

## Valemetostat: First approval as a dual inhibitor of EZH1/2 to treat adult T-cell leukemia/lymphoma

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**SUMMARY** Adult T-cell leukemia/lymphoma (ATL) is a mature T-cell lymphoma with a poor prognosis. Accumulating trimethylation of histone H3 lysine 27 (H3K27me3) caused by upregulated function of either enhancer of zeste homologue 2 (EZH2) or its homolog EZH1 plays an essential role in the maintenance of transcriptional repression in ATL. Selective inhibition of EZH2 may complementarily induce EZH1 activation, so dual targeting EZH1/2 is a rational strategy in developing potent antitumor agents. Valemetostat is the first dual EZH1/2 inhibitor approved for treatment of aggressive ATL in Japan in September 2022. Several other dual EZH1/2 inhibitors such as HH2853, HM97594, and HM97662 have also demonstrated potential in treating malignant tumors. Dual targeting EZH1/2 may have promising antitumor action in hematological malignancies and solid tumors.

**Keywords** valemetostat, adult T-cell leukemia/lymphoma, EZH1, EZH2

Adult T-cell leukemia/lymphoma (ATL) is a mature T-cell lymphoma that is highly prevalent in southwestern Japan, the central and southern United States, and other regions due to chronic infection with human T-cell lymphotropic virus type 1 (HTLV-1) (1,2). In Japan, there are approximately one million HTLV-1 carriers in whom the estimated lifetime risk of developing ATL is 6-7% for men and 2-3% for women, and an estimated 1,000 deaths from ATL annually (3,4). ATL is classified into two indolent types (smoldering and favorable chronic) and three aggressive types (acute, lymphoma, and unfavorable chronic). Newly diagnosed aggressive ATL is mainly treated with conventional chemotherapy such as CHOP (a combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone) or a CHOP-like regimen, followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT) if criteria are met (3). In the past few years, mogamulizumab and lenalidomide has been used as salvage therapy for relapsed or refractory ATL (5). Although various treatment options are now available, the prognosis for ATL is still dismal, with a 4-year survival rate of 16.8% for acute ATL, 19.6% for lymphoma-ATL, 26.6% for unfavorable chronic ATL, 62.1% for favorable chronic ATL, and 59.8% for smoldering ATL (3). A novel strategy is urgently required for treatment of ATL.

Valemetostat, a dual inhibitor of enhancer of zeste homolog (EZH) 1 and EZH2 developed by Daiichi

Sankyo, was approved for treatment of patients with relapsed or refractory ATL in Japan in September 2022 (6). This approval was based on the results of an open-label, single-arm, phase 2 trial in which 25 patients with relapsed or refractory ATL who had received a median of 3 prior lines of therapy had an overall response rate (ORR) of 48.0%, including complete remission in 5 patients and partial remission in 7 (7). Of note, 24 patients that had previously received mogamulizumab treatment had an ORR of 45.8% (complete remission in 4 patients and partial remission in 7) (7). Treatment-emergent adverse events including thrombocytopenia, anemia, alopecia, dysgeusia, neutropenia, lymphopenia, leukopenia, decreased appetite, and pyrexia were manageable and tolerated (7). Larger scale clinical studies are warranted to further investigate the efficacy and safety of valemetostat in the treatment of relapsed or refractory ATL.

In addition to dysregulation of transcription due to a genetic abnormality, abnormal epigenetic regulation of transcription plays an important role in carcinogenesis and cancer development. Trimethylation of histone H3 lysine 27 (H3K27me3), which is catalyzed by polycomb repressive complex 2 (PRC2), is a suppressive histone mark of chromatin condensation and gene silencing (8). In ATL, H3K27me3-mediated gene repression was reported to be correlated with poor prognostic markers (9). EZH1 or EZH2 functions as an enzymatically active

core subunit of PRC2 to methylate Lys-27 on histone 3 (H3K27) by transferring a methyl group from the cofactor *S*-adenosyl-*L*-methionine (8). The oncogenic role of EZH2 has attracted considerable attention since overexpression or somatic mutations (gain-of-function) of EZH2 has been found in many solid cancers and hematologic malignancies (10-13). Different types of EZH2 inhibitors that diminish the abundance of H3K27me3 and thus unleash the expression of tumor suppressive genes have been synthesized and tested for cancer treatment thus far. Tazemetostat is an EZH2 inhibitor that was approved for treatment of metastatic or locally advanced epithelioid sarcoma and relapsed follicular lymphoma in the US in 2020 (14,15). That said, some H3K27me3-high malignancies are reported to be relatively tolerant to EZH2 inhibitors (16). Yamagishi *et al.* noted a relationship between mutual interference and the compensatory function of co-expressed EZH1 and EZH2 in malignant lymphomas, suggesting a rationale for dual targeting EZH1 and EZH2 (16). A study has indicated that EZH1/2 dual inhibitors were superior to an EZH2 selective inhibitor in suppressing trimethylation of H3K27 and tumor cell proliferation both *in vitro* and *in vivo* (17). In ATL, EZH1 and EZH2 were found to be independently required for tumor cell proliferation (16), indicating the necessity of targeting both EZH1/2 in treatment of ATL.

The efficacy and safety of valemetostat in treating relapsed/refractory peripheral T-cell lymphoma (PTCL) and B-cell lymphoma is currently being investigated in two phase II clinical trials (18). Valemetostat displayed acceptable safety and encouraging preliminary efficacy in treatment of relapsed/refractory PTCL in a phase I study (19). Forty-five patients had an ORR of 55.6%, including a complete response in 11 and a partial response in 14 (19). Valemetostat is also being evaluated to treat tumors characterized by an SMARCB1/INI1 deficiency (a SWI/SNF mutation), such as malignant rhabdoid tumors, epithelioid sarcoma, or synovial sarcoma as are frequently observed during childhood and adolescence, in a phase I trial (20). Besides valemetostat, several other dual EZH1/2 inhibitors such as HH2853, HM97594, and HM97662 have demonstrated potential in treating malignant tumors. HH2853 is currently being tested for its efficacy and safety in treating relapsed or refractory non-Hodgkin's lymphoma in a phase 1/2 trial (21-23). Dual targeting EZH1/2 may have promising antitumor action in hematological malignancies and solid tumors.

**Funding:** None.

**Conflict of Interest:** The authors have no conflicts of interest to disclose.

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Received October 16, 2022; Revised October 23, 2022;  
Accepted October 26, 2022.

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Released online in J-STAGE as advance publication October 28, 2022.