GMI-1271, a Potent E-Selectin Antagonist, in Combination with Chemotherapy in Relapsed/Refractory AML: A Novel, Well-Tolerated Regimen with a High Remission Rate


Background

For those achieving CR in Phase 1
The incidence and severity of mucositis was low overall, with one Grade 3/4 event reported.

E-selectin inhibition by GMI-1271 disrupts this interaction.

E-selectin is expressed on endothelium in the bone marrow, and sLex expressed on AML cells (blasts and LSCs).

Methods

A Phase 1/2 open-label trial evaluated GMI-1271 together with cytotoxic induction and consolidation chemotherapy in adult patients with R/R AML. This phase included assessment of safety, tolerability, PK, biomarkers and anti-leukemic activity.

Results

Eligible patients (R/R AML) had an ECOG score of 0-2, received ≤2 prior induction regimens, absolute blast count ≤25% (revised to ≤20% after dose levels), no active infections, and adequate renal and hepatic function. One prior HCT was allowed.

GMI-1271 was administered with chemotherapy (24 hrs prior, throughout, and 48 hrs following chemotherapy). In Phase 1, DLT was defined as any non-hematologic or hematologic toxicity beyond D2 in the absence of disease or Grade 2-4 non-hematologic toxicity beyond D3. In Phase 2, DLT was defined as any non-hematologic toxicity beyond D2 in the absence of disease or Grade 2-4 non-hematologic toxicity beyond D3 and/or a >25% reduction in WBC count. The percentage of blasts expressing the E-sel ligand was more than 10% in those achieving full CR (Fig. 3). A positive finding was strongly associated with achieving full CR (Fig. 3).

Effectivity

• The response rate (CR/CRi) was 41% and higher than expected given the high-risk prognostic and other disease features. After a single course of induction chemotherapy with GMI-1271 (Phase 1), a higher CR/CRi rate (47%) was seen compared to historical controls (Feldman 2005; Greenberg 2004). Phase 2 adds consolidation for possible deepening of remission and improved duration of response.

• Durability of response is encouraging and sufficient to allow patients to proceed to stem cell transplant (NHS to date)

Safety

• 60-day mortality was low (9%).

• The incidence and severity of mucositis was low overall, with one Grade 3/4 event reported.

Biomarker

• Patients with a greater percentage of blasts expressing the E-sel ligand were more likely to be able to achieve PFS and OS, but no specific biomarker outcome provides strong evidence of clinical proof of concept. Future studies plan to explore how the expression of the E-sel ligand on leukemic cells can be exploited to improve outcomes.

The United States Food and Drug Administration recently granted Breakthrough Therapy designation to GMI-1271 for the treatment of adult patients with relapsed/refractory acute myeloid leukemia. Planning is underway for a randomized controlled trial.

Conclusion

Safety Outcomes

Table 1: Response in AML as reported by the European Leukaemia Net (Deleu, Blood 2010)

RP2D: Recommended Phase 2 Dose; 10 mg/kg

Mechanism of Action

Treatment Schema

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More information on this and related Glycomimetics projects can be obtained at glycominetics.com

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