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LAM-003, a novel oral heat shock protein 90 inhibitor for treatment of acute myeloid leukemia, including wild-type and FMS-like tyrosine kinase 3 (FLT3)-mutant disease

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Introduction

- Acute myeloid leukemia (AML) is a heterogeneous disease characterized by abnormal proliferation and accumulation of myeloid cells in the bone marrow.
- Mutation of the FLT3 receptor is one of the most common genetic alterations, occurring in ~30% of all patients with AML.
- FLT3 inhibitors that target the constitutively active mutant receptor have recently been approved (e.g., midostaurin, gilteritinib).

- However, not all patients respond, and those who do inevitably relapse due to acquisition of secondary FLT3 mutations, upregulation of other molecular pathways, or the influence of the bone marrow microenvironment.
- In vitro studies demonstrate that inhibiting heat shock protein 90 (HSP90), a major chaperone protein, is effective in reducing AML blast viability.

- We describe nonclinical studies of LAM-003, a novel, orally bioavailable HSP90 inhibitor produg, for the treatment of AML.

LAM-003 Displays Potent Activity in Wild-Type (WT) AML and in FLT3-Mutant AML

LAM-003 decreases survival of mice in an MOLM-14 (FLT3-ITD) systemic AML model. Mice were inoculated with MOLM-14 cells and treated with either vehicle, LAM-003 (75 mg/kg), or LAM-003 plus venetoclax (20 mg/kg). Mice were treated with a loading dose of LAM-003 on day 0, followed by continued treatment every other day. Mice treated with LAM-003 alone have significantly improved survival compared to vehicle and LAM-003 plus venetoclax. LAM-003 plus venetoclax also shows improved survival compared to vehicle, but not significantly compared to LAM-003 alone.

LAM-003 Inhibition of HSP90 Results in Degradation of Mutant FLT3 and Blocks Oncogenic Signaling in FLT3-Mutant AML Cells

Mechanism of LAM-003 and venetoclax Synergy

Conclusions

- LAM-003 displays antileukemic activity in both WT and FLT3-mutant AML, with preferential activity observed in FLT3-mutant cells.
- LAM-003, through inhibition of HSP90, degrades FLT3-mutant receptor with mutations that confer resistance to FLT3 inhibitors.
- LAM-003 disrupts stomal factor signaling that confer resistance to FLT3 inhibitors.
- LAM-003 exhibits potent synergy with venetoclax in both WT and FLT3-mutant AML.
- Based on these findings, a dose-ranging study is evaluating LAM-003 safety, pharmacokinetics, pharmacodynamics, and efficacy in patients with relapsed AML.

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Disclosures

N.B.S., S.L., S.G., J.S., B.M., P.Y., and H.L. are employees at Al Therapeutics. T.X. is on the Al Therapeutics advisory board. J.R. is a Director of Al Therapeutics. L.M. is a consultant for Al Therapeutics. Al Therapeutics is the owner of LAM-003/ALM-003 patents.