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

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Background

Treatment of patients with acute myeloid leukemia (AML) remains a significant challenge. Poor outcomes result from low response rates and short duration of remission when achieved. Although cytotoxic chemotherapy remains standard treatment, 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 leukemic 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, contributing to chemotherapy resistance. (Chien 2013; Winkler 2016) Leukemic cells in patients with relapsed AML have 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$^{a/x}$) and 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 confers increased sensitivity to cytotoxic agents 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. Induction 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 reduce chemotherapy-induced damage to the mucosa in a murine model by blocking secondary migration of inflammatory macrophages, thereby 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 now describe a phase 1/2 trial of GMI-1271 plus MEC (mitoxantrone, etoposide, cytarabine) induction and consolidation for the treatment of relapsed/refractory (R/R) AML.

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. Objectives included assessment of safety, tolerability, PK, biomarkers and anti-leukemic activity.

Phase 1 dose escalated single cycle GMI-1271 across 3 pharmacologically active dose levels (5-20 mg/kg) combined with MEC (mitoxantrone, etoposide, cytarabine). Once the recommended phase 2 dose (RP2D, 10 mg/kg) was selected, Phase 2 dose expansion continued enrolling patients with R/R AML and added the option for responders to proceed to 1 cycle of consolidation with GMI-1271 combined with a reduced course of MEC.

- **Eligible patients (R/R AML) had an ECOG score of 0-2, received ≤2 prior induction regimens, absolute blast count <20K (raised to <40K after 2 dose levels), no active CNS disease, and adequate renal and hepatic function. One prior HSCT was allowed.**

GMI-1271 was administered with chemotherapy (24 hrs prior, throughout, and 48 hrs post induction or consolidation). In Phase 1, DLT was defined as myelosuppression beyond day 42 in the absence of disease or Grade 3 non-hematologic toxicity attributable to GMI-1271 and not resolving to Grade 2 by day 42. Samples were collected for biomarkers at baseline and at key study milestones (end of treatment, relapse). Patients were followed for leukemia remission, durability of remission, transplant, and survival.

Results

Demographics

Subgroup, reported as n (%)	Phase 1	Phase 2	Total	RP2D*
Enrollment to Date	**19**	**40**	**59**	**47**
Age, median (range)	**51 (26-77)**	**62 (27-84)**	**59 (26-84)**	**58 (26-84)**
Male	**13 (68)**	**26 (65)**	**39 (66)**	**29 (62)**
Refractory	**6 (32)**	**11 (28)**	**17 (29)**	**12 (26)**
Relapsed, All	**13 (68)**	**29 (73)**	**42 (71)**	**35 (74)**
Relapsed <6 months	6 (32)	15 (38)	21 (36)	**18 (38)**
Relapsed 6-12 months	4 (21)	6 (15)	10 (17)	**6 (13)**
Relapsed ≥12 months	3 (16)	8 (20)	11 (19)	**11 (23)**
Prior Therapies				
HSCT	4 (21)	5 (13)	9 (15)	**6 (13)**
1 Induction Regimen	13 (68)	26 (65)	39 (66)	**31 (66)**
≥2 Induction Regimens	6 (32)	14 (35)	20 (34)	**16 (34)**
Cytogenetic risk group (SWOG)				
Favorable	0	0	0	**0**
Intermediate	9 (47)	15 (38)	24 (41)	**19 (40)**
Unfavorable	10 (53)	22 (55)	32 (54)	**25 (53)**
Unknown	0	3 (8)	3 (5)	**3 (6)**
FLT3-ITD mutated	**2 (11)**	**5 (13)**	**7 (12)**	**7 (15)**
Extramedullary disease	**1 (5)**	**1 (3)**	**2 (3)**	**2 (4)**
ECOG Performance Status				
0	6 (32)	15 (38)	21 (36)	**18 (38)**
1	6 (32)	20 (50)	26 (44)	**22 (47)**
2	7 (36)	5 (13)	12 (20)	**7 (15)**

*RP2D = Recommended Phase 2 Dose, 10 mg/kg

Clinical Outcomes

Outcome, reported as n (%)	Phase 1	Phase 2	Total	RP2D
n Completing Induction Period	**19**	**35**	**54**	**42**
Response*				
CR/CRi	**9 (47)**	**13 (37)**	**22 (41)**	**18 (43)**
Complete Remission (CR)	9 (47)	11 (31)	20 (37)	**16 (38)**
CR with incomplete recovery (CRi)	0	2 (6)	2 (4)	**2 (5)**
CR/CRi/MLFS/PR	**10 (53)**	**17 (49)**	**27 (50)**	**22 (52)**
Morphologic Leukemia-Free State (MLFS)	1 (5)	2 (6)	3 (6)	**2 (5)**
Partial Remission (PR)	0	2 (6)	2 (4)	**2 (5)**
Persistent Disease	**9 (47)**	**18 (51)**	**27 (50)**	**20 (48)**
All-Cause Mortality 30 days**	**0**	**1 (3)**	**1 (2)**	**1 (2)**
All-Cause Mortality 60 days**	**2 (11)**	**2 (6)**	**4 (7)**	**3 (7)**

Phase 1: 5/9 in CR proceeded to HSCT.
Phase 2: 2/11 in CR; 1/2 in MLFS; and 1/2 in PR proceeded to HSCT to date.

A total of 9 patients have proceeded to HSCT, 5 in the Phase 1 arm and 4 thus far in the Phase 2 arm.

****All-cause mortality is cumulative. Deaths were at Day 27, 33, 55, and 56, and all occurred after documentation of persistent disease.**

Subgroup	CR/CRi Rate n (%) of subgroup			
	Phase 1	Phase 2	Total	RP2D
n Completing Induction Period	**19**	**35**	**54**	**42**
Primary Refractory	**3/6 (50)**	**2/11 (18)**	**5/17 (29)**	**2/9 (22)**
Relapsed	**6/13 (46)**	**11/29 (38)**	**17/42 (40)**	**16/33 (48)**
Relapsed <6 months	2/6 (33)	4/15 (27)	6/21 (29)	**6/18 (33)**
Relapsed 6-12 months	1/4 (25)	2/6 (33)	3/10 (30)	**2/6 (33)**
Relapsed ≥12 months	3/3 (100)	5/8 (63)	8/11 (73)	**8/9 (89)**
Age <60 years	**7/14 (50)**	**6/14 (43)**	**13/28 (46)**	**11/21 (52)**
Age ≥60 years	**2/5 (40)**	**7/21 (33)**	**9/26 (35)**	**7/21 (33)**
Cytogenetic risk group (SWOG)				
Favorable risk	0	0	0	**0**
Intermediate risk	5/9 (56)	6/13 (46)	11/22 (50)	**9/17 (53)**
Unfavorable risk	4/10 (40)	7/20 (35)	11/30 (37)	**9/23 (39)**
FLT3-ITD mutated	**1/2 (50)**	**2/5 (40)**	**3/7 (43)**	**3/7 (43)**
Extramedullary disease	**1/1 (100)**	**1/1 (100)**	**2/2 (100)**	**2/2 (100)**

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

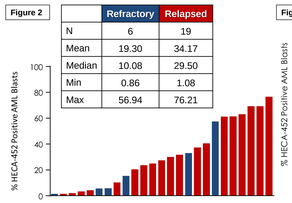
Correlative Biomarkers in Phase 2

The majority of patients had detectable E-sel ligand on the leukemic cell surface, indicating presence of this marker is common in the AML population under study (Fig. 2). Where E-sel binding is a putative mechanism for protection of blasts from chemotherapy, it might be expected that the population of cells with higher levels of the E-sel ligand are the source of relapse. We observed that the percentage of blasts with the ligand was indeed higher in the group with relapsed disease, although not significantly so (Fig. 3).

The percentage of blasts expressing the E-sel ligand was higher in those achieving remission (CR/CRi) compared to non-responders (PD/PR/MLFS). This finding was strongest in those achieving full CR (Fig. 4), yet remained significant for the group achieving CR/CRi (Fig. 5).

Figure 2

	Refractory	Relapsed
N	6	19
Mean	19.30	34.17
Median	10.08	29.50
Min	0.86	1.08
Max	56.94	76.21



Leukemic blasts were defined by flow on the basis of CD45+ and SSC. Baseline E-sel ligand on leukemic cells in the bone marrow was detected using HECA-452 for identification of the Sle^x binding site on the cell surface.

Figure 3

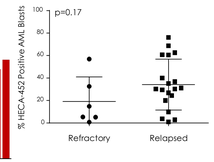


Figure 4

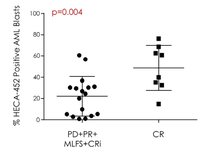
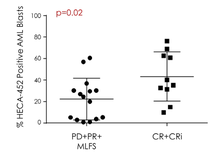


Figure 5



Survival and Durability of Response

Phase 1:

- **Median overall survival (all) is 7.6 mo.**
- **For those achieving CR in Phase 1:**
  - **7/9 have responses lasting ≥6 mo.**
  - **Median disease free survival is 11.1 mo.**
  - **Median follow up in this group is 12.6 mo, with median survival not yet reached.**
- **Of the 5 who proceeded to stem cell transplant, 3 remained in remission one year after entering study**

Phase 2 enrollment completed and follow up continues.

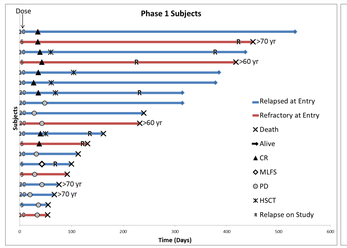


Figure 6: Phase 1 Survival

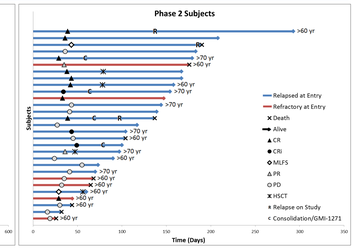


Figure 7: Phase 2 Survival (Evaluable Patients to Date)

Safety Outcomes

Safety Findings:

- **N=41 for whom detailed AE data reported and monitored at time of cut-off**
- **No DLT was seen in Phase 1**
- **All patients tolerated GMI-1271 combined with MEC chemotherapy well**
- **Types and rates of AEs were typical for induction chemotherapy in this population**
- **Oral mucositis/stomatitis occurred at lower rates and intensity than expected for MEC induction chemotherapy**

Common Grade 3/4 Adverse Events	Phase 1	Phase 2	Total	RP2D
Evaluable Patients	**19**	**22**	**41**	**29**
Cardiac	**2 (11)**	**5 (23)**	**7 (17)**	**5 (17)**
Colitis	**2 (11)**	**0**	**2 (5)**	**0**
GI	**2 (11)**	**3 (14)**	**5 (12)**	**3 (10)**
Hematologic	**10 (53)**	**12 (55)**	**22 (54)**	**15 (52)**
Anemia	5 (26)	6 (27)	11 (27)	**7 (24)**
Neutropenia	2 (11)	4 (18)	6 (15)	**4 (14)**
Thrombocytopenia	8 (42)	10 (45)	18 (44)	**12 (41)**
Hepatic	**0**	**5 (23)**	**5 (12)**	**5 (17)**
Hypophosphatemia	**4 (21)**	**1 (5)**	**5 (12)**	**1 (3)**
Infectious	**15 (79)**	**18 (82)**	**33 (80)**	**23 (79)**
Bacteremia	3 (16)	4 (18)	7 (17)	**5 (17)**
Febrile neutropenia	7 (37)	11 (50)	18 (44)	**13 (45)**
Sepsis	6 (32)	4 (18)	10 (24)	**5 (17)**
Renal failure, acute	**0**	**2 (9)**	**2 (5)**	**2 (7)**
Respiratory	**4 (21)**	**3 (14)**	**7 (17)**	**4 (14)**
Hypoxia	4 (21)	2 (9)	6 (15)	**3 (10)**
Non-Fatal Respiratory failure	0	1 (5)	1 (2)	**1 (3)**
Tumor lysis syndrome	**0**	**1 (5)**	**1 (2)**	**1 (3)**

Cardiac: Atrial fibrillation, cardiac arrest/failure, diastolic dysfunction, prolonged QT, hypertension, hypotension, ventricular tachycardia
Hepatic: increased transaminases, increased bilirubin, liver injury

Adverse Events: Oral Mucositis	Phase 1	Phase 2	Total	RP2D
Evaluable Patients	**19**	**22**	**41**	**29**
Grades 1/2*	**3 (16)**	**7 (32)**	**10 (24)**	**8 (28)**
Mouth ulceration	0	1 (5)	1 (2)	**1 (3)**
Mucosal inflammation	0	3 (14)	3 (7)	**3 (10)**
Oral Pain	0	1 (5)	1 (2)	**1 (3)**
Stomatitis/oral mucositis	3 (16)	2 (9)	5 (12)	**3 (10)**
Grades 3/4*	**0**	**1 (5)**	**1 (2)**	**1 (3)**

*AE grade definitions follow CTCAE v4.03.

Count Recovery	Phase 1	Phase 2	Total	RP2D
n Achieving CR/CRi	**9**	**13**	**22**	**18**
Time to Count Recovery, Median (Range) in Days				
ANC >500	33 (23-42)	32 (24-69)	32 (23-69)	**32 (23-69)**
ANC >1000	36 (23-45)	37 (26-65)	36 (23-65)	**36 (23-65)**
Platelets >100K	34 (26-43)	37 (24-64)	36 (24-64)	**36 (24-64)**

Mechanism of Action

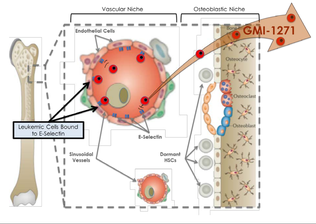
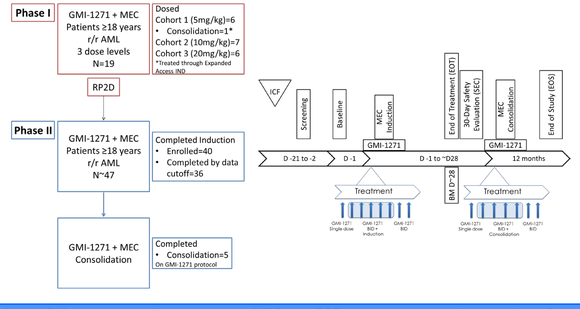


Figure 1: E-selectin-mediated adhesion

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



Conclusions

Efficacy:

- **The response rate (CR/CRi) was 41% and higher than expected given the high-risk cytogenetic and other disease features. After a single course of induction treatment with GMI-1271 (Phase 1), a higher CR/CRi rate (47%) was seen compared to historical controls of similar populations treated with MEC (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 (N=9 to date).**

Safety:

- **60-day mortality was low (7%).**
- **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 achieve complete remission. This biomarker outcome provides strong evidence of clinical proof of concept. Future studies plan to explore how 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.

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