Trials in Progress: A Phase 3 Trial to Evaluate the Efficacy of Uproleselan (GMI-1271) with Chemotherapy In Patients with Relapsed/Refractory 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).

- 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-κB), 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

Key Findings in Phase I/II Trial

- ≥218 to ≤575 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
  - HSCT >4 months
  - No acute GvHD Grade 2
  - No active chronic GvHD requiring immunosuppressive therapy
- Must be medically eligible for chemotherapy
- ECOG performance status ≤2

Figure 1: Mechanism of Action

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

Saline injected

Uproleselan

Winkler, et al. 2014

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


Figure 4a: Overall Survival in All Patients Receiving RP2D

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

Key Criteria for Study Entry

- Uproleselan/placebo treatment:
  - Pre-chemotherapy: 24 hours prior to first dose of chemotherapy at 800 mg
  - During chemotherapy: 800 mg Q12h x 5 days
  - Post-chemotherapy: 800 mg Q12h x 2 days

Patients will receive the single priming dose of uproleselan/placebo at 800 mg given 24 hours prior to first dose of chemotherapy, every 12 hours (± 1 hour) on chemotherapy days and 2 days following the last dose of chemotherapy

Treatment

- No active chronic GvHD requiring immunosuppressive therapy
- Must be medically eligible for chemotherapy
- ECOG performance status ≤2

Current Enrollment

This trial is expected to enroll 380 patients across approximately 8 countries in North America, Europe, and Australia (Figure 5). The first patient was enrolled in November 2018.

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

Exploratory endpoints:
- MRD assessment
- E-selectin ligand expression on leukemic blast cells, plasma soluble E-selectin

References


For further information please contact: cfoederman@glycomimetics.com

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