Valemetostat for Relapsed or Refractory B-Cell Lymphomas: Primary Results from a Phase 1 Trial

#1731

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PURPOSE

- To describe the safety and tolerability of valemetostat tosylate (valemetostat) in patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphomas (B-NHLs) and T-cell NHLs (T-NHLs) enrolled in the DS3201-A-J101 (“J101”; NCT02732275) trial
- To report primary clinical outcomes for the subgroup of patients with R/R B-NHLs, including diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL)

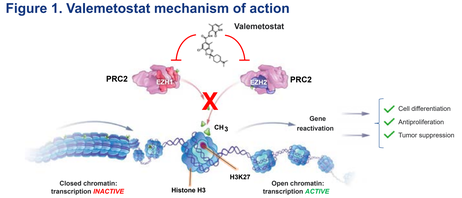
CONCLUSIONS

- Valemetostat monotherapy demonstrated encouraging preliminary clinical activity with durable responses (duration of response [DOR] > 1.5 years) in patients with R/R B-NHLs
- The safety profile of valemetostat was acceptable; cytopenias were common but manageable and did not require treatment discontinuation
- Results for patients in this trial with R/R T-NHLs are described in an abstract by Jacobsen et al. (abstract #303) at this congress
- Ongoing trials of valemetostat monotherapy in patients with R/R B-NHLs include a phase 2 trial in France and Belgium (NCT04842877) and a phase 1/2 trial of valemetostat plus rituximab and lenalidomide (R^2) in the US (NCT05683171)

BACKGROUND

- B-NHLs, including DLBCL and FL, are among the most common NHLs
- Enhancer of zeste homolog (EZH)2 and its close homolog EZH1 catalyze the trimethylation of histone H3 at lysine 27 (H3K27me3), leading to transcriptional repression[1,2]
  - EZH2 is involved in mediating B-cell development, and many NHLs are correlated with EZH2 dysregulation[3,4]
  - *EZH2* gain-of-function (GOF) mutations at tyrosine 641 are known to occur in germinal center B-cell–like DLBCL and FL; one study estimated the occurrence of this mutation to be 22% and 7%, respectively, and other studies have indicated that it may be more common[5,6]
  - Preclinical models suggest that EZH1 compensates for the loss of EZH2 in lymphoma cells[7,8]
- Valemetostat is a novel, potent, and selective dual inhibitor of EZH2 and EZH1 (**Figure 1**) approved in Japan for the treatment of R/R adult T-cell leukemia/lymphoma (ATLL)[9,10]
- J101 is a multicenter, open-label, single-arm, phase 1 trial of valemetostat in patients with R/R B-NHLs and T-NHLs

Figure 1. Valemetostat mechanism of action



PRC2, polycomb repressive complex 2.

METHODS

Study design

- Adult patients eligible for participation in the J101 trial had confirmed B- or T-NHL as defined by the World Health Organization 2016 classification criteria and had relapsed from, were refractory to, or ineligible for standard therapies
- The trial included a dose-escalation part followed by a dose-expansion part (**Figure 2**)
- Patients with a histological diagnosis of B- or T-NHL were enrolled in the dose-escalation part and received valemetostat once daily (QD) at doses of 150–300 mg in continuous 28-day treatment cycles

Efficacy analysis

- Efficacy assessments included objective response rate (ORR), complete response (CR) rate, and DOR based on the International Working Group (IWG) 2007 response criteria

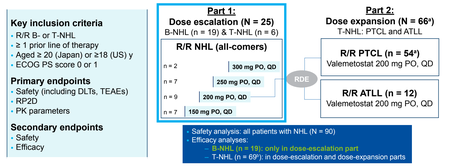
Pharmacokinetic (PK) analysis

- Serial blood samples were collected on days 1 and 15 of cycle 1 to assess plasma PK of valemetostat

Pharmacodynamic analysis

- Gene mutation analysis was performed on DNA samples collected at baseline in a subset of patients with B-NHLs by next-generation sequencing using the Oncomine™ Comprehensive Assay (Thermo Fisher Scientific; Waltham, MA), version 1

Figure 2. Study design, key inclusion criteria, and endpoints of the J101 trial



[a]Number includes the 1 patient excluded from all analyses due to a good clinical practice (GCP) violation; [a]Number excludes 2 patients without measurable lesions at baseline.
DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; PO, by mouth; PTCL, peripheral T-cell lymphoma; RDE, recommended dose for expansion; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event.

RESULTS

Patient characteristics

- Overall, the trial enrolled 91 patients with R/R NHLs
  - One patient was excluded from analysis sets due to a GCP violation
- The primary trial cutoff occurred on Dec 31, 2022
- Nineteen patients with R/R B-NHLs were enrolled in Part 1 (dose escalation) of the trial and had received ≥ 1 dose of valemetostat, including 7 patients with DLBCL, 7 with FL, 3 with indolent B-NHL, and 2 with other B-NHLs (**Table 1**)
  - Median number of prior therapies was 2 (range 0–6), and no patient in this cohort had received prior hematopoietic cell transplantation (HCT)

Disposition

- As of the primary trial cutoff, study treatment was ongoing in 2 (11%) patients with B-NHLs and had been discontinued in 17 (89%) patients
  - Reasons for discontinuation included progressive disease (PD; 8 [42%] patients), clinical progression (2 [11%]), adverse events (1 [5%]), physician decision (1 [5%]), and withdrawal by patient (5 [26%])

Table 1. Baseline demographics and disease characteristics

Characteristic	B-NHL (n = 19)	T-NHL (n = 71)	Total (N = 90)
Age (years), median (range)	66.0 (44–88)	68.0 (26–83)	67.5 (26–88)
Sex, n (%)			
Male	10 (53)	43 (61)	53 (59)
Female	9 (47)	28 (39)	37 (41)
Country of enrollment, n (%)			
US	0	44 (62)	44 (49)
Japan	19 (100)	27 (38)	46 (51)
ECOG PS score, n (%)			
0	15 (79)	29 (41)	44 (49)
1	4 (21)	41 (58)	45 (50)
≥ 2[a]	0	1 (1)	1 (1)
Cancer type, n (%)			
B-NHL	19 (100)	0	19 (21)
DLBCL	7 (37)	0	7 (8)
FL	7 (37)	0	7 (8)
Indolent B-cell lymphoma excluding FL	3 (16)	0	3 (3)
Mantle cell lymphoma	1 (5)	0	1 (1)
LPL	1 (5)	0	1 (1)
T-NHL	0	71 (100)	71 (79)
PTCL	0	57 (80)	57 (63)
ALCL	0	2 (3)	2 (2)
AITL	0	23 (32)	23 (26)
PTCL, NOS	0	26 (37)	26 (29)
Other T-cell lymphoma	0	6 (8)	6 (7)
ATLL	0	14 (20)	14 (16)
EZH2 GOF mutation, n (%)	1 (11)[b]	0[c]	1 (2)[d]
Prior lines of therapy, median (range)	2 (0–6)	2 (1–8)	2 (0–8)
Prior HCT, n (%)	0	18 (25)	18 (20)
Assigned valemetostat dose, n (%)			
150 mg/day	3 (16)	4 (6)	7 (8)
200 mg/day	7 (37)	67 (94)	74 (82)
250 mg/day	7 (37)	0	7 (8)
300 mg/day	2 (11)	0	2 (2)

[a]One patient with an ECOG PS score of 4 was eligible for the study at the time of screening; [b]*EZH2* mutation status assessed in 9 patients with B-NHLs; [c]*EZH2* mutation status assessed in 41 patients with T-NHLs; [d]*EZH2* mutation status assessed in a total of 50 patients.
AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; LPL, lymphoplasmacytic lymphoma; NOS, not otherwise specified.

Efficacy in B-NHL

- The ORR in patients with R/R B-NHL was 47% (9/19; 95% confidence interval [CI], 24.4–71.1)
  - Clinical responses were observed in 3/7 patients with DLBCL and 4/7 patients with FL; 1 patient in each of these groups achieved CR (**Table 2**)
    - An *EZH2* GOF mutation was identified in 1/5 evaluable patients with FL; this patient achieved a partial response (PR)
- Treatment duration and clinical response for individual patients is shown in **Figure 3**
- Of 19 patients, 9 (47%) achieved reductions of ≥ 50% from baseline in the sum of target lesion areas during valemetostat treatment (**Figure 4**)

Safety and tolerability

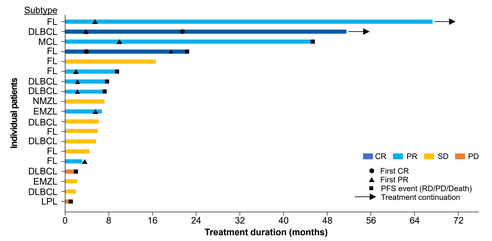
- All 90 patients with B-NHLs or T-NHLs experienced at least 1 TEAE, including 78 (87%) who had treatment-related TEAEs

Table 2. Clinical responses in patients with R/R B-NHLs

Response	All B-NHL (N = 19)
Best overall response, n (%)	
CR	2 (11)
PR	7 (37)
SD	8 (42)
PD	2 (11)
ORR,[a] % (n/N)	47 (9/19)
[95% CI][b]	[24.4, 71.1]
Time to response, median, months	3.7
(Range)	(1.9–10.1)
DOR,[c] median, months	18.4
[95% CI][b]	[5.3, NR]
Follow-up time,[d] median, months	49.2
[95% CI][e]	[0.03, 64.0]

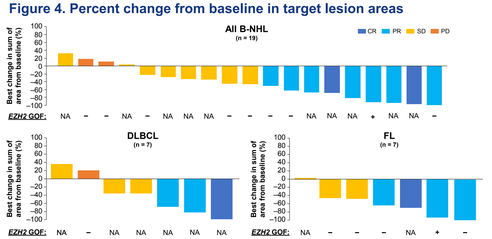
[a]Clinical response defined per IWG 2007 response criteria. ORR was the proportion of patients achieving CR or PR; [b]95% CI based on Clopper–Pearson method; [c]Median DOR was estimated using Kaplan–Meier methods; [d]Median follow-up time was estimated using reverse Kaplan-Meier methods; [e]CI was computed using Brookmeyer—Crowley method.
NR, not reached; SD, stable disease.

Figure 3. Exposure duration and best clinical responses



EMZL, extranodal marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; RD, relapsed disease.

Figure 4. Percent change from baseline in target lesion areas



NA, unknown.

- The most common TEAEs (any grade) were decreased platelet count (64%), dysgeusia (50%), anemia (43%), decreased neutrophil count (34%), and alopecia (33%; **Table 3**)
- The most common grade ≥ 3 TEAEs were cytopenias, including decreased neutrophil count (24%), platelet count (24%), and lymphocyte count (19%; **Table 4**)
- Treatment-emergent serious adverse events (SAEs) occurred in 39 (43%) patients; 32 (36%) patients had SAEs of ≥ grade 3
- TEAEs required treatment discontinuation for 7 (8%) patients, dose reduction for 9 (10%) patients, and treatment interruption for 42 (47%) patients
- Maximum tolerated dose was not reached between 150 and 300 mg/day based on the modified continual reassessment method (mCRM). RP2D/RDE was determined to be 200 mg/day based on the mCRM, safety findings, preliminarily efficacy, and PK/pharmacodynamic analyses

Table 3. TEAEs (all grades) that occurred in ≥ 15% of patients with NHLs

Preferred term, n (%)	Valemetostat dose 150 mg/day (n = 7)	200 mg/day (n = 74)	250 mg/day (n = 7)	300 mg/day (n = 2)	All dose levels (N = 90)
Platelet count decreased[a]	5 (71)	44 (59)	7 (100)	2 (100)	58 (64)
Dysgeusia	4 (57)	34 (46)	6 (86)	1 (50)	45 (50)
Anemia[b]	3 (43)	31 (42)	3 (43)	2 (100)	39 (43)
Neutrophil count decreased[c]	2 (29)	24 (32)	3 (43)	2 (100)	31 (34)
Alopecia	3 (43)	23 (31)	4 (57)	0	30 (33)
White blood cell count decreased[d]	1 (14)	20 (27)	4 (57)	2 (100)	27 (30)
Diarrhea	2 (29)	20 (27)	4 (57)	0	26 (29)
Lymphocyte count decreased[e]	3 (43)	12 (16)	6 (86)	2 (100)	23 (26)
Nausea	2 (29)	18 (24)	1 (14)	0	21 (23)
Fatigue[f]	2 (29)	14 (19)	2 (29)	0	18 (20)
Alanine aminotransferase increased	2 (29)	13 (18)	2 (29)	0	17 (19)
Aspartate aminotransferase increased	1 (14)	13 (18)	1 (14)	0	15 (17)
Pyrexia	0	13 (18)	2 (29)	0	15 (17)
Decreased appetite	2 (29)	13 (18)	0	0	15 (17)
Cough	0	14 (19)	0	0	14 (16)

[a]Platelet count decreased includes Medical Dictionary for Regulatory Activities (MedDRA) preferred terms Thrombocytopenia and Platelet count decreased; [b]Anemia includes Anemia, Hemoglobin decreased, and Red blood cell count decreased; [c]Neutrophil count decreased includes Neutropenia and Neutrophil count decreased; [d]White blood cell count decreased includes Leukopenia and White blood cell count decreased; [e]Lymphocyte count decreased includes Lymphopenia and Lymphocyte count decreased; [f]Fatigue includes Asthenia and Fatigue.

Table 4. TEAEs (grade ≥ 3) that occurred in ≥ 3 patients with NHLs

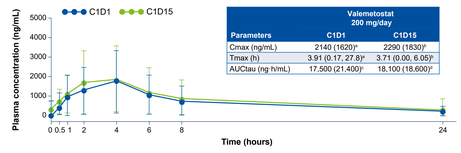
Preferred term, n (%)	Valemetostat dose 150 mg/day (n = 7)	200 mg/day (n = 74)	250 mg/day (n = 7)	300 mg/day (n = 2)	All dose levels (N = 90)
Neutrophil count decreased[a]	0	18 (24)	2 (29)	2 (100)	22 (24)
Platelet count decreased[b]	2 (29)	17 (23)	1 (14)	2 (100)	22 (24)
Lymphocyte count decreased[c]	2 (29)	10 (14)	5 (71)	0	17 (19)
Anemia[d]	2 (29)	11 (15)	1 (14)	1 (50)	15 (17)
White blood cell count decreased[e]	1 (14)	10 (14)	1 (14)	1 (50)	13 (14)
Gamma-glutamyltransferase increased	1 (14)	4 (5)	1 (14)	0	6 (7)
Hypertension	0	5 (7)	0	0	5 (6)

[a]Neutrophil count decreased includes MedDRA preferred terms Neutropenia and Neutrophil count decreased; [b]Platelet count decreased includes Thrombocytopenia and Platelet count decreased; [c]Lymphocyte count decreased includes Lymphopenia and Lymphocyte count decreased; [d]Anemia includes Anemia, Hemoglobin decreased, and Red blood cell count decreased; [e]White blood cell count decreased includes Leukopenia and White blood cell count decreased.

PK

- PK parameters and the concentration-time profile of valemetostat 200 mg/day are presented in **Figure 5**
  - Valemetostat showed variability in exposure between patients
  - Peak valemetostat plasma concentration occurred at a median time to reach maximum plasma concentration (Tmax) of approximately 4 hours
  - Accumulation of valemetostat plasma exposure was minimal

Figure 5. PK parameters and time course of mean plasma valemetostat concentrations on C1D1 and C1D15 at 200 mg/day in patients with NHLs



[a]n = 74; [b]n = 66; [c]n = 65; [d]n = 58.
Cmax and AUCtau values in table represent mean (standard deviation [SD]); Tmax value in table represents median (minimum, maximum). Data points in graph represent mean ± SD.
AUCtau, area under the plasma concentration-time curve during the dosing interval; C1D1, cycle 1 day 1; C1D15, cycle 1 day 15; Cmax, maximum plasma concentration.

Gene mutations in patients with B-NHLs

- Among 9 patients with available data, GOF mutations were identified in 3 patients and loss-of-function mutations in 2 patients (**Figure 6**)

Figure 6. Gene mutations identified in patients with B-NHLs

Gene mutation analysis was performed on DNA samples collected at baseline in a subset of patients (n = 9) with B-NHLs.
LOF, loss-of-function.

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