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

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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 remains standard treatment for those who can tolerate such regimens, novel agents are needed to improve clinical outcomes.

Binding of leukemic blasts to E-selectin (E-sel), an adhesion molecule expressed constitutively in bone marrow endothelium, supports leukemia cell quiescence and protection from cell cycle-dependent chemotherapy. (Winkler 2012; Rashidi 2016) Further, AML-stromal interactions mediated by E-sel activate leukemic cell survival pathways and contribute to chemotherapy resistance. (Chien 2013; Winkler 2016) Leukemic cells in patients with relapsed AML have proportionally higher expression of the E-sel ligand than in patients with newly diagnosed AML, suggesting that these cells may contribute to the likelihood of relapse. (Chien, 2013)

GMI-1271 is a novel antagonist of E-sel, rationally designed to mimic the carbohydrate structures of the E-sel ligand binding epitope (sialyl Le$^{a/x}$) which can putatively disrupt leukemic blast adhesion and activation, down-regulate cell survival pathways, and enhance chemotherapy response. Nonclinical data collectively suggest that GMI-1271-mediated disruption of E-sel interactions between the endothelium and AML blasts confers increased sensitivity to cytotoxic agents both by preventing AML cells from remaining in the bone marrow niche and by attenuating stroma-induced resistance to chemotherapy. Xenograft and syngeneic *in vivo* models demonstrate that addition of GMI-1271 decreases tumor burden and enhances survival beyond chemotherapy alone. (Winkler 2014; Chien 2012)

Additionally, chemotherapy is independently associated with E-sel up-regulation in the bone marrow and other tissues. Chemotherapy-induced damage to gut and intestinal mucosa is substantially aggravated by secondary macrophage infiltration; erosion of the mucosal lining concurrent with neutropenia is a likely contributor to sepsis and mortality, prolonged hospitalization, and impact on quality of life. GMI-1271 has been shown to block secondary migration of inflammatory macrophages to chemotherapy-damaged mucosa in a murine model, protecting from weight loss and improving survival. (Winkler 2012; 2013)

GMI-1271 has been assessed for safety and pharmacokinetics (PK) in Phase 1 healthy volunteer trials, with a benign safety profile and predictable, dose-proportional PK to date. (Devata 2015) We performed a phase 2 trial of GMI-1271 together with intensive induction and consolidation for the treatment of elderly patients with newly diagnosed AML.

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. Objectives included assessment of safety, tolerability, PK, biomarkers and anti-leukemic activity. Eligible patients had an ECOG score of 0-2, baseline WBC <40K/μL, no active CNS disease, and adequate renal and hepatic function. Secondary AML and treatment-related AML were included. Prior treatment of MDS was allowed.

GMI-1271 (10 mg/kg) was administered with chemotherapy (a single sentinel dose 24 hrs prior, twice daily throughout, and 48 hrs post induction or consolidation). Induction chemotherapy consisted of infusional cytarabine and idarubicin (7+3); a second cycle of induction (5+2) was allowed if Day 15 bone marrow confirmed residual leukemia. The first 3 patients were assessed for dose-limiting toxicity (DLT) during induction; following these first 3 patients, subsequent responders (CR) could receive consolidation with GMI-1271 plus intermediate dose cytarabine for up to 3 cycles.

DLT was defined as myelosuppression in the absence of disease or related Grade 3 non-hematologic toxicity beyond day 42. Baseline E-sel ligand expression on leukemic blasts in the bone marrow (CD45/SSC by flow) is reported. Patients were followed for leukemia remission, durability of remission, transplant, and survival.

Mechanism of Action

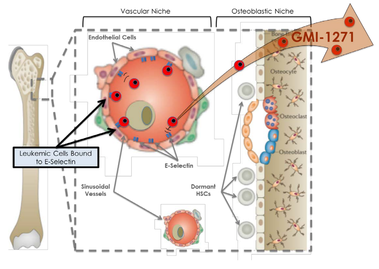


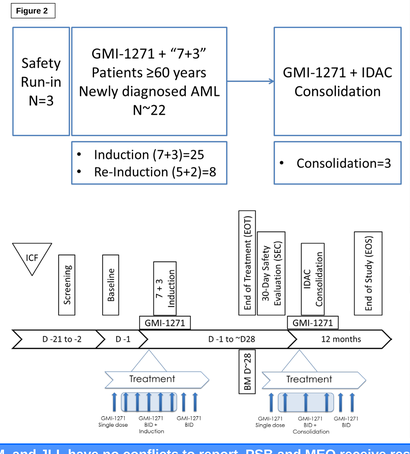
Figure 1: E-selectin-mediated adhesion

E-selectin is expressed on endothelium in the bone marrow, and binds to a trisaccharide domain common to both sLe^a and sLe^x expressed on AML cells (blasts and LSCs).

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

Treatment Schema

Figure 2



Results

Demographics

Subgroup	n (%)
Enrollment	**25**
Age, median (range)	**67 (60-79)**
Male	**14 (56)**
Newly diagnosed, All	**25 (100)**
de novo	11 (44)
Secondary AML[#]	14 (56)
Cytogenetic risk group (SWOG)	
Favorable	1 (4)
Intermediate	15 (60)
Unfavorable	8 (32)
Unknown	1 (4)
FLT3-ITD mutated	**1 (4)**
ECOG Performance Status	
0	13 (52)
1	10 (40)
2	1 (4)

[#] Included patients with:
- Prior MDS
- Prior CMML-1 or CMML-2
- Prior Myelofibrosis
- Treatment-related AML

Interim Clinical Outcomes

Outcome	n (%)
n Completing Induction Period	**25**
n Receiving Re-Induction (5+2)	**8 (32)**
Response*	
CR + CRi	**17 (68)**
Complete Remission (CR)	13 (52)
CR with incomplete recovery (CRi)	4 (16)
CR + CRi + MLFS	**20 (80)**
Morphologic Leukemia-Free State (MLFS)	3 (12)
Persistent Disease	**3 (12)**
Proceeded to HSCT, n (%)	**3 (12)**
Indeterminate (Died; not assessed)	**2 (8)**
All-Cause Mortality 30 days, n (%)**	**2 (8)**
All-Cause Mortality 60 days, n (%)**	**2 (8)**

*Response criteria in AML as reported by the International Working Group (Cheson, JCO 2003) and the European Leukaemia Net (Dohner, Blood 2010)

**All-cause mortality is cumulative. Deaths were from sepsis, at Day 3 and 23.

AML Subgroup	CR/CRi* Rate n (%) of subgroup
n Completing Induction Period	**25**
de novo	8/11 (73)
Secondary AML	9/14 (64)
Cytogenetic risk group (SWOG)	
Favorable risk	1/1 (100)
Intermediate risk	10/15 (67)
Unfavorable risk	5/8 (63)
FLT3-ITD mutated	**1/1 (100)**

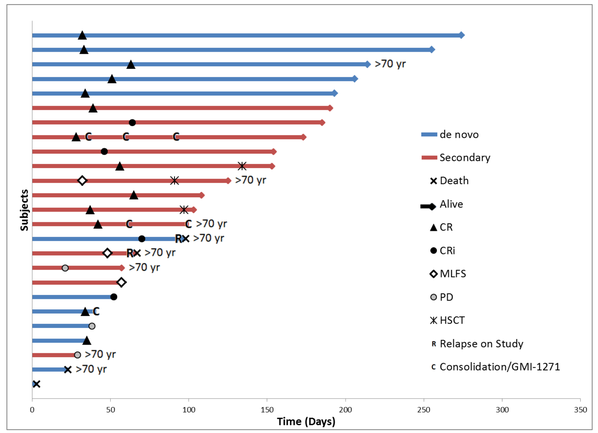


Figure 5: Swimmers plot showing interim outcome and survival as of data cutoff.

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

Interim Safety Outcomes

Adverse Events: Grade 3/4	n (%)
Evaluable Patients	**17**
Cardiac Atrial fibrillation; Chest pain	**2 (12)**
Colitis	**1 (6)**
GI Decreased appetite; malnutrition	**2 (12)**
Hematologic	**6 (35)**
Anemia	2 (12)
Neutropenia	3 (18)
Thrombocytopenia	2 (12)
White blood cell count decreased	3 (18)
Hepatic Cholecystitis	**1 (6)**
Infectious	**14 (82)**
Febrile neutropenia	9 (53)
Pneumonia	3 (18)
Pyrexia	1 (6)
Sepsis	3 (18)
Vaginal infection	1 (6)
Lab Abnormalities Hypocalcemia; Hypokalemia; Hypophosphatemia	**3 (18)**
Rash	**1 (6)**
Respiratory	**4 (24)**
Pleural effusion	1 (6)
Pulmonary edema	2 (12)
Respiratory failure	2 (12)
Tumor lysis syndrome	**1 (6)**

*AE grade definitions follow CTCAE v4.03.

Safety Summary
- N=17 for whom detailed AE data reported and monitored at time of cut-off
- GMI-1271 combined with chemotherapy was well tolerated
- The first 3 patients were assessed for Dose Limiting Toxicities; none were observed
- AEs were typical for induction chemotherapy in this population; most Grade 3/4 AEs resolved during treatment phase.
- Oral mucositis/stomatitis occurred at lower rates and intensity than expected for induction chemotherapy in this population. No cases of Grade 3/4 oral mucositis were observed.

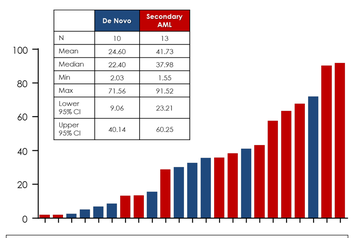
Adverse Events: Oral Mucositis	n (%)
Evaluable Patients	**17**
Grades 1/2*	**3 (18)**
Mouth ulceration	1 (6)
Pharyngeal mucositis	1 (6)
Stomatitis	1 (6)
Grades 3/4*	**0**

Time to Count Recovery	Median Days (Range)
n Completing Induction	**25**
ANC >500	28 (15-51)
ANC >1000	27 (22-51)
Platelets >100K	28 (22-51)

Time to count recovery is reported for those achieving CR or CRi with first induction (7+3) only.

Biomarker Data

Figure 3



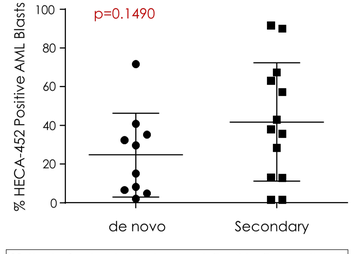
Expression of E-selectin ligand on leukemic cell surface, as detected by flow cytometry

Figure 3 shows percentage of blasts expressing E-sel ligand for evaluable patients.

Figure 4 shows median and range of blasts expressing E-sel ligand for those with de novo disease and those with secondary disease.

The majority of patients had detectable E-sel ligand on the leukemic cell surface, indicating presence of this marker is common in AML.

Figure 4



Methods: Leukemic blasts were defined by flow on the basis of CD45+ and SSC. Baseline E-sel ligand expression on leukemic cells in the bone marrow was assessed using HECA452 for identification of the SLe^x binding site on the cell surface.

Subsequent Therapy & Interim Duration of Remission

Interim follow up is reported for 12 patients evaluable for 6-month outcomes:
- 9 out of 12 achieved CR/CRi
- Disease Free Survival is 100% at 6 months: all 9 remain in remission

Ability to Proceed to Subsequent Therapy: Interim Analysis	n
n Evaluable (6 Month Follow Up)	**12**
CR/CRi	**9**
Consolidation with GMI-1271/IDAC	1
Consolidation with IDAC off study	3
Other Consolidation off study	1
HSCT	2
Subsequent therapy unknown	2
MLFS	**2**
HSCT	1
No subsequent therapy	1
PD	**1**
Subsequent therapy unknown	1

Conclusions

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 transplant.
- 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.

Safety:
- 60-day mortality was low (8%).
- The incidence and severity of mucositis was low overall, with no Grade 3/4 events reported.

Biomarker:
- Detection of the E-sel ligand on blasts was higher in secondary AML, which may account for the high CR/CRi rate in this population (64%).

Planning is underway for randomized controlled trials.

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