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An Open-Label, Single-Arm, Phase 2 Trial of Valemetostat in Relapsed or Refractory Adult T-Cell Leukemia/Lymphoma

Tracking no: BLD-2022-016862R1

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Abstract:
Adult T-cell leukemia/lymphoma (ATL) is an aggressive non-Hodgkin lymphoma with poor prognosis and few treatment options for patients with relapsed, recurrent, or refractory disease. We evaluated the efficacy and safety of valemetostat, a potent EZH1 and EZH2 inhibitor, in treating relapsed/refractory (R/R) ATL. This multicenter phase 2 trial (NCT04102150; https://clinicaltrials.gov/ct2/show/NCT04102150; DS3201-A-J201) enrolled patients with R/R aggressive ATL (acute, lymphoma, unfavorable chronic type). Patients received valemetostat 200 mg/day until progressive disease or unacceptable toxicity. The primary endpoint was overall response rate (ORR) centrally assessed by an independent efficacy assessment committee (IEAC). Secondary endpoints included best response in disease compartments, duration of response (DOR), pharmacokinetics, and safety. Twenty-five patients (median age, 69.0) with a median of 3 prior lines of therapy were enrolled; 24 had prior mogamulizumab treatment. The primary endpoint was met with a centrally reviewed ORR of 48.0% (90% CI, 30.5% to 65.9%), including 5 complete and 7 partial remissions. Patients pretreated with mogamulizumab had an ORR of 45.8% (4 complete and 7 partial remissions). IEAC-assessed median DOR was not reached (NR; 95% CI, 1.87 months to NR). Treatment-emergent adverse events (TEAEs) were manageable. TEAEs that occurred in ≥20% of patients included thrombocytopenia, anemia, alopecia, dysgeusia, neutropenia, lymphopenia, leukopenia, decreased appetite, and pyrexia. Grade ≥3 TEAEs included thrombocytopenia, anemia, lymphopenia, leukopenia, and neutropenia. Valemetostat demonstrated promising efficacy and tolerability in heavily pretreated patients, warranting further investigation in treating R/R ATL.

Conflict of interest: COI declared - see note

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Title: An Open-Label, Single-Arm, Phase 2 Trial of Valemetostat in Relapsed or Refractory Adult T-Cell Leukemia/Lymphoma

Running head: Efficacy and safety of valemetostat in R/R ATL

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Key Points

- This phase 2 study assessed the efficacy and safety of the dual EZH1 and EZH2 inhibitor valemetostat in patients with R/R ATL.
- Valemetostat 200 mg orally once daily demonstrated promising efficacy and manageable toxicity in heavily pretreated patients.

Abstract (230/250 words)

Adult T-cell leukemia/lymphoma (ATL) is an aggressive non-Hodgkin lymphoma with poor prognosis and few treatment options for patients with relapsed, recurrent, or refractory disease. We evaluated the efficacy and safety of valemetostat, a potent EZH1 and EZH2 inhibitor, in treating relapsed/refractory (R/R) ATL. This multicenter phase 2 trial (NCT04102150; https://clinicaltrials.gov/ct2/show/NCT04102150; DS3201-A-J201) enrolled patients with R/R aggressive ATL (acute, lymphoma, unfavorable chronic type). Patients received valemetostat 200 mg/day until progressive disease or unacceptable toxicity. The primary endpoint was overall response rate (ORR) centrally assessed by an independent efficacy assessment committee (IEAC). Secondary endpoints included best response in disease compartments, duration of response (DOR), pharmacokinetics, and safety. Twenty-five patients (median age, 69.0) with a median of 3 prior lines of therapy were enrolled; 24 had prior mogamulizumab treatment. The primary endpoint was met with a centrally reviewed ORR of 48.0% (90% CI, 30.5% to 65.9%), including 5 complete and 7 partial remissions. Patients pretreated with mogamulizumab had an ORR of 45.8% (4 complete and 7 partial remissions). IEAC-assessed median DOR was not reached (NR; 95% CI, 1.87 months to NR). Treatment-

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emergent adverse events (TEAEs) were manageable. TEAEs that occurred in ≥20% of patients included thrombocytopenia, anemia, alopecia, dysgeusia, neutropenia, lymphopenia, leukopenia, decreased appetite, and pyrexia. Grade ≥3 TEAEs included thrombocytopenia, anemia, lymphopenia, leukopenia, and neutropenia. Valemetostat demonstrated promising efficacy and tolerability in heavily pretreated patients, warranting further investigation in treating R/R ATL.

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Introduction

Adult T-cell leukemia/lymphoma (ATL) is an aggressive non-Hodgkin lymphoma (NHL) subtype that arises from T cells infected with human T-lymphotropic virus type 1 (HTLV-1).[1-3] HTLV-1 is endemic to Japan, the Caribbean, Central and South America, Africa, the Middle East, and Australia. Recent reports indicate that ATL constitutes ≥30% of all T-cell lymphoma cases in Japan.[4-6] ATL is classified into 4 clinical subtypes (acute, lymphoma, chronic, and smoldering), with acute, lymphoma, and unfavorable chronic subtypes among the most aggressive.[4] Current standard first-line treatment for aggressive ATLs is multiagent chemotherapy including VCAP-AMP-VECP (vincristine, cyclophosphamide, doxorubicin and prednisone; doxorubicin, ranimustine, and prednisone; and vindesine, etoposide, carboplatin, and prednisone).[1-3,7] Even for those who respond to first-line chemotherapy, the response is usually not durable, and the prognosis of patients with aggressive ATL remains poor (median survival is ≤1 year).[8,9] Early up-front allogenic hematopoietic stem cell transplant (allo-HSCT) is considered for aggressive ATL.[10,11] However, the median age at diagnosis (68 years), donor availability, patient comorbidities, and infectious complications during induction treatment severely limit eligibility for allo-HSCT.[10,12-14] In addition, more than half of patients who receive allo-HSCT cannot achieve long-term survival due to relapse and/or treatment-related toxicities, requiring further treatment.[9]

Recently, new agents have been incorporated into the armamentarium for relapsed/refractory (R/R) ATL.[15,16] A phase 2 study of the defucosylated anti-CCR4 antibody, mogamulizumab, resulted in an overall response rate (ORR) of 50%.[16] A separate phase 2 study of lenalidomide, an immunomodulator and inhibitor of E3 ubiquitin ligase, yielded an ORR of

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42%.[15] Another phase 2 study of tucidinostat (HBI-8000; chidamide), a histone deacetylase inhibitor, in R/R ATL with mogamulizumab pretreatment resulted in an ORR of 30%.[17] These agents received regulatory approval in Japan. Despite these options, response rates in patients with aggressive ATLs remain low, and patients continue to experience relapse. Development of novel therapies is therefore critical for patients with R/R ATL.

Enhancer of zeste homolog 2 (EZH2) and EZH1 are the principal histone methyltransferases of the polycomb repressive complex 2 (PRC2) and initiate chromatin folding through trimethylation of histone H3 lysine 27, resulting in transcriptional repression.[18-22] Although EZH2-selective inhibitors have been developed, EZH1 compensation for EZH2 loss necessitates the implementation of dual inhibitory agents.[23,24] Valemetostat tosylate (valemetostat) is a novel, potent, and selective dual inhibitor of EZH1 and EZH2 with strong antitumor properties.[24] Interim analyses from a phase 1 study in the US and Japan of valemetostat monotherapy showed that 200 mg daily (QD) valemetostat had an acceptable safety profile with signs of preliminary efficacy in patients with R/R NHLs, including ATL (NCT02732275; DS3201-A-J101).[25] Based on these encouraging results, we conducted a phase 2 trial to assess efficacy and safety of valemetostat 200 mg QD in patients with R/R ATL for purposes of obtaining regulatory approval in Japan.

Methods

Patient Eligibility

Patients aged ≥20 years with cytologically or pathologically diagnosed R/R ATL (acute, lymphoma, or unfavorable chronic type as assessed at the time of diagnosis) with antibody-

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confirmed HTLV-1 infection were eligible. Unfavorable chronic ATL was defined as having ≥1 of the following factors: low serum albumin, high lactate dehydrogenase, or high blood urea nitrogen concentration.[7] Patients needed to have relapsed, recurrent, or refractory disease after prior mogamulizumab therapy or, if mogamulizumab was contraindicated or not tolerated, ≥1 systemic therapy with cytotoxic chemotherapy. Patients with an Eastern Cooperative Oncology Group performance status of 0-2 and ≥1 measurable lesion were eligible. Eligibility criteria further included a neutrophil count ≥1000/μL, platelet count ≥75,000/μL, hemoglobin ≥8.0 g/dL, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN), bilirubin ≤1.5 × ULN, and serum creatinine ≤1.5 × ULN or creatinine clearance ≥30 mL/min. Patients with central nervous system involvement of ATL at screening, chemotherapy or molecularly targeted therapy within 21 days, history of allo-HSCT, or recent autologous HSCT within 12 weeks before enrollment were excluded. Corticosteroids over 10 mg/day were not permitted. Patients treated with investigational drugs within 28 days or a history of EZH inhibitor treatment were excluded.

Study Design

DS3201-A-J201 (NCT04102150) was a multicenter, single-arm, open-label, phase 2 clinical trial for patients with R/R ATL. The objectives of this study were to evaluate the efficacy and safety of valemetostat monotherapy in patients with R/R ATL. Relapsed disease was defined as disease progression after achieving complete remission (CR) or unconfirmed complete remission (CRu) following prior chemotherapy. Recurrent disease was defined as disease progression after achieving partial remission (PR) with prior chemotherapy. Disease was considered refractory if patients required a treatment switch after achieving stable disease (SD)

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or had experienced disease progression after prior treatment. The primary endpoint was centrally reviewed ORR, defined as the proportion of participants whose best response was CR, CRu, or PR as assessed by an independent efficacy assessment committee (IEAC).[26] Secondary endpoints included investigator-assessed ORR, best response in disease compartments, CR rate, tumor control rate (TCR), time to response (TTR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), pharmacokinetics, and safety. Details of pharmacokinetic methodology are described in the Supplemental Methods.

Patients were treated with valemetostat 200 mg QD orally under fasting conditions (≥2 hours before or ≥1 hour after a meal) on continuous 28-day cycles until progressive disease (PD) or unacceptable toxicity. Patients receiving strong CYP3A inhibitors or P-glycoprotein (P-gp) inhibitors had a valemetostat dose reduction to 100 mg QD. Those receiving drugs with a strong inhibitory effect on both CYP3A and P-gp received a reduced dose of 50 mg QD.

Efficacy and Safety Assessments

All patients treated with ≥1 dose of valemetostat were included in the efficacy analysis. Initial antitumor response was assessed 4 weeks after the first dose of valemetostat, and the response was subsequently assessed every 8 weeks. After 48 weeks, assessments were conducted every 12 weeks thereafter. Efficacy assessments were conducted by an IEAC. Patient best responses and best change in tumor burden by disease compartment were quantified across treatment. Nodal or measurable extranodal lesions were assessed with computed tomography scans, and sums of the products of the greatest diameters were quantified. Skin lesions were evaluated visually and through calculation using the modified severity-weighted assessment tool.[27] Disease in peripheral blood was evaluated based on

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white blood cell count, lymphocyte count, and abnormal lymphocyte count. Antitumor response was assessed in accordance with the antitumor response assessment criteria, which were slightly modified from the response assessment criteria for ATL.[26] The modification was made such that there was no requirement for each criterion to be present for ≥4 weeks.

The safety analysis consisted of patients treated with ≥1 dose of valemetostat. The Medical Dictionary for Regulatory Activities version 23.1 was used to code all adverse events (AEs). Safety was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analyses

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). The 90% CI for ORR was calculated using the Clopper-Pearson method. The Kaplan-Meier method was used to estimate the survival distribution function for time-to-event analyses. DOR calculated for responders was defined as the time from first response to relapsed disease (RD)/PD or death from any cause, whichever occurred first. PFS was measured from the start of treatment until RD/PD based on overall response assessment or death. OS was defined from the time of study treatment start to death regardless of cause. TTR was defined as time from the start of study treatment to first assessed response (CR, CRu, or PR). TCR consisted of the proportion of patients whose best response was CR, CRu, PR, or SD.

Sample Size

The threshold ORR was set to 5%, primarily because no established treatment exists for target patients. The expected ORR was set to 30% based primarily on a prior study of

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lenalidomide in R/R ATL.[15] A binomial 1-sided exact test was performed to test the null hypothesis at a 5% significance level (H_0: ORR <0.05); 21 patients were needed for 90% power.

Study Oversight

This study was sponsored by Daiichi Sankyo Co. Ltd. (Tokyo, Japan) and was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines as outlined by the International Conference on Harmonisation E6 requirements. All protocols were approved by the institutional review board at each participating center. Academic investigators and sponsors were responsible for the study design. All patients who participated in this trial provided written informed consent before enrollment.

Results

Patients

Twenty-eight patients were screened, and 25 (12 male, 13 female) were enrolled between November 2019 and October 2020 across 12 sites in Japan. Baseline patient and disease characteristics are summarized in **Table 1**. The median age was 69.0 years (range, 59-84). This study enrolled 16, 6, and 3 patients with acute, lymphoma, or unfavorable chronic type R/R ATL, respectively. ATL status included 8 patients (32%) with relapsed, 6 patients (24%) with recurrent, and 11 patients (44%) with refractory disease. The median time since last ATL treatment was 60 days (range, 23-1400). All 25 patients had received treatment for ATL, with a median of 3 prior lines of therapy (range, 1-8). Twenty-four patients had received mogamulizumab treatment; 1 patient with CCR4-negative ATL had no prior mogamulizumab therapy. Six patients (24%) were refractory to mogamulizumab-containing regimens. Eight

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patients (32%) had received lenalidomide. Seventeen patients (68%) discontinued the study drug; 14 patients (56%) discontinued because of disease progression. Two patients (8%) discontinued study treatment due to AEs, and 1 patient (4%) discontinued study treatment per physician decision.

Efficacy

At data cutoff (April 24, 2021), the median follow-up was 6.5 months. The IEAC-assessed/median TTR was 1.4 months (range, 1.0-5.6). The study met its primary endpoint, with a centrally reviewed IEAC-assessed ORR of 48.0% (p<.0001; 12/25; 90% CI, 30.5% to 65.9%), including a CR rate of 20.0% (5/25) and a PR rate of 28.0% (7/25) (**Table 2**). The ORR by subtype was 62.5% (10/16) for acute, 16.7% (1/6) for lymphoma, and 33.3% (1/3) for unfavorable chronic. Notably, the ORR of patients pretreated with mogamulizumab was 45.8% (11/24) (90% CI, 28.2% to 64.2%). The ORR of patients refractory to mogamulizumab-containing therapies was 50.0% (3/6). An ORR of 50% (90% CI, 15.7% to 84.3%) was achieved in patients with prior lenalidomide treatment (4/8). The ORR by disease status was 37.5% (3/8) for relapsed, 66.7% (4/6) for recurrent, and 45.5% (5/11) for refractory disease (**Table 2**). The TCR was 88.0% (95% CI, 68.8% to 97.5%).

Efficacy was further assessed by disease compartment. The IEAC-assessed best percentage change in tumor burden by disease compartment is depicted in **Fig 1**. A ≥50% reduction from baseline was observed in nodal or extranodal lesions in 9 of 20 patients (5 CRs, 2 CRus, 2 PRs) (**Fig 1A**), in the skin compartment in 3 of 6 patients (1 CR, 2 PRs) (**Fig 1B**), and in peripheral blood in 8 of 9 patients (2 CRs, 6 PRs) (**Fig 1C**). One patient with skin lesions did not undergo assessment after the initial baseline measurement and was not included in the

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analysis. The treatment duration with clinical outcomes of the 25 patients is shown in **Fig 2A**. At data cutoff, 8 patients were receiving ongoing study treatment. Notably, 4 of 10 patients who achieved SD were able to receive valemetostat for ≥6 months following treatment initiation. Furthermore, responses were converted from PR to CR in 2 patients. The median DOR was not reached (NR) (95% CI, 1.87 months to NR) (**Fig 2B**), and 6 of 12 responders (50%) had an ongoing response. Although immature, the median PFS and OS were 7.4 months (95% CI, 3.0 to not estimable) and 16.4 months (95% CI, 6.5 to 16.4), respectively.

Efficacy outcomes per investigator assessment were consistent with IEAC-adjudicated results. Investigator-assessed ORR was 56.0% (90% CI, 37.9% to 73.0%), including 24.0% CR (6/25), 4.0% CRu (1/25) and 28.0% PR (7/25). The investigator-assessed CR rate was 28.0% (7/25).

Pharmacokinetics

Serial and trough blood samples were collected for plasma valemetostat concentration measurements (**Supplemental Fig 1**). The mean maximum plasma concentration (C_{max}) of total valemetostat (2230 ng/mL on cycle 1 day 1 and 2300 ng/mL on cycle 1 day 15) and unbound valemetostat (81.7 ng/mL on cycle 1 day 1 and 84.9 ng/mL on cycle 1 day 15) was achieved in median time to C_{max} (T_{max}) of 2 to 4 hours (**Supplemental Table 1**). At steady state (cycle 1 day 15), the mean area under the plasma concentration-time profile during dosing interval (AUC_{tau}) was 20,800 ng·h/mL for total valemetostat and 584 ng·h/mL for unbound valemetostat. The mean accumulation ratios for AUC_{tau} of total and unbound valemetostat were 1.19 and 1.27, respectively, indicating mild accumulation after continuous daily dosing at 200 mg.

Safety

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Table 3 summarizes treatment-emergent adverse events (TEAEs) and frequency of the most common TEAEs. All patients treated with valemetostat experienced TEAEs. Common hematologic TEAEs were thrombocytopenia (80%), anemia (52%), neutropenia (28%), lymphopenia (24%), and leukopenia (20%). Grade ≥3 hematologic TEAEs reported in ≥10% of patients were thrombocytopenia (32%), anemia (32%), lymphopenia (16%), leukopenia (12%), and neutropenia (12%). Common nonhematologic TEAEs included alopecia (40%), dysgeusia (36%), decreased appetite (20%), and pyrexia (20%). Serious TEAEs occurred in 8 (32%) patients. Cardiac failure led to discontinuation in 1 patient; other serious TEAEs resolved without discontinuation of the study drug. This study prespecified 3 AEs of special interest (AESI), which included combined elevations of aminotransferases and bilirubin (ALT and/or AST ≥3×ULN and blood bilirubin ≥2×ULN), secondary malignancy, and thrombocytopenia. No patient met the criteria for AESI, except for thrombocytopenia. Secondary malignancies, including hematologic malignancy or myelodysplastic syndrome, were not observed.

Of 3 patients who experienced grade 4 thrombocytopenia (platelet count, $<25 \times 10^9$/L), the median time to onset of postbaseline platelet reduction occurred early during treatment at 21 days from the first dose, with a median time to recovery (platelet count, $\geq 25 \times 10^9$/L) of 3 days. Three of 20 patients who experienced thrombocytopenia required dose modification (discontinuation, 1 patient; dose interruption, 2 patients). Thrombocytopenia in most of the remaining 17 patients was transient and resolved without dose modification. Five patients required platelet transfusions for thrombocytopenia, and 3 patients required a red blood cell transfusion for anemia. TEAEs led to dose reduction in 2 patients (8%). Five patients (20%) experienced TEAEs that required dose interruption. Two patients (8%) who had achieved SD

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discontinued study treatment due to AEs such as cardiac failure and thrombocytopenia, respectively. No treatment-related deaths occurred.

The median dose intensity of valemetostat was 199.33 mg/day. The median duration of treatment was 4.3 months (range, 0.8-14.9).

Discussion

In this study, we observed clinically relevant efficacy and tolerable safety of valemetostat in patients with R/R ATL after prior systemic therapy, including mogamulizumab or ≥1 prior systemic therapy with cytotoxic chemotherapy in patients intolerant of, or ineligible for, mogamulizumab. The primary endpoint was met, with an IEAC-assessed ORR of 48.0%, including a CR rate of 20.0% and PR rate of 28.0%. Importantly, valemetostat was effective in patients pretreated with mogamulizumab and those with disease refractory to mogamulizumab—ORRs of 45.8% and 50.0%, respectively. We noted an ORR of 50.0% in patients previously treated with lenalidomide.

ATL carries a very poor prognosis among various histologic subtypes of T-cell lymphomas.[3,4,8,9,28,29] Few treatment options are available for patients with R/R ATL, highlighting the considerable need for novel therapies. In separate studies that included subsets of patients pretreated with mogamulizumab, the ORRs with lenalidomide and tucidinostat monotherapy were 18% (2/11) and 30% (7/23), respectively.[15,17] Our findings demonstrated clinically meaningful efficacy of valemetostat in heavily pretreated R/R ATL and support valemetostat as a treatment option for patients experiencing PD after prior therapy, including mogamulizumab.

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In contrast to follicular lymphoma or diffuse large B-cell lymphoma, EZH2 gain-of-function mutations are not observed in ATL; however, overexpression of EZH2 and PRC2 dysfunction are common in ATL.[30-32] Molecular therapeutics targeting EZH2 have been explored in the treatment of NHLs, except for ATL.[33,34] Compared with the EZH2-selective inhibitor tazemetostat, valemetostat strongly reduced H3K27 trimethylation through inhibition of EZH1 and EZH2, driving re-expression of repressed genes.[24] Valemetostat demonstrated greater attenuation of ATL cell growth *in vitro* at lower concentrations than tazemetostat and GSK126, primarily because of dual inhibition of EZH1 and EZH2.[24] We continue to evaluate the biological underpinnings of valemetostat's mechanism of action through assessments of key biomarkers and comprehensive gene mutation and expression analyses of ATL cells.

Responses to valemetostat were observed across disease compartments, subtypes (acute, lymphoma, or chronic), and statuses (relapsed, recurrent, or refractory). Notably, valemetostat yielded an ORR of 50% in nodal or extranodal lesions, which is higher than that seen in phase 2 studies of mogamulizumab (25%, 3/12) and lenalidomide (31%, 5/16).[15,16] In patients with aggressive acute type ATL, the ORR was 62.5% (10/16) in response to valemetostat compared with 43% (6/14) and 33% (5/15) with mogamulizumab and lenalidomide, respectively.[15,16] This study included 11 patients with refractory disease (SD or PD) to last prior therapy; the ORR in this population was 45.5%. However, in the phase 2 study of mogamulizumab, only patients who had achieved response to the last previous therapy were included.[15] In the phase 2 study of lenalidomide, only 2 patients with SD to prior therapy were included.[14] The shorter time since last ATL treatment (median, 60 days) in the current study compared with those in the phase 2 studies for other agents (234.5 days for lenalidomide and

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89 days for tucidinostat) reflects the inclusion of patients with refractory disease and more aggressive features. Furthermore, the higher median of 3 prior lines of therapy (range, 1-8) in this study compared with 2 for lenalidomide (range, 1-4) and 2 for tucidinostat is similarly reflective of aggressive ATL.

The safety profile was consistent with the phase 1 study of valemetostat.[25] Among the most common TEAEs were cytopenias, which included thrombocytopenia, the most common grade ≥3 severe TEAE. Many thrombocytopenia events resolved without dose reduction or interruption. All other TEAEs were manageable with supportive care and/or dose modification, indicating a manageable and acceptable safety profile for valemetostat in patients with R/R ATL.

This study had several limitations. Patients who had received prior allo-HSCT were excluded as part of the study design because of potential worsening of graft-vs-host disease (GVHD). Future studies could assess the impact of valemetostat in patients with prior allo-HSCT. Additionally, it is unknown how valemetostat therapy would affect outcomes of subsequent allo-HSCT treatment because no patient underwent allo-HSCT after study drug discontinuation. Prior treatment with mogamulizumab in patients undergoing allo-HSCT is associated with high rates of severe GVHD and mortality, mainly because of long-term depletion of CCR4-expressing regulatory T cells.[35] The effects of valemetostat on immune function in patients remains to be elucidated. Furthermore, the follow-up period of the current study is limited. Long-term follow-up is warranted to fully understand the efficacy and safety of valemetostat in patients with R/R ATL. Lastly, the number of patients included in this study was limited, although sample size was sufficient to evaluate our hypothesis and the number of patients enrolled in this study was

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comparable with that in the phase 2 studies of other agents for ATL, a relatively rare disease, even in Japan where HTLV-1 is endemic.[15-17] Because of this small number of patients, there are limitations to examining the effect of this agent in each subgroup. Future follow-up studies will be necessary to fully understand the efficacy of these agents in the treatment of ATL.

Collectively, valemetostat shows promise in treating relapsed, recurrent, or refractory ATL in patients with an extensive treatment history, including mogamulizumab. The combination of clinical efficacy, antitumor properties, and acceptable safety profile of valemetostat in our phase 2 study provides rationale for further investigation of this agent in ATL.

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Authorship

Contribution: K. Izutsu, A. Utsunomiya, K. Tsukasaki, H. Yamada, K. Tobinai, K. Yonekura, and K. Ishitsuka conceived and designed this study. K. Tobinai and K. Ishitsuka supervised the study. K. Izutsu, H. Yamada, and N. Adachi, wrote the manuscript. K. Izutsu, S. Makita, K. Nosaka, M.

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Yoshimitsu, A. Utsunomiya, S. Kusumoto, S. Morishima, K. Tsukasaki, T. Kawamata, T. Ono, S. Rai, H. Katsuya, J. Ishikawa, K. Yonekura, and K. Ishitsuka contributed to patient accrual. K. Izutsu, H. Yamada, K. Kato, M. Tachibana, and K. Ishitsuka contributed to data analysis and interpretation. Y. Kakurai provided statistical support. All authors reviewed, edited, and approved the final version of the manuscript.

Conflict-of-interest disclosure: K. Izutsu has received honoraria from Eisai, Chugai, Janssen, AstraZeneca, Novartis, Bristol-Myers Squibb, Kyowa Kirin, AbbVie, Ono Pharmaceutical, Eli Lilly, MSD, Daiichi Sankyo, Symbio, and Takeda and research funding from Eisai, Chugai, Janssen, AstraZeneca, Novartis, AbbVie, Daiichi Sankyo, Pfizer, Yakult, Genmab, Beigene, and Incyte. K. Izutsu has had an advisory or consulting role with Eisai, AbbVie, and Genmab. S. Makita has received honoraria from Celgene/Bristol-Myers Squibb, Chugai Pharma, Daiichi Sankyo/UCB Japan, Eisai, Novartis, Takeda, CSL Behring, and Meiji Seika Pharma. S. Makita has had an advisory or consulting role at Celgene/Bristol-Myers Squibb and Takeda. M. Yoshimitsu has received honoraria from Takeda, Bristol-Myers Squibb/Medarex, Novartis, CSL Behring, Chugai Pharma, Otsuka, and Daiichi Sankyo. M. Yoshimitsu has had an advisory or consulting role at Takeda. A. Utsunomiya has received honoraria from Bristol-Myers and Meiji Seika Pharma. A. Utsunomiya has had an advisory or consulting role with JIMRO and Otsuka Medical Devices. S. Kusumoto has received honoraria from Chugai Pharmaceutical Co., Ltd., Kyowa Kirin Co. Ltd., and Daiichi Sankyo/UCB Japan and research funding from Chugai Pharmaceutical Co., Ltd, Kyowa Kirin Co., Ltd., and Daiichi Sankyo/UCB Japan. S. Morishima has received honoraria from Pfizer, Janssen, AbbVie, Nippon Shinyaku, Bayer, Chugai Pharma, Sanofi, Kyowa Kirin, Takeda, and Daiichi Sankyo. K. Tsukasaki has received honoraria from Chugai Pharmaceutical Co

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Footnotes

De-identified individual participant data (IPD) and applicable supporting clinical trial documents may be available upon request at https://vivli.org/. In cases where clinical trial data and supporting documents are provided pursuant to Daiichi Sankyo's company policies and procedures, Daiichi Sankyo will continue to protect the privacy of our clinical trial participants. Details on data sharing criteria and the procedure for requesting access can be found at this web address: https://vivli.org/ourmember/daiichi-sankyo/

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Figure Legends

Figure 1. **Best percent change in tumor burden by disease compartment as assessed by IEAC**. Best percent change in tumor burden for nodal or extranodal lesions (A), skin lesions (B), and peripheral blood (C) in patients treated with valemetostat. Dashed line indicates a 50% reduction in tumor burden from baseline.

Figure 2. **Treatment duration with clinical outcomes and duration of response.** The swimmer plot (A) summarizes treatment duration of individual patients and best response. Patients ongoing in the study are denoted by arrows. The Kaplan-Meier plot depicts the duration of response (B). Tick marks denote censored patients.

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505 **Table 1. Baseline patient and disease characteristics.**

Patient Characteristics	Patients (N=25)
Age, median (range), years	69.0 (59-84)
Female	13 (52.0)
ECOG performance status	
0	13 (52.0)
1	10 (40.0)
2*	2 (8.0)
Median time since last ATL treatment, days (range)	60.0 (23-1,400)
Median prior lines of therapy	3 (1-8)
Prior mogamulizumab therapy	
Yes	24 (96.0)
No	1 (4.0)
Refractory to mogamulizumab-containing therapy	6 (24.0)
Prior lenalidomide therapy	
Yes	8 (32.0)
No	17 (68.0)
Prior anthracycline-based therapy	
Yes	24 (96.0)
No	1 (4.0)
Prior HSCT	
No	25 (100.0)
ATL subtype	
Acute	16 (64.0)
Lymphoma	6 (24.0)
Unfavorable chronic	3 (12.0)

506

507 ATL, adult T-cell leukemia/lymphoma; ECOG, Eastern Cooperative Oncology Group; HSCT,
508 hematopoietic stem cell transplantation.
509 *One patient had an ECOG performance status of 2 at initial screening but advanced to a status
510 of 3 on day 1 cycle 1.

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Table 2. **Summary of patient best responses as assessed by an independent efficacy assessment committee.**

Population	N	ORR, n (%)	CR, n (%)	CRu, n (%)	PR, n (%)	SD, n (%)	RD/PD, n (%)
All patients	25	12 (48.0)	5 (20.0)	0	7 (28.0)	10 (40.0)	3 (12.0)
ATL subtype							
Acute	16	10 (62.5)	5 (31.3)	0	5 (31.3)	4 (25.0)	2 (12.5)
Lymphoma	6	1 (16.7)	0	0	1 (16.7)	5 (83.3)	0
Unfavorable chronic	3	1 (33.3)	0	0	1 (33.3)	1 (33.3)	1 (33.3)
Disease site							
Nodal or extranodal lesions	20	10 (50.0)	6 (30.0)	2 (10.0)	2 (10.0)	7 (35.0)	3 (15.0)
Skin lesions	7	3 (42.9)	1 (14.3)	NE	2 (28.6)	3 (42.9)	12 (48.0)
Peripheral blood	9	8 (88.9)	2 (22.2)	NE	6 (66.7)	1 (11.1)	0
Disease status							
Relapsed	8	3 (37.5)	1 (12.5)	0	2 (25.0)	4 (50.0)	1 (12.5)
Recurrent	6	4 (66.7)	1 (16.7)	0	3 (50.0)	2 (33.3)	0
Refractory	11	5 (45.5)	3 (27.3)	0	2 (18.2)	4 (36.4)	2 (18.2)
Prior mogamulizumab treatment							
Yes	24	11 (45.8)	4 (16.7)	0	7 (29.2)	10 (41.7)	3 (12.5)
No	1	1 (100.0)	1 (100.0)	0	0	0	0
Prior lenalidomide treatment							
Yes	8	4 (50.0)	0	0	4 (50.0)	3 (37.5)	1 (12.5)
No	17	8 (47.1)	5 (29.4)	0	3 (17.6)	7 (41.2)	2 (11.8)

Relapsed disease: received ≥1 prior chemotherapy, achieved CR or CRu, and subsequently experienced disease progression. Recurrent disease: received ≥1 prior chemotherapy, achieved PR, and subsequently experienced disease progression. Refractory: received ≥1 prior chemotherapy, achieved SD, required a treatment switch, or received ≥1 prior chemotherapy and subsequently experienced disease progression.

ATL, adult T-cell leukemia/lymphoma; CR, complete remission; CRu, unconfirmed complete remission; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial remission; RD, relapsed disease; SD, stable disease.

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Table 3. Summary of treatment-emergent adverse events occurring in ≥20% of patients and grade ≥3 events regardless of relation to valemetostat treatment.

All Adverse Events		
AE type, n (%)	**(N=25)**	
TEAEs	25 (100.0)	
TRAEs	24 (96.0)	
Serious TEAE*	8 (32.0)	
Serious TRAEs	7 (28.0)	
Grade ≥3 TEAEs	15 (60.0)	
Grade ≥3 TRAEs	14 (56.0)	
TEAEs leading to reduction	2 (8.0)	
TRAEs leading to reduction	2 (8.0)	
TEAEs leading to interruption	5 (20.0)	
TRAEs leading to interruption	4 (16.0)	
TEAEs leading to discontinuation	2 (8.0)	
TRAEs leading to discontinuation	2 (8.0)	
Most Common TEAEs		
Hematologic, n (%)	**All Grades (≥20%)**	**Grade ≥3**
Thrombocytopenia†	20 (80.0)	8 (32.0)
Anemia‡	13 (52.0)	8 (32.0)
Neutropenia§	7 (28.0)	3 (12.0)
Lymphopenia‖	6 (24.0)	4 (16.0)
Leukopenia¶	5 (20.0)	3 (12.0)
Nonhematologic, n (%)	**All Grades (≥20%)**	**Grade ≥3**
Alopecia	10 (40.0)	0 (0)
Dysgeusia	9 (36.0)	0 (0)
Decreased appetite	5 (20.0)	2 (8.0)
Pyrexia	5 (20.0)	0 (0)

AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

*Acute kidney injury, cardiac failure, cytomegalovirus chorioretinitis, cytomegalovirus infection reactivation, febrile neutropenia, hepatic function abnormal, hypercalcemia, lower gastrointestinal hemorrhage, overdose, thrombocytopenia, pneumonia, and venous thrombosis limb occurred in 1 patient each.

†Encompasses the preferred terms thrombocytopenia and platelet count decreased.

‡Encompasses the preferred terms anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased.

§Encompasses the preferred terms neutropenia and neutrophil count decreased.

‖Encompasses the preferred terms lymphopenia and lymphocyte count decreased.

¶Encompasses the preferred terms leukopenia and white blood cell count decreased.

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Figure 1

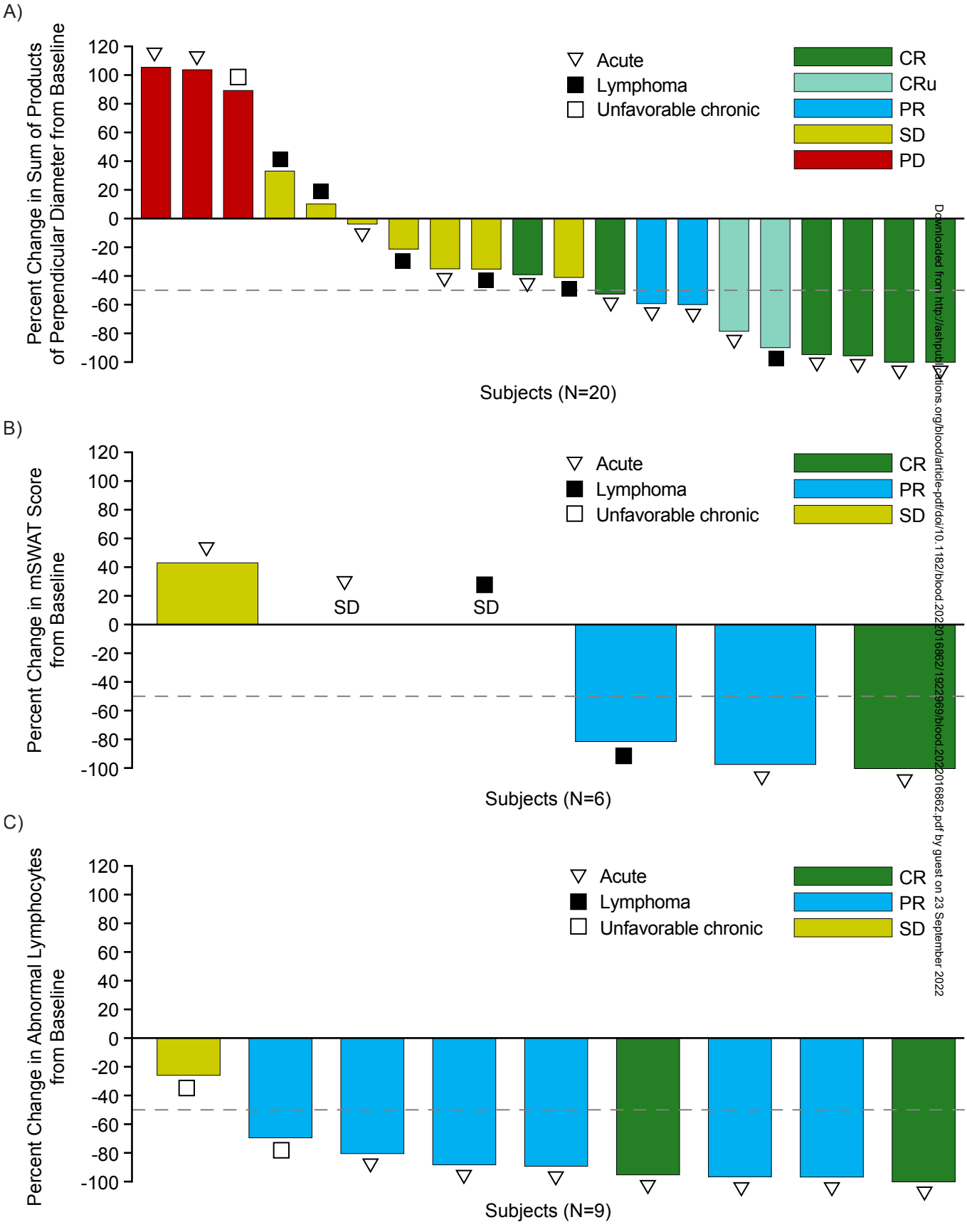

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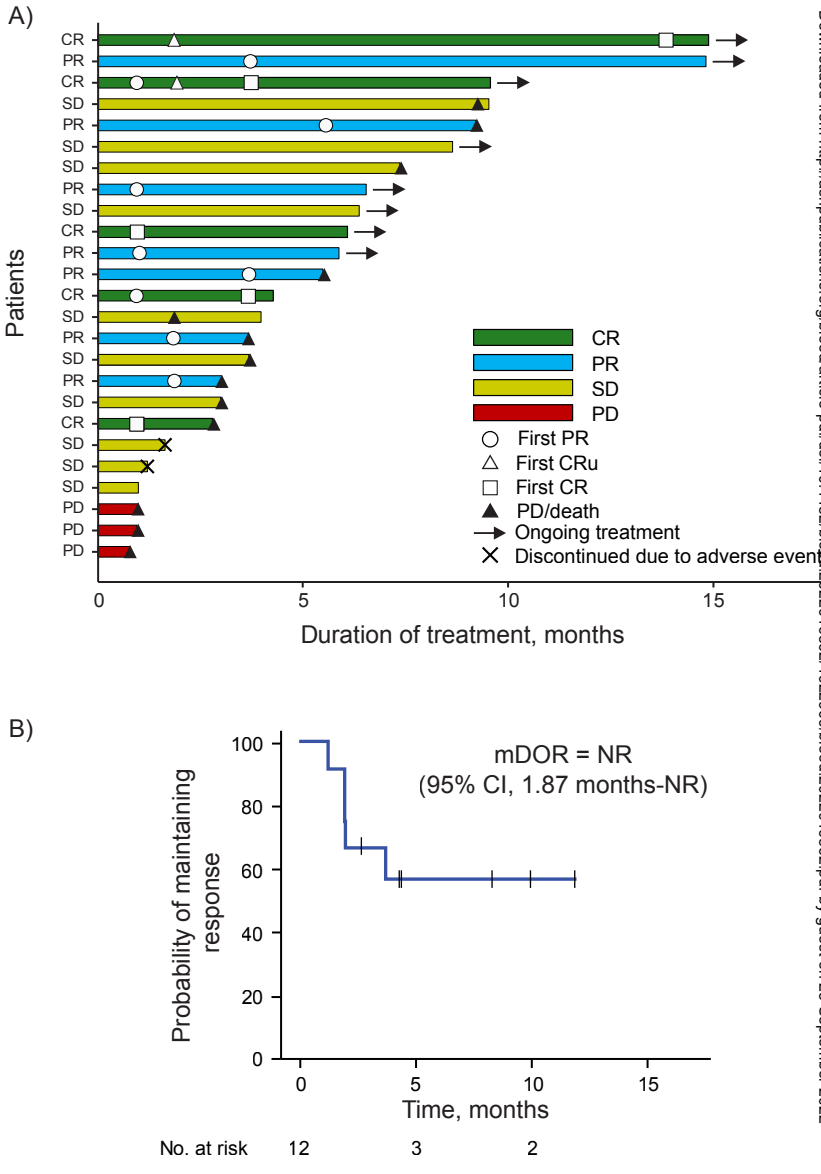
Figure 2



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