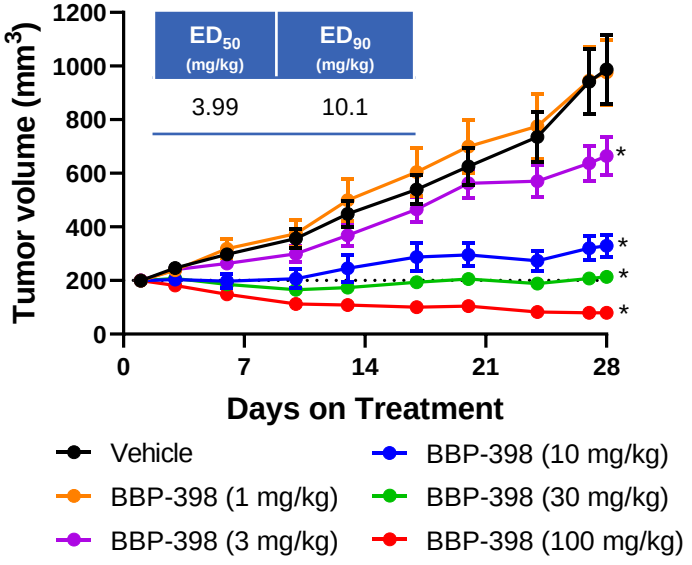
ED_{90} in the HCC827 ($EGFR^{ex19del}$ & $EGFR^{amp}$) CDX model confirms time over pERK IC_{50} of ~16 hours drives efficacy

Time of [BBP-398] over pERK IC_{50}



NOD/SCID mice dosed QDx1, PO

HCC827 ($EGFR^{ex19del}$ & $EGFR^{amp}$) - NSCLC CDX

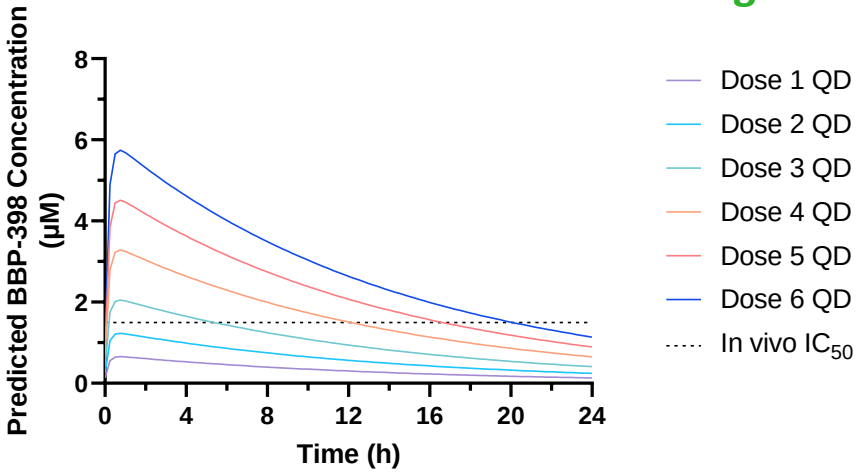


All groups dosed QD, PO
Two-way mixed-effects ANOVA: *p < 0.0001 vs vehicle

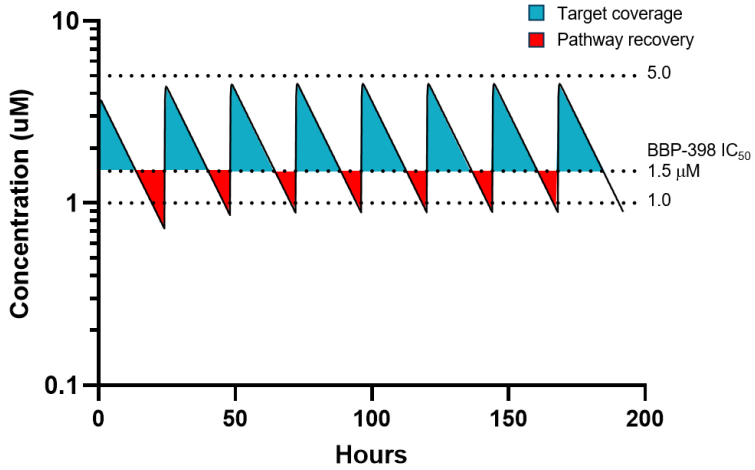
Analysis of HCC827 efficacy and PD shows that ~16 hours over pERK IC_{50} drives efficacy

Predicted steady-state plasma concentration-time profiles following once daily oral administration of BBP-398

Predicted human plasma levels of BBP-398 from allometric scaling

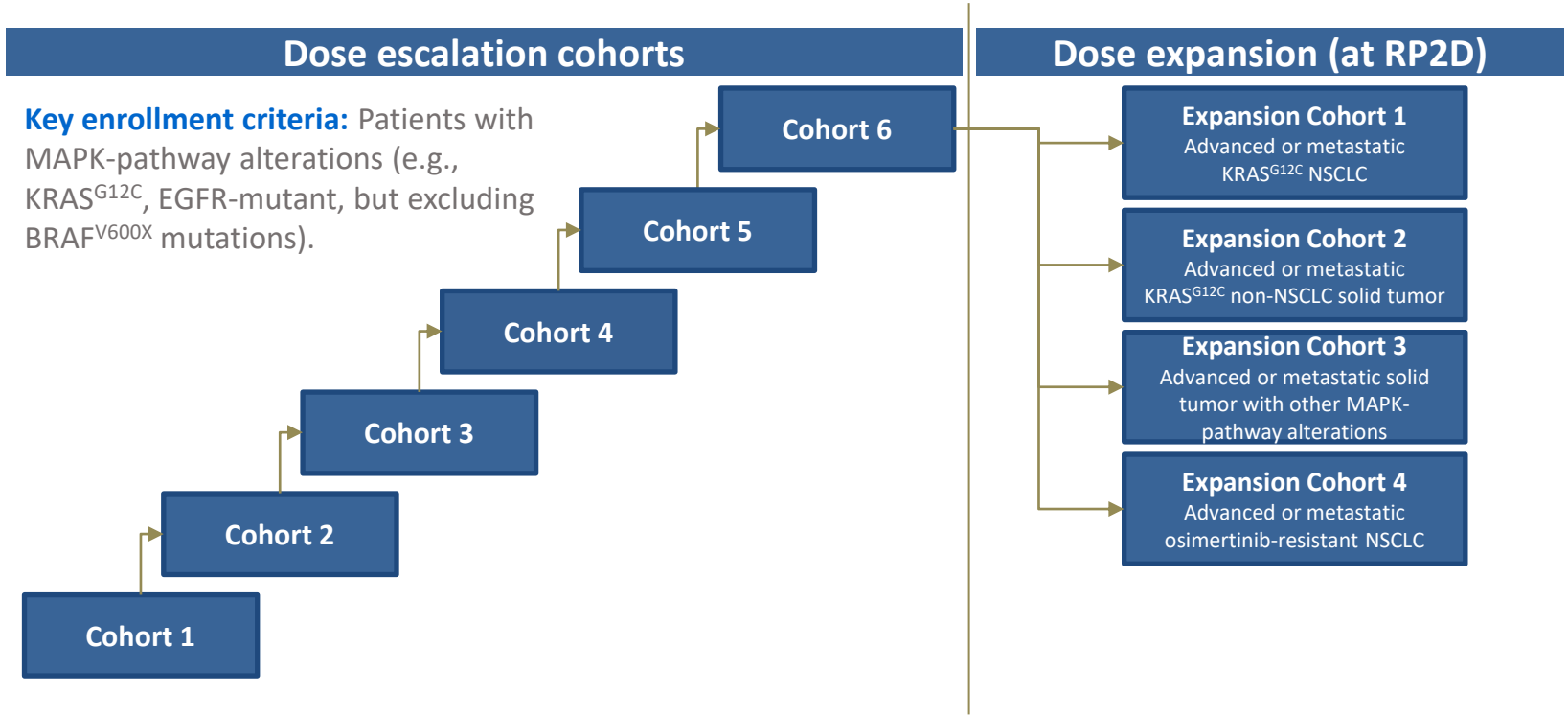


BBP-398 steady-state PK simulation for optimal efficacy



Maintenance at or above in vivo IC_{50} for >16 hours of the dosing interval is anticipated with continuous once daily dosing

A BOIN Phase 1 dose escalation with BBP-398 is ongoing: Observed PK/PD is in-line with preclinical predictions



Summary

- BBP-398 is a potent and selective SHP2 inhibitor that demonstrates pathway inhibition across a panel of cell lines with active MAPK signaling
- BBP-398 exhibits monotherapy efficacy in RTK/KRAS-driven xenograft models and synergizes with sotorasib and osimertinib to inhibit in vivo tumor growth
- Pharmacodynamic analysis of target coverage following BBP-398 dosing strongly suggests that ~16 hrs of IC_{50} coverage and daily pathway recovery are best for therapeutic index
- Predicted human steady-state plasma concentration-time profiles suggest continuous once daily oral dose of BBP-398 may achieve the desired therapeutic index
- A BOIN Phase 1 dose escalation with BBP-398 is ongoing: Observed PK/PD is consistent with our preclinical prediction