Valemetostat, an EZH1/2 inhibitor, suppresses HTLV-1 infection in a humanized mouse model

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Background:
We have previously shown that EZH2, which is involved in H3K27me3 histone methylation, is overexpressed in ATL cells, and that the EZH1/2 dual inhibitor Valemetostat (DS-3201) reduces ATL cell viability. In order to clarify the involvement of H3K27me3 histone methylation in the process of HTLV-1 infection and ATL onset, we investigated the effect of Valemetostat administration against HTLV-1 infection in a humanized mouse model.

Methods:
Humanized mice, prepared by intra–bone marrow injection of CD133+ human hematopoietic stem cells, were infected with HTLV-1 by intraperitoneal injection of HTLV-1 infected Jurkat cells. Valemetostat was administrated with feed during the course of infection. Proviral load (PVL) and expressions of CD7 and CADM1 on the peripheral blood cells were analyzed according to the HAS-flow analysis for HTLV-1 infection and disease progression.

Results:
In 9 weeks of infection, 12 out of 14 animals in the drug-free group were infected with HTLV-1 and 5 died, whereas 3 out of 13 drug-administered mice were found HTLV-1 positive and 2 died later. In the course of infection, CD7 expression on the HTLV-positive CADM1$^+$ CD4$^+$ T-cells in mice without drug

administration was diminished in parallel with the disease progression, as observed in the case of ATL. On the other hand, the drug administration retarded the reduction of CD7 expression on the $CADM1^+$ $CD4^+$ T-cells as well as the increase in the number of infected cells in peripheral blood.

Conclusion:
Administration of Valemetostat suppressed the HTLV-1 infection in humanized mouse model. Furthermore, the drug suppressed the transition from $CD7^+CADM1^+$ fraction (D fraction) to $CD7^-CADM1^+$ fraction (N fraction) in HTLV-1 infected $CD4^+$ T-cells, which reflects to the disease progression of ATL. Thus, the results suggest that H3K27me3 histone methylation is involved in the progression of ATL at the step of D to N transition in HAS-flow analysis system.

Disclosure of Interest Statement:
Nothing to disclose.