A Phase I Study of Uproleselan Combined with Azacitidine and Venetoclax for the Treatment of Older or Unfit Patients with Treatment Naïve Acute Myeloid Leukemia

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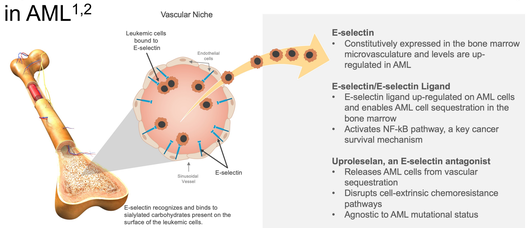
Introduction

Uproleselan is a novel E-selectin inhibitor with activity in AML[1,2]

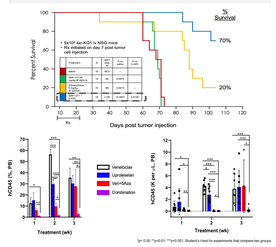


E-selectin
- Constitutively expressed in the bone marrow microvasculature and levels are up-regulated in AML

E-selectin/E-selectin Ligand
- E-selectin ligand up-regulated on AML cells and enables AML cell sequestration in the bone marrow
- Activates NF-kB pathway, a key cancer survival mechanism

Uproleselan, an E-selectin antagonist
- Releases AML cells from vascular sequestration
- Disrupts cell-extrinsic chemoresistance pathways
- Agnostic to AML mutational status

- Uproleselan was added to MEC in R/R AML and also added to 7+3 in treatment naïve AML. The combinations were well tolerated and demonstrated promising efficacy[3]
  - Higher expression of E-selectin was associated with improved outcomes
- Uproleselan added to azacitidine improved survival in a mouse AML xenograft model[4]
- Uproleselan added to azacitidine and venetoclax mobilized leukemia cells, improved survival, and reduced leukemia cell burden in an HMA-resistant AML PDX model[5]



Objectives and Endpoints

Primary

To assess the safety and tolerability of uproleselan combined with azacitidine and venetoclax in older or unfit patients with treatment naïve AML (Endpoints: safety, AE by CTCAE v5.0, R2PD)

Secondary

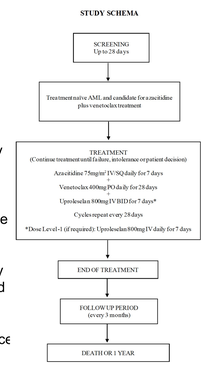
To evaluate the preliminary efficacy of uproleselan combined with azacitidine and venetoclax (Endpoints: MFC MRD-ve CR/CRi, ORR, TI, DoR, EFS, RFS, OS)

Exploratory

To evaluate correlative biomarkers and mechanisms of response of uproleselan combined with azacitidine (Endpoints: E-selectin ligand expression on blasts; efficacy endpoints in pt subsets)

Study Design

- Ongoing single center Phase 1 trial of frontline Upro in combination with Aza/Ven in older or unfit AML pts (NCT04964505).
  - Dose de-escalation portion using a modified 3+3 dose de-escalation design with DLT assessed in cycle 1 to determine RP2D (6-12 patients)
  - After RP2D determined, a 19-patient dose expansion portion to evaluate preliminary efficacy using rate of MFC MRD negative CR/CRi to determine sample size
- Key eligibility criteria included: age > 18 years, AML diagnosis by WHO 2016 criteria and eligibility for frontline Aza/Ven
- Ven ramp up in cycle 1 including TLS monitoring and prophylaxis; a bone marrow biopsy was done after every cycle until MLFS+; Upro was given for up to 6 cycles and decreased to daily after achieving MLFS+; dose modifications and delays were allowed
- Treatment continues until relapse/progression, intolerance or patient decision to stop



Results

Patient Disposition

- Data cut off 6/26/2022
- Data from the dose optimization portion and initial dose expansion are presented
- All patients completed cycle 1
  - Median time on study 126 days (range 32-179)
  - Median number of treatment cycles received 3 (range 1-6)
- No DLTs were observed
  - There were no deaths in the first 30 days (30d mortality 0%)
  - There was one death from sepsis in the first 60 days (60d mortality 13%)
- Two patients remain on treatment
- All patients achieving MLFS or better response had dose modifications and/or cycle delays
- Six patients have discontinued study therapy
  - Patient decision (n=4), Death (n=2)

Demographics

Enrolled Patients	n=8
Age Median (Range)	78 (70-81)
Sex	
Male	2 (25%)
Female	6 (75%)
ECOG PS	
0	3 (38%)
1	3 (38%)
2	2 (25%)
WHO 2016 Subtype	
Therapy-related myeloid neoplasm, AML	3 (38%)
AML with mutated RUNX1	2 (25%)
AML, NOS	1 (13%)
AML with MRC	1 (13%)
AML with mutated NPM1	1 (13%)
AML Subtype	
De Novo	4 (50%)
Secondary	4 (50%)

Enrolled Patients	n=8
ELN 2017 Risk	
Favorable	0 (0%)
Intermediate	2 (25%)
Adverse	6 (75%)
Cytogenetics	
Normal	3 (38%)
Complex	3 (38%)
Other	2 (25%)
Molecular	
RUNX1	4 (50%)
BCOR	2 (25%)
TET2	2 (25%)
TP53	1 (13%)
NPM1	1 (13%)
FLT3-ITD (high AR)	1 (13%)
IDH2	1 (13%)
PHF6	1 (13%)
DDX41	1 (13%)
ASXL1	1 (13%)
NF1	1 (13%)
IKZF1	1 (13%)
U2AF1	1 (13%)
NRAS	1 (13%)
ETV6	1 (13%)

Treatment Emergent Adverse Events

All patients had at least one TEAE of any grade and of grade 3 or higher; 2 patients experienced grade 5 events (sepsis; malignant neoplasm - AML), both unrelated

AE Regardless of Attribution in at least 2 patients	Any Grade (% of total pts)	Grade 3-4 (% of total pts)
Anemia	6 (75)	6 (75)
Platelet count decreased	6 (75)	6 (75)
Anorexia	4 (50)	0
Nausea	4 (50)	0
Neutrophil count decreased	4 (50)	4 (50)
Fatigue	3 (38)	0
Hypocalcemia	3 (38)	0
Hyponatremia	3 (38)	1 (13)
Blood lactate dehydrogenase increased	2 (25)	0
Creatinine increased	2 (25)	0
Febrile neutropenia	2 (25)	2 (25)
Hyperglycemia	2 (25)	1 (13)
Hypernatremia	2 (25)	0
Hypophosphatemia	2 (25)	0
Sepsis	2 (25)	1 (13)
Superficial thrombophlebitis	2 (25)	0
Urinary tract infection	2 (25)	1 (13)

AE At Least Possibly Related to Study Treatment in at least 2 patients	Any Grade (% of total pts)	Grade 3-4 (% of total pts)
Anemia	6 (75)	6 (75)
Platelet count decreased	6 (75)	6 (75)
Nausea	4 (50)	0
Neutrophil count decreased	4 (50)	4 (50)
Fatigue	3 (38)	0

AE At Least Possibly Related to Uproleselan in at least 2 patients	Any Grade (% of total pts)	Grade 3-4 (% of total pts)
Nausea	2 (25)	0

Serious Adverse Events

4 patients (50%) experienced a total of 9 SAE

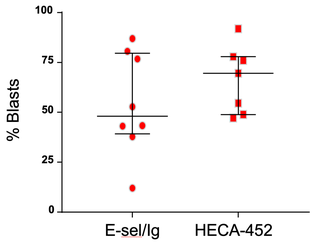
SAE Regardless of Attribution	Any Grade (% of total pts)	Grade 3-4 (% of total pts)	Grade 5 (% of total pts)
Platelet count decreased	2 (25)	2 (25)	0
Fracture	1 (13)	1 (13)	0
Heart failure	1 (13)	1 (13)	0
Lung infection	1 (13)	1 (13)	0
Sepsis	1 (13)	0	1 (13)
Skin infection	1 (13)	1 (13)	0
Malignant Neoplasm (Disease Progression AML)	1 (13)	0	1 (13)

SAE At Least Possibly Related to Study Treatment	Any Grade (% of total pts)	Grade 3-4 (% of total pts)	Grade 5 (% of total pts)
Platelet count decreased	2 (25)	2 (25)	0
Skin infection	1 (13)	1 (13)	0

SAE At Least Possibly Related to Uproleselan	Any Grade (% of total pts)	Grade 3-4 (% of total pts)	Grade 5 (% of total pts)
None	0	0	0

Correlatives

E-Selectin ligand was detected in all patients at baseline



	Baseline %E-sel/Ig	Baseline %HECA-452
N	8	7
Min	11.99	47.14
25% percentile	39.13	48.87
Median	47.98	69.58
75% percentile	79.58	77.91
Max	86.93	91.88
Mean	54.12	66.55
r	0.889	

Note:
- Correlation with efficacy is ongoing
- E-selectin ligand expression in >10% was associated with improved outcomes in R/R AML patients treated with MEC plus Uproleselan[3]

Results

Responses

Response (n=8)	n (%)
CR	5 (63)
CRi	1 (13)
CR/CRi*	6 (75)
MFC MRD negative CR/CRi	4 (50)
MLFS	2 (25)
MLFS or better response	8 (100)

*5 of 6 CR/CRi responses occurred after cycle 1

Response (n=8)	Cytogenetics	Molecular
MFC MRD negative CR	Complex, including del(5q)	TP53, IDH2
MFC MRD negative CR	Complex	TET2, U2AF
MFC MRD negative CR	Normal	DDX41 double
MFC MRD negative CRi	Normal	FLT3-ITD, NPM1, DNMT3A, BCOR
MFC MRD positive CR	t(1;17)	RUNX1, ASXL1, IKZF1, NF1 double, CBL
MFC MRD positive CR	Normal	RUNX1, PHF6, TET2 double
MLFS	Complex, including del(5q), del(7q)	RUNX1
MLFS	del(5q)	RUNX1, BCOR, ETV6, NRAS

Conclusions

- Preliminary results from this Phase I study of Uproleselan in combination with Aza/Ven in pts with untreated AML ineligible for induction chemotherapy demonstrate:
  - Tolerable safety profile
    - No DLTs were observed
    - The most common Grade 3-4 AE and SAE were hematologic
    - Dose modifications and/or cycle delays were common
  - Promising preliminary efficacy
    - 50% rate of MFC MRD negative CR/CRi
    - All patients achieved an MLFS or better response
- Enrollment is ongoing
- Two additional study sites are planned

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