Alliance A041701 - A randomized phase 2/3 study of conventional chemotherapy +/- uproleselan (GMI-1271) in older adults with acute myeloid leukemia receiving intensive induction chemotherapy

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ABSTRACT

Uproleselan (GMI-1271) is a novel antagonist of E-selectin, an adhesion molecule expressed on endothelial cells. E-selectin is expressed transiently in the normal vasculature during an inflammatory response and constitutively in the bone marrow (BM). Binding of E-selectin (E-sel) to sialyl Lex, the E-sel ligand (E-sel-L), on the leukemic cell surface activates cell survival pathways and promotes chemotherapy resistance in AML. In preclinical models, blockade of E-selectin with uproleselan disrupts the activation of cell survival pathways and enhanced the efficacy of chemotherapy across multiple AML tumor models. Furthermore, uproleselan protected against chemotherapy induced mucositis by regulating macrophage trafficking to the site of injury in the gut lining. A previous phase I/II study of uproleselan added to chemotherapy in patients with untreated AML (older adults ≥60 yrs) and relapsed/refractory AML (≥ 18yrs) showed promising remission rates (CR/CRi) and survival outcomes, and reduced rates of mucositis. In the newly diagnosed older patients, high remission rates were achieved overall (CR/CRi 72%) and for the high risk subgroup with sAML (CR/CRi 69%). In this phase 2/3 study, we will test the addition of uproleselan to a standard daunorubicin/cytarabine regimen in older adults with previously untreated AML (ClinicalTrials.gov Identifier: NCT03701308).

The study will enroll patients age ≥ 60 with untreated acute myeloid leukemia. Patients with acute promyelocytic leukemia, activating mutations in FLT3, or evidence of CNS involvement are excluded. Subjects are randomized to 7+3 induction (cytarabine + daunorubicin) +/- uproleselan . Subjects achieving a CR/CRi may receive up to 3 cycles of consolidation with intermediate dose cytarabine 2gm/m2 IV d1-5 +/- uproleselan. The primary phase II endpoint is to compare the event-free survival (EFS). A sample size of 262 patients was selected for the phase II to detect an improvement in median EFS from 7 months to 11 months (HR= 0.64) with > 95% power, using a log rank test. The phase III primary endpoint will compare overall survival. For the phase III, a sample size of 335 evaluable patients per arm (670 total inclusive of patients enrolled in phase II) will provide >90% power to detect an improvement in median OS from 12 months to 16 months (HR= 0.75), using a log-rank test. Correlative studies will measure E-selectin ligand on AML blasts, soluble E-selectin and will also measure MRD after remission induction by mutiparameter flow cytometry. A comprehensive geriatric assessment will identify baseline measures associated with EFS and develop a risk model to predict OS among older adults receiving intensive AML therapy. The study is endorsed by SWOG and ECOG-ACRIN and opened to enrollment on 1/16/2019.

RATIONALE

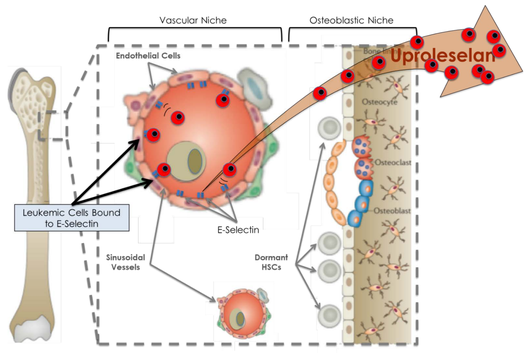


Figure 1. Mechanism of Action. E-selectin is constitutively expressed in bone marrow vascular and binds to E-selectin ligands on AML blasts promoting environment-mediated drug resistance. Uproleselan (GMI-1271) is an E-selectin antagonist which disrupts the protective interaction between tumor cells and bone marrow microenvironment and blocks trafficking of neutrophils / monocytes to area to endothelial injury reducing chemotherapy-associated mucositis.

BACKGROUND

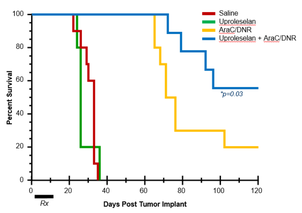


Figure 2. Addition of uproleselan to chemotherapy prolongs survival in AML tumor model. Female NOD SCID mice injected with 5x10^6 U937 cells (n=10-11/group) and treated with chemotherapy +/- Uproleselan 2 days after injection (Winkler et al. Blood. 2014;122:2)

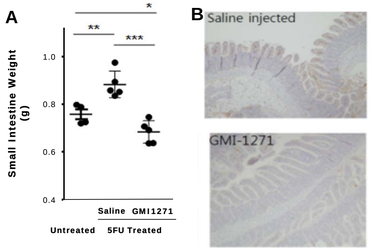


Figure 3. Uproleselan protects against chemotherapy-induced mucositis. (A) Decreased weight loss in mice treated with 5-FU + Uproleselan (20 mg/kg bid) x 5 days. (B) Uproleselan blocks migration of inflammatory F4/80+Ly-6C+ macrophages to intestine. (Winkler et al. Blood 2013:122:21)

Outcome	Subjects, n (%)
N Completing Induction Period	25
BONE MARROW RESPONSE	
CR	13 (52)
CR/CRi	17 (68)
ORR (CR/CRi/MLFS/PR)	20 (80)
All-Cause Mortality 0-30 days	2 (8)
All-Cause Mortality 0-60 days	3 (12)
AML Type	
De novo	9/12 (75)
Secondary AML	8/13 (62)
ELN Risk Category	
Favorable risk	3/3 (100)
Intermediate risk	4/7 (57)
Adverse risk	8/12 (67)

Oral Mucositis Adverse Event	Subjects, n (%)
Evaluable Patients	25
Grades 1/2*	5 (20)
Grades 3/4*	0

Table 1. GMI1271-201 Phase I/II Study of Uproleselan in AML. Results of phase II cohort comprised of older adults with newly diagnosed AML treated with Uproleselan in combination with 7+3. (DeAngelo et al. Blood 2016 128:4049)

STUDY DESIGN

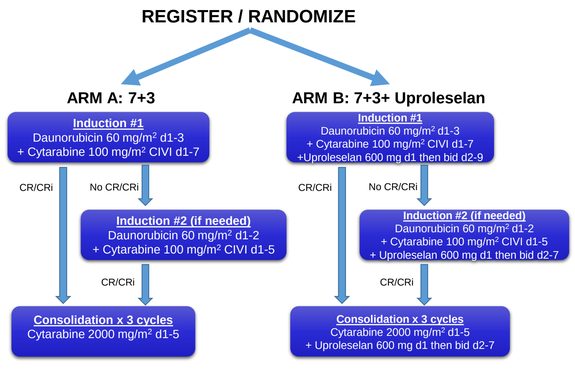


Figure 4. Study Schema

Eligibility Criteria

- Age ≥ 60 years
- Diagnosis of AML based on 2017 WHO criteria excluding APL with PML-RARA
- No activating mutation in Fms-like tyrosine kinase-3 (FLT3)
- No evidence of CNS involvement of AML
- No prior chemotherapy for MDS or AML including hypomethylating agents or lenalidomide
- Total Bilirubin ≤ 3 x upper limit of normal (ULN)
- Creatinine ≤ 3 x upper limit of normal (ULN) OR Creatinine Clearance ≥ 30 mL/min/1.73m2

Primary objectives:

Phase II: Compare the event-free survival (EFS) of daunorubicin, cytarabine plus uproleselan versus daunorubicin and cytarabine in subjects ≥ age 60 with previously untreated acute myeloid leukemia.

Phase III: Compare the overall survival (OS) of the daunorubicin, cytarabine plus uproleselan to daunorubicin and cytarabine in this patient population.

STATISTICAL CONSIDERATIONS

Phase II: Sample size of 131 evaluable patients per arm (262 total) provides 96% power to detect an improvement in median EFS from 7 months to 11 months (a hazard ratio of 0.64), using a one-sided log-rank test at a significance level of 10%.

Phase III: Sample size of 335 evaluable patients per arm (670 total) provides 90% power to detect an improvement in median OS from 12 months to 16 months (a hazard ratio of 0.75), using a one-sided log-rank test at a significance level of 2.5%. The overall power for the phase II/III design is 86% (=0.96*0.9).

CORRELATIVE STUDIES

Geriatric Assessment

- Performed at baseline, end of induction, end of consolidation
- Evaluate changes in physical, emotional, social and cognitive health
- Quantify associations between baseline assessment and overall survival
- Explore association between frailty categorized by a geriatric assessment-derived cumulative deficit burden frailty index and overall survival

Minimal Residual Disease testing

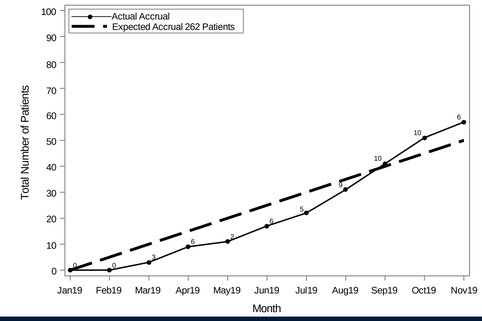
- Multiparameter flow cytometry using “Difference from Normal” technique performed at end of induction and end of consolidation
- Correlated with clinical outcomes

E-selectin ligand / Soluble E-selectin

- Performed by flow cytometry and ELISA at baseline and end of induction
- Correlated with clinical outcomes

STUDY ACCRUAL

Protocol was activated on January 16, 2019.
As of December 4, 2019, 59 patients have been enrolled.



ACKNOWLEDGMENTS

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