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HH102007 is a highly selective and potent PARP1 inhibitor and trapper

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Abstract

PARP1 plays a critical role in DNA repair and represents the pivotal target of first-generation PARP inhibitors to show so-called "synthetic lethal" efficacy in patients with DNA repair deficiency. PARP2 shares high homology with PARP1, but its inhibition has been linked to hematological toxicity caused by PARP inhibitors with no selectivity between PARP1 and PARP2. AstraZeneca developed next-generation PARP inhibitors with better selectivity on PARP1 over PARP2, AZD5305 and AZD9574, both of this new class, are presently in early phase clinical trials.

We discovered a highly selective and potent PARP1 inhibitor, HH102007, which was studied extensively using AZ compounds as comparators. In our setting, AZD5305 was more potent than AZD9574 in PARP1-DNA trapping, cell proliferation inhibition and in vivo anti-tumor efficacy, while AZD9574 had a much higher selectivity on PARP1 enzymatic inhibition over PARP2, which led to less hematological toxicity in rat and a wider therapeutic window in preclinical models.

HH102007 showed even better selectivity on PARP1 than both compounds in PARPs enzymatic assays. We also showed that HH102007 can form a tighter PARP1-DNA trapping than AZD9574, leading to better potency in DNA damage, immune activation and cancer cell proliferation as AZD5305. HH102007 achieved tumor regression in MDA-MB-436 xenografts at a lower dose than AZD9574, and showed synergistic efficacy in combination with carboplatin in SUM149PT, which was insensitive to AZD9574. As for hematological toxicity, HH102007 up to 25 mg/kg did not reduce reticulocyte in rat while AZD5305 at 1 mg/kg caused reticulocyte reduction in a head-to-head comparison. In summary, HH102007 is a potent PARP1 inhibitor and trapper, with better selectivity and therapeutic window than both AZ compounds.

Target/ Approach	• PARP1 inhibitor • Oral small molecule
Potential Indications	• Ovarian Cancer • Breast Cancer • Prostate Cancer • Pancreatic Cancer • Other HR-deficient cancers
Mutation/ aberration	• BRCA1/2-mutations • DNA homologous recombination repair-deficient
Status/ Milestone	• PCC

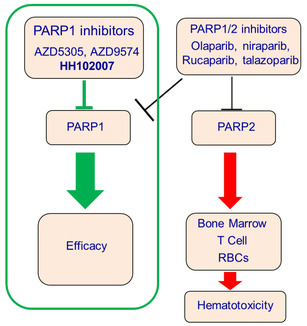

Figure 1. MoA of PARP1 inhibitor HH102007.

Results

➢ **HH102007 is a potent and selective PARP1 inhibitor**

We discovered HH102007, a selective PARP1 inhibitor. In a panel of PARPs, HH102007 only showed robust inhibition on PARP1 and mild on PARP7 (table 1). Its selectivity between PARP1 and PARP2 is better than both AZ compounds.

HH102007 also showed a tighter formation of PARP1-DNA trapping complex than AZD9574 after 3 h treatment (table 2 and fig 2). Its potent enzymatic and trapping activity led to a better cell proliferation inhibition than AZD9574 in a panel of cell lines with BRCAm (breast cancer) or high PARP1 expression (SCLC) (table 3 and fig 3).

Table 1. Selective inhibition on PARP1 by HH102007 vs. other PARP1 inhibitors.

IC_{50} (nM)	Olaparib	AZD5305	AZD9574	HH102007
PARP1	0.95	0.46	0.87	0.32
PARP2	0.34	10	672	326
PARP3	4.4	3400#	>100000*	>5000
PARP5A	643	>89000#	>100000*	>5000
PARP5B	785			4997
PARP6	561	26000#	>100000*	>5000
PARP7	69	42	>5000	183
PARP12	1244			>5000
PARP15	1623			1081
Fold Selective PARP1/2	0.39	22	772	1003

*Staniszewska, Anna D., et al. Clinical Cancer Research (2023).
#Johannes, Jeffrey W., et al. Journal of Medicinal Chemistry 64.19 (2021): 14498-14512.

Table 2. PARP1-DNA trapping by HH102007 at multiple time points.

Profile		AZD5305	AZD9574	HH102007
PARP1 trapping EC_{50} (nM)	60 min	11.34	30.10	**34.69**
	120 min	24.65	153.35	**65.87**
	180 min	35.98	296.55	**102.74**
	Potency decline (180 min/60 min)	3.17	9.85	**2.96**

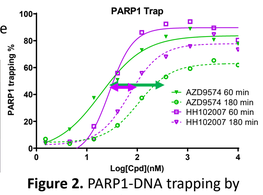

Figure 2. PARP1-DNA trapping by HH102007 and AZD9574

Table 3. Proliferation inhibition by HH102007 in a panel of cell lines.

Cell lines IC_{50} (nM)		Olaparib	AZD5305	AZD9574	HH102007
DLD-1 (BRCA2 KO)		27	1.8	17	**3.0**
Breast_BRCAm	MDA-MB-436	9.2	1.2	7.2	**2.6**
	HCC1395	40	0.9	14	**3.6**
	SUM149PT	219	44	2999	**70**
SCLC_PARP1 high	NCI-H69	200	20	234	**13**
	NCI-H209	172	1.9	45	**3.4**
	NCI-H446	660	9.0	452	**4.9**

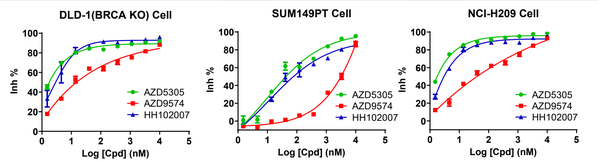

Figure 3. Cell proliferation in DLD-1 (BRCA KO), SUM149PT and NCI-H209 with HH102007 and other PARP1 inhibitors

➢ **HH102007 has better *in vivo* efficacy than AZD9574**

In MDA-MB-436, a tumor model sensitive to PARP inhibitors, HH102007 showed better efficacy at 0.6 and 2 mg/kg than AZD9574 at some doses (fig 4 up). HH102007 caused significant tumor regression in all mice at all doses tested (fig 4 down).

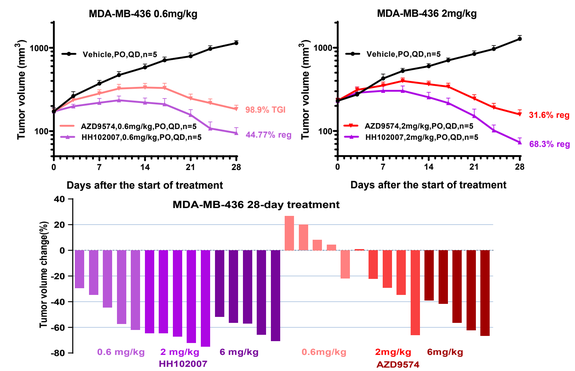

Figure 4. *In vivo* efficacy of HH102007 and AZD9574 in MDA-MB-436 xenograft model at 0.6 and 2 mg/kg (up) and waterfall plot of tumor volume changes in individual animals

➢ **HH102007 has synergy with carboplatin**

We also found that HH102007 has a better in vitro potency than AZD9574 in SUM149PT. And HH102007 also showed synergistic efficacy with carboplatin in this cell line while AZD9574 did NOT (fig 5 left and middle). A xenograft study further demonstrated this synergistic efficacy *in vivo* (fig 5 right).

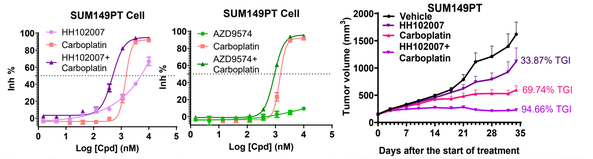

Figure 5. *In vitro* (left) and *in vivo* (right) efficacy of HH102007 and AZD9574 in SUM149PT in combination with carboplatin

➢ **HH102007 has better therapeutic window**

Reduction of reticulocyte is believed to be relevant to PARP2i-induced bone marrow suppression. Olaparib and AZ5305 inhibited reticulocyte at their efficacious doses, the two compounds also inhibited growth of rat body weights (fig 6). HH102007 did NOT show obvious toxicity in this rat study as AZD9574 (fig 6).

A therapeutic window is defined as comparing human equivalent dose (HED) and free drug exposure to cause tumor regression in mice and reticulocyte reduction in rat. HH102007 exhibited a better therapeutic window even than AZD9574, AZD5305 and Olaparib (fig 7 and table 4).

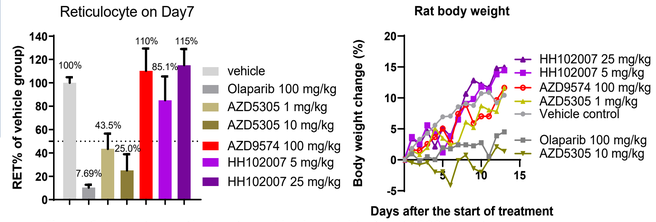

Figure 6. Impact on reticulocyte and body weight of HH102007 in rat.

Figure 7. Therapeutic windows of HH102007 compared with AZ PARP inhibitors

Conclusions

HH102007 is a potent and selective PARP1 inhibitor and trapper. It showed better potency and efficacy than AZD9574, as well as synergy with chemotherapy. It did not induce obvious hematological toxicity in rats and indicated a better therapeutic window than other PARP inhibitors in pre-clinical setting.

The pre-clinical candidate of our PARP1 inhibitor is an analog of HH102007 with improved drug-like property. IND clearance will be expected by Q1 2025.

Table 4. Profiling of HH102007 with other PARP inhibitors.

Profile	Parameter	Olaparib	AZD5305	AZD9574	HH102007
Potency & selectivity	PARP1 (nM)	0.95	0.46	0.87	**0.32**
	PARP2 (nM)	0.34	10	672	**326**
	Fold Selective PARP1/2	0.39	22	772	**1003**
Cellular potency IC_{50} (nM)	DLD-1 (BRCA2 KO)	27	1.8	17	**3.0**
	MDA-MB-436	9.2	1.2	7.2	**2.6**
	SUM149PT	219	44	2999	**70**
	NCI-H209	172	1.9	45	**3.4**
Efficacy	MDA-MB-436 TGI/ORR on day 28	TR>80% at 100 mg/kg*	TR>80% at 0.1 mg/kg*	TR 31% at 2 mg/kg	**TR 45% at 0.6 mg/kg**
Hemato-toxicity	Reticulocyte% on day 7	-92.31 at 100 mg/kg	-56.55 at 1 mg/kg	+10.41 at 100 mg/kg	**+15 at 25 mg/kg**
Therapeutic Index	Fold of Tox/efficacy with HED/free drug AUC	<2/<1.61	<20/<1.71	>100/>76.5	**>83/>715**

*Lluzzi G. Clin Cancer Res; 28(21) November 1, 2022

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