GMI-1271, a Potent E-Selectin Antagonist, Combined with Induction Chemotherapy in Elderly Patients with Untreated AML: A Novel, Well-Tolerated Regimen with a High Remission Rate

Daniel J. DeAngelis1, Brian A. Jonas2, Dale L. Bixby2, Pamela S. Becker2, Michael E. O'Dwyer4, Anjali S. Advanji2, Paula Martlon2, John L. Magnani2, Helen M. Thackray5, Jane L. Liesveld1

1Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts; 2Department of Medicine, Division of Hematology, and Oncology, UC Davis Comprehensive Cancer Center, Sacramento, California; 3Department of Internal Medicine, Division of Hematology and Oncology, University of Michigan, Ann Arbor, Michigan; 3Division of Hematology, University of Washington, Seattle, Washington; 4Department of Haematology, National Cancer Hospital, Singapore, Galway, Ireland; 5Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio; 5Princess Alexandra Hospital, Brisbane, Australia; 6GlycoMimetics, Rockville, Maryland; 7Department of Medicine, Hematology/Oncology, University of Rochester Medical Center, Rochester, New York.

Background

Treatment of elderly patients with acute myeloid leukemia (AML) remains a significant challenge. Poor outcomes result from morbidity and mortality during intensive induction chemotherapy and short duration of remission when achieved. Although cytotoxic chemotherapy is a standard treatment for those who can tolerate such regimens, novel agents are needed to improve clinical outcomes.

Methods

A Phase 2, open-label trial evaluated GMI-1271 together with anthracycline-based induction and consolidation chemotherapy in adult patients ≥60 years of age with newly diagnosed AML. Patients were followed for leukemia remission, durability of remission, subsequent therapy, and survival.

Results

Efficacy:

- The response rate (CR/CRi) was 68% and higher than expected given the high risk disease features.
- Responses are seen in all risk subgroups.
- Durability of response is encouraging and sufficient to allow eligible patients to proceed to stem cell transplantation.
- Follow-up is short (median 6.9 mos), but for the 12 patients evaluable at 6 months, 9/12 achieved CR/CRi and all those remain in remission.
- 60-day mortality was low (8%).
- The incidence and severity of mucositis was low overall, with no Grade 3+ events reported.

Toxicity:

- GMI-1271 is a novel antagonist of E-selectin, rationally designed to mimic the carbohydrate structures of the E-selectin ligand binding epitope (sLea) which can potentially disrupt leukocyte blast adhesion and degranulation, and thus improve chemotherapy response. Nonclinical data collectively suggest that GMI-1271 mediated disruption of E-selectin interactions between the endothelium and blasts decreases sensitivity to cytotoxic agents both by preventing AML cells from binding to the bone marrow niche and by attenuating stroma-induced resistance to chemotherapy. Xenograft and syngeneic models demonstrate that addition of GMI-1271 decreases tumor burden and enhances survival beyond chemotherapy alone.

Phase 2 enrollment is complete; all patients have completed induction chemotherapy and initial response assessment. Median overall survival has not been reached.

Conclusions

GMI-1271 demonstrated significant improvements in safety and efficacy in elderly patients with AML. This regimen was well tolerated, enabling a high CR rate and long remission duration. Further studies are warranted to evaluate the potential of GMI-1271 as a component in combination therapy for AML.