Landmark and longitudinal exposure-response analyses for multiple efficacy and safety endpoints to justify the clinical dose of valemetostat for adult T-cell leukemia/lymphoma

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Objectives

Valemetostat (DS-3201, EZHARMIA®) is an orally administered dual inhibitor of enhancer of zeste homolog (EZH) 1 and EZH2, which was approved for the treatment of patients with relapsed/refractory (R/R) adult T-cell leukemia/lymphoma (ATL) in Japan in September 2022 and is under development for other cancers. The objectives of this work were to determine (i) the valemetostat exposure range which provided satisfactory efficacy and acceptable safety or tolerability in R/R ATL patients, (ii) whether there were any clinically identifiable subpopulations that would warrant a dosing regimen other than the recommended dose (200 mg QD), and iii) a dose adjustment guidance due to platelet count decreased.

Methods and results

Landmark Exposure-Response Analyses

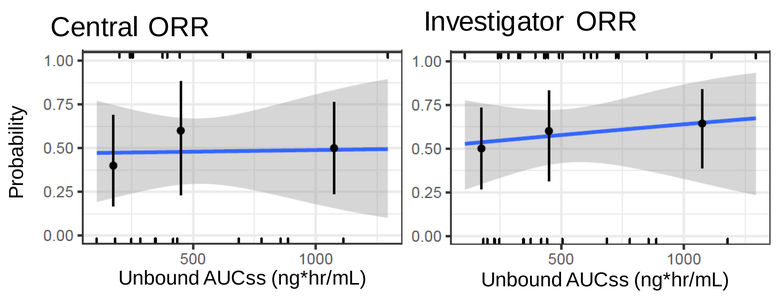
- The analysis was conducted using data from Studies DS3201-A-J101 and DS3201-A-J201 with non-Hodgkin's lymphoma (NHL), including ATL. Patients with ATL were included for efficacy endpoints and the whole population of NHL were analyzed for safety with wider dose range (**Table 1**).

Table 1 Summary of dataset assessed in the landmark exposure-response analyses by endpoint

Endpoint	Population	N	Dose (mg)	Note
ORR by central assessment	ATL	25	200 mg	Efficacy
ORR by investigator	ATL	39	150-200 mg	Efficacy
Anemia (Grade >=3)	NHL	102	150-300 mg	Safety
Neutrophil count decreased (Grade >=3)	NHL	102	150-300 mg	Safety
Platelet count decreased (Grade >=3)	NHL	102	150-300 mg	Safety
Dose reduction due to AEs	NHL	102	150-300 mg	Safety
Dose interruption due to AEs	NHL	102	150-300 mg	Safety
Any AEs with Grade >=3	NHL	102	150-300 mg	Safety

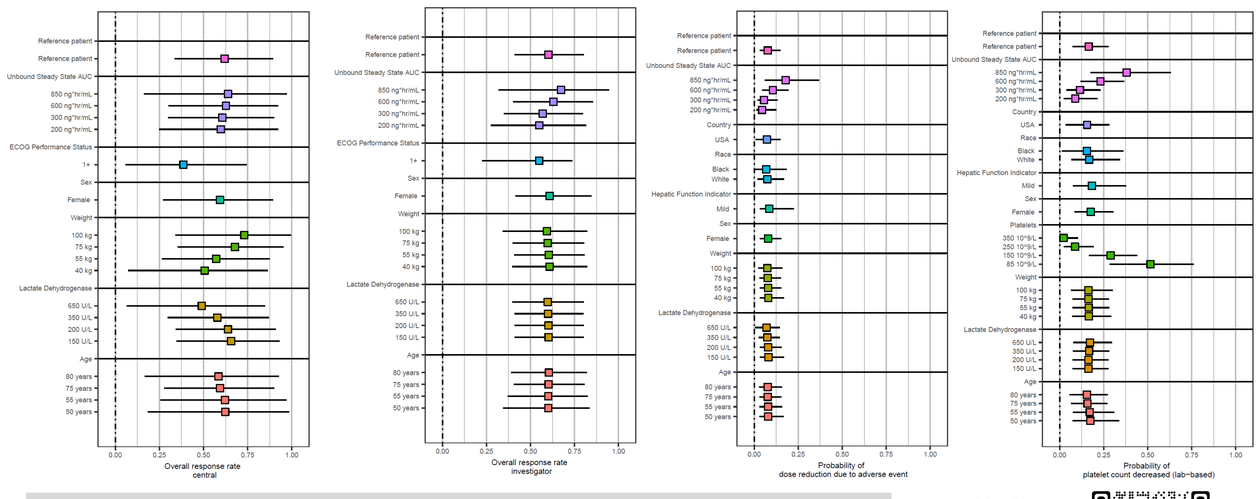
- Slightly positive association with exposure was observed for efficacy endpoints while it was steeper for all safety endpoints (**Fig. 1**).
- Each of these outcome variables were dichotomous, therefore logistic regression was performed.
- The candidate covariates were investigated by full model approach with regularized estimation of covariate effects via Spike and Slab priors in a Bayesian framework.
- For all endpoints, positive exposure-response relationship was confirmed (**Fig. 2**).

Fig. 1 Observed exposure-response relationship for selected endpoints. Solid blue lines and gray areas represent smoothing curves and the 95% confidence intervals, respectively.



- Only the baseline blood counts for the corresponding safety outcomes were identified as covariates with substantial impact (**Fig. 2**).
- The models were also used to establish a region of practical equivalence (ROPE), that provides satisfactory efficacy and acceptable safety.
  - Satisfactory efficacy: probability of objective response of greater than 30% for typical patients
  - Acceptable safety: probability of dose reduction due to AE of less than 50% for 90% of patients
- A ROPE of (0 to 1255 ng*hr/mL) and modified ROPE with direct empirical support of (184 to 887 ng*hr/mL) were estimated as target exposure ranges (**Fig. 3 left**).
- Simulations suggested that 200 mg QD dosing is most likely to achieve exposures within the modified ROPE for subpopulations of interest (**Fig. 3 right**).
- These analyses were conducted using R 4.0.3.

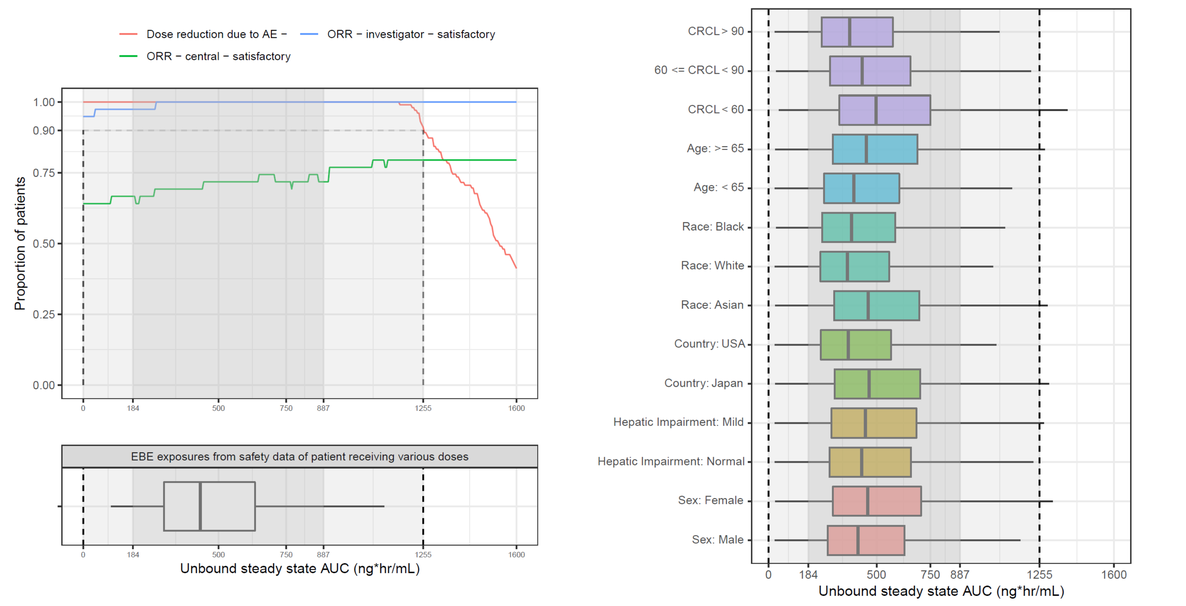
Fig. 2 Effect of exposure (unbound AUC at steady state) and covariates on selected outcomes



QR code for this poster (left), and summary of Spike and Slab methodology for covariate effect estimation (right)

Methods and results (cont.)

Fig. 3 Estimated ROPE based on the definition (**left**) and expected exposure range of sub-population administered 200 mg QD (**right**). The light and dark gray areas indicate the ROPE and modified ROPE, respectively.



Longitudinal Exposure-Response Analysis (Platelet)

- Platelet dynamics over time was modeled in order to assess a dose adjustment guidance due to platelet count decreased.
- After applying exclusions of extreme data, the longitudinal analysis dataset included 101 patients contributing 2313 platelet observations; most observations (82.2%) were collected from the 71 Japanese patients.
- Platelets initially declined then spontaneously recovered to a new steady state under continued, daily dosing with valemetostat (**Fig. 4**).
- The final model included two proliferation compartments, both representing the stem cells and the proliferating precursors cells in the bone marrow with different sensitivity to valemetostat (**Fig. 5**).
- The longitudinal model predicted 2.36% of simulated subjects who experienced Grade 4 platelet count decreased when the following dose adjustment guidance was applied, while 8.45% without dose adjustment (**Fig. 6**).
  - The initial dose of 200 mg will be reduced to one-level (50 mg) lower after second and third incidence, respectively, then, the treatment will be terminated after fourth incidence.
- These analyses were conducted using NONMEM® 7.5 and R 4.0.3.

Fig. 4 Observed platelet count data after administration of valemetostat by exposure level

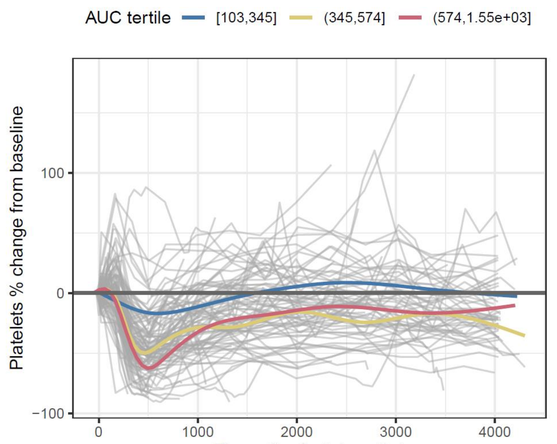


Fig. 5 Schematic representation of the longitudinal exposure-response model for platelet count decreased

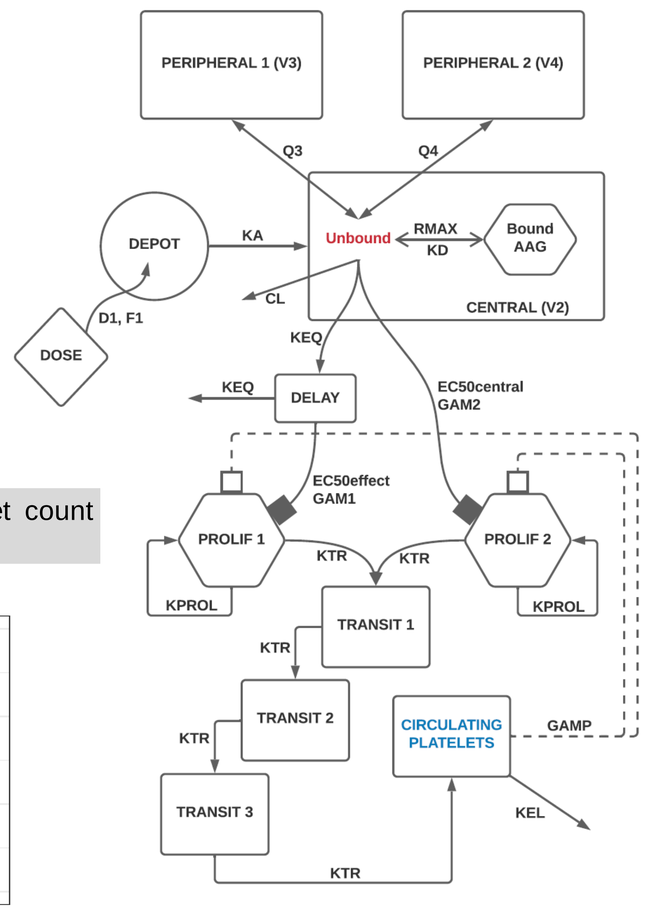
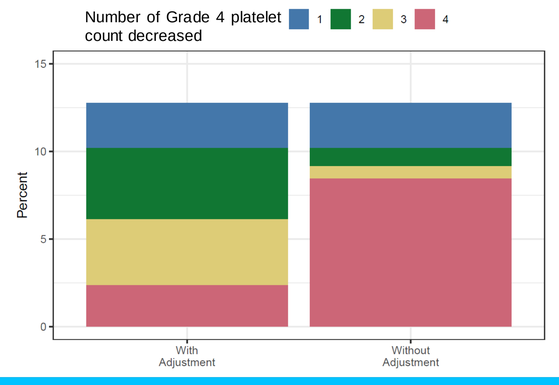


Fig. 6 Predicted frequency of Grade 4 platelet count decreased with or without dose adjustment



Conclusions

- The landmark analyses confirmed the positive exposure-response relationship for all endpoints and established the target exposure range (ROPE), that provides satisfactory efficacy and acceptable safety of recommended dose (200 mg QD) of valemetostat.
- The longitudinal analysis adequately characterized the time-course of platelet counts with spontaneous partial recovery from the nadir. The adaptive simulation predicted the risk of recurrent G4 platelet count decreased with or without dose adjustment. The dose adjustment guidance based on platelet count was justified.
- These analyses justified the recommended dose of 200 mg QD and dose adjustment for patients with R/R ATL.