684TiP

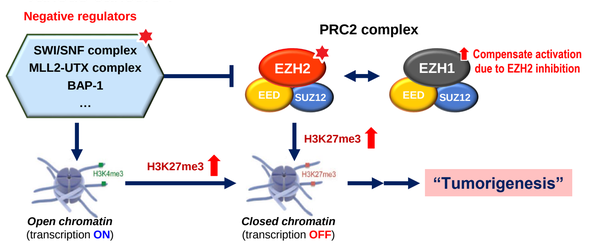
A Phase I, Open-Label, Multicenter, Dose Escalation and Expansion Study of HM97662 (EZH1/2 dual inhibitor) as a Single Agent in Patients with Advanced or Metastatic Solid Tumors

Bhumsuk Keam[1], Jin-Hee Ahn[2], Kidong Kim[3], Sung-Hoo Hong[4], Vinod Ganju[5], Lisi Elizabeth Lim[6], Vineet Kwatra[7], Amy Body[8,9], Paul Dong Rhee[10], Sooa Jung[10], Jiyeon Yoon[10], Eunhye Baek[10], Young Su Noh[10]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [2]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam-Si, Gyeonggi-Do, Republic of Korea; [4]Department of Urology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [5]Peninsula and Southeast Oncology, Level 3 Frankston Private, 24-28 Frankston Flinders Road, Frankston, VIC 3199, Australia; [6]Department of Medical Oncology, Ballarat Regional Integrated Cancer Centre, Ballarat, Victoria, Australia; [7]Cancer Research South Australia, Adelaide, South Australia, Australia; [8]Department of Medicine, Nursing and Health Sciences, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC 3800, Australia; [9]Department of Oncology, Monash Medical Centre, Monash Health, Clayton, VIC 3168, Australia; [10]Department of ONCO Clinical Research and Development, Hanmi Pharmaceutical Co., Ltd., Seoul, Republic of Korea

BACKGROUND

- Enhancer of zeste homolog 2 (EZH2) and its close homolog EZH1 are pivotal components of the polycomb repressive complex 2 (PRC2), which is critical for the maintenance of epigenetic repression. These proteins mediate the tri-methylation of histone H3 at lysine 27 (H3K27me3), a modification associated with transcriptional silencing of genes involved in crucial cellular processes such as the cell cycle and differentiation. Dysregulation of EZH2, often through gain-of-function mutations or overexpression, leads to excessive H3K27me3 levels, contributing to tumorigenesis and poor clinical outcomes in various cancers[1].

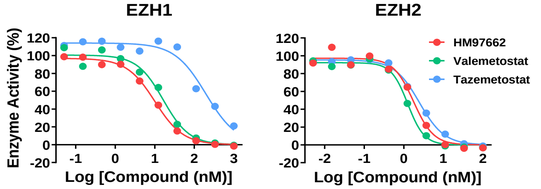


Target chromatin remodelers	**Aberrations** (representative types or components)
PRC2 complex	**EZH2 GOF mutation** (Y641/A677/A687), **EZH2 overexpression**
Negative regulators (LOF mutation)	**SWI/SNF complex** (ARID1A, SMARCB1, SMARCA4/2, PBRM1…), **MLL2-UTX complex** (KDM6A…), **BAP1**

- In addition to EZH2, EZH1 can compensate for its function, particularly in contexts where EZH2 is depleted. This compensation highlights the potential of targeting both EZH1 and EZH2 to achieve a more effective inhibition of PRC2 activity.
  - It is indicated that dual inhibition may provide enhanced anti-tumor effects compared to inhibiting EZH2 alone, as it may more effectively restore the expression of tumor-suppressive genes[2,3].
- Furthermore, alterations in components of the SWI/SNF chromatin remodeling complex, such as ARID1A, SMARCA4, and SMARCB1, have been shown to interact synergistically with EZH2 inhibition[4].
- Given these insights, we developed HM97662, a novel dual inhibitor of EZH1 and EZH2.
  - Preclinical studies have demonstrated that HM97662 effectively inhibits the methyltransferase activity of both wild-type EZH1 and EZH2, as well as various GOF mutant forms of EZH2, at nanomolar concentrations[5].
- With these promising results, a first-in-human Phase I study of HM97662 was initiated to evaluate its safety, pharmacokinetics, and early efficacy in patients with advanced or metastatic solid tumors.

PHARMACOLOGICAL ACTIVITY

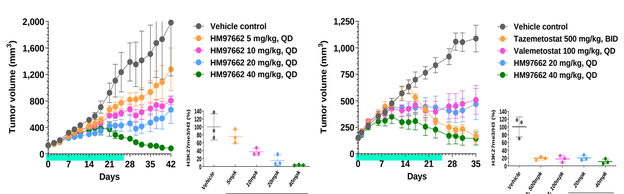
❖ Inhibition of EZH1 and EZH2 catalytic activity



PRC2 complex	Inhibition (IC_{50}, nM)		
	HM97662	Valemetostat	Tazemetostat
EZH1 WT	**16**	30	188
EZH2 WT	**2.1**	1.2	2.8
Selectivity ratio (EZH1/EZH2)	**7.6**	25	67

❖ Antitumor activity and H3K27me3 regulation

HT-1376 (Urothelial bladder cancer, UBC)



† *HM97662 were treated once daily via oral gavage for 28 consecutive days in BALB/c nude mice subcutaneously inoculated with HT-1376 bladder cancer cell line (p<0.01 or p<0.001 vs. vehicle, determined by ANOVA followed by Dunnett's test)*

† *H3K27me3 / H3 (%) of each groups were determined in tumor after the oral administration of HM97662 on Day 14*

STUDY DEGISN

- This is a Phase I, open-label, multicenter study enrolling patients with advanced or metastatic solid tumors
- The study is comprised of 3 parts:
  - Part 1, Dose-Escalation: HM97662 will be administered orally at escalating doses once daily (QD)
  - Part 2, Dose-Ranging (randomized): More than one feasible dose will be selected and may be evaluated in 10 patients (with alterations in components of the SWI/SNF complex) per dose level
  - Part 3, Dose-Expansion: Stage 1 will enroll 10 patients per indication-specific cohort. In Stage 2, an additional 15 patients will be enrolled per indication-specific cohort if the specified criteria are met

Study Objectives	
Primary	➢ Safety and tolerability of HM97662 ➢ Maximum tolerated dose (MTD) or recommended Phase II dose (RP2D) of HM97662
Secondary	➢ Pharmacokinetics (PK) of HM97662 ➢ Preliminary anti-tumor efficacy of HM97662 administered in patients with (SWI/SNF complex) and without genomic alterations
Exploratory	➢ Relationships between PK, PD, biomarker variables, safety and efficacy

Key Eligibility Criteria

- Standard of Care (SoC) failed / intolerant advanced or metastatic solid tumors
- No prior EZH1/2 dual inhibitor
- ECOG performance status 0 or 1
- Adequate hematological, renal, and hepatic function

Part 1: Dose-Escalation *(n=3~6 / cohort)*

- Dose level 7: 350 mg
- Dose level 6: 300 mg
- Dose level 5: 250 mg
- Dose level 4: 200 mg
- Dose level 3: 150 mg
- Dose level 2: 100 mg
- Dose level 1: 50 mg

Part 2: Dose-Ranging

- Standard of Care (SoC) failed / intolerant advanced or metastatic solid tumors with **alterations in SWI/SNF complex**

R 1:1 → Dose level B / Dose level A

** Number of doses to be randomized will be determined based on a comprehensive review of the results from the Part 1*

Part 3: Dose-Expansion

- Cohort 1: Indication 1, n=10 → Indication 1, n=15
- Cohort 2: Indication 2, n=10 → Indication 2, n=15

** **Indication will be selected considering:** 1) Prevalence, 2) Competitive landscape, 3) Preclinical results, 4) Initial clinical results*

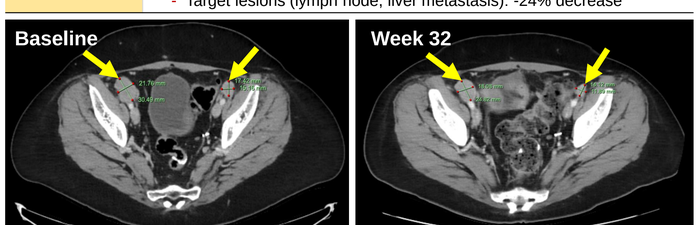
(🔴) Evaluation of compelling efficacy + acceptable safety

CASE REPORT *(with Clinical Benefit)*

Data as of: Sep. 2024

❖ Metastatic Ovarian Carcinoma (53 yrs / Female / ECOG PS 0)

Initial Diagnosis	➢ **Ovarian Carcinoma (High-grade serous) / Stage IV (May 2021)**
Prior Therapy (Metastatic setting)	➢ 1L: Carboplatin + Gemcitabine (Mar ~ Jul 2023, PR) ➢ 2L: Carboplatin + Liposomal Doxorubicin (Nov ~ Nov 2023, UNK)
Study Treatment	➢ Dose-Escalation Part: HM97662 200 mg (QD); Treatment for 8+ months
Best Response	➢ Stable Disease (SD) - Target lesions (lymph node, liver metastasis): -24% decrease



STUDY STATUS

- Patient accrual for this Phase I clinical study (NCT05598151) is being conducted in the Republic of Korea (4 sites) and Australia (4 sites)
- First Patient-In (FPI) was in January 2023, and the study has accrued 19 patients to date (September 2024) in Part 1 (Dose-Escalation)
- HM97662 showed manageable safety profile up to date (September 2024) with no Dose-Limiting Toxicities (DLTs) observed to date

Reference

1) Kim, K. H., et al. (2016). Nature Medicine, 22(2), 128-134
2) Bitler, B. G., et al. (2015). Nature Medicine, 21(3), 231-238
3) Lee, S. H., et al. (2022). BMB Reports, 55(12), 595-601
4) Rehman, H., et al. (2022). JCI Insight, 7(16), e155899
5) Jung, S. H., et al. (2021). Cancer Res 81(13): 1142

❖ ***B.K*** *reports advisory board with Handok, Trial Informatics, ImmuneOncia, NeoImmuneTech, and BeiGene; invited speaker with MSD, Eli Lilly, and LG Chem; local PI with MSD, AstraZeneca, Ono Pharmaceutical, and Bayer.*

❖ **Hanmi Pharm. Co., Ltd. / bhumsuk@snu.ac.kr, pauldong.rhee@hanmi.co.kr**