HJM-353: A Potent, Selective and Orally Bioavailable EED Inhibitor with Robust Anti-tumor Activities

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Introduction

- Polycythemal Repressive Complex 2 (PRC2), a mutimeric complex that catalyzes the methylation of histone H3 at lysine 27 with core subunits EZH2, EED and SUZ12, functions as an epigenetic modulator in regulating cell proliferation and development. Dysregulation of the PRC2 complex is implicated in hematological and solid malignancies and shown to correlate with poor prognosis in cancers.
- EZH2 inhibitor Tazemetostat (EPZ-6438) has been approved by FDA for the treatment of advanced epithelial sarcoma and follicular lymphoma. However, acquired mutations in EZH2 and the complementary activity of EZH1 might impair the effectiveness of this class of PRC2 inhibitors.
- Targeting the allosteric subunit EED represents a new strategy to fully inhibit PRC2 activity and address the limitations of EZH2 inhibition.
- HJM-353 is a potent, selective and orally bioavailable EED inhibitor with robust anti-tumor activities, and good DMPK properties.

Activity of HJM-353 on Tazemetostat-Resistant Cell

Figure 2 A: Validation of constructed Tazemetostat-resistant rhabdoid G401 cell line (EZH2-Y111N). HJM-353 level could not be reduced after Tazemetostat (EPZ-6438) treatment at 0.37 μM; B: Anti-proliferation activities of HJM-353 and Tazemetostat on G401 WT and EZH2-Y111N mutated cells after 15-day incubation. HJM-353 is not affected by this resistant mutation, while IC50 values of Tazemetostat shifted over 80-fold.

DMPK Profiles and Pre-clinical Evaluation of HJM-353

Microsomal stability CM (μM/min/mg, μelu,μM/mg protein)<7.5/6.7/7.5/15.4/7.5 Plasma stability t1/2 (min, μM/h)IC50 33.8 nM

Enzymatic inhibition of PRC2 (EZH1 or 2)

Concentration (nM)% Inhibition
EZH1 IC50 21 nM
EZH2 IC50 15 nM

Histone Methylation activity

Plasma Free Conc (μM)IC50 or IC50 > 10μM

In vivo Activity of Anti-tumor Activity Evaluation in CDX Models

Figure 3 A: HJM-353 showed highly anti-tumor activity in B cell NHL Karpas422 CDX model, induced tumor complete regression as low as 5 mg/kg, BID dosage; B: HJM-353 showed quite similar tumor growth suppression in xKATO III gastric cancer CDX model as MAK683 and Tazemetostat.

In vivo Activity of HJM-353

Figure 1 A: HJM-353 inhibits EED-H3K27me3 peptide binding activity, determined by AlphaScreen assay; B: HJM-353 inhibits enzymatic histone methyltransferase activity of PRC2 (EZH2) and PRC2 (EZH2) equally, determined by AlphaLISA assay; C: HJM-353 effectively inhibits PRC2 activity in G401 cell, indicated by reduction of cellular H3K27me3 level, determined by quantified analysis of Western Blot results after 3-day incubation; D: HJM-353 potently inhibits WSU-DLCL2 cell proliferation after 9-day incubation, viable cell numbers were counted by Vi-CELL.

PK/PD Study in Karpas422 CDX Model

Figure 4 A: HJM-353 reduced H3K27me3 levels dose-dependently in Karpas422 tumor samples, after 14-day twice daily dosing; B: Quantification and normalized WB results, correlated well with HJM-353 plasma free concentrations at 4 hours after 1st dose on Day 14; C: mRNA levels of two PRC2 targeted genes upregulated dose-dependently in Karpas422 tumor samples.

Conclusion

- In summary, HJM-353 demonstrated potent in vitro and in vivo anti-tumor activities, good drug-like properties and PK/PD correlation, efficacious on Tazemetostat-resistant tumor cells as well (in vivo data is not shown).
- GLP toxicity studies were completed, and IND filing is expected in 2022 Q3.