Synergistic Effects of HM97662 as an EZH1/2 Dual Inhibitor Combined with DNA-Damaging Agents on Malignant Lung Cancers Harboring SMARCA4-Deficiency

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Abstract #7055

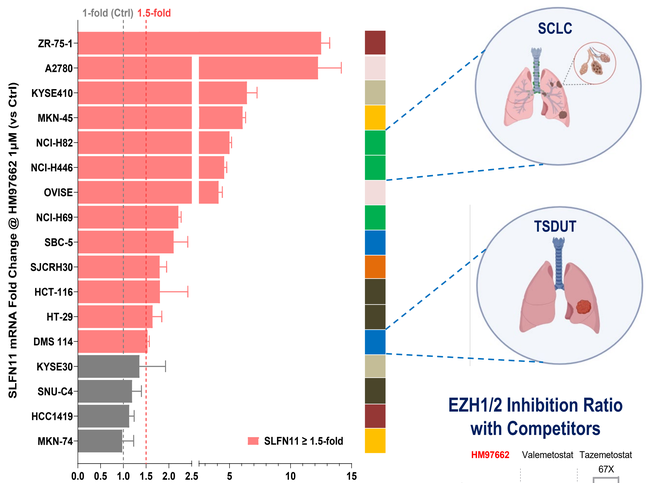
Introduction

EZH (enhancer of zeste homolog) is a histone methyltransferase that catalyzes the trimethylation of H3K27 and functions as a catalytic subunit of the polycomb repressive complex 2 (PRC2). Through epigenetic regulation, EZH modulates the transcription of tumor suppressor genes, thereby contributing to cancer cell survival, proliferation, metastasis, and drug resistance.[1)] In particular, the enzymatic activity of EZH2 is strongly associated with poor clinical outcomes, indicating that EZH2 has high therapeutic potential in cancer treatment. Under normal conditions, EZH1 and EZH2 function complementarily to support PRC2 and maintain epigenomic homeostasis. However, inhibiting EZH2 alone can trigger compensatory activation of EZH1, reducing benefit and enabling resistance. Thus, dual inhibition of EZH1 and EZH2 is a rational strategy to overcome resistance *via* broad PRC2 suppression across the tumor microenvironment.

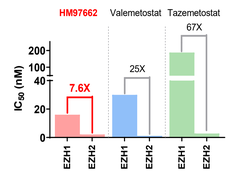
Thoracic SMARCA4-deficient undifferentiated tumor (TSDUT) which has been classified in 2021 by World Health Organization (WHO) at first, is a newly defined, high-grade malignancy with undifferentiated/rhabdoid features, marked aggressiveness, and poor prognosis.[2)] It is molecularly characterized by SMARCA4 deficiency or concurrent loss of SMARCA2, which are key subunits of the SWI/SNF complex that are often mutated and show synthetical lethal relationships in various cancers. Owing to its rarity and histological heterogeneity, diagnosis is challenging, and standard treatments are lacking; TSDUT frequently recurs after surgery, shows radio-resistance, and responds poorly to chemotherapy. Notably, EZH1/2 inhibition may enhance SLFN11-mediated sensitivity to DNA-damaging agents (DDAs), offering a promising therapeutic avenue through combination.[3)]

SLFN11 Modulation by EZH1/2 Dual Inhibitor

Broad Combination Potential of HM97662 with DDAs Across Multiple Indications



EZH1/2 Inhibition Ratio with Competitors

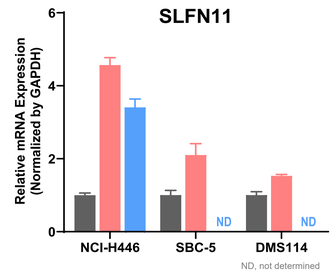


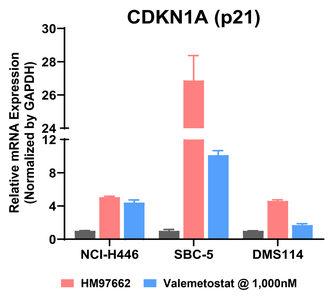
- SCLC: accounts for approximately 13–15% of all lung cancers and is a highly aggressive subtype that grows rapidly, metastasizes early, and is strongly associated with smoking
- TSDUT: high-grade malignancy with undifferentiated/rhabdoid features, marked aggressiveness, and poor prognosis

Combination Efficacy with DNA-Damaging Agents in Thoracic SMARCA4-Deficient Undifferentiated Tumor (TSDUT)

Induction of Chemosensitivity-Related Genes

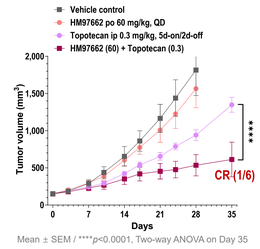
(*In vitro* Rationale for the Combination with DDAs in SCLC/TSDUT Cell Lines)



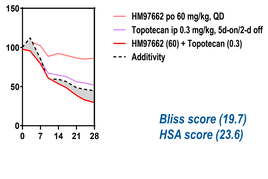


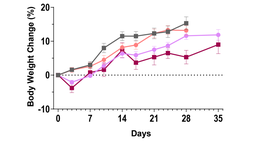
SBC-5 (SMARCA4/2 loss)

Combined with Topotecan



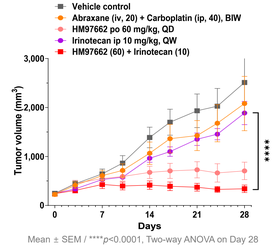
Mean ± SEM / ****p<0.0001, Two-way ANOVA on Day 35



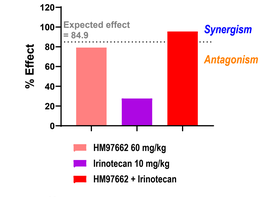


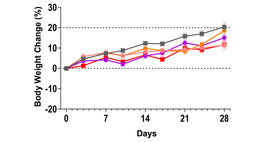
DMS114 (SMARCA4/2 loss)

Combined with Irinotecan

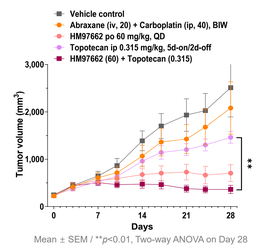


Mean ± SEM / ****p<0.0001, Two-way ANOVA on Day 28

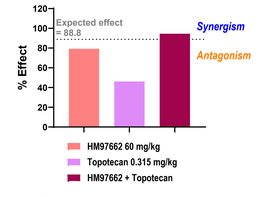


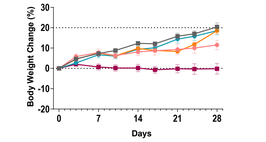


Combined with Topotecan



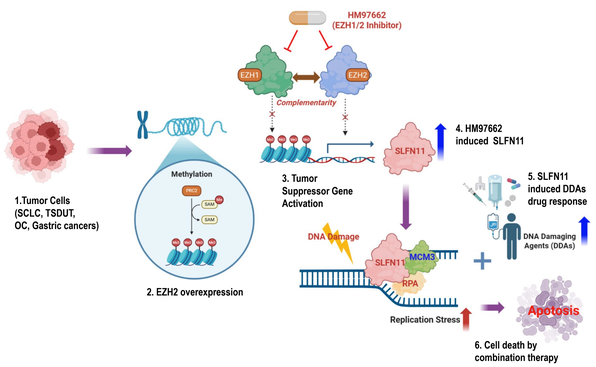
Mean ± SEM / **p<0.01, Two-way ANOVA on Day 28





Scientific Rationale for Combination with DDAs [4)]

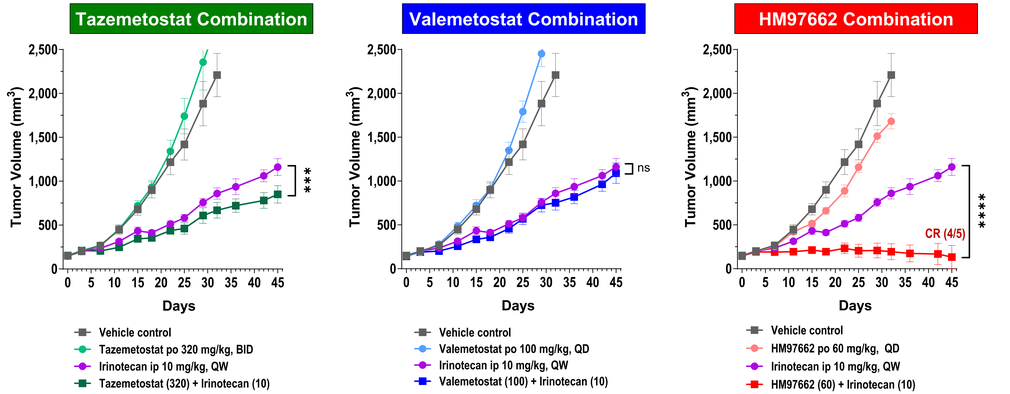
HM97662 Combined with DNA-Damaging Agents for Cancer Treatment

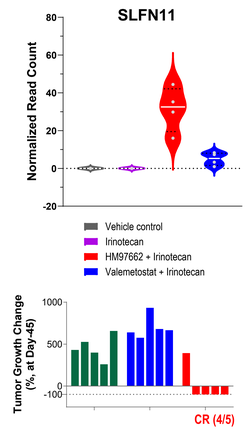


Combination Efficacy with DNA-Damaging Agent in SCLC

NCI-H446 (SMARCA4 mut)

Mean ± SEM / ***p<0.001, ****p<0.0001, ns=not significant, Two-way ANOVA on Day 45





Concluding Remarks

- HM97662, an EZH1/2 dual inhibitor, showed a wide and strong growth inhibitory effect in various solid cancer cell lines.
- Moreover, HM97662 exhibited potent antitumor activities in xenograft mouse models with various solid cancer cells especially small cell lung cancer, and Thoracic SMARCA4-deficient undifferentiated tumor (TSDUT).
- Furthermore, HM97662 induced the activation of chemo sensitivity-related genes such as SLFN11 and enhanced the drug response to DDAs, thereby promoting cell death through a combination strategy. Therefore, HM97662 showed synergistic effects with DDAs such as topoisomerase 1 inhibitors in associated tumor xenograft models.
- Currently, a FIH Phase 1 dose escalation and ranging study of HM97662 in advanced or metastatic solid tumors is underway in KR/AU (NCT05598151).

References

1. Margueron, R., Reinberg, D., et al. *Nature*, 469, **2011**, 343-349;
2. Field, N. R., Marsh, D. J., et al. *Cancer Letters*, 605, **2024**, 217282;
3. Zhou, K., Zhuang, L., et al. *Front. Oncol.* 15, **2025**, 1582738;
4. Zoppoli, G., Regiraz, M., et al. *PNAS*. 109, **2012**, 15030-15035;
5. The graphical representations were generated with BioRender.com.

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