

# 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

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

## Objectives

- Evaluate the safety and efficacy of seclidemstat in combination with azacitidine in patients (pts) with higher-risk MDS and CMML with failure to HMA therapy

## Methods

### Inclusion Criteria

- Age ≥18 years of age
- Diagnosis of MDS or CMML by WHO
- Int-1 to High risk by IPSS
- No response after 6 cycles of HMA or relapse or progression after any number of cycles
- ECOG PS ≤2
- CrCr >50ml/min
- AST/ALT ≤3xULN, BR≤2xULN

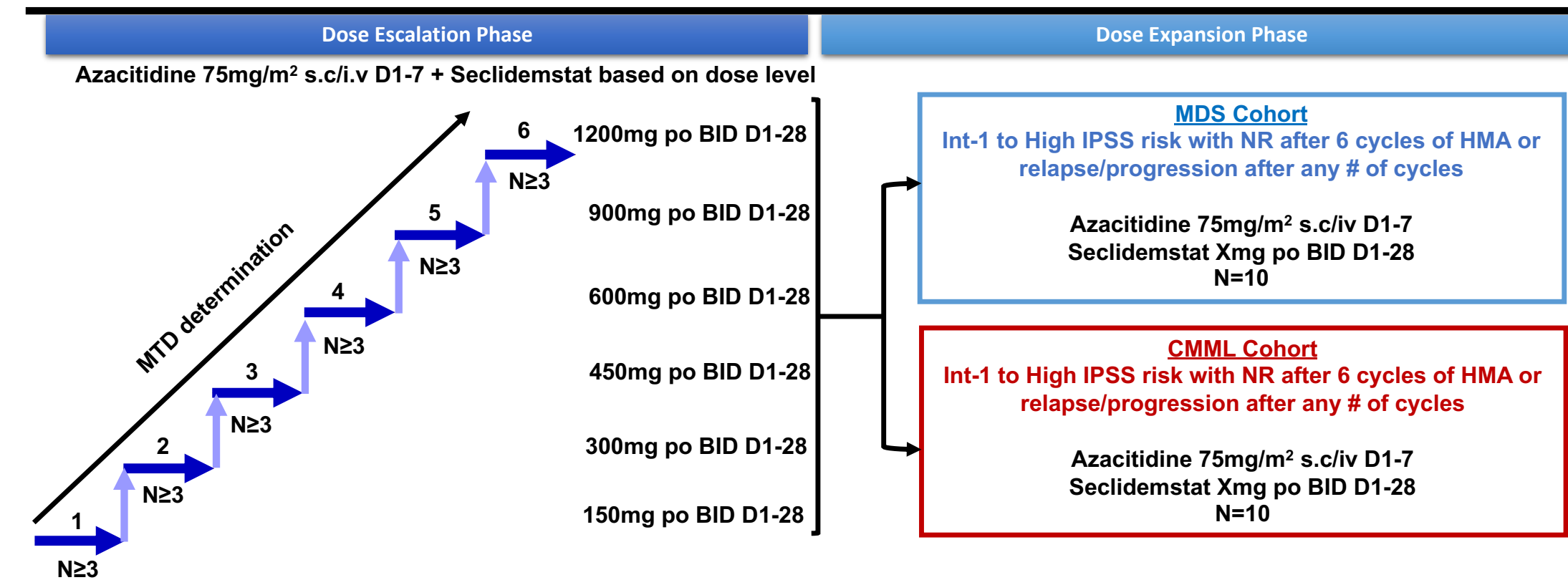
### Study Design

- Phase I/II study of seclidemstat in combination with azacitidine
- Initial Phase I dose escalation evaluating up to 6 dose levels of seclidemstat (Figure 1)
- Phase II dose expansion at selected dose level of seclidemstat
- Cycles every 28 days
- Maximum cohort of N=35 pts
- Stopping rules for toxicity and response

### Study Endpoints

- Primary objective: safety, tolerability, MTD and overall response
- Secondary objective:
  - Overall survival, duration of response, leukemia-free survival
  - Correlative studies during dose expansion phase

**Figure 1. Study Design**



## Results

### Patient Characteristics

- Nine patients enrolled as of October 2022.
- Patient characteristics detailed in Table 1

**Table 1. Patient Characteristics**

Patient	Age (years)	Diagnosis	WBC (x10 <sup>9</sup> /L)	ANC (x10 <sup>9</sup> /L)	Hgb (g/dL)	Plt (x10 <sup>9</sup> /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

ANC: Absolute neutrophil count. Hgb: Hemoglobin. Plt: platelet count. BM: bone marrow. MDS: myelodysplastic syndrome. T-MDS: Therapy-related MDS. CMML: chronic myelomonocytic leukemia

### Toxicities

- Early mortality of 0%
- No DLTs at current dose level.
- Adverse events detailed in Table 2.
- 6 (67%) patients experienced reversible elevation of Cr → initial week of therapy with azacitidine
- Cardiac rhythm/ECG abnormalities in 3 patients

**Table 2. Adverse Events**

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
Diarrhea	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

### Efficacy

- 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 (Table 3)
- 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

**Table 3. Responses by dose level**

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

CR: Complete response. pCyr: partial cytogenetic response. mCR: marrow complete response. HI: hematological improvement. NR: no response. SD: stable disease. NE: not evaluable for response (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
- Need for further experience to determine safety and efficacy of higher doses of seclidemstat

## Contact Details

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