Synthetic lethal strategy of an EZH1/2 dual inhibitor, HM97662, for the treatment of ARID1A-mutated solid cancers

Gunwoo Lee, Seung Hyun Jung, Seon Yeong Han, Jooyun Byun, Yu-Yon Kim, Miyoung Lee, Junghwa Park, Sunyoung Lim, Hyesun Han, Sang Hyun Lee, and Young Gil Ahn

Hanmi Pharmaceutical Co., Ltd., Seoul, Republic of Korea

Abstract #3240

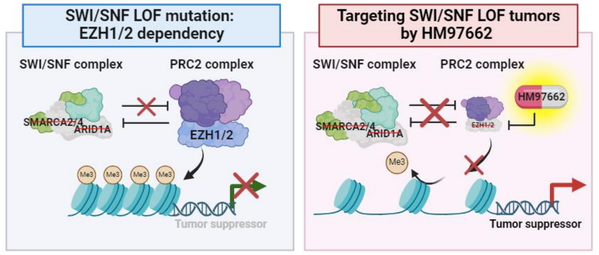
Introduction

Enhancer of zeste homolog 2 (EZH2), an enzymatic subunit of polycomb repressive complex 2 (PRC2), is known to catalyze tri-methylation of histone H3 at lysine 27 (H3K27me3), leading to repression of the transcription of its target genes involved in cell cycle regulation, cell proliferation, cell differentiation, and tumor suppression[1]. It has been proposed that epigenetic regulators could serve as novel drug targets, and EZH2 is one of the targets with considerable therapeutic potential. Although the methyltransferase activity of PRC2 is mainly contributed by EZH2, EZH1 also plays a compensatory role in maintaining tri-methylation of H3K27 and directly binds to chromatin, modulating its condensation[2]. These emphasize that blocking both EZH1 and EZH2 might have greater anti-tumor effect than EZH2 alone.

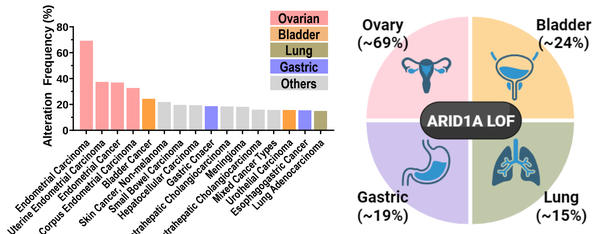
It has been shown that loss-of-function (LOF) mutations of component proteins in SWI/SNF chromatin remodeling complex, including PBRM1, ARID1A, SMARCA4, and so on, are synthetic lethal with inhibition of the histone methyltransferase EZH2. Especially, ARID1A-mutated solid tumors are vulnerable to EZH2 inhibition[3–5]. Given that ARID1A is mutated in approximately 10% of all tumor types, inhibiting EZH2 activity could be a promising therapeutic strategy for cancer patients with this mutation[6].

Here, we propose the anti-tumor potency of HM97662, an EZH1/2 dual inhibitor, in diverse solid cancer cell lines carrying SWI/SNF mutations. Additionally, we demonstrate its effectiveness in xenograft mouse models with ARID1A-mutant solid tumors, exploiting a synthetic lethal approach.

Synthetic Lethal Strategy of an EZH1/2 Inhibitor, HM97662

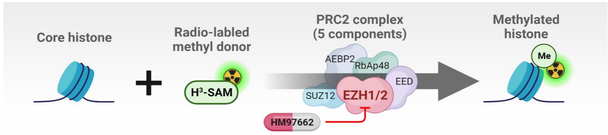


Alteration frequency of ARID1A in solid tumors

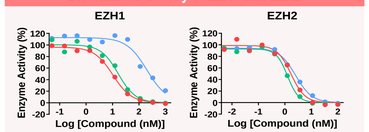


cBioPortal: Curated set of non-redundant studies (70,665 samples)

Potency and Selectivity on EZH1/2 Enzyme

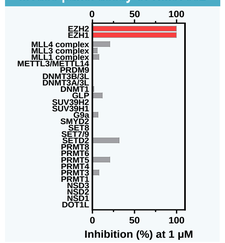


Biochemical activity of EZH1 and EZH2



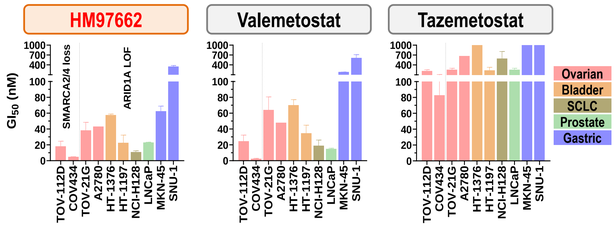
PRC2 complex	Inhibition (IC_{50}, nM)		
	HM97662	Valemetostat	Tazemetostat
EZH1 WT	16	30	188
EZH2 WT	2.1	1.2	2.8

MTase panel assay of HM97662

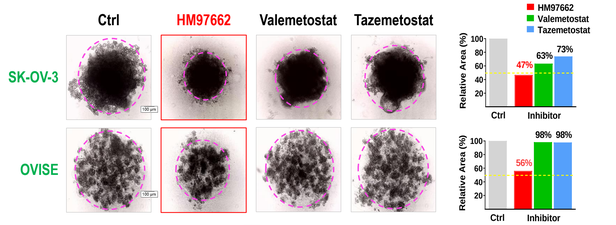


Anti-proliferative Effect against Cancer Cell Lines

A. Long-term proliferation assay in SWI/SNF-mutated cancers

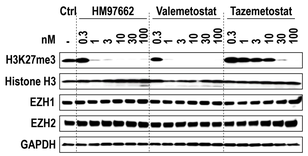


B. 3D spheroid formation assay in ARID1A-mutated ovarian cancers

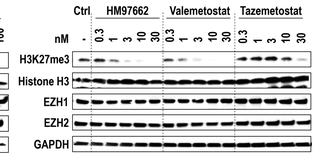


H3K27me3 Target Modulation

A. HT-1376



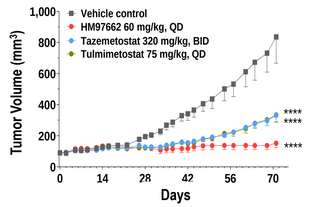
B. TOV-21G



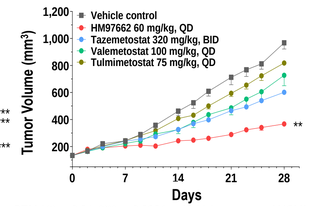
Cancer type	Cell line	Genetic alteration	H3K27me3 Inhibition (IC_{50}, nM)		
			HM97662	Valemetostat	Tazemetostat
Bladder	HT-1376	ARID1A LOF	0.9	0.5	12
Ovarian	TOV-21G	ARID1A LOF	1.2	1.6	27

Anti-tumor Efficacy in ARID1A LOF Xenograft Models

A. Bladder HT-1197 model

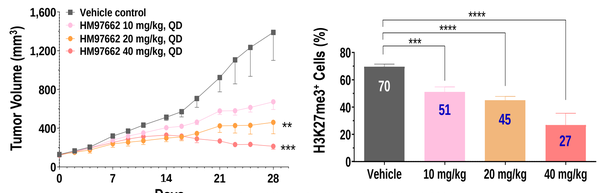


B. Ovarian TOV-21G model

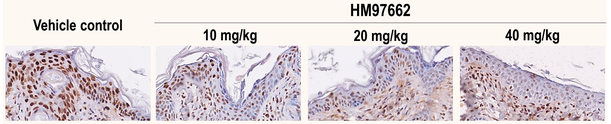


Mean ± SEM / ** p<0.01, **** p<0.0001 vs Vehicle, one-way ANOVA

C. Bladder HT-1376 model w/ PD marker H3K27me3 in skin



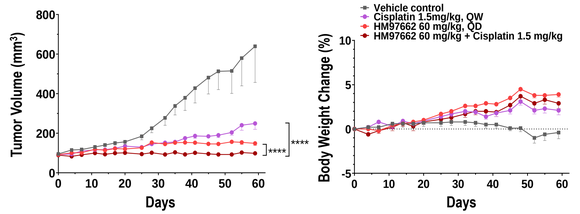
Mean ± SEM / ** p<0.01, *** p<0.001, **** p<0.0001 vs Vehicle, one-way ANOVA



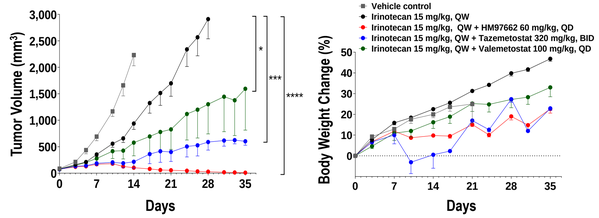
400x, H3K27me3 in the skin after 28 days of administration

SoC Combination to Maximize Anti-cancer Effect

A. Bladder HT-1197 model



B. SCLC NCI-H128 model



Mean ± SEM / * p<0.05, *** p<0.001, **** p<0.0001 vs SoC alone, t-test

Concluding Remarks

- HM97662, an EZH1/2 dual inhibitor, showed a wide and strong growth inhibitory effect in various solid cancer cell lines harboring ARID1A mutation.
- HM97662 also potently repressed tri-methylation of H3K27 both in vitro and *in vivo* tumor models with ARID1A LOF mutation.
- HM97662 exhibited potent anti-tumor activities in xenograft mouse models with various ARID1A-mutated solid cancers including ovarian and bladder cancer.
- Furthermore, HM97662 showed great synergistic effects with SoC in bladder and small cell lung cancer.
- Taken together, these preclinical studies demonstrated that HM97662 holds promising therapeutic potential for ARID1A-mutated solid cancers.
- Currently, a first-in-human phase 1 dose escalation study of HM97662 in advanced or metastatic solid tumors in underway in KR/AU (NCT05598151).

References

1. Huang K. et al., *Cell Cycle.* **2020,** *19(7),* 758;
2. Soo Hyun L. et al., *BMB Rep.* **2022**, *55*, 595;
3. Alldredge J.K. et al., *Gynecol Oncol Res Pract.* **2017**, *4*, 17;
4. Bitler B.G. et al., *Nat Med.* **2015**, *21(3)*, 231;
5. Rehman H. et al., *JCI Insight.* **2022**, *7(16)*, e155899;
6. Fontana B. et al., *Front Oncol.*, **2023**, *13*, 1136248.

Acknowledgements

This research was supported by Korea Drug Development Fund funded by Ministry of Science and ICT, Ministry of Trade, and Energy, and Ministry of Health and Welfare (HN21C1077, Republic of Korea).