Antitumor Activity of a Novel Reversible LSD1 Inhibitor, HM97211 in Preclinical Models of SCLC

InHwan Bae, JiSook Kim, WonJeoung Kim, JiYoung Song, Hyeongki Kim, Guangmo Nampoong, Joo-Yun Byun, HyunJeong Kang, TaeHun Song, Ho Jeong Lee, YoungHoon Kim, YoungGil Ahn, KweeHyun Sun and SunJin Kim

Hanmi Research Center, Hanmi Pharmaceutical Co. Ltd., South Korea

Abstract

Global changes in the epigenetic landscape are known as the hallmark in cancer. The histone demethylases lysine-specific demethylase 1 (LSD1) is one of the novel targets for the therapy of various malignant diseases and LSD1 overexpression is associated with poor prognosis in various cancers. LSD1-mediated epigenetic modification is known to play a key role in the regulation of gene expression by removing the methyl groups from methylated lysine 4 and lysine 9 of histone H3. Alterations in histone methylation lead to aberrant silencing of multiple gene expression involving tumor survival and in cell cycle. Moreover, epigenetic deregulation plays a critical role in pathogenesis of various types of cancers such as acute myeloid leukemia (AML) and non-small cell lung cancer (SCLC). Herein, this study introduces a small drug profile of the novel LSD1 inhibitor by reversible binding on LSD1.

In vitro Cellular Activity

Anti-proliferation Effects of HM97211 in SCLC Cell Lines

Cell Lines | GI50 (nM) | Vehicle
---|---|---
NCI-H526 | 24 | 100
NCI-H1417 | 24 | 100

In vitro Enzyme Activity

Enzymes | IC50 (nM) | LSD1
---|---|---
LSD2 | 1,000 | 64
MAO-A | >100,000 | 20,000
Other enzymes | >1,000 | >1,000

Inhibition of Interaction between LSD1 and INSM1

Mode of Action

Reversible LSD1 Inhibitor, HM97211 by Jump-dilution Assay

In vitro Enzyme Activity

Transcriptional Regulation

Biomarker Evaluation

ASCL1 Down-regulation & Histon H3 Methylation

Antitumor Efficacy

NCI-H1417 Xenograft Model

NCI-H526 Xenograft Model

PK/PD Profile

Conclusions

Time after HM97211 (30 mg/kg) administration of Day 4 in NCI-H1417 xenograft

Pharmacokinetic parameters of HM97211 was calculated from the plasma concentration-time data by a non-compartmental method using Pharsight WinNonlin. Tumor tissue was prepared for PD analysis.

HM97211 is a novel reversible LSD1 inhibitor with a histone competitive inhibition mechanism.

HM97211 enhanced not only global methylation of H3K4 but also apoptotic signaling in NCI-H1417 cell line.

HM97211 altered expression of neuroendocrine factor ASCL1, inducing programmed cell death in SCLC cells.

In NCI-H1417 xenograft models, daily oral administration of HM97211 induced tumor regression with remarkable toxicity. HM97211 enhanced efficacy of standard of care agents in human SCLC xenograft models.

Analyses of tumor samples revealed the important role of potent small molecule LSD1 inhibitor in neuroendocrine-associated transcription and cell proliferation of SCLC.

HM97211 can potentially provide clinical benefits and a favorable safety profile for the treatment of SCLC patients.

References

2. Burrows MD et al., Cell Reports 2016, 16, 1269-1277.
3. Fujino K et al., Am J Pathol. 2015, 186, 3586-3577.

Author Disclosures

All Authors: Employees in Hanmi Pharmaceutical Co. Ltd.

Hanmi Pharmaceutical Co. Ltd. (http://www.hanmipharm.com)