A Phase 1 Trial of Valemetostat in Patients With Relapsed or Refractory (R/R) Acute Myeloid Leukemia (AML) or Acute Lymphocytic Leukemia (ALL)

AML-385

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PURPOSE

- To determine the safety, tolerability, and maximum tolerated dose (MTD) and recommended dose for expansion (RDE) of valemetostat tosylate (valemetostat) in patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL) enrolled in a phase 1 clinical trial

CONCLUSIONS

- Valemetostat monotherapy demonstrated acceptable and manageable safety in patients with R/R AML and R/R ALL
  - The most common treatment-emergent adverse events (TEAEs) were mainly gastrointestinal events (diarrhea, nausea, decreased appetite, and vomiting)
  - The most common Grade ≥ 3 TEAEs and most common serious adverse events (SAEs) were mainly infections (febrile neutropenia, pneumonia, sepsis, and cellulitis)
- Orally administered valemetostat was rapidly absorbed; plasma concentration was dose-dependent, and the time to maximum plasma concentration (T_{max}) was reached in 2–4 hours
- Preliminary efficacy analyses showed 2 responders with AML (1 complete remission with incomplete blood count recovery [CRi] and 1 partial response [PR]; n = 22), and 1 responder with ALL (complete response [CR]; n = 6)

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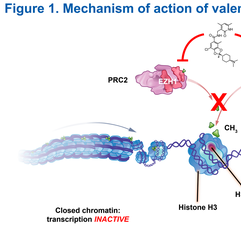
BACKGROUND

- Despite relatively high rates of initial response with induction therapies, up to 80% of patients with AML eventually relapse or develop refractory disease[1,2]
- Alternative treatment options are needed to improve outcomes for patients with R/R AML[3–5]
- Enhancer of zeste homolog (EZH)2 and its close homolog EZH1 catalyze the trimethylation of histone H3 at lysine 27 (H3K27me3) (**Figure 1**); overexpression of *EZH2* and global H3K27me3 accumulation result in abnormal epigenetic regulation and altered transcriptome in various cancers[6–8]
  - *EZH2* plays a dual role as a tumor suppressor in normal hematopoiesis and as an oncogene in lymphoma and AML[6,7]

Figure 1. Mechanism of action of valemetostat



CH3, trimethyl group; PRC2, polycomb repressive complex 2.

- Valemetostat is a novel, potent, and selective dual inhibitor of EZH2 and EZH1 that suppresses aberrant H3K27me3, thereby promoting antitumorigenic processes[9,10]
  - Valemetostat monotherapy is approved in Japan for the treatment of R/R adult T-cell leukemia/lymphoma and peripheral T-cell lymphoma[11]
- In preclinical models of AML, valemetostat has been shown to reduce leukemic stem cells (LSCs) and delay disease progression
  - Quiescent LSCs are highly dependent on EZH1 and EZH2; valemetostat has a synergistic effect against LSCs[12]
- The phase 1, non-randomized, multicenter, open-label, dose-escalation and -expansion DS3201-A-U102 study (NCT03110354) assessed valemetostat monotherapy in patients with R/R AML or ALL

METHODS

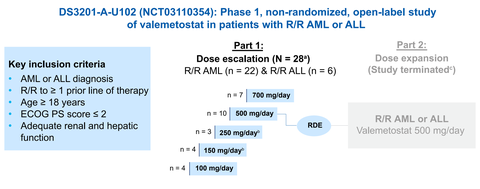
Study design

- Patients aged ≥ 18 years with confirmed AML or ALL (World Health Organization 2008 criteria[13]) that had failed any prior induction therapy regimen or had relapsed after prior therapy were enrolled at 6 sites in the United States
- The trial prospectively included a dose-escalation part followed by a dose-expansion part (**Figure 2**)
  - The dose-escalation part assessed valemetostat at escalating doses of 100–700 mg/day in continuous 28-day treatment cycles; dose-escalation was guided by a Bayesian logistic regression model
  - The dose-expansion part would further assess valemetostat at RDE

Endpoints

- Primary endpoints:
  - Dose-escalation: safety and tolerability assessment of valemetostat in patients with R/R AML or ALL, and determination of MTD and RDE
  - Dose-expansion: confirmation of safety and tolerability of valemetostat at the RDE in patients with R/R AML or ALL

Figure 2. Study design, key inclusion criteria, and endpoints of the U102 trial



[a]All the enrolled patients were included in the safety and PK data sets; 1 patient in the 500 mg cohort and 1 patient in the 700 mg cohort were excluded from the full analysis set; [b]All patients in the 150 mg and 250 mg cohorts had AML. [c]This study was terminated at the end of the dose-escalation part due to slow accrual.
ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; MTD, maximum tolerated dose; PK, pharmacokinetics; RDE, recommended dose for expansion; R/R, relapsed/refractory.

- Secondary endpoints included pharmacokinetics (PK), overall response rate (ORR), duration of response (DOR), and overall survival (OS)
- Safety was assessed by investigator reporting of TEAEs from first dose through 30 days after last dose of study drug
  - In the dose-escalation part, safety assessment for dose-limiting toxicities (DLTs) was performed after cycle 1, day 28
- Clinical response was assessed in bone marrow aspirates collected at screening, on day 8, and at the start of each subsequent treatment cycle
  - Clinical responses were defined using revised International Working Group (IWG) 2003 response criteria for AML[14] or National Comprehensive Cancer Network (NCCN) 2016 response criteria for ALL[15]
  - ORR was the proportion of patients achieving CR, CRi/complete remission with incomplete platelet recovery (CRp), or PR
  - DOR was defined as the time from first objective response until confirmed disease progression
- OS was defined as the time from enrollment until death from any cause

RESULTS

Patient enrollment and disposition

- Overall, 28 patients with R/R AML (n = 22) and ALL (n = 6) were enrolled from April 2017 through March 2021, all in the dose-escalation portion
- Median treatment duration at data cutoff (March 9, 2021) was 34 days (range, 4–331)
- At data cutoff, all 28 patients had discontinued study treatment; the primary reasons for discontinuation were progressive disease (n = 11, 39%), failure to achieve response (n = 8, 29%), TEAEs (n = 4, 14%), death (n = 2, 7%), start of new therapy (n = 1, 4%), and other (n = 2, 7%)

Demographics and baseline characteristics

- Median age was 61.5 years (range 20–85; **Table 1**)
- Median prior lines of therapy was 3 (range 1–10) for patients with AML and was 2 (range 2–3) for patients with ALL
- Most patients (n = 21, 75%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 1 at baseline

Safety and tolerability

- All 28 patients experienced at least 1 TEAE (**Table 2**)
  - Grade ≥ 3 TEAEs were reported in 24 (86%) patients, including treatment-related Grade ≥ 3 events in 7 (25%) patients
- TEAEs required treatment discontinuation for 7 (25%) patients and dose reduction for 3 (11%) patients

Table 1. Baseline demographics

Characteristic	Total (N = 28)
Age, years, median (range)	61.5 (20–85)
Sex, n (%)	
Male	10 (36)
Female	18 (64)
Race, n (%)	
White	22 (79)
Black or African American	2 (7)
Asian	2 (7)
Other	2 (7)
ECOG PS score, n (%)	
0	3 (11)
1	21 (75)
2	4 (14)
Prior lines of therapy, median (range)	2 (1–10)
Time since diagnosis, days, median (range)	536 (40–1548)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Overview of TEAEs in the valemetostat dose-escalation trial

Parameters	Valemetostat dose					All dose levels (N = 28)
	100 mg/day (n = 4)	150 mg/day (n = 4)	250 mg/day (n = 3)	500 mg/day (n = 10)	700 mg/day (n = 7)	
Any TEAE, n (%)	4 (100)	4 (100)	3 (100)	10 (100)	7 (100)	28 (100)
Grade ≥ 3 TEAE	3 (75)	3 (75)	3 (100)	9 (90)	6 (86)	24 (86)
TEAEs leading to dose reduction	0	0	0	1 (10)	2 (29)	3 (11)
TEAEs leading to treatment discontinuation	2 (50)	0	0	3 (30)	2 (29)	7 (25)
Any TRAE, n (%)	2 (50)	2 (50)	1 (33)	5 (50)	6 (86)	16 (57)
Grade ≥ 3 TRAE	0	1 (25)	0	3 (30)	3 (43)	7 (25)
TRAEs leading to dose reduction	0	0	0	1 (10)	2 (29)	3 (11)
TRAEs leading to treatment discontinuation	0	0	0	2 (20)	1 (14)	3 (11)
Any SAE, n (%)	3 (75)	3 (75)	3 (100)	7 (70)	6 (86)	22 (79)
Grade ≥ 3 SAE	3 (75)	3 (75)	3 (100)	7 (70)	6 (86)	22 (79)
Treatment-related SAE, n (%)	0	1 (25)	0	2 (20)	2 (29)	5 (18)
Grade ≥ 3 treatment-related SAE	0	1 (25)	0	2 (20)	2 (29)	5 (18)

SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related TEAE.

- Fatal (Grade 5) TEAEs were reported in 3 patients, including (n = 1 each) respiratory failure and sepsis, intracranial hemorrhage, and sepsis; these were not considered to be related to study drug
- The most common TEAEs were diarrhea and nausea (43% each), followed by vomiting and decreased appetite (36% each) (**Table 3**)
- SAEs occurred in 22 (79%) patients (**Table 4**)
- One patient experienced 2 events of differentiation syndrome as confirmed by Montesinos criteria[16]

Table 3. TEAEs (all grades) that occurred in ≥ 20% of patients

Preferred term	Valemetostat dose, n (%)					All dose levels (N = 28)
	100 mg/day (n = 4)	150 mg/day (n = 4)	250 mg/day (n = 3)	500 mg/day (n = 10)	700 mg/day (n = 7)	
Diarrhea	0	2 (50)	2 (67)	4 (40)	4 (57)	12 (43)
Nausea	1 (25)	2 (50)	1 (33)	4 (40)	4 (57)	12 (43)
Vomiting	0	1 (25)	0	6 (60)	3 (43)	10 (36)
Decreased appetite	2 (50)	0	1 (33)	2 (20)	5 (71)	10 (36)
Febrile neutropenia	1 (25)	3 (75)	1 (33)	2 (20)	2 (29)	9 (32)
Hypomagnesemia	0	1 (25)	1 (33)	4 (40)	2 (29)	8 (29)
Dysgeusia	0	0	1 (33)	4 (40)	2 (29)	7 (25)
Headache	2 (50)	1 (25)	0	1 (10)	3 (43)	7 (25)
Hypokalemia	0	2 (50)	0	2 (20)	2 (29)	6 (21)
Hypotension	0	0	1 (33)	2 (20)	3 (43)	6 (21)
Pneumonia	3 (75)	2 (50)	0	1 (10)	0	6 (21)

TEAE, treatment-emergent adverse event.

Table 4. Summary of SAEs

Preferred term	Valemetostat dose					All dose levels (N = 28)
	100 mg/day (n = 4)	150 mg/day (n = 4)	250 mg/day (n = 3)	500 mg/day (n = 10)	700 mg/day (n = 7)	
Any treatment-emergent SAE, n (%)	3 (75)	3 (75)	3 (100)	7 (70)	6 (86)	**22 (79)**[c]
SAEs reported in ≥ 3 patients, n (%)						
Febrile neutropenia	1 (25)	2 (50)	1 (33)	2 (20)	2 (29)	8 (29)
Pneumonia	3 (75)	2 (50)	0	1 (10)	0	6 (21)
Sepsis	1 (25)	1 (25)	0	1 (10)	1 (14)	4 (14)
Cellulitis	0	1 (25)	0	0	2 (29)	3 (11)

SAE, serious adverse event.

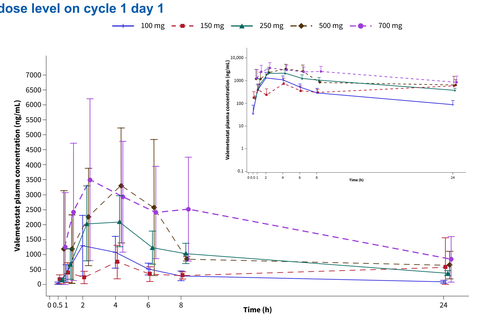
Maximum Tolerated Dose

- The 500 mg/day dose level was determined to be the MTD and selected as the RDE, but the study was closed following completion of the dose-escalation due to low enrollment

PK parameters

- Valemetostat was rapidly absorbed, and plasma concentration increased proportionately to the administered dose (**Figure 3**)
- Median T_{max} ranged from 2 to 4 hours

Figure 3. Linear and semi-log mean valemetostat plasma concentrations by dose level on cycle 1 day 1



Efficacy

- The efficacy-evaluable set included 26 (93%) patients
  - Two patients (1 each in the 500 mg and 700 mg cohorts) were excluded from the efficacy analyses due to missing post-baseline bone marrow assessments
- In the AML cohort (n = 20), 2 patients achieved CRi (n = 1) and PR (n = 1); both responding patients were in the 500 mg dose cohort and had core binding factor AML (CBF-AML)
- In the ALL cohort (n = 6), 1 patient in the 700 mg cohort achieved CR

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