Materials and Methods

**BM Leukemia Burden**

GMI-1359 Blocks Adhesion of Leukemic Cells and Enhances FLT3 Inhibitor Efficacy in a Murine AML Model

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1. Zhang, W., Mu, H., Zhang, Q., Patel, N. B., Pate, F., E. W., Magnani, J. L., and Andreiff, M.
2. Active mutations of the FLT3 tyrosine kinase such as the most common alterations in acute myeloid leukemia (AML) and they are associated with very poor disease prognosis[1]. Targeted therapy for FLT3-mutated AML patients using small molecule FLT3 inhibitors (e.g., sorafenib) has showed clinical success in reducing leukemic blasts in peripheral blood. However, this therapeutic strategy has limited effect on leukemic stem cells residing in the bone marrow (BM) microenvironment[2,3]. The BM microenvironment is enriched with cytokines and adhesion molecules such as CXCR4 and E-selectin, which are believed to provide AML cells protection against chemotherapeutic agents[4]. Furthermore, CXCR4-mediated therapy has achieved successful anti-leukemia effects[5,6]. Therefore, we hypothesized that blocking CXCR4 and E-selectin concomitantly along with FLT3 inhibitor could eliminate the protection provided by the BM microenvironment in designated AML patients. We recently reported that targeting CXCR4/E-selectin with the dual inhibitor GMI-1359 (GlycoMimetics, Inc., Rockville, MD) showed significant prolongation of survival of mice engrafted with FLT3-ITD-mutant MV4-11 leukemia cells[7]. In the present study, we further investigated and characterized this activity.

Results

**GMI-1359 Blocks Adhesion of Leukemic Cells to E-selectin and SDF-1α In Vitro**

Combination of GMI-1359 with Sorafenib Reduces Leukemia Burden in Vivo

Combination of GMI-1359 with Sorafenib Enhances In Vivo Leukemia Cell Elimination from Bone Marrow

**GMI-1359 Effectively Mobilizes Leukemia Cells into Circulation in a Murine FLT3-ITD-mutated Leukemia Model**

**GMI-1359 Blocks Adhesion of Leukemic Cells to E-selectin and SDF-1α In Vitro**

**GMI-1359 Effectively Mobilizes Leukemia Cells into Circulation in a Murine FLT3-ITD-mutated Leukemia Model**

**Conclusions**

- GMI-1359 significantly promoted mobilization of leukemia cells from BM into circulation in a murine AML model.
- Combination of GMI-1359 with sorafenib markedly reduced leukemia burden and eliminated leukemic cells in bone marrow in a FLT3-ITD-mutated MOLM14-engrafted AML murine model.

References