The vascular niche is involved in regulating leukemic stem cells in murine chronic myelogenous leukemia

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**Disclosures for Investigators**

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Presentation includes discussion of the following off-label use of a drug or medical device: GMI-1271
Targeting of the osteoblastic niche can eradicate LSC in CML

- Resistance to imatinib
- Disease relapse
- Disease progression

Krause DS et al., 2013, Nat Med; 19(11):1513
An osteoblastic and a vascular hematopoietic stem cell niche are distinguished

Krause DS, Scadden DT, Preffer FI, 2013, Cytometry Part B; 84(1): 7
Adhesion pathways employed by normal HSC and LSC in the BM

- E-selectin inhibitor?
- E-selectin promotes HSC proliferation


E-selectin is exclusively expressed on endothelial cells
The E-selectin-specific antagonist GMI-1271

- Successor of the pan-selectin antagonist Rivipansel (GMI-1070), now in phase 2 clinical trial for vaso-occlusive crisis of sickle cell disease

- In clinical trial for AML to decrease adhesion of acute myeloid leukemia blasts to E-selectin

- Improves survival in mice after high-dose chemotherapy by alleviating mucositis and accelerating neutrophil recovery

- May be beneficial in inhibiting metastasis and thromboembolic complications
Retroviral BM transduction/transplantation model

Donor: 5-FU 200 mg/kg

packaging cell

prestimulation (IL-3, IL-6, SCF)
and ex vivo transduction

The tumor burden is reduced in mice treated with the E-selectin antagonist GMI-1271 +/- imatinib.

Day 0
- Transplantation

Days 10-28
- Daily Treatment with
  - vehicle
  - imatinib 100 mg/kg p.o.
  - GMI-1271 20 mg/kg i.p.
  - GMI-1271+imatinib

### Leukocyte count in peripheral blood

- **Vehicle**
- **Imatinib**
- **GMI**
- **GMI+IM**

**P-values:**
- **P=0.02**
- **P=0.07**
- **P=0.02**

### GFP⁺ (BCR-ABL1⁺) myeloid cells in peripheral blood

- **Vehicle**
- **Imatinib**
- **GMI**
- **GMI+IM**

**P-values:**
- **P=0.03**
- **P=0.04**
- **P=0.02**
Spleen weights are reduced in mice treated with GMI-1271 plus imatinib.
GMI-1271 +/- imatinib leads to prolongation of survival in some mice

Survival benefit is not due to increased mobilization of BCR-ABL1+ myeloid cells or LSC to peripheral organs
GMI-1271-treatment significantly reduces BCR-ABL1+ leukemic stem cells
The tumor burden is reduced in secondary recipients of GMI1271-treated BM

Secondary transplantation of CML BM cells from treated primary donor mice to assess LSC frequency, self-renewal and repopulation efficiency
Treatment with GMI-1271 and imatinib reduces the cycling of BCR-ABL1+ LKS cells

P = 0.03
Conclusions

• The E-selectin inhibitor GMI-1271 +/- imatinib reduces tumor burden in a murine model of CML.

• GMI-1271 +/- imatinib prolongs survival in approximately 20% of mice with CML.

• GMI-1271 reduces LSC in CML and, consequently, tumour burden in secondary recipients.

• GMI-1271 reduces the cycling of CML stem cells.

• Modulation of the vascular niche and in particular E-selectin may be a possible strategy to target LSC in CML, in particular when imatinib is discontinued.