Discovery and Characterization of HH100937, a potent and selective SOS1 inhibitor demonstrates synergistic efficacy in combination with KRAS/MAPK therapies

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Abstract

Besides marketed inhibitors targeting KRAS G12C, novel therapies are needed to effectively treat cancer patients harboring other KRAS mutations. SOS1, a guanine nucleotide-exchange factors (GEFs), plays a critical role in catalyzing the conversion of KRAS from its GDP- to GTP-bound form, regardless of KRAS mutation status and represents a promising therapeutic target for all KRAS-driven tumors (fig. 1). Up to date, several SOS1 inhibitors have entered early phase clinical trials. But a more potent SOS1 inhibitor with improved drug-like properties is still needed to prove efficacy as monotherapy or in combination with other drugs targeting the KRAS/MAPK pathway.

We discovered a potent SOS1 inhibitor, HH100937 that effectively disrupted the interaction between SOS1 and wild-type KRAS or with G12C, G12D or G12V mutations. HH100937 exhibited lower IC50s than BI-3406 and MTRX0902 in blocking ERK phosphorylation and cancer cell proliferation, leading to better anti-tumor efficacies in xenografts than reference compounds at same doses. HH100937 also showed synergistic effect with AMG510 in cancer cells with KRAS G12C mutation but refractory to AMG510. The combination of HH100937 and AMG510 in xenografts led to tumor regression in all mice, while some tumors did not response well to AMG510 monotherapy. Our SOS1 inhibitor also exhibited synergistic effect with HH2710, a clinical-stage ERK inhibitor, in a broad panel of cancer cells with KRAS mutations.

The pharmacological potency of HH100937 was highly selective over SOS2, other kinases tested or other targets in a safety panel of 47 targets. HH100937 was well tolerated in 28-day DRF study in rats and dogs up to 250 mg/kg QD and 30 mg/kg QD, respectively. The AUC of drug exposure in DRF studies was approximately three to six times higher than that at the efficacious dose. HH100937 also showed favorable DMPK properties in mice, rats and dogs, and acceptable safety profiles in vitro.

Taken together, HH100937 is a highly potent and selective SOS1 inhibitor with better anti-tumor activities than some SOS1 inhibitors at clinical stage. It can be developed as mono therapy or in combination with other KRAS/MAPK targeting therapies.

Target/ Approach	• SOS1-RAS interaction inhibitor • Oral small molecule
Potential Indications	• RAS-mutant NSCLC, colon and pancreatic cancers *via* combination therapy • Cancers with other MAPK pathway alterations • Other diseases with MAPK pathway alterations
Status/ Milestone	• IND-enabling study

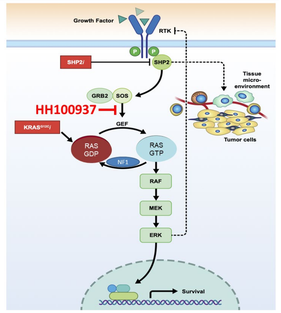

Figure 1. MoA of SOS1 inhibitor HH100937.

Results

➢ **HH100937 has better potency and drug-like property**

We discovered HH100937, a selective SOS1 inhibitor. In a panel of in vitro enzymes and kinases tests, HH100937 showed robust inhibition on SOS1 interaction with KRAS of wild-type and distinct mutations (table 1), but no activity on SOS2, kinases, ion channels, enzymes in 47 Safety Panel (table 1 and fig 2).

Compared to MTRX0902, a SOS1 inhibitor in phase 1 study, HH100937 show stronger maximum inhibition on p-ERK, better in vivo efficacy and more balanced DMPK properties for solid tumors. (table 2)

Table 1. selective inhibition on SOS1 by HH100937.

Target inhibition (IC_{50}, nM)	HH100937
SOS1::KRAS WT	**7.3**
SOS1::KRAS G12C	**7.4**
SOS1::KRAS G12D	**6.9**
SOS1::KRAS G12V	**11.7**
SOS2: KRAS G12D	**>10000**

HH100937 Kinase Potency	
EGFR IC_{50} (nM)	3630
FGFR3 IC_{50} (nM)	>10000
KDR IC_{50} (nM)	>10000

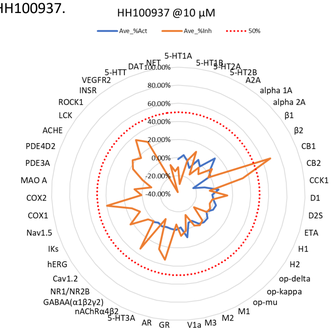

Figure 2. Profiling of HH100937 in 47 Safety Panel

Table 2. Profiling of HH100937 in comparison with MRTX0902.

Profile	Cpd ID	HH100937	MRTX0902#
Potency	SOS1::KRAS IC_{50} (nM)	7	9.8
	pERK IC_{50} /IC_{90} (nM)	76/460	57/ Imax<90%
	T/C% in LN229 (50 mg/kg, BID)	28%	~75%
ADME	$V_{d,ss}$ (m/r/d,L/kg)	2.5/3.48/1.08	0.28/0.28/0.48
	In vivo CL (m/r/d/mk, mL/min/kg)	14/18/3/17.7	4.4/14.4/7.6/NA
	T1/2 in vivo (h, m/r/d)	2.22/3.32/4.56	1.3/0.62/0.86
	F% (m/r/d)	52/35/30	69/83/38
Safety	CYPs IC_{50} (1A2/2C9/2C19/2D6/3A4, μM)	>50/6.1/15.9/>50/>50	NA/NA/NA/3.6
	hERG IC_{50} (μM)	>10	>10
	Mini-Ames	Neg	NA

NA: not available # data from J. Med. Chem. 2022, 65, 14, 9678–9690

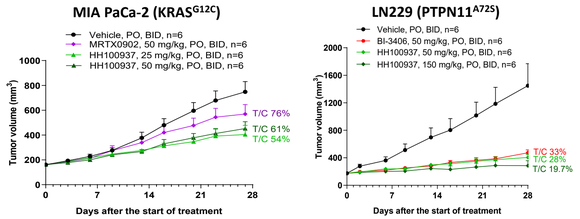

Figure 3. In vivo efficacy of HH100937 in MIA PaCa-2 (left) and LN229 (right) xenograft models.

Table 3. Pharmacokinetic profiles following 27 days in MIA Paca-2 model.

Compound	Dosing regimen	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	MRT (h)	AUC_{0-24} (ng·h/mL)
MRTX0902	50 mg/kg, *po*, *bid*	1.30	1.00	32033	3.48	258526
HH100937	25 mg/kg, *po*, *bid*	1.83	2.00	2123	4.09	26463
	50 mg/kg, *po*, *bid*	2.71	1.00	4957	4.72	54745

➢ **HH100937 has better in vivo efficacy**

We profiled in vivo efficacy of HH100937 in MIA PaCa-2 and LN229 xenograft models. (fig 3).

In MIA PaCa-2, a tumor with KRAS G12C mutation, HH100937 showed better efficacy at 25 and 50 mg/kg than MRTX0902 at 50 mg/kg. The PK tests also indicated that HH100937 reached this efficacy at a much lower exposure than MRTX0902 (table 3).

We also demonstrated that HH100937 had a better efficacy than MRTX0902 in LN229, a tumor with PTPN11 mutation. (MRTX0902 data in Mirati 2022 AACR presentation)

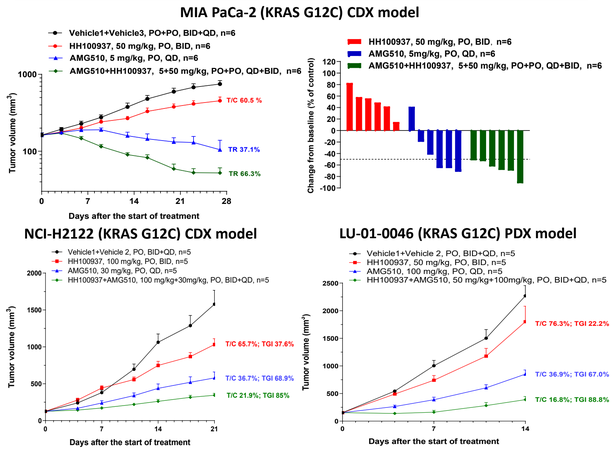

Figure 4. In vivo efficacy of HH100937 in combination with AMG510 in xenograft models. tumor growth in MIA PaCa-2 (up left) and tumor inhibition in individual animals (up right), tumor growth in NCI-H2122 (down left) and LU-01-0046 (down right)

➢ **SOS1 inhibitors have synergy with MAPK pathway inhibitors**

We tested synergistic effect of SOS1 with MAPK inhibitors with HH100937 and its lead compound HH000043.

HH100937 showed synergy with AMG510, a KRAS G12C inhibitor, on p-ERK inhibition (fig5, up left) and in vivo efficacy in three xenograft models with KRAS G12C mutations. Especially in MIA PaCa-2 model, combination of HH100937 and AMG510 caused significant tumor regression in all mice (fig 4, up).

HH000043 showed synergy with HH2710, a ERK1/2 inhibitor in clinical stage, in p-ERK/p-RSK and cell proliferation of tumors with KRAS mutations. Notably, HH000043 can block a negative feedback loop on p-ERK re-activation by ERK inhibitor and further downregulate p-RSK (fig 5 down left and right).

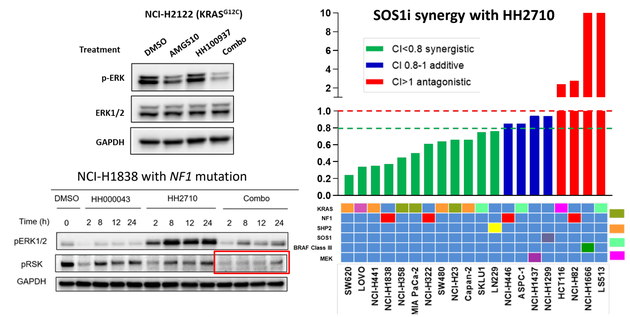

Figure 5. In vitro potency of HH100937 or HH000043 in combination with AMG510 and HH2710 in MAPK pathway blockage (left) and cell proliferation with HH2710 (right).

Conclusions

Haihe preclinical candidate HH100937 is a potent and selective SOS1 inhibitor, with favorable efficacy and DMPK in animal models. Our SOS1 inhibitors show good synergy with KRAS G12C inhibitor and other MAPK inhibitors, suggesting potential combination strategy for clinical development.

We have completed a 28-day dose-finding toxicity study of HH100937 in rats and dogs. The compound was well tolerated with a significant therapeutic window compared to its efficacy dose and exposure. IND clearance will be expected by the end of 2024.

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