Development of GMI-1359, a Novel Agent Targeting Tumor-Microenvironment Cross-talk in Bone Metastatic Breast Cancer

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Introduction

Pre-clinical and clinical data suggest that the bone marrow (BM) environment provides breast cancer (BC) cells a protective haven against chemotherapeutic insult, endocrine therapies, and immune recognition. Novel agents that intercept cross-talk between BC cells and the host could therefore improve the depth of response to therapies and potentially increase overall survival in metastatic BC. We have previously shown that bone metastatic BC cells reside in perivascular niches expressing high levels of stromal-derived factor 1 alpha (SDF-1α) and E-selectin, two molecules for which emerging data have demonstrated a significant role in metastatic BC progression[1]. Our prior pre-clinical studies have shown that E-selectin inhibition specifically prevents circulating BC cells from homing to the BM, whereas CXCR4 (SDF-1α receptor) blockade mobilizes micrometastasis from the marrow into circulation, where they may be sensitized to chemotherapeutic cell kill. Given the normal role of these molecules in host immune responses, E-selectin/CXCR4 blockade has additional potential to impact the tumor immune microenvironment.

Project Objectives:

- Analyze the effect of GMI-1359, a novel dual inhibitor of E-selectin and CXCR4, on the proportions of regulatory immune cells within the bone marrow and primary tumor in a pre-clinical, syngeneic model of breast cancer.
- Initiate a Phase 1b clinical trial of GMI-1359 in hormone receptor positive metastatic breast cancer patients.

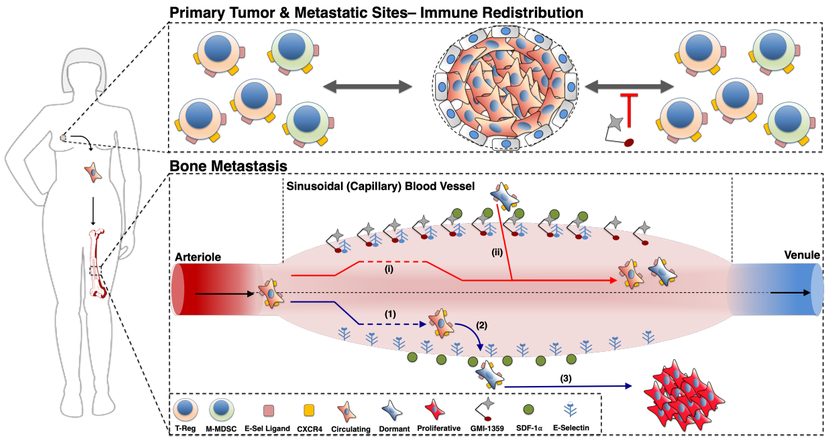


Fig. 1. GMI-1359 effects on breast cancer metastasis and regulatory immune cell infiltration. Schematic model of E-selectin and SDF-1α mediated BCC metastasis and GMI-1359 mediated antagonism of this process in pre-clinical models. BCCs home to sinusoidal (capillary) vascular niches in the bone marrow in an E-selectin-dependent manner[1] (**1**). Disseminated tumor cells may remain dormant for prolonged periods in this SDF-1α+ niche, where CXCR4 anchors them to the niche (**2**), while BCC proliferation occurs in other (non-sinusoidal) regions of the bone marrow (**3**). GMI-1359, a dual inhibitor of E-selectin and SDF-1α, significantly diminished BCC entry into the bone (**i**), and successfully promoted mobilization of established disease out of the pro-dormancy niche (**ii**). Immune regulatory cells (regulatory T-cells and myeloid derived suppressor cells) express E-selectin ligands and CXCR4 which can affect their trafficking within tumors. GMI-1359 therefore has the potential to alter the immune profile within tumors.

References:

1. *Price TT*, et al ***Sci Trans Med*** 2016.
2. NCT04197999.

Trial Design

Phase 1b, Single and Multiple Dose, Open-Label Trial of i.v GMI-1359

Eligibility Criteria:

- Metastatic HR+ breast cancer
- Stable or minimal evidence of progression on endocrine therapy +/- a CDK4/6 inhibitor
- Total accrual – 6 Patients

OBJECTIVES AND ENDPOINTS

Primary Objective	Secondary Objectives	Exploratory Objectives
• Safety/tolerance of GMI-1359 for single ascending doses and multi-dose administration	• Plasma PKs after single ascending and multiple dose administration • PD markers of on-target effect: - CD34 cell mobilization - Serum E-sel levels • Tumor cell mobilization by CTC analyses pre- and post- GMI-1359	• Response by RECIST criteria • Circulating and BM immune cell subset analyses • Circulating tumor cell Ki67, viability, CXCR4 expression • Serum/plasma markers of bone turnover, endothelial activation • RNAseq analyses on bone marrow disseminated tumor cells

Trial Schema

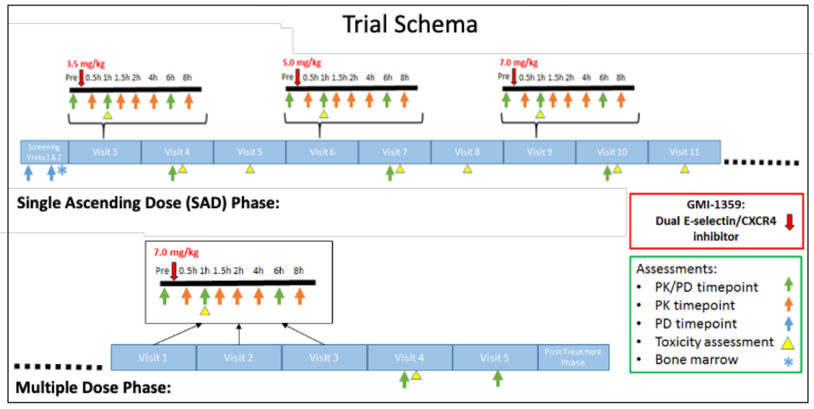
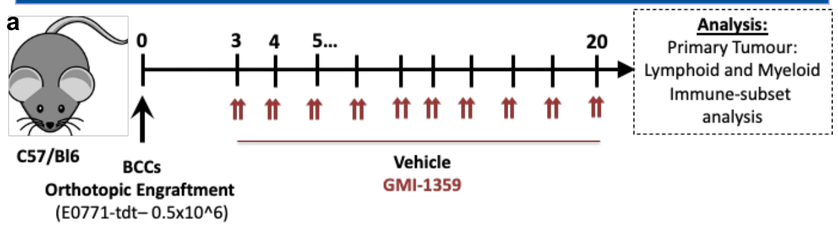


Fig. 2. Schema of GMI-1359 Phase 1b clinical trial[2].

Results: Pre-clinical



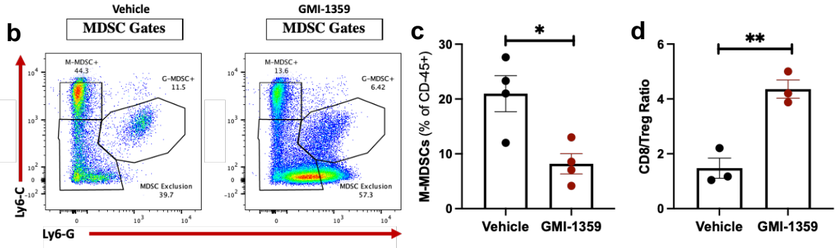


Fig. 3. GMI-1359 effects regulatory immune cell distribution in a syngeneic model of breast cancer. (**a**) Schematic of treatment and analysis strategy. (**b-d**) Flow cytometry data. GMI-1359 decreases intratumoral monocytic-myeloid derived suppressor cells (M-MDSC) and induces a favorable CD8 effector/T regulatory cell ratio. (***G-MDSC***: CD3-,CD19-,CD45+,CD-11b+,Ly6-G+ / ***M-MDSC***: CD3-,CD19-,CD45+,CD-11b+,Ly6-C*high*).

Results: Clinical

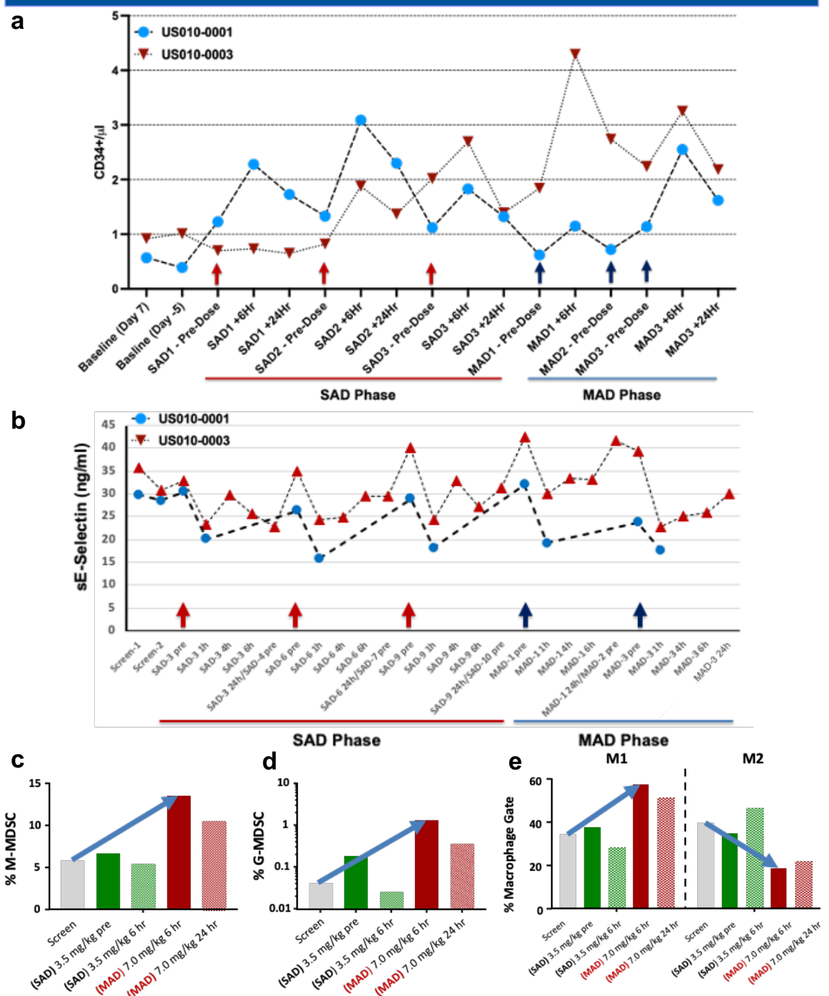


Fig. 4. Preliminary Phase 1b Clinical trial data. (**a & b**) **Pharmacodynamic markers:** Quantification of CXCR4+ hematopoietic progenitor cell number (CD34+/µl) and soluble E-selectin levels (sEsel ng/ml) in the blood of two patients (USD010-0001 & USD010-0003) at various time points pre- and post-treatment during single and multiple dose phases. At all dose levels, GMI-1359 promotes mobilization of CD34+ cells into the bloodstream and reduces soluble E-selectin in serum, demonstrating dual functionality of the compound. (**c-e**) **Immune subset analysis:** Effect of GMI-1359 on the redistribution of MDSCs into peripheral blood and the polarization of macrophage phenotype from M2 to M1 (***gMDSC***: CD11b+ CD33dim HLA-DR- CD15+ cells; ***mMDSC***: CD11b+ CD33+ HLA-DRlow/- CD14+ cells).

Conclusion

- To date, 4/6 total patients have been enrolled and 2/6 patients have completed their treatment course.
- No dose-limiting toxicity has been observed.
- Evidence of on-target effects of GMI-1359 have been observed in patients, including CD34+ mobilization and decreased soluble E-selectin levels following drug dosing.
- In pre-clinical mouse models and in a pilot analysis of the first patient enrolled in this clinical trial, favorable changes in immune subset profiles were observed.
- Ongoing clinical and preclinical work will define the efficacy of GMI-1359 to enhance responses to chemo and immune therapies.