Uproleselan Added to Cladribine Plus Low Dose Cytarabine (LDAC) in Patients with Treated Secondary Acute Myeloid Leukemia (TS-AML)

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Abstract

Background:

Treated secondary AML (TS-AML), arising after prior HMA-treated MDS, is associated with very poor prognosis (Complete Remission [CR] rates 15-30% and median Overall Survival [OS] 6-8 months). E-selectin ligand is highly expressed on AML blasts in the leukemic microenvironment and may be a marker of cell survival and resistance to chemotherapy. Exposure of leukemic blasts to HMAs has been shown to increase their expression of E-selectin ligand. Uproleselan is an E-selectin antagonist that overcomes resistance to chemotherapy in AML (Barbier, *Nat Commun* 2020).

We sought to study the combination of low-intensity chemotherapy with Cladribine + LDAC (CLAD/LDAC) with uproleselan to overcome local and microenvironmental resistance and improve outcomes in this difficult subset.

Methods:

This is Phase Ib/II clinical trial (NCT04848974) to evaluate the safety, tolerability, and explore the efficacy of Uproleselan added to Cladribine and LDAC. A 3+3 dose-escalation approach was implemented to evaluate 2 different dose levels for Cladribine (CLAD)+ LDAC; each 4-week cycle consists of Uproleselan (at a fixed dose of 800mg intravenously [IV]) added to IV CLAD 5 days (3.75mg/m2 and 5mg/m2; level -1 and 1, respectively) and subcutaneous LDAC twice daily 10 days (15mg, and 20mg; level -1 and 1, respectively) during induction; consolidation was similar except it was with 3-days of CLAD, for up to 6 cycles. Patients (Pts) aged ≥18 years with a diagnosis of TS-AML with adequate organ function, who have not received therapy for their AML were enrolled. TS-AML is defined as AML arising from a previously treated myeloid neoplasm. Presence of the E-selectin ligand was assessed using Flow Cytometry (FC). Composite Complete Response (cCR) included pts in CR, CRi, CRp and MLFS.

Results:

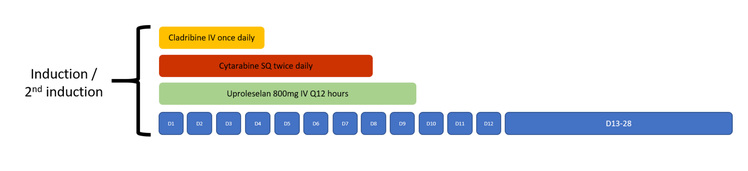
15 pts have been treated, with 12 pts currently evaluable: 10 (66.7%) were male and the median age was 71 years (range, 58-80); at the start of therapy, the median bone marrow blasts were 26% (20-78%), median WBC was 2.2x10^9/L (0.6-20.1), median platelets were 26x10^9/L (4-667), and median creatinine was 1.03mg/dL (0.49-1.52). Pts had received a median of 1 (1-3) treatments prior to AML transformation. Prior diagnoses were: therapy-related Myelodysplastic Syndrome (t-MDS), Chronic Myelomonocytic Leukemia (CMML), MDS and MDS/MPN in 4 (26.7%), 5 (33.3%), 5 (33.3%) and 1 (6.7%) respectively; all had received HMA, 8 (53%) additionally had Venetoclax and 3 (20%) had stem cell transplantation (SCT) prior to enrolling. All pts had unfavorable features by ELN 2017. The most frequent mutations were: ASXL1, NRAS, TP53, TET2, SRSF2 and RUNX1 in 6 (40%), 6 (60%), 5 (33%), 5 (33%), 5 (33%) and 4 (27%) pts each. 6 pts were evaluable for E-selectin ligand expression; the median expression was 64% (43%-95%) and median MFI was 26.2 (14-263). The most common SAEs were ≥ grade 3 neutropenic fever (70%), (including 2 grade 5 events), grade 3 bleeding (10%), and grade 2 thrombosis (5%). There were no dose-limiting toxicities observed on dose levels -1 or 1. Two pts treated on dose level -1 died during the study follow-up due to sepsis within the first 4-weeks during induction. Median time to 0.5x10^9/L neutrophil and 50x10^9/L platelets recovery was 29 (17-39) and 38 (33-48) days, respectively. The median follow-up is 3.3 months. 12 pts were evaluable for response at the time of analysis. The ORR was 58% (7/12), including 2 (17%) PR, 2 (17%) MLFS, 1 (8%) CR, 1 (8%) CRi, and 1 (8%) CRp. There was a reduction in BM blasts in 8 pts (67%). 7 (58%) pts were taken off protocol due to progression, 2 (17%) for death, 1 (8%) for allogeneic SCT and 2 (17%) continued in remission. Three of the pts (60%) with CRc (3/5) achieved negative MRD, and one underwent SCT and is still alive. Median OS and EFS were 5.4 and 1.4 months respectively; 4-month RFS (CRi, CRp, and MLFS) was 75%. The median cycles received was 1 (1-3), median cycles at which the best response was achieved was 1 (1-2). The 4-month OS were 100% and 69% among responders vs. non-responders, respectively (p=0.13), and the 4-month EFS were 67% and 14% respectively (p<0.01). The ORR was 57% (4/7) (p=0.92) and 33% (1/3) (p=0.31) among pts who had prior venetoclax exposure or prior SCT, respectively.

Conclusions:

The combination of Cladribine + LDAC with Uproleselan was overall well tolerated with few treatment-related AEs. The combination produced an ORR of 62% in a high-risk, refractory population whose prognosis is very dismal. The relationship of E-selectin ligand expression, response to treatment, and outcomes is being analyzed.

Background

- Vascular niche hijack from AML blast is mediated through **E-selectin upregulation**
- E-selectin and blast interaction triggers cell **regeneration**, **survival** and **chemoresistance** through AKT/mTOR/NFκB



Study Design

Phase Ib/II, single-center, single-arm trial

Primary objective

- To determine the safety, tolerability, and recommended phase II dose (RP2D) of uproleselan combined with cladribine + low dose cytarabine (LDAC) in patients with treated-secondary AML (TS-AML)

Eligibility criteria

- Patients with a diagnosis of treated secondary-AML (TS-AML) who have not received therapy for their AML.
- TS-AML is defined as AML arising from a previously treated antecedent myeloid neoplasm (myelodysplastic syndrome or myeloproliferative neoplasm that has been previously treated with hypomethylating agents).
- Patients must be at least 7 days from their last therapy for the antecedent myeloid neoplasm
- Age >/= 18 years.
- 5. Adequate liver function (total bilirubin < 2mg/dL, AST and/or ALT <3 x ULN – or <5 x ULN if related to leukemic involvement), kidney function (creatinine < 1.5 x ULN), known cardiac ejection fraction of > or = 45% within the past 6 months.
- ECOG performance status of ≤ 2.
- A negative urine or serum pregnancy test is required within 1 week for all women of childbearing potential.

Treatment Plan

	Dose Escalation Table	
Dose level	Cladribine (mg/m^2 IV daily on days 1-5)*	Cytarabine (mg SQ twice daily on days 1-10)
1	5	20
-1	3.75	15

Baseline Characteristics

	n= 15 (%)
Male	10 (66.7)
Age - median (range)	71 (58-80)
ECOG - 0 - 1 - 2	 1 (6.7) 10 (66.7) 4 (26.7)
BM Blasts - median (range)	26 (20-78)
Prior treatments - median (range) - Ven - SCT	1 (1-3) 8 (53) 3 (20)
CG - Complex - Diploid - Other	 7 (47) 5 (33) 3 (20)
Previous Malignancy - MDS - CMML - MDS/MPN	 9 (60) 5 (33) 1 (7)
Follow-up	3.3 months

Safety profile

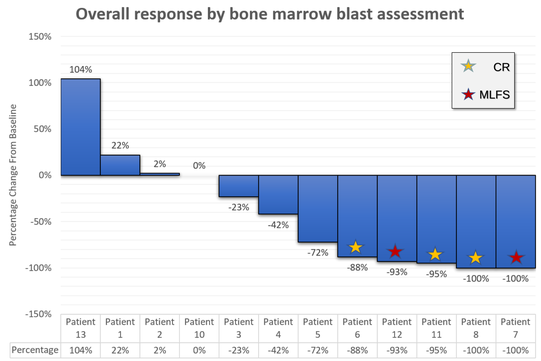
Adverse Events	All n=21 n (%)	Dose level -1 G 1-2 n=1	Dose level -1 G ≥3 n=6	Dose level 1 G 1-2 n=1	Dose level 1 G ≥3 n=13
Neutropenic fever	15 (70%)	0	5	0	10
Nausea*	1 (5%)	1	0	0	0
Hypotension	1 (5%)	0	1	0	0
Cystitis	1 (5%)	0	0	0	1
Bleeding	2 (10%)	0	0	0	2
Thrombosis	1 (5%)	0	0	1	0
Time to **ANC** ≥0.5x10^9/L Median (range)		29 (17-39) days			
Time to **PLT** ≥50x10^9/L Median (range)		38 (33-48) days			

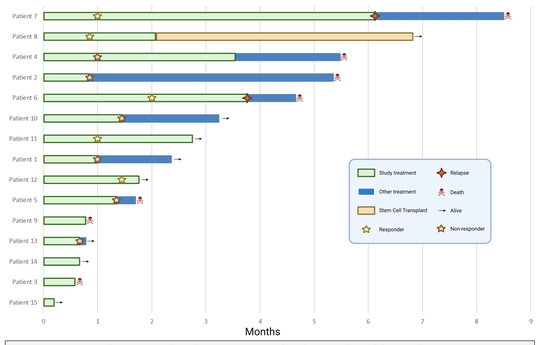
*Related to study treatment
G Grade. ANC Absolute Neutrophil Count. PLT Platelets.

Summary

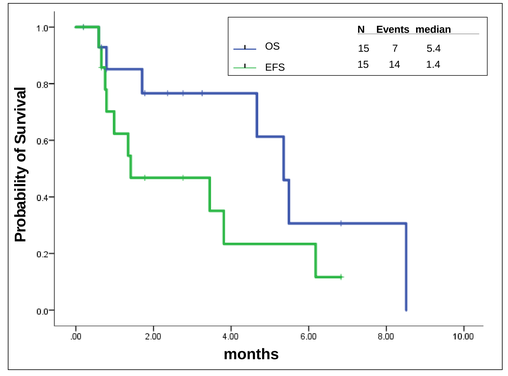
- The combination of Cladribine + LDAC + Uproleselan is well tolerated
- Responses irrespective of previous HMA and Venetoclax exposure were seen.
- Targeting the vascular niche in AML is another feasible approach in treatment, that may overcome resistance

Results

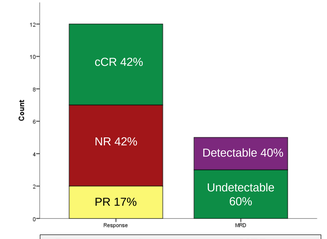




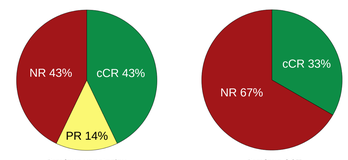
Swimmers plot for response in the analyzable patients



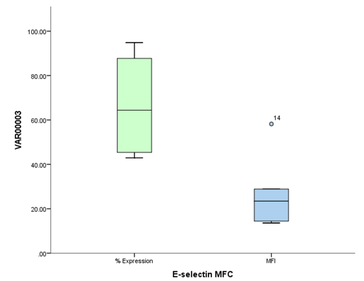
OS and EFS for all the patients treated



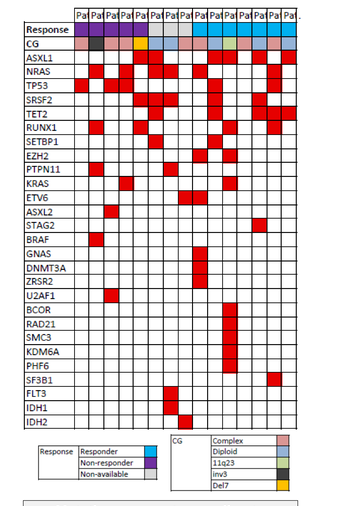
Distribution of responses and MRD in the analyzable patients



Responses according to previous Venetoclax or SCT exposure



E-selectin expression by Flow Cytometry



Mutations present according to responses