INTRODUCTION

Oral HM43239 is in development for the treatment of acute myeloid leukemia (AML) because of its capacity to potently inhibit kinases that drive myeloid malignancies, including diverse forms of the FLT3, SYK, JAK, and c-KIT kinases. Wildtype FLT3 is overexpressed in most AML patients, and approximately 30% of newly diagnosed adult AML patients harbor internal tandem duplications (ITDs) or point mutations in the tyrosine kinase domain (TKD). These mutations drive aberrant activation of downstream proliferation pathways and are associated with a high risk of relapse. Likewise, the c-KIT tyrosine kinase domain (TKD). These mutations drive aberrant activation of downstream SYK, JAK/STAT5, ERK, and other rescue signaling pathways. This rationale supports the development of HM43239.

OBJECTIVE

Evaluate the activity of HM43239, an orally active drug, as a Myeloid Kinome Inhibitor in human AML models.

METHOD

Biochemical kinase assays were performed by Thermo Fisher Scientifics and DiscoverX USA. The effects of HM43239 on cell proliferation (IC50), growth rate (GR50), and concentration at half-maximal effect (GEC50) were determined using the MTS assay with vehicle controls1. Cell-based inhibition of target kinase activity was performed using dose-dependent drug treatments. The effects of HM43239 on cell survival, proliferation, and downstream signaling were assessed using flow cytometry, western blot analysis, and immunohistochemistry.

Effect of HM43239 and Gilteritinib on the Interactions of Bone Marrow Stroma with AML in Orthotopic Mice Model

HM43239 is more potent than gilteritinib in orthotopic murine model of AML. Mice were administered 2% D1FLT3-ITD or MOLM-14 FLT3-ITD/F691L cells and allowed to populate the bone marrow for 7 days, after which drugs were administered orally QD for 12 to 14 days. Representative images of IHC were collected using a Dako REAL Envision Detection System (400x) and quantified with a Vectra 3 Pathology Imaging Analyzer (200x images). Positive DAB % was calculated using GraphPad PRISM®.

CONCLUSIONS

• HM43239 inhibits wild type and mutant forms of FLT3 at low nM concentrations.
• HM43239 inhibits phospho-FLT3, phospho-SYK, phospho-EKR1/2 and phospho-JAK/STAT5 that participate in signaling and rescue pathways.
• HM43239 has potential to kill cells and tumors resistant to other FLT3 inhibitors.
• HM43239, at doses that are well tolerated, demonstrates in vivo efficacy on tumors resistant to other FLT3 inhibitors.
• A Phase 1/2 trial (NCT03859574) of HM43239 in R/R AML patients is ongoing.

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REFERENCES


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