High E-selectin Ligand Expression Contributes to Chemotherapy-Resistance in Poor Risk Relapsed and Refractory (R/R) Acute Myeloid Leukemia (AML) Patients and can be Overcome with the Addition of Uproleselan

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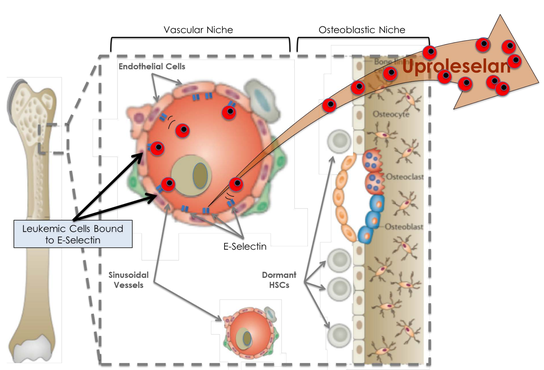
Background I. Mechanism of Action



E-selectin:
- Constitutively expressed in the bone marrow microvasculature
- Binds to the E-selectin ligands on AML cells
- Promotes environment-mediated drug resistance (EMDR)

Uproleselan, an E-selectin antagonist:
- Inhibits activation of cancer survival pathways (e.g., NF-kB)
- Reduces chemotherapy-associated mucositis (Figure 2)
- Prolongs survival over chemotherapy alone in animal models
- Protects normal HSCs by enhancing quiescence and ability for self-renewal

Figure 1: Disruption of E-selectin binding to LSC significantly reduces LSC survival and enhances chemotherapy sensitivity in animal model

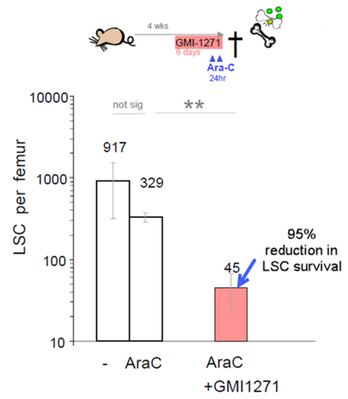


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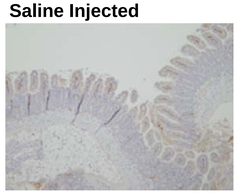
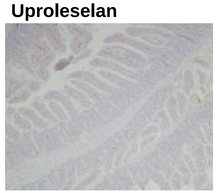
Figure 2: Uproleselan Protects Against Chemotherapy-Induced Mucosal Injury in Mice

Saline Injected



Uproleselan



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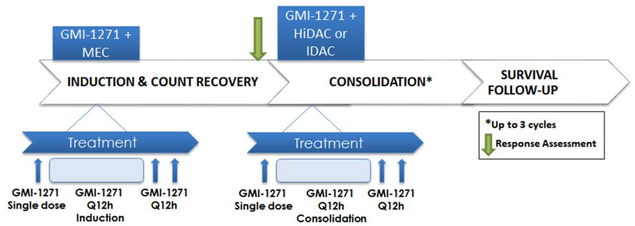
Phase I/II Study Design

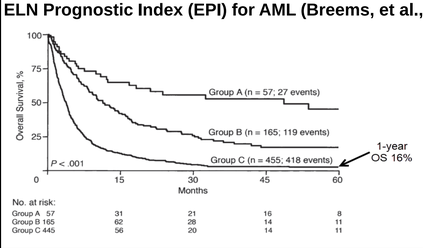
Eligible patients – Relapsed/Refractory:
- ≥18 years old
- Primary refractory AML, ≤2 prior inductions (one with anthracyclines)
- OR in first or second relapse
- HSCT was allowed, >4 months prior (no GVHD)
- Hemodynamically stable/adequate organ function



Methods

E-selectin ligand expression detection by flow cytometry
- Multicolor flow cytometry was used to examine binding of the HECA452 antibody that recognizes sialyl Lewis a/x
- The blast population was gated by forward vs. side scatter, followed by CD45 vs. side scatter. LSCs were determined from this gate and defined as CD34+CD38-CD123+. Flow cytometry was performed using FACScanto with FACSDiva (BD Biosciences. San Jose, CA) and data analysis was conducted with FlowJo software (Tree Star, Inc.).

ELN Prognostic Index (EPI) for AML (Breems, et al., 2005)



Prognostic factors include:
- Relapse-free interval (RFI)
- SWOG
- Age at study entry
- Stem-cell transplantation before study entry

Results

Table 2: Demographics

		Total R/R Patients N (%)	HECA ≥10% N (%)*	HECA <10% N (%)*
No. of Patients		66	22	14
Age, y.o.	≥65	19 (29)	6 (27)	5 (36)
Diagnosis at study entry	Refractory	22 (33)	7 (32)	8 (57)
	1st relapse	32 (48)	**13 (59)**	4 (29)
	2nd relapse	10 (15)	2 (9)	2 (14)
Relapse-free interval (RFI): 0-6 mos		46 (70)	**13 (59)**	13 (93)
Cytogenetic Risk Category: Unfavorable		39 (59)	**13 (59)**	6 (43)
Prior HSCT: Yes		12 (18)	2 (9)	0 (0)
EPI Poor/2nd Salvage		52 (79)	**16 (72)**	11 (79)

Table 3: Clinical Outcomes

	Total R/R patients N=66 (%)	HECA ≥ 10% N=22 (%)*	HECA < 10% N=14 (%)*
CR/CRi	26/66 (39)	**10/22 (45)**	4/14 (29)
CR	22/66 (33)	**8/22 (36)**	3/14 (22)
CRi	4/66 (6)	2/22 (9)	1/14 (7)
PD	33/66 (50)	9/22 (41)	9/14 (64)
Evaluable MRD: Negative**	11/16 (69)	**6/8 (75)**	0/2 (0)
Median OS (months)	8.1	**12.7**	5.2
Probability of One Year OS (%)	36.4	**54.5**	14.3

*Data on E-sel ligand was available in 36 patients at the study entry
**Numbers of evaluable MRD in all R/R, HECA ≥10%, and HECA <10% patients are 16, 8, and 2, respectively

Background II. Data from the Completed Phase I/II Study in Patients with R/R AML (DeAngelo, et al., Blood 2018)

We have previously reported CR/CRi rate of 39% (RP2D: 41%)
- Overall survival (OS) of 8.1 months in all R/R patients (RP2D: 8.8 months)
- E-sel-L expression ≥10% on leukemic blasts correlated with improved OS of 12.7 months (Figure 5)
- Low rates of severe oral mucositis

Figure 3: Overall Survival in R/R AML Patients Receiving RP2D

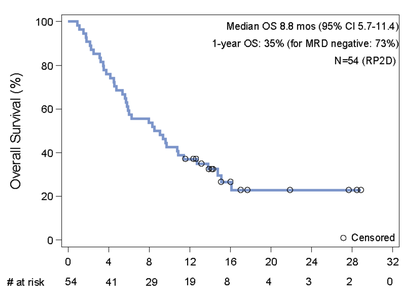


Figure 4: E-selectin Ligand Detectable on Blasts in All R/R AML Patients

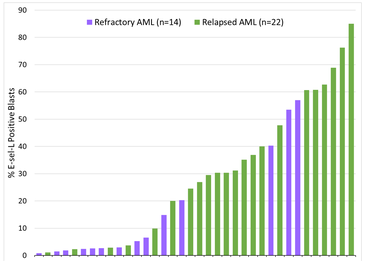


Figure 5: Overall Survival in High E-sel-L Expression and Low E-sel-L Expression on LSC from R/R Patients

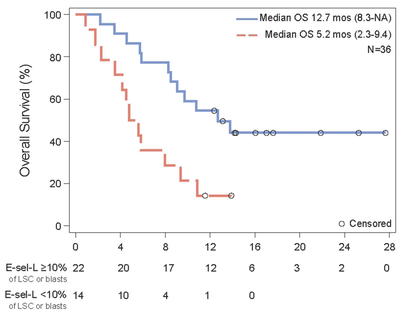


Table 1: Comparative Data in R/R AML

Population	Phase 2/3 Primary Outcome Measure	Uproleselan Phase 1/2 Results	Historical Comparators		
			Publication	Design	Result
Relapsed/ Refractory AML	Overall Survival (months)	**8.8 months**	Ravandi, et al. (2014)	Vosaroxin + Hidac vs. Hidac	6.1 months (Hidac)
			Feldman, et al. (2005)	Lintuzumab + MEC vs. MEC	5.2 months (MEC)
			Roboz, et al. (2014)	Elacytarabine vs. Investigator choice	3.4 months (Investigator choice)

References

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Conclusions

- E-selectin ligand high expressers (≥10%) had unfavorable features based on EPI risk and expected one year survival of <20%
- High E-selectin ligand expression (≥10%) in LSCs:
  - 66% of patient samples
  - More common in relapse vs primary refractory AML patients
- The addition of Uproleselan to MEC resulted in promising outcomes in patients with high E-selectin ligand expression and poor risk, giving a one year OS probability of 54.5% and a median OS of 12.7 months.

Conflict of Interest Disclosures: DJD, DLB, and PM have no conflicts to report. JLL, MEO, and PSB received research funding, and BAJ and ASA were paid consultants over the past 2 years for GlycoMimetics, Inc. WEF, JLM, MC, EJF, and HMT are employees of, and have equity ownership in, GlycoMimetics, Inc.
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