The Dual E-selectin/CXCR4 Antagonist GMI-1359 Exerts Anti-leukemia Efficacy Against FLT3-ITD-mutated Acute Myeloid Leukemia in A Patient-derived Xenograft Murine Model

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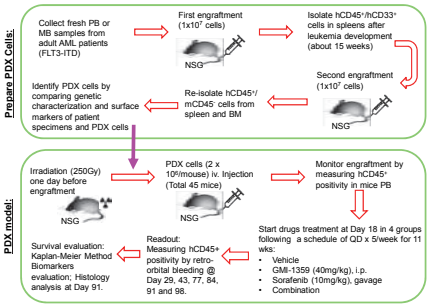
Abstract: 3519

Background

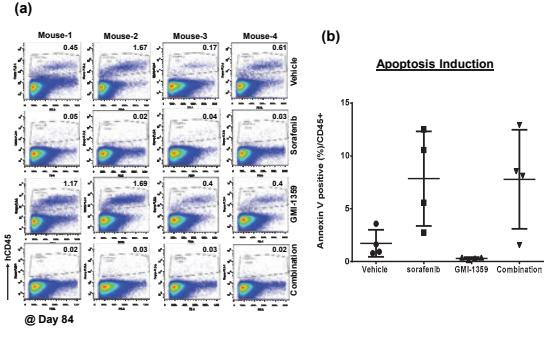
Acute myeloid leukemia (AML) is a molecularly heterogeneous disease with poor clinical outcome. Targeted therapy of FMS-like tyrosine kinase-3 (*FLT3*)-mutated AML patients using small molecular inhibitors including sorafenib showed clinical success in reducing leukemia blasts in peripheral blood. However, they have limited effect on leukemic stem cells in the bone marrow (BM) microenvironment *(1, 2)*. The BM is presumed to be the reservoir for leukemia stem cells (LSCs) that persist during targeted therapy and mediate disease relapse. The interaction of leukemic blasts with the BM microenvironment is mediated by receptor-ligand axes such as CXCR4/SDF-1, E-selectin/HECA-452, and cell-cell contact have also been associated with drug resistance in *FLT3* mutated AML *(3-5)*. We recently reported that targeting CXCR4/E-selectin with the dual inhibitor GMI-1359 (GlycoMimetics, Inc., Rockville, MD) showed efficient mobilization of leukemia cells in to the circulation, and significant prolonged survival of mice in a *FLT3*-ITD mutant AML cells-xenografted murine model *(6, 7)*. In the present study, we further evaluated the anti-leukemia effects of GMI-1359 in a patient-derived xenograft (PDX) murine model. We demonstrated that GMI-1359 enhances normal hematopoiesis in the BM in addition to its anti-leukemia effects, either alone or combined with sorafenib treatment.

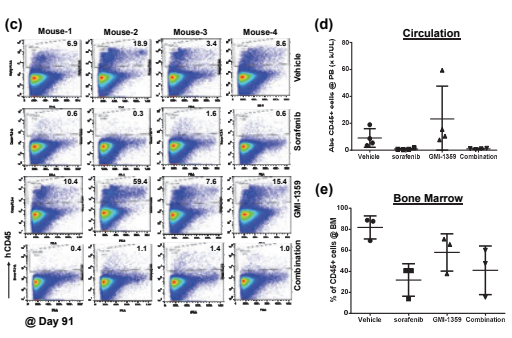
Materials and Methods



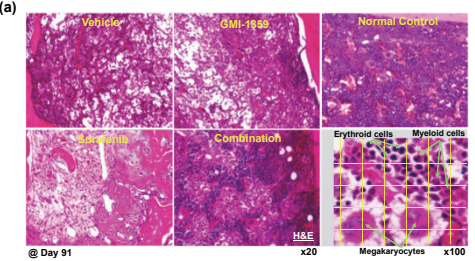
Results

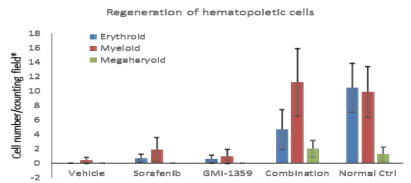
1) *GMI-1359 Mobilizes Leukemic Cells to Circulation, Which Are Them Effectively Eliminated by Combined Treatment with Sorafenib*



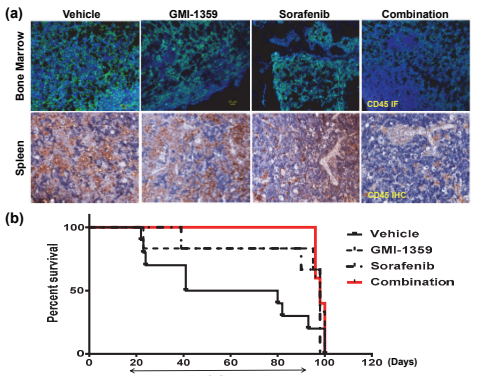


2) The Combination of GMI-1359 and Sorafenib Profoundly Increases Erythropoiesis, Myelopoiesis and Megakaryopoiesis in Bone Marrow





3) *The Combination of GMI-1359 with Sorafenib Reduces Leukemic Cells Burden in Organs*



Conclusions

- **The dual CXCR4/E-selectin inhibitor GMI-1359, alone or in combination with the FLT3 ITD inhibitor sorafenib, demonstrated anti-leukemia effects in a PDX model of FLT3 ITD-mutated AML.**
- **The combination of the dual CXCR4/E-selectin inhibitor GMI-1359 with sorafenib also strikingly increased normal hematopoiesis in the bone marrow.**
- **Mechanism is being investigated.**

References

1. W. Zhang *et al.*, *J.Natl.Cancer Inst.* **100**, 184-198 (2008).
2. G. Borthakur *et al.*, *Haematologica* **96**, 62-68 (2011).
3. A. Peled, S. Tavor, *Theranostics.* **3**, 34-39 (2013).
4. J. M. Horacek, *et al.*, *Biomed.Pap.Med.Fac.Univ Palacky.Olomouc.Czech.Repub.* **157**, 277-279 (2013).
5. S. M. Garrido *et al.*, *Experimental Hematology* **29**, 448-457 (2001).
6. Zhang et al., ASH Abstract #3790, 2015.
7. Zhang et al., AACR Abstract #3284, 2016.

* No conflict of interest disclosure.