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
- Inhibits activation of cancer survival pathways (e.g., NF-kB), disrupting EMDR within bone marrow
- Protects survival over chemotherapy alone in animal models (Figure 2a)
- Protects normal HSCs by enhancing quiescence and ability for self-renewal

Exploratory endpoints

- Binds to the E-selectin ligands on AML cells
- Reduces chemotherapy-associated mucositis (Figure 2a)
- MRD assessment
- Prolongs survival over chemotherapy alone in animal models (Figure 2b)
- E-selectin ligand expression on leukemic blast cells, plasma

Endpoints

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

Key secondary endpoints

- Rate of severe oral mucositis
- Rate of HSCT
- Rate of CR and CRh

Uproleselan Relapsed/Refractory AML Phase 3 Trial Design

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

- High E-sel-L expression on leukemic blasts correlated with improved OS (Figures 4a and 4b)
- High rates of MRD negativity
- Improved overall survival (OS) of 8.8 months (historical control 5.2 months, Feldman, et al 2005) (Figure 3)
- Breakthrough Therapy Designation granted by FDA for R/R population (NCT03616470)
- Additional trials planned for front-line older newly diagnosed AML (NCT03701308)

2005) (Figure 3)

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

Key findings in Phase III trial

- Key findings in R/R population:
  - 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)

Treatment Schema

Chemosensitization

- MEC: Mitoxantrone, etoposide and cytarabine; FAI: Fludarabine, cytarabine and idarubicin; HiDAC/IDAC: High-dose cytarabine with or without idarubicin

Key Criteria for Study Entry

- Prior transplant (HSCT) is allowed
- ≥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 (≥25% blasts in bone marrow) at least 28 days after initiation of induction therapy
  - ECOG performance status ≤2
- 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

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. MEO, BC, CC, and PSB own common stock and/or equity in GlycoMimetics, Inc.

ClinicalTrials.gov Identifier: NCT03616470

References


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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

Current Enrollment

North America
- Canada
- United States

Europe
- Ireland
- Netherlands
- France
- Spain

Australia

For more information, please call 1-866-889-5607.