HM97662, a Novel EZH1/2 Dual Inhibitor, in Patients with Advanced or Metastatic Solid Tumors: Initial Results from a First-In-Human Phase I Study

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BACKGROUND

- Epigenetic dysregulation, particularly aberrant histone modifications, plays a pivotal role in cancer pathogenesis and progression. The polycomb repressive complex 2 (PRC2), comprised of EZH2 and EZH1, catalyzes histone H3 lysine 27 trimethylation (H3K27me3), leading to transcriptional silencing of tumor suppressor genes and cell cycle regulators[1]. EZH2 overexpression and gain-of-function mutations are frequently observed across diverse solid malignancies, contributing to oncogenesis and poor clinical outcomes[2,5].
- While EZH2-selective inhibitors have shown clinical promise, emerging evidence suggests that EZH1 can functionally compensate for EZH2 depletion, potentially limiting therapeutic efficacy[3]. Dual inhibition of both EZH1 and EZH2 may enhance anti-tumor effects by preventing compensatory mechanisms[4].
- HM97662 represents a novel, potent dual inhibitor of EZH1 and EZH2 with demonstrated robust preclinical efficacy against both wild-type and gain-of-function mutant EZH2 variants. This first-in-human phase I study (NCT05598151) evaluates the safety, tolerability, pharmacokinetics, and preliminary anti-tumor activity of HM97662 in patients with advanced or metastatic solid tumors.

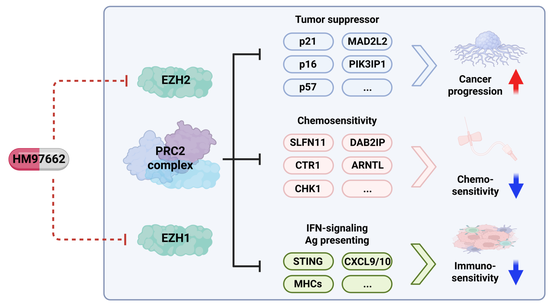


Figure 1. HM97662 Dual EZH1/2 Inhibition Modulates Oncogenic Pathways

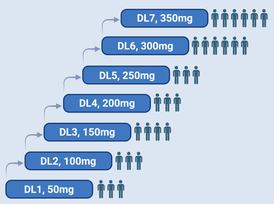
METHODS

Figure 2. Phase I Study Design

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

Key Eligibility Criteria
- Age 18 years or older
- 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

- ***HM-EZHI-101 P1 study is ongoing in the AUS, KOR***
- ***3+3 Dose escalation design***
- ***Dosing frequency: Once daily (QD)***



Primary objective:
- Safety and tolerability of HM97662
- MTD or RP2D of HM97662

Secondary objective:
- PK characteristics of HM97662
- Preliminary anti-tumor activity of HM97662

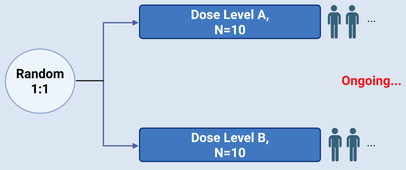
Exploratory objective:
- Relationships between PK, PD, biomarker variables, safety and efficacy

Part 2: Dose-Ranging
(n=10 / Dose Level)

Key Eligibility Criteria
- Standard of Care (SoC) failed / intolerant advanced or metastatic solid tumors with alterations in SWI/SNF complex
- ≥1 measurable lesion
- Available tumor sample for biomarker analysis

** Remaining eligibility criteria are the same as those used in the dose-escalation part*

- ***Two dose levels are under evaluation***
- ***Number of doses to be randomized was determined based on a comprehensive review of Part 1 results***



Part 3: Dose-Expansion
(n=10~25 / Cohort)

Further exploring efficacy and safety in indication-specific cohorts

DL= Dose Level; MTD= Maximum Tolerated Dose; RP2D= Recommended Phase 2 Dose; PK= Pharmacokinetics; PD= Pharmacodynamics; ECOG= Eastern Cooperative Oncology Group

BASELINE CHARACTERISTICS

- As of 11 June 2025, 28 patients with solid tumor were treated across 7 dose levels (50 to 350 mg) (Table 1).
- Median prior lines of therapy were 4.0 (range: 0–7); 23 patients (82.1%) had received ≥2 lines of prior anti-tumor treatment.
- The most common tumor types included ovarian (n=6, 21.4%), pancreatic (n=4, 14.3%), and lung cancer (n=3, 10.7%).
- Although enrollment in the dose-escalation part was not restricted by genetic alterations, 39.3% (n=11) of patients harbored SWI/SNF complex alterations.

Table 1. Baseline Characteristics

Characteristics	Total (N = 28)
Age, Median (range) (years)	69.0 (28-87)
Sex, n (%)	
Male	13 (46.4)
Female	15 (53.6)
Race, n (%)	
Asian	14 (50.0)
White	14 (50.0)
Baseline ECOG, n (%)	
0	10 (35.7)
1	18 (64.3)
Prior systemic anti-tumor therapy, n (%)	
Median (range)	4.0 (0-7)
<2	5 (17.9)
≥2	23 (82.1)

Characteristics	Total (N = 28)
Cancer type, n (%)	
Adrenal gland	1 (3.6)
Bladder	2 (7.1)
Breast	1 (3.6)
Gastroesophageal junction	1 (3.6)
Head and neck	1 (3.6)
Lung	3 (10.7)
Ovary	6 (21.4)
Pancreas	4 (14.3)
Skin	1 (3.6)
Other*	8 (28.6)
SWI/SNF complex alteration, n (%)	
ARID1A	3 (10.7)
SMARCB1	2 (7.1)
SMARCA4	5 (17.9)
Other	1 (3.6)

* Includes two cases of malignant mesothelioma and one case each of ureter, pericardium, mandible, undifferentiated uterine sarcoma, extraskeletal sarcoma, and uterine tumor.

SAFETY AND TOLERABILITY

- No dose-limiting toxicity (DLT) occurred up to DL5 (250 mg). One patient each experienced a DLT(s) at DL6 (300 mg) and DL7 (350 mg).
- 26 (92.9%) patients experienced at least one treatment-emergent adverse events (TEAEs); 13 (46.4%) had ≥ Grade 3 TEAEs. The most common (≥20%) TEAEs were nausea (n=15, 53.6%), thrombocytopenia (n=14, 50.0%), diarrhoea (n=12, 42.9%), anaemia (n=10, 35.7%), and vomiting (n=10, 35.7%).
- Treatment-related adverse events (TRAEs) occurred in 21 (75.0%) patients; 9 (32.1%) had ≥ Grade 3 TRAEs. The most common (≥20%) TRAEs were thrombocytopenia (n=14, 50.0%), nausea (n=12, 42.9%), diarrhoea (n=11, 39.3%), vomiting (n=9, 32.1%), and anaemia (n=7, 25.0%).
- TEAEs leading to dose modification occurred in 13 (46.4%) patients, and no TEAEs leading to discontinuation of study drug were reported.

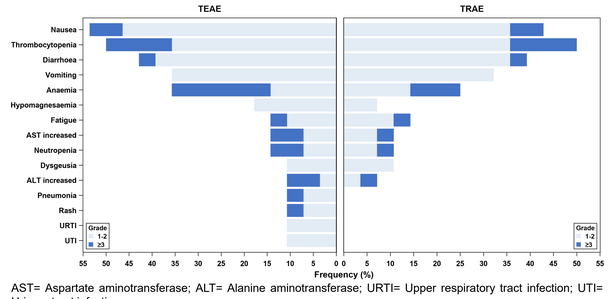
Table 2. Overall Summary of Adverse Events

Type of AEs, n (%)	Total (N = 28)
TEAEs	26 (92.9)
TEAEs with Grade ≥3	13 (46.4)
SAEs	7 (25.0)
TRAEs	21 (75.0)
TRAEs with Grade ≥3	9 (32.1)
DLTs*	2 (8.7)
TEAEs leading to dose modification	13 (46.4)
TEAEs leading to treatment discontinuation	0 (0.0)
TEAEs leading to death	0 (0.0)

Preferred Term, n (%)	Total (N = 28)
Most frequently reported TEAEs (≥10%)	
Nausea	15 (53.6)
Thrombocytopenia	14 (50.0)
Diarrhoea	12 (42.9)
Anaemia	10 (35.7)
Vomiting	10 (35.7)
Hypomagnesaemia	5 (17.9)
Aspartate aminotransferase increased	4 (14.3)
Fatigue	4 (14.3)
Neutropenia	4 (14.3)
Alanine aminotransferase increased	3 (10.7)
Dysgeusia	3 (10.7)
Pneumonia	3 (10.7)
Rash	3 (10.7)
Upper respiratory tract infection	3 (10.7)
Urinary tract infection	3 (10.7)

* Incidence is based on DLT evaluable population

Figure 3. The Most Common TEAEs (≥10%) and TRAEs (≥5%)



AST= Aspartate aminotransferase; ALT= Alanine aminotransferase; URTI= Upper respiratory tract infection; UTI= Urinary tract infection

AEs were graded according to National Cancer Institute Common Terminology Criteria for AE (NCI-CTCAE) v5.0.

EFFICACY

Confirmed objective response:
- One patient with SMARCA4-deficient uterine sarcoma achieved a confirmed partial response (PR) at 300 mg, with tumor shrinkage of –39% at cycle 5.

Durable disease stabilization:
- One patient with ovarian cancer at 200 mg achieved prolonged stable disease (SD), remaining on treatment for >20 cycles (>18 months) with best tumor shrinkage of –26%.

Disease control across tumor types:
- Clinical benefit (PR + SD) was observed across multiple tumor types, including ovarian cancer, uterine sarcoma, pancreatic cancer, and NSCLC, demonstrating broad anti-tumor activity of HM97662 in diverse solid malignancies.

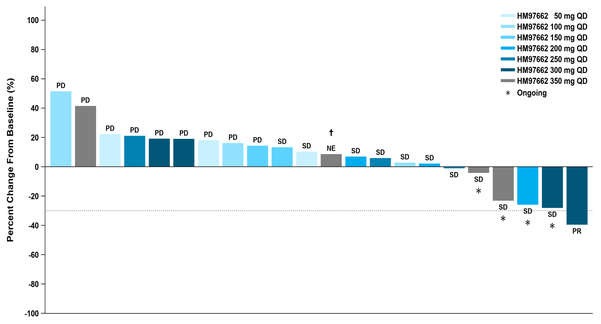
Activity in biomarker-selected populations:
- Notable clinical benefit was observed in tumors harboring chromatin remodeling pathway alterations (e.g., SMARCA4 deficiency, SMARCB1 mutation, etc.), consistent with the proposed mechanism of EZH1/2 dual inhibition.

Table 3. Overall Summary of Efficacy

Response \ Dose, mg QD	50 (N=3)	100 (N=3)	150 (N=4)	200 (N=3)	250 (N=3)	300 (N=6)	350 (N=6)
Best overall response (BOR), n(%)							
Complete Response (CR)	0	0	0	0	0	0	0
Partial Response (PR)	0	0	0	0	0	1 (16.7)	0
Stable Disease (SD)	1 (33.3)	1 (33.3)	1 (25.0)	3 (100)	2 (66.7)	1 (16.7)	2 (33.3)
Progressive Disease (PD)	2 (66.7)	2 (66.7)	2 (50.0)	0	1 (33.3)	2 (33.3)	1 (16.7)
Not Evaluable (NE)	0	0	1 (25.0)*	0	0	2 (33.3)*	3 (50.0)*
Objective Response Rate (ORR)							
n (%)	0	0	0	0	0	1 (16.7)	0
95% CI	0, 70.8	0, 70.8	0, 60.2	0, 70.8	0, 70.8	0.4, 64.1	0, 45.9
Disease Control Rate (DCR)							
n (%)	1 (33.3)	1 (33.3)	1 (25.0)	3 (100)	2 (66.7)	2 (33.3)	2 (33.3)
95% CI	0.8, 90.6	0.8, 90.6	0.6, 80.6	29.2, 100	9.4, 99.2	4.3, 77.7	4.3, 77.7

* No post-baseline tumor assessment (disease progression leading to death or subject withdrawal) or SD duration criterion not met.

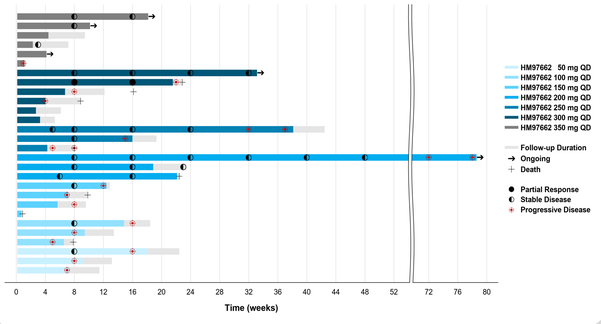
Figure 4. Best Percentage Change from Baseline (Waterfall plot)



Confirmed best overall response; subject without measurable post-baseline assessment excluded.

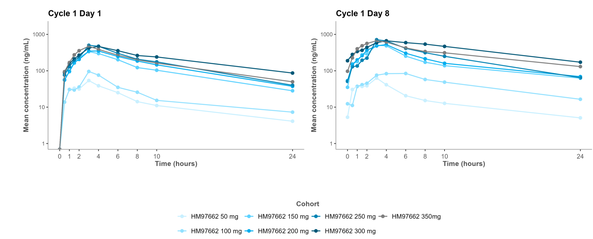
† SD at assessment; duration criterion not met.

Figure 5. Treatment Duration and Response Assessment (Swimmer plot)



PHARMACOKINETICS (PK)

Figure 6. Mean Plasma Concentration–Time Profiles of HM97662

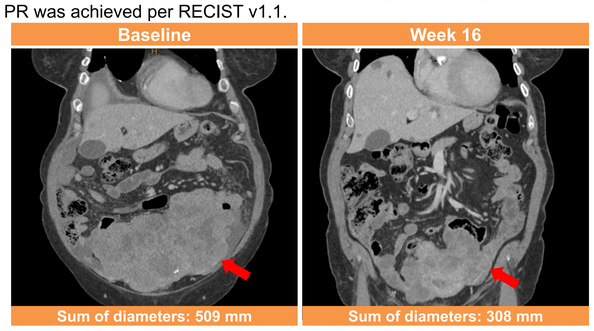


- PK data were collected from 28 patients across 7 dose levels.
- HM97662 exposure generally increased with dose; a similar pattern was observed on C1D1 and C1D8.

CASE REPORTS

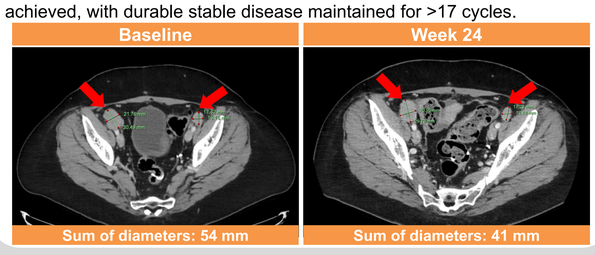
1. 67-year-old female with SMARCA4-deficient Uterine Sarcoma (Figure 7)

After receiving 4 cycles of HM97662 treatment (300 mg QD), a confirmed PR was achieved per RECIST v1.1.



2. 53-year-old female with Ovarian Cancer (Figure 8)

Treated at 200 mg QD, a maximum tumor reduction of –26% was achieved, with durable stable disease maintained for >17 cycles.



Concluding Remarks

- **HM97662 demonstrated a manageable safety profile**, with no discontinuations due to treatment-emergent adverse events.
- **Preliminary pharmacokinetic data showed increased exposure with higher dose levels**.
- **Durable clinical activity was observed across multiple solid tumor types**, highlighting the therapeutic potential of EZH1/2 dual inhibition.
- **Responses in tumors with SWI/SNF complex alterations provided mechanistic support**, suggesting a role for biomarker-informed strategies.
- **HM97662 is emerging as a promising therapeutic option for patients with advanced solid tumors**, warranting further clinical evaluation.

References

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** The graphical representations were generated with BioRender.com*

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