THE UNIVERSITY OF TEXAS
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A Phase I/II Study of Seclidemstat, an LSD1 Inhibitor, and Azacitidine for Patients with Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia

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Background and Rationale

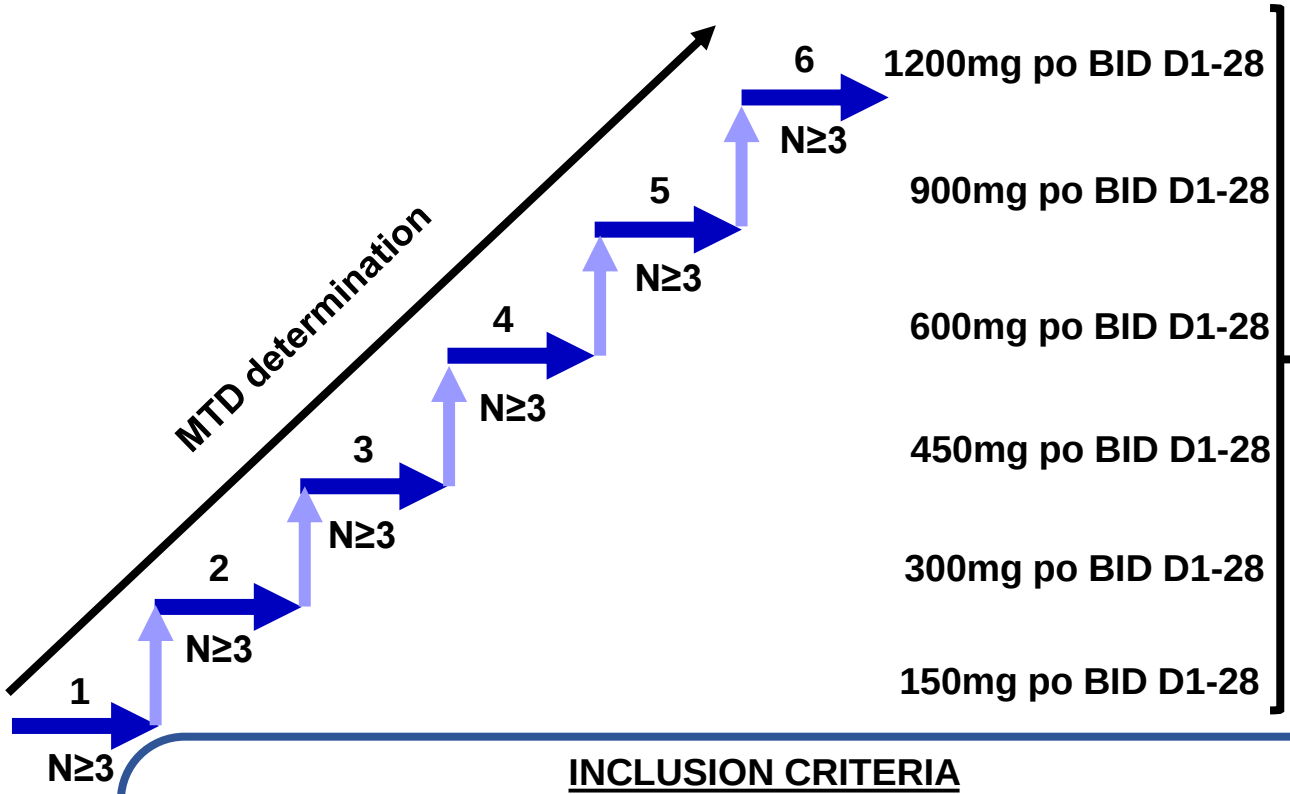
- **Epigenetic modifications are essential for gene expression regulation**
- **Aberrant DNA and histone methylation is a hallmark of MDS and CMML pathogenesis and progression[1]**
- **Hypomethylating agents active via epigenetic modifications and induction of differentiation[2]**
- **Poor outcomes after HMA failure → OS of 4-6 months[3]**
- **Lysine specific demethylase 1 (LSD1) implicated in maintenance of pluripotency and proliferation genes**
- **LSD1 inhibition promotes differentiation of blast cells and has antileukemic effect[4]**
- **Evaluation of synergistic effect of LSD1 inhibition with azacitidine in MDS/CMML warranted**

1. Issa Clin Caner Research 2007, 2. Shen et al JCO 2010, 3. Jabbour et al Cancer 2010, 4.Fiskus et al Leukemia 2014.

Study Design

Dose Escalation Phase

Azacitidine 75mg/m² s.c/i.v D1-7 + Seclidemstat based on dose level



Dose Expansion Phase

MDS Cohort

Int-1 to High IPSS risk with NR after 6 cycles of HMA or relapse/progression after any # of cycles

Azacitidine 75mg/m² s.c/iv D1-7
Seclidemstat Xmg po BID D1-28
N=10

CMML Cohort

Int-1 to High IPSS risk with NR after 6 cycles of HMA or relapse/progression after any # of cycles

Azacitidine 75mg/m² s.c/iv D1-7
Seclidemstat Xmg po BID D1-28
N=10

INCLUSION CRITERIA

- **Age >18 years**
- **Diagnosis of MDS or CMML by WHO with Int-1 to High IPSS**
- **NR after 6 cycles of HMA or relapse/progression after any # cycles**
- **ECOG PS ≤2**
- **CrCr >50ml/min**
- **AST/ALT ≤3xULN, BR≤2xULN**

Primary Objective: Safety, tolerability, MTD and activity (ORR)

Secondary objectives: OS, duration of response, LFS, RFS

Patient Characteristics

Patient	Age (years)	Diagnosis	WBC ($x10^9$/L)	ANC ($x10^9$/L)	Hgb (g/dL)	Plt ($x10^9$/L)	BM Blasts (%)	Karyotype	Mutations	Risk Category	Prior Therapies
1	74	T-MDS	2.9	1.5	12.6	68	10	Complex	*TP53*	IPSS: Int-2 IPSS-R: Very high	Decitabine
2	73	T-MDS	19.6	13.13	7.6	35	10	Complex	*TP53*	IPSS: High IPSS-R: Very High	Azacitidine+venetoclax Decitabine
3	75	T-MDS	6.6	0.58	11.5	111	10	+8	*DNMT3A, ZRSR2, RUNX1 BCOR, TP53*	IPSS: Int-2 IPSS-R: High	Decitabine Allo-SCT Azacitidine
4	75	CMML	5.6	1.18	9.2	50	6	Misc	*ASXL1, RUNX1, STAG2, TET2, EZH2*	IPSS: Int-2 CPSS-Mol: High	Azacitidine
5	78	MDS	5	3.3	6.4	95	3	Normal	*ASXL2, SRSF2, DNMT3A, NF1, TET2, TP53, TET2*	IPSS: Int-1 IPSS-R: High	Azacitidine+ipilimumab Decitabine
6	67	MDS	1.7	1.11	7.2	35	10	Normal	*SF3B1, BCOR*	IPSS: Int-1 IPSS-R: High	Decitabine
7	80	CMML	31.3	13.46	8.4	60	8	+8,del(20q)	*NRAS, SRSF2, BRAF, JAK3, STAG2, ASXL1*	IPSS: High CPSS-Mol: High	Azacitidine
8	76	CMML	1.8	0.27	13.7	78	15	Misc	*ASXL1, GATA2*	IPSS: High IPSS-Mol: Int01	Decitabine Decitabine+venetoclax
9	68	MDS	17.1	10.43	9.6	362	1	Inv(3)	*JAK2, SF3B1*	IPSS: Int-1 IPSS-R: Int	Lenalidomide Ruxolitinib Azacitidine Luspatercept

Seclidemstat dose level: 150mg bid D1-28 | 300mg bid D1-28 | 450mg bid D1-28

Toxicity and Safety

Adverse event	Grade 1-2 (N of patients)	Grade 3 or more (N of patients)
Infection	0	3
Hypotension	3	1
Atrial fibrillation	1	1
Creatinine elevation	6	0
Nausea	6	0
Constipation	5	0
Vomiting	4	0
Abdominal pain	3	0
Cough	3	0
Diarreha	3	0
Dizziness	3	0
Dyspnea	3	0
Fatigue	3	0
Myalgia	3	0
Fever	2	0
Right bundle branch block	1	0
QT prolongation	1	0

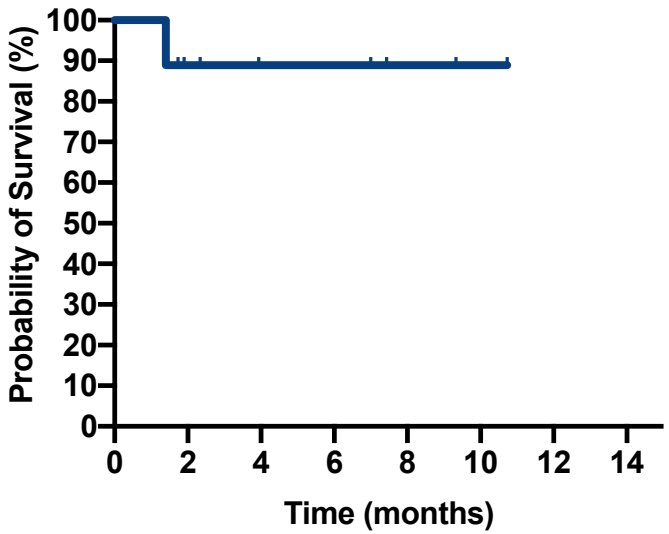
- Early mortality (8 weeks) of 0%
- No DLTs at current dose level
- 6 (67%) patients experienced reversible elevation of Cr → initial week of therapy with azacytidine
- Cardiac rhythm/ECG abnormalities in 3 patients

Response

- Median follow up: 3.9 months (95% CI 0-10.4 months)
- Median number of cycles: 3 (1-7)
- ORR: 50% (4/8) including 1 CR, 2 mCR+HI and 1 mCR
- Median number of cycles to best response: 2 (1-2)
- Patient disposition:
  - 2 patients off study due to progression
  - 1 to undergo allo-SCT
  - 1 due to no response
  - 5 patients on study

Acc	Dose Level	Seclidemstat dose	Response
1	1	150mg bid	CR + pCyR
2			PD
3			NR
4	2	300mg bid	mCR+HI
5			NR
6			mCR
7	3	450mg bid	mCR+HI
8			SD
9			NE

NE: Too early for response evaluation.



Conclusions

- **Combination of azacitidine and seclidemstat safe at current dose levels**
- **Early signs of activity in high-risk HMA failure population:**
  - **ORR 50%**
  - **1 CR, 2 mCR+HI, 1 mCR**
- **Evaluation of biomarkers of response planned in dose expansion to help patient selection**
- **Need for further experience to determine safety and efficacy of higher doses of seclidemstat**