As a novel epigenetic modulator, EZH1/2 dual inhibitor HM97662 exhibits antitumor efficacy in hematological malignancies and overcomes EZH2 inhibitor-mediated resistance

Abs. no. 801

Jooyun Byun, Seung Hyun Jung, Young Su Noh, Young Gil Ahn, Inyoung Choi
Hanmi Pharmaceutical Co. Ltd., Seoul, Republic of Korea

Introduction

EZH1 and EZH2, the catalytic subunits of the Polycomb Repressive Complex 2 (PRC2), mediate chromatin remodeling and play a crucial role in lymphoid development, with deregulation contributing to malignancy. In diffuse large B-cell lymphoma (DLBCL), gain-of-function mutations in EZH2 (e.g., Y641X) enhance H3K27 trimethylation, leading to epigenetic silencing of differentiation genes and promoting lymphomagenesis. EZH2 overexpression also represses tumor suppressors, contributing to malignant transformation. However, selective EZH2 inhibition may trigger compensatory EZH1 activation, potentially limiting efficacy and driving resistance. Thus, dual inhibition of EZH1/2 offers a promising strategy to overcome resistance by broadly modulating PRC2 activity within the tumor microenvironment. HM97662, a novel EZH1/2 dual inhibitor developed by Hanmi Pharma, is under evaluation in a Phase 1 clinical trial.

Methods

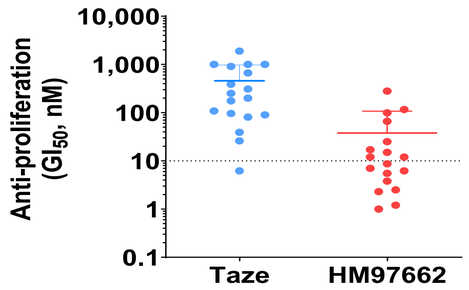
- Anti-proliferation assay: Cell viability was assessed using the CellTiter-Glo® Luminescent Cell Viability Assay (Promega)
- Immunoblot: EZH1, EZH2 (Cell Signaling), trimetylation and GAPDH (Santa Cruz) were used for detecting protein expression
- Resistance cell line construction: KARPAS-422 cells were continuously exposed with Tazemetostat *in vitro* for 12 weeks
- *In vivo* efficacy: HM97662 was orally administrated once daily in KARPAS-422 and TazemetostatR mice model (IACUC approved)

Results

Pharmacological features of HM97662

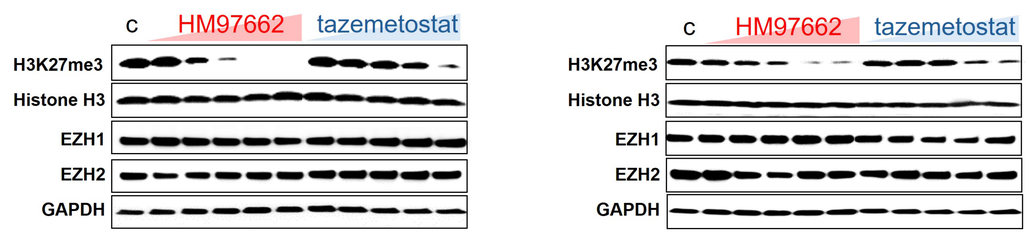
HM97662 shows a superior potency compared to Tazemetostat

Drugs	Enzyme inhibition activity (IC_{50}, nM)		
	EZH1	EZH2	$EZH2^{Y641F}$
Tazemetostat	188	2.8	2.7
HM97662	16	2.1	1.4



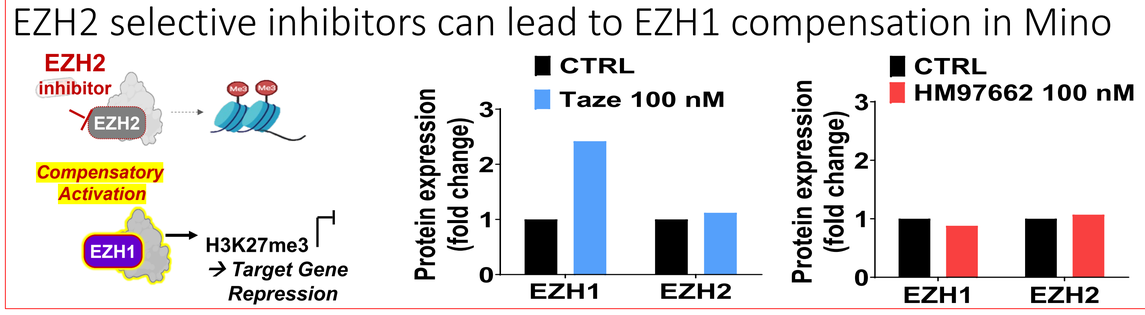
H3K27me3 methylation in KARPAS-422 and MM1.S cells

Dose-dependently inhibits global H3K27 tri-methylation



Limitation of EZH2 selective epigenetic modulator

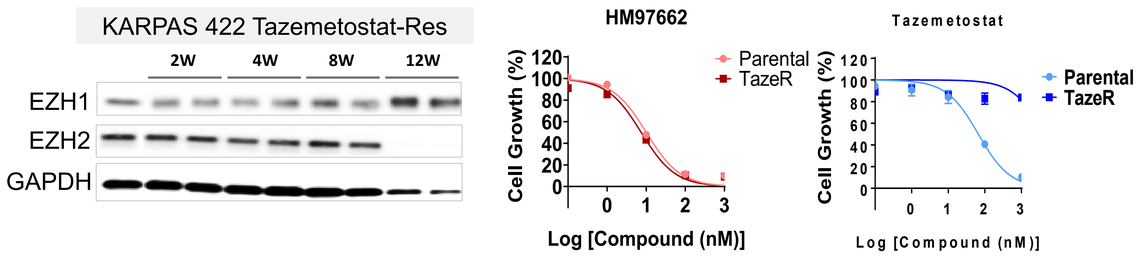
EZH2 selective inhibitors can lead to EZH1 compensation in Mino



Results

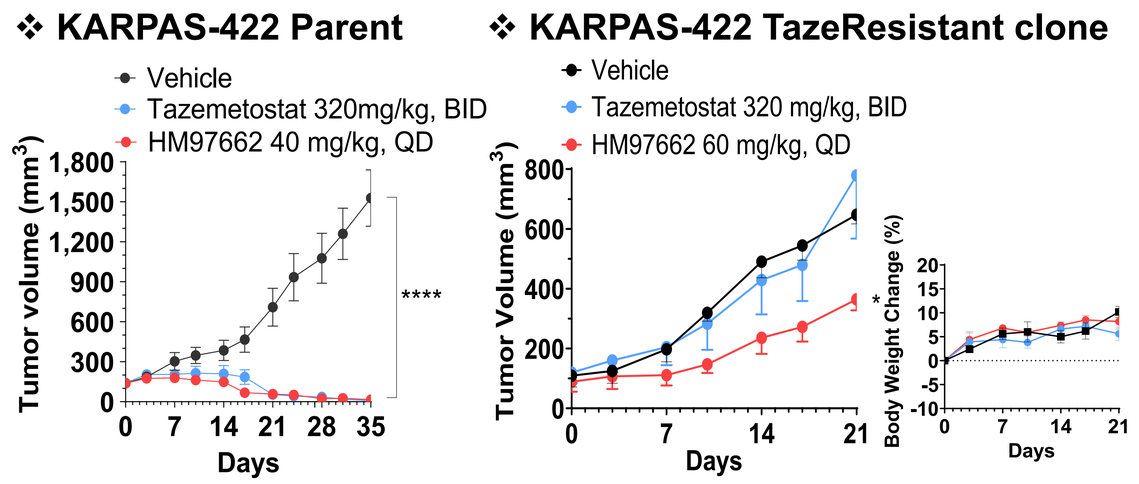
Strategy for overcoming the EZH2*i*-induced resistance

Long-term treatment of Tazemetostat in KARPAS-422 DLBCL cells induces EZH1 expression by compensation mechanism. EZH1/2 dual inhibitor overcomes its bypass/resistant mechanism



Anti-tumor efficacy of HM97662 in KARPAS-422 parent and -TazeResistant DLBCL xenograft mice models

HM97662 exhibits superior potency in KARPAS-422 ($EZH2^{Y641N}$) as well as in KARPAS-422 Taze-resistance xenograft mice model



Conclusions

EZH2 is a clinically validated epigenetic target that plays a key role in silencing tumor suppressor genes. However, selective inhibition of EZH2 leads to a compensatory upregulation of EZH1, which contributes to the development of resistance and limits long-term efficacy. To overcome this limitation, we developed HM97662, a next-generation EZH1/2 dual inhibitor with enhanced inhibitory activity against EZH1.

HM97662 exhibits effective target modulation, including inhibition of H3K27me3 and B-cell differentiation, demonstrating its robust epigenetic remodeling capacity. Importantly, HM97662 showed strong antitumor activity in KARPAS-422 Tazemetostat-resistant xenograft mice models. Currently, HM97662 is in a first-in-human dose-escalation study (NCT05598151) aiming to validate its clinical potential as a durable and broad-spectrum epigenetic therapy.

Acknowledgement

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)

References / Bibliography

AACR /ESMO/ISSX/Bio-IT conference since 2021
Blood Reviews 2022 (56) Franck Morcshharuser et al.
Nature 2012 (492) Michael T. McCabe et al.