A Double-Blind, Placebo-Controlled, Phase 3 Registration Trial to Evaluate the Efficacy of Uproleselan (GMI-1271) with Standard Salvage Chemotherapy in Patients with Relapsed/Refractory (R/R) Acute Myeloid Leukemia

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Background

Uproleselan (GMI-1271), an E-selectin antagonist, disrupts the relationship between tumor cells and bone marrow microenvironment (Figure 1)

E-selectin
- Constitutively expressed in the bone marrow microvasculature
- Binds to the E-selectin ligands on AML cells
- Promotes environment-mediated drug resistance (EMDR) of leukemic cell

Uproleselan, an E-selectin antagonist:
- Inhibits activation of cancer survival pathways (e.g., NF-kB), disrupting EMDR within bone marrow
- Reduces chemotherapy-associated mucositis (Figure 2a)
- Prolongs survival over chemotherapy alone in animal models (Figure 2b)
- Protects normal HSCs by enhancing quiescence and ability for self-renewal

Figure 1: Mechanism of Action

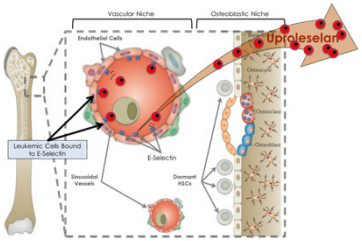
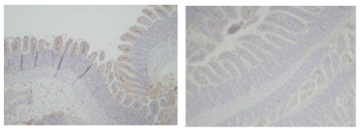
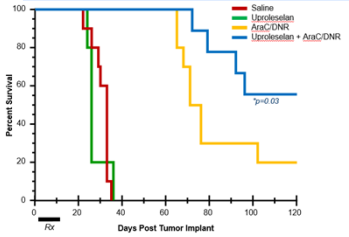


Figure 2a: Uproleselan Protects Against Chemotherapy-Induced Mucosal Injury in Mice



Winkler, et al. 2014

Figure 2b: Uproleselan in Combination with Chemotherapy Prolongs Survival in AML Tumor Model



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Key Findings in Phase I/II Trial

Phase I/II AML trial in relapsed/refractory (R/R) AML (uproleselan + MEC) and newly diagnosed older AML (uproleselan + '7+3') was completed.

- Key findings in R/R population:
  - Higher remission rate (CR/CRi) of 39% (historical control 28%, Feldman, et al. 2005)
  - High rates of MRD negativity
  - Improved overall survival (OS) of 8.8 months (historical control 5.2 months, Feldman, et al. 2005) (Figure 3)
  - High E-sel-L expression on leukemic blasts correlated with improved OS (Figures 4a and 4b)
  - Low rates of severe oral mucositis
- Breakthrough Therapy Designation granted by FDA for R/R population (NCT03616470)
- Additional trials planned for front-line older newly diagnosed AML (NCT03701308)

Figure 3: Overall Survival in All Patients Receiving RP2D

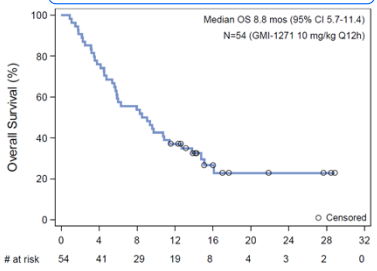


Figure 4a: E-selectin Ligand Detectable on Blasts in All Patients

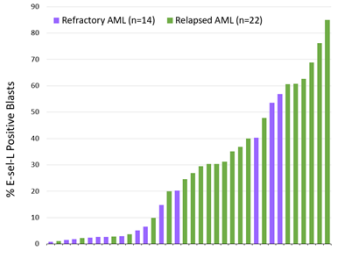
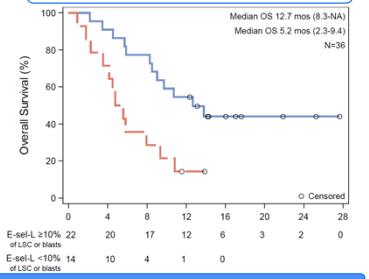


Figure 4b: Overall Survival in High E-sel-L Expression vs. Low E-sel-L Expression



Key Criteria for Study Entry

- ≥18 to ≤75 years old
- Primary refractory AML defined as follows:
  - Must have received 1 (and only 1) prior induction regimen containing both an anthracycline and cytarabine*
  - Persistent disease (≥5% blasts in bone marrow) at least 28 days after initiation of induction therapy
    -- OR --
  - Relapse from a first remission (CR, CRi, CRp) lasting for <90 days
- Relapsed AML defined as follows:
  - First or second relapse untreated with cytotoxic regimen*
  - Secondary refractory AML is not allowed
- Prior transplant (HSCT) is allowed
  - Allogeneic HSCT >4 months
  - Autologous HSCT >3 months
  - No acute GVHD ≥ Grade 2
  - No active chronic GVHD requiring immunosuppressive therapy
- Must be medically eligible for chemotherapy
- ECOG performance status ≤2

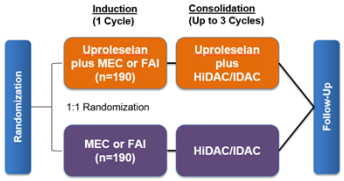
***Targeted inhibitors are not considered cytotoxic chemotherapy for the purpose of the study:**
- **FLT3 inhibitors**
- **IDH1/IDH2 inhibitors**
- **HMA +/- venetoclax**

Endpoints

Primary Endpoint:
- To evaluate OS achieved with uproleselan administered with chemotherapy versus chemotherapy alone

Key secondary endpoints	Exploratory endpoints
• Rate of severe oral mucositis • Rate of HSCT • Rate of CR and CRh	• MRD assessment • E-selectin ligand expression on leukemic blast cells, plasma soluble E-selectin

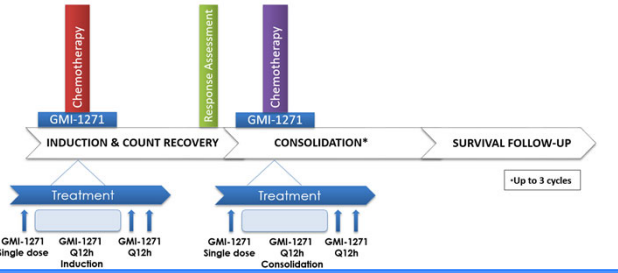
Uproleselan Relapsed/Refractory AML Phase 3 Trial Design



After completion of the induction period and response assessment, every effort should be made to transplant eligible subjects. For those in remission and being actively assessed for transplant, consolidation on trial while awaiting transplant is strongly encouraged.

MEC: Mitoxantrone, etoposide and cytarabine; FAI: Fludarabine, cytarabine and idarubicin; HiDAC/IDAC: High-dose or Intermediate-dose cytarabine; based on investigator's choice

Treatment Schema



Current Enrollment

This trial is expected to enroll 380 patients across approximately 9 countries in North America, Europe, and Australia (Figure 5). The first patient was enrolled in November 2018.

Figure 5: Participating Countries

References

DeAngelo DJ, et al. Blood 2018; 132:331; DeAngelo DJ, et al. Blood 2017; 130:894; Feldman E, et al. J Clin Oncol 2005; 23 (18):4110; Angelini DE, et al. Blood 2016;128:3826; Cheson BD, et al. J Clin Oncol 2003;21 (24):4642-4649; Chien S, et al. Blood 2013;122:2161; Chien S, et al. Blood 2012;120:4092; Devata S, et al. Blood 2015;126:1004; Dohner H, et al. Blood 2010;115 (3):453-474; Rashidi A, DiPersio JF. Ther Adv Hematol 2016;7:4051; Winkler IG, et al. Nat Med 2012;18(11):1651-7; Winkler IG, et al. Blood 2013;122:2266; Winkler IG, et al. Blood 2014;124:620; Winkler IG, et al. Blood 2016; 128:2823.

Conflict of Interest Disclosures: DJD, HE, PM, GH, BC, BB, and MA have no conflicts to report. MEO, JLL, and PSB received research funding, and BAJ and ASA were paid consultants over the past 2 years for GlycoMimetics, Inc. WF, MC, JM, HT, and EF are employees of, and have equity ownership in, GlycoMimetics, Inc.
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More information on this and related GlycoMimetics projects can be obtained at glycomimetics.com