

Oral histone deacetylase inhibitor tucidinostat (HBI-8000) in patients with relapsed or refractory adult T-cell leukemia/lymphoma: Phase IIb results

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Abbreviations: AE, adverse event; allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATLL, adult T-cell leukemia/lymphoma; CI, confidence interval; CR, complete response; DOR, duration of response; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; IOERC, Independent Overall Efficacy Review Committee; NHL, non-Hodgkin's lymphoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PTCL, peripheral T-cell lymphoma; R/R, relapsed or refractory; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event.

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Abstract

This multicenter, prospective phase IIb trial evaluating the efficacy and safety of tucidinostat (HBI-8000) in patients with relapsed or refractory (R/R) adult T-cell leukemia/lymphoma (ATLL) was undertaken in Japan. Eligible patients had R/R ATLL and had failed standard of care treatment with chemotherapy and with mogamulizumab. Twenty-three patients received tucidinostat 40 mg orally twice per week and were included in efficacy and safety analyses. The primary end-point was objective response rate (ORR) assessed by an independent committee. The ORR was 30.4% (95% confidence interval [CI], 13.2, 52.9). Median progression-free survival was 1.7 months (95% CI, 0.8, 7.4), median duration of response was 9.2 months (95% CI, 2.6, not reached), and median overall survival was 7.9 months (95% CI, 2.3, 18.0). All patients experienced adverse events (AEs), which were predominantly hematologic and gastrointestinal. Incidence of grade 3 or higher AEs was 78.3%; most were laboratory abnormalities (decreases in platelets, neutrophils, white blood cells, and hemoglobin). Tucidinostat was well tolerated with AEs that could be mostly managed with supportive care and dose modifications. Tucidinostat is a meaningful treatment option for R/R ATLL patients; further investigation is warranted.

KEYWORDS

ATLL, HBI-8000, HDAC inhibitor, ORR, tucidinostat

1 | INTRODUCTION

Adult T-cell leukemia/lymphoma caused by latent infection of HTLV-1 is a mature T-cell malignancy that is highly aggressive and difficult to treat.¹ Worldwide, approximately 15–20 million people are estimated to be infected with HTLV-1.² Infection with HTLV-1 is endemic in several regions, including southwestern Japan, sub-Saharan Africa, the Caribbean, South America, parts of the Middle East and Australo-Melanesia,³ and also in some areas of Europe.⁴ Japan has one million HTLV-1 carriers.⁵

Worldwide, at least 3000 new cases of ATLL are diagnosed each year.⁶ A rising incidence of ATLL has been reported in nonendemic regions such as the United States,⁷ especially in urban communities with Caribbean and Latin American populations.⁸ The median age of ATLL patients in the United States is 54 years,⁹ whereas in Japan it is around 68 years.¹⁰

Adult T-cell leukemia/lymphoma generally has a poor prognosis, with shorter OS than other common subtypes of PTCL.¹¹ Aggressive types of ATLL are associated with a particularly poor prognosis (median OS approximately 8–10 months); the median OS of indolent types is approximately 5 years.¹² In Japan, approximately 1000 people die from ATLL each year.¹³

In Japan, the Practical Guidelines for Hematological Malignancies 2018 recommended multidrug combination chemotherapy for aggressive ATLL (acute type, lymphoma type, and unfavorable chronic type) that progresses rapidly.¹⁴ For aggressive ATLL, chemotherapy with the multiagent protocol modified

VCAP-AMP-VECP regimen (mLSG15) has been recommended as first-line treatment in Japan based on the results of a phase III trial, however, the prognosis after treatment is still poor.¹⁴ In the phase III study JCOG9801, the PFS rate at 1 year with mLSG15 was 28% and survival at 3 years was 24%, with median survival of 13 months.¹⁵ Mogamulizumab, a defucosylated anti-CC chemokine receptor 4 Ab, is approved as first-line therapy in combination with chemotherapy for untreated aggressive ATLL.¹⁶ For R/R ATLL, mogamulizumab monotherapy and lenalidomide monotherapy have been approved in Japan.^{16,17}

As the response to intensive chemotherapy is not generally durable, and cumulative toxicities discourage the use of long-term intensive chemotherapy, early allo-HSCT is recommended after response to first-line therapy.¹⁸ Allogeneic HSCT has the potential to cure some patients with aggressive ATLL, but carries the risk of transplant-related mortality,¹⁹ and the clinical outcome of allo-HSCT after PD is poor.²⁰ Patient age is a key factor in determining the eligibility of allo-HSCT and the type of conditioning regimen,²¹ and allo-HSCT is less likely to be an option for elderly patients. As the age of ATLL patients in Japan at diagnosis has been increasing,¹⁰ treatment options for elderly patients are needed.

Especially challenging is the management of patients with R/R aggressive ATLL.¹ The prognosis for these patients is dismal, although the use of lenalidomide or mogamulizumab has produced some encouraging results.²² Options for treatment of R/R ATLL are very limited and might include a clinical trial, best supportive care, or an alternative therapy not previously used.^{23,24} The low survival

rates in patients with ATLL and the lack of curative therapy present an unmet medical need for which we should explore new targeted therapies.²²

T-cell lymphomas have been responsive to HDACi,²⁵ and several HDACi have achieved marketing approval, including tucidinostat (HBI-8000; chidamide in China). Tucidinostat is a benzamide HDACi of HDAC isoenzymes 1, 2, 3, and 10 selectively. There are three distinct mechanisms of action associated with tucidinostat: direct tumor suppression, immunomodulation, and epigenetic modification of cellular functions.^{26,27} Histone deacetylase inhibitors cause apoptosis of ATLL cells,²⁸ precancerous lymphocytes infected with HTLV-1, or HTLV-1 transfected cell lines. Therefore, tucidinostat presents a novel mechanism of action that does not overlap with approved drugs to treat R/R ATLL.

The antitumor effect of tucidinostat in ATLL was investigated using cell lines derived from Japanese patients with ATLL and primary tumor cells obtained directly from patients with ATLL. In most cases tucidinostat induced apoptosis in both cell lines and primary ATLL cells.²⁹ Tucidinostat stimulates accumulation of acetylated histones H3 and H4 in tumor cells, which can increase the gene expression of various tumor suppressors, such as p53 and p21. Tucidinostat inhibits proliferation and cell viability in both ATLL-derived cell lines and primary ATLL cells freshly obtained from ATLL patients.²⁹ These preclinical observations support the hypothesis that tucidinostat will be efficacious in ATLL.

Clinical studies of tucidinostat have been undertaken mainly in patients with T-cell lymphomas.^{30,31} A phase I study in Japanese patients with R/R NHL, including ATLL patients, showed a manageable safety profile, and 40 mg twice per week was selected for subsequent clinical development. An encouraging efficacy signal was observed in patients with ATLL (three of four patients with ATLL achieved PR), along with an acceptable tolerability/safety profile.³¹

The aim of the current phase IIb study was to evaluate the efficacy and safety of tucidinostat in patients with R/R ATLL. This is the first study for patients with R/R aggressive ATLL with a treatment history of mogamulizumab. The recommended dose of tucidinostat was selected based on the previous Japanese phase I study in R/R NHL, which is slightly higher than the chidamide (HBI-8000) approved dose for PTCL in China. The data described herein led to the approval of tucidinostat in 2021 by Japan's Ministry of Health, Labour and Welfare for R/R aggressive ATLL.

This paper reports the results of the final analysis when all patients had completed follow-up assessments.

2 | MATERIALS AND METHODS

2.1 | Patients

The study cohort included Japanese adult patients with R/R aggressive ATLL (acute, lymphoma or unfavorable chronic types, histologically or cytologically diagnosed) after receiving prior therapy

with mogamulizumab, or at least one systemic therapy with cytotoxic chemotherapy if intolerance/contraindication for mogamulizumab was observed, and for whom no other standard treatment could be considered appropriate. Patients had to have at least one evaluable ATLL lesion, ECOG performance status³² of 0–2, estimated life expectancy of more than 3 months, no previous organ transplantation, no previous allo-HSCT, no autologous HSCT within 12 weeks of starting the study drug, and no active infection or heart abnormalities/arrhythmias.

2.2 | Study design

This was a phase IIb, open-label, single-arm, nonrandomized study to evaluate the efficacy and safety of tucidinostat in patients with R/R ATLL (registered at [ClinicalTrials.gov](https://clinicaltrials.gov) as NCT02955589). It was performed in accordance with International Council for Harmonization Good Clinical Practice Guideline³³ and the Declaration of Helsinki,³⁴ and was approved by the institutional review board/independent ethics committee at each study site.

After informed consent, eligible patients were to ingest 40mg tucidinostat approximately 30min after a meal twice per week. A treatment cycle was defined as 28 consecutive days. Tucidinostat treatment was to be continued until PD or the occurrence of unacceptable toxicities despite appropriate dose reduction, treatment interruption, and/or supportive care.

The primary efficacy end-point of the study was ORR, which was analyzed in the per-protocol set. Secondary end-points included PFS, DOR, and ORR in each ATLL subtype.

2.3 | Assessments

Response to treatment and progression of ATLL was evaluated according to modified criteria of the International Consensus Meeting.²³ Best responses were determined from the efficacy assessments conducted at end of the 4th week, the 8th week after first study dose, and then every 8 weeks from the 8th week through the study period. An IOERC of hematologic oncologists reviewed all data related to disease status, including evaluation of imaging studies by Independent Radiology Review, a modification of the Severity-Weighted Assessment Tool score for skin lesions,³⁵ peripheral blood findings (abnormal lymphocytes), and applicable clinical observations.

Safety and tolerability were evaluated by the occurrence of AEs, clinical laboratory tests, vital signs, physical examination, and electrocardiograms. Treatment-emergent AEs were graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03,³⁶ and a Data Safety Monitoring Board reviewed data on safety signals. Survival status was followed until death or end of study, 12 months after the last dose of study drug of the last patient.

2.4 | Statistical analyses

The target sample size was 22 patients to have at least 18 evaluable patients for efficacy analysis. The target ORR for this study was 30%. To show a response rate of more than 5% in 18 subjects, the power was 80% at a 5% significance level and a two-sided alpha.

First and final analyses were planned. The first analysis was for the purpose of regulatory submission and planned to be carried out when all patients completed end of treatment assessment. The final analysis was planned to be carried out when all patients completed follow-up assessments.

3 | RESULTS

The study was conducted from November 2016 to November 2019.

3.1 | Patients

A total of 23 eligible Japanese patients from 18 study sites were treated with at least one dose of tucidinostat and included in analyses.

All patients had advanced ATLL with rapidly progressing disease. All but one patient had ECOG performance status 0–1. The median time from initial diagnosis was 1.5 years. The median time from the last treatment before the first dose of the study drug was 89 days (range, 30–496 days; mean, 131 days). All patients had previously received chemotherapy and mogamulizumab in combination or sequentially. In fact, 73.9% (17/23) already had at least two lines of treatment. Furthermore, 13.0% (3/23) had five or more regimens. Overall, 21.7% (5/23) of patients had disease progression during their last treatment and were thus classified as refractory (Table 1). The median number of tucidinostat treatment cycles was 1.3 (range, 0.3–13.9 cycles).

3.2 | Efficacy

The primary end-point of ORR was determined to be 30.4% (7/23), confirmed independently by the IOERC. Of the seven patients with a response, one had CR and six reached PR. Results were similar when based on the investigator response assessment (34.8%). Disease control (CR, PR, or SD) was reported in 12 of the 23 patients (52.2%) (Table 2).

When analyzed by ATLL subtype, ORR in acute ATLL was 46.2%, in lymphoma ATLL ORR was 12.5%, and there was no response in the two patients with unfavorable chronic ATLL (Table 2).

A tumor response (CR or PR) was observed in nodal and extranodal target lesions in 30.0% (6/20), in skin lesions in 62.5% (5/8), and in peripheral blood (abnormal lymphocytes) in 60.0% (3/5) (Table 3).

Subgroup analysis showed a tendency for higher ORR in patients with acute type disease, of female gender, younger than 75 years,

TABLE 1 Demographic data and disease history of 23 Japanese patients with relapsed or refractory adult T-cell leukemia/lymphoma (ATLL)

Characteristic (unit)	Statistic	(N = 23)
Age (years)	Median (range)	72.0 (60–89)
Sex		
Male	n (%)	15 (65.2)
Female	n (%)	8 (34.8)
ECOG performance status		
0	n (%)	12 (52.2)
1	n (%)	10 (43.5)
2	n (%)	1 (4.3)
ATLL disease subtype		
Acute	n (%)	13 (56.5)
Lymphoma	n (%)	8 (34.8)
Unfavorable chronic	n (%)	2 (8.7)
Duration since initial diagnosis (years)	Median (range)	1.50 (0.31–21.95)
ATLL subset based on response to last previous treatment ^a		
Relapsed	n (%)	5 (21.7)
Recurrent	n (%)	13 (56.5)
Refractory	n (%)	5 (21.7)
Number of patients with mogamulizumab therapy	n	23
Chemotherapy plus mogamulizumab therapy	n (%)	11 (47.8)
Mogamulizumab monotherapy	n (%)	12 (52.2)
Number of days from last previous treatment	Median (range)	89.0 (30–496)
Number of previous chemotherapy regimens including target therapy	Median (range)	2.0 (1–5)
5 or more	n (%)	3 (13.0)
2 or more	n (%)	17 (73.9)

Abbreviations: n, number of patients; N, number of patients in analysis set.

^aRelapsed, response to last previous treatment was complete response and unconfirmed complete response; Recurrent, response to last previous treatment was partial response and stable disease; Refractory: response to last previous treatment was progressive disease.

who had undergone fewer than three prior regimens, and prior mogamulizumab combination therapy (Figure 1).

The ORR was higher in patients who were classified with relapsed ATLL (80.0%; 4/5) compared with recurrent ATLL (23.1%; 3/13); patients with refractory ATLL had no response.

Secondary end-points were confirmed by the IOERC. Median PFS was 1.7 months (95% CI, 0.8, 7.4) (Figure 2).

Median DOR was 9.2 months (95% CI, 2.6, not reached); four patients had PD and three were censored (Figure 3).

	Best overall response	n (%)
Objective response	(CR or PR)	7 (30.4%) (95% CI, 13.2, 52.9)
Best response	CR	1 (4.3)
	PR	6 (26.1)
	SD	5 (21.7)
	PD	11 (47.8)
Acute ATLL		13
	ORR (CR or PR)	6 (46.2)
	CR	1 (7.7)
	PR	5 (38.5)
	SD	2 (15.4)
Lymphoma ATLL		8
	ORR (CR or PR)	1 (12.5)
	PR	1 (12.5)
	SD	2 (25.0)
	PD	5 (62.5)
Unfavorable chronic ATLL		2
	ORR (CR or PR)	0 (0.0)
	SD	1 (50.0)
	PD	1 (50.0)
Relapsed ATLL		5
	ORR (CR or PR)	4 (80.0)
	CR	1 (20.0)
	PR	3 (60.0)
	SD	1 (20.0)
Recurrent ATLL		13
	ORR (CR or PR)	3 (23.1)
	PR	3 (23.1)
	SD	2 (15.4)
	PD	8 (61.5)
Refractory ATLL		5
	ORR (CR or PR)	0 (0.0)
	SD	2 (40.0)
	PD	3 (60.0)

Abbreviations: CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

ORR (%) (n/N, 95% CI)	Response of target lesions % (n/N, 95% CI)		
	Nodal/extranodal	Skin	Peripheral blood
30.4 (7/23; 3.2, 52.9)	30.0 (6/20; 11.9, 54.3)	62.5 (5/8; 24.5, 91.5)	60.0 (3/5; 14.7, 94.7)

Abbreviations: CI, confidence interval; ORR, overall response rate.

TABLE 2 Tumor response overall and by adult T-cell leukemia/lymphoma (ATLL) subtype and ATLL disease status in Japanese patients treated with tucidinostat (N = 23)

TABLE 3 Response to tucidinostat treatment by target lesion type in Japanese patients with adult T-cell leukemia/lymphoma (N = 23)

Exploratory end-points included median time to treatment response of 3.1 months. Median OS was 7.9 months (95% CI, 2.3, 18.0); 16 (69.6%) patients died and seven (30.4%) were censored at the last

date confirmed alive (Figure 4). Nineteen of 23 patients had other anti-ATLL treatments such as lenalidomide and mogamulizumab after the completion of this study treatment.

FIGURE 1 Forest plot of objective response rates (ORR) by subgroups among 23 Japanese patients with relapsed or refractory adult T-cell leukemia/lymphoma (ATLL) treated with tucidinostat

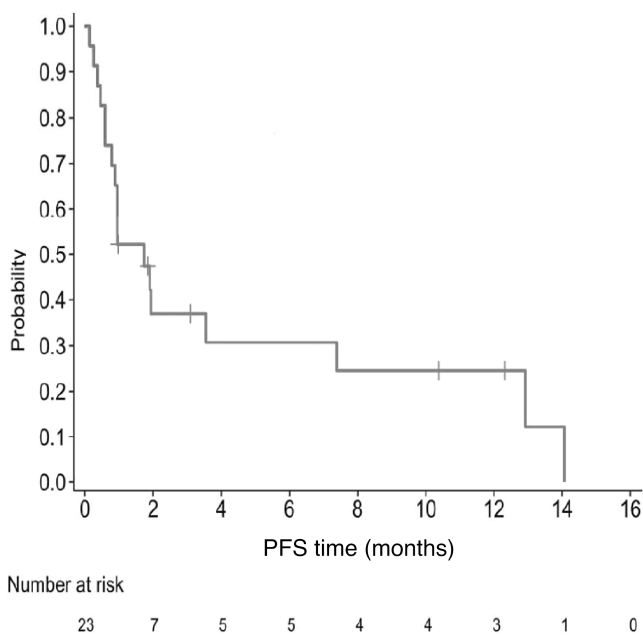
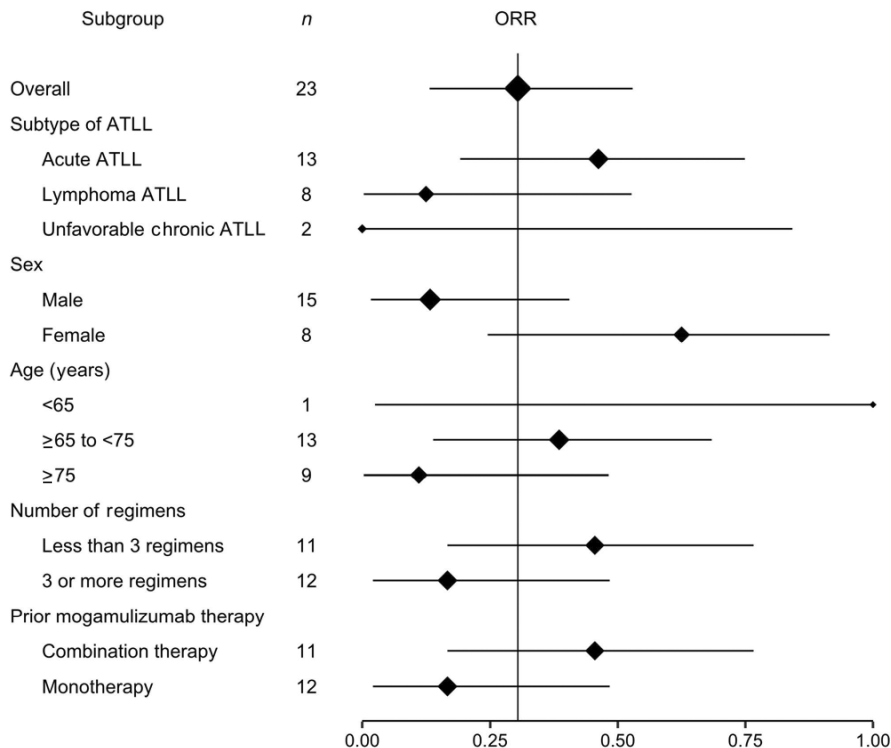


FIGURE 2 Progression-free survival (PFS) among 23 Japanese patients with relapsed or refractory adult T-cell leukemia/lymphoma treated with tucidinostat. Kaplan–Meier plot of PFS probability over time (months), with numbers of patients at risk

3.3 | Safety

All 23 patients had TEAEs that were considered related to study drug; most frequently hematologic (mainly platelet count decreased, neutrophil count decreased, white blood cell count decreased, and

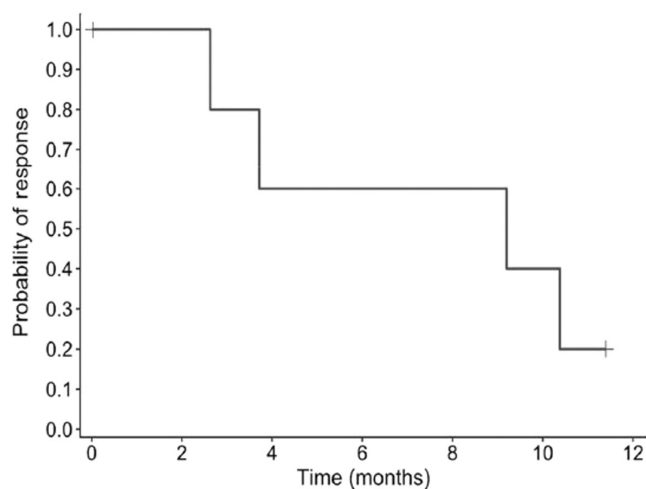


FIGURE 3 Duration of response among 23 Japanese patients with relapsed or refractory adult T-cell leukemia/lymphoma treated with tucidinostat. Kaplan–Meier plot of duration of response probability over time (months)

anemia) and gastrointestinal (mainly decreased appetite, malaise, and diarrhea). The incidence of grade 3 or higher TEAEs was 78.3%; most were laboratory abnormalities, the majority of which were decreases in platelets, neutrophils, and white blood cells, and anemia (Table 4). Changes in hematologic parameters of platelet count, white blood cell count, neutrophils, and hemoglobin were, in most cases, improved by study drug interruption or reduction and patients resumed dosing.

Seven patients (30.4%) experienced SAEs (urinary tract infection, *Pneumocystis jirovecii* pneumonia, palpitations, platelet count

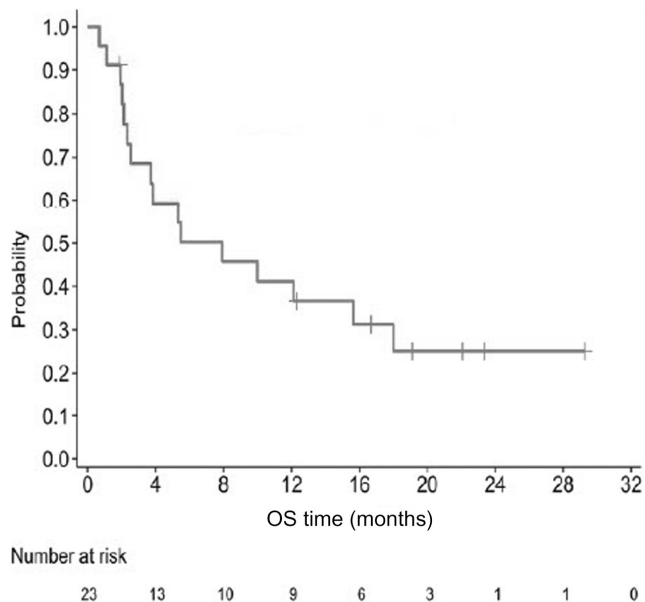


FIGURE 4 Overall survival (OS) among 23 Japanese patients with relapsed or refractory adult T-cell leukemia/lymphoma treated with tucidinostat. Kaplan–Meier plot of OS probability over time (months), with numbers of patients at risk

decreased [in two patients], acute respiratory failure, interstitial lung disease, neutrophil count decreased); all but acute respiratory failure were considered to be related to study drug. All SAEs resolved except for the case of grade 1 palpitations. Nine patients (39.1%) discontinued the study drug due to a TEAE. Four patients discontinued because grade 3 or 4 platelet count decreased or thrombocytopenia did not recover to grade 1 within 2 weeks as required in the study protocol. One patient discontinued because grade 3 or higher neutrophil count decrease recurred at 20 mg, the lowest dose defined in the study protocol. The remaining four patients discontinued due to grade 3 or higher nonhematological AEs (interstitial lung disease, *P. jirovecii* pneumonia, fatigue, γ -glutamyltransferase/alkaline phosphatase increased). The most frequent TEAEs leading to dose reduction/interruption and/or drug discontinuation were neutrophil count decreased and platelet count decreased. No patient died as a result of an AE.

4 | DISCUSSION

This is the first prospective study for the treatment of patients with R/R aggressive ATLL who had previously been treated with chemotherapy and mogamulizumab and patients with refractory ATLL. Tucidinostat 40 mg twice per week, given orally, showed an ORR of 30.4% by the IOERC and 34.8% by investigator assessment. As a post hoc analysis, the ORR in patients with relapsed or recurrent ATLL was 38.9% (7/18). This result is comparable to phase II studies of the currently available treatments in Japan. Mogamulizumab was reported to produce an ORR of 50% in patients with relapsed ATLL,³⁷ and an ORR of mogamulizumab in a study of mogamulizumab

versus investigator's choice of chemotherapy in patients who were refractory or relapsed after at least one prior systemic therapy was 34% by investigator assessment and 28% by independent review.³⁸ Lenalidomide was reported to produce an ORR of 42% in patients with relapsed or recurrent ATLL.¹⁷ In our study, 78.3% of patients had two or more prior treatment regimens, and 17.4% had five or more; five (22%) of the enrolled patients were refractory to their previous chemotherapy. In addition, the median time since last ATLL treatment was 89.0 days in our study, but 234.5 days in the lenalidomide study,¹⁷ suggesting that patients with more aggressive ATLL were enrolled in our study.

Tucidinostat showed an acceptable safety profile. The most common AEs were hematological, such as thrombocytopenia, neutropenia, leukopenia, and anemia, and these laboratory abnormalities also constituted the grade 3 or higher TEAEs. Some patients discontinued the study drug due to hematological AEs according to the treatment discontinuation guidelines. As patients were treated with multiple cancer treatments before entering this study, previous treatments might have increased the hematological toxicities necessitating discontinuation of the study drug. The most of hematological AEs are manageable with dosing interruption or reduction in a timely manner in conjunction with preemptive supportive care.

The hematological toxicities of HDACi are well known, and AEs reported in the present study were similar to those in other HDACi studies. A phase II study of romidepsin in patients with PTCL showed the most common grade 3 or higher TEAEs to be lymphopenia (74%), neutropenia (54%), leukopenia (46%), and thrombocytopenia (38%).³⁹ A phase II study of vorinostat in patients with NHL or mantle cell lymphoma showed that 80% of patients experienced grade 3/4 AEs, most frequently thrombocytopenia and neutropenia, all of whom recovered after dose reduction, interruption, or discontinuation and adequate supportive measures.⁴⁰ A previous study of tucidinostat in China showed that most AEs of grade 3 or higher were thrombocytopenia (22%), leukopenia (13%), and neutropenia (11%).³⁰ The typical AEs of HDACi such as thrombocytopenia, neutropenia, and anemia have been reported as transient and reversible,⁴¹ which were also observed in our study.

Few other chemotherapeutic drugs offer durable disease control in ATLL patients; therefore, new treatment options are needed. Mogamulizumab was approved based on a phase II study in patients who had relapsed after their last anti-ATLL therapy,³⁷ therefore efficacy of mogamulizumab in refractory ATLL was not examined in the phase II study. Mogamulizumab in combination with intensive chemotherapy mLSG15 improves CR but was found to be potentially associated with a less favorable safety profile, particularly for infectious and skin-related events.¹⁶ A postmarketing survey of mogamulizumab⁴² showed a shorter median survival (5.5 months) than in the prospective clinical study reported by Ishida et al.³⁷ as well as safety management challenges with regard to infusion reactions and skin disorders.⁴² Lenalidomide was approved based on the results of a phase II study in patients with "relapsed or recurrent" ATLL whether or not they had previously received mogamulizumab, and showed two responders among 11

TABLE 4 Treatment-emergent adverse events (TEAEs) related to tucidinostat in more than 10% of study patients with adult T-cell leukemia/lymphoma, and any TEAEs grade 3 or higher ($N = 23$)

Preferred term	Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Number of patients with at least one TEAE	23 (100.0)	9 (39.1)	9 (39.1)
Platelet count decreased	15 (65.2)	4 (17.4)	5 (21.7)
Neutrophil count decreased	11 (47.8)	7 (30.4)	2 (8.7)
White blood cell count decreased	9 (39.1)	7 (30.4)	0 (0.0)
Anemia	8 (34.8)	4 (17.4)	0 (0.0)
Decreased appetite	8 (34.8)	0 (0.0)	0 (0.0)
Malaise	7 (30.4)	0 (0.0)	0 (0.0)
Diarrhea	5 (21.7)	0 (0.0)	0 (0.0)
Weight decreased	4 (17.4)	1 (4.3)	0 (0.0)
Dysgeusia	4 (17.4)	0	0 (0.0)
Thrombocytopenia	3 (13.0)	2 (8.7)	1 (4.3)
Nausea	3 (13.0)	0 (0.0)	0 (0.0)
Hypoalbuminemia	3 (13.0)	0 (0.0)	0 (0.0)
Fatigue	2 (8.7)	2 (8.7)	0 (0.0)
Lymphocyte count decreased	2 (8.7)	1 (4.3)	0 (0.0)
Gamma-glutamyltransferase increased	2 (8.7)	1 (4.3)	0 (0.0)
Hyponatremia	2 (8.7)	0 (0.0)	1 (4.3)
Neutropenia	1 (4.3)	0 (0.0)	1 (4.3)
Febrile neutropenia	1 (4.3)	1 (4.3)	0 (0.0)
Hemoglobin decreased	1 (4.3)	1 (4.3)	0 (0.0)
Device-related infection	1 (4.3)	1 (4.3)	0 (0.0)
<i>Pneumocystis jirovecii</i> pneumonia	1 (4.3)	1 (4.3)	0 (0.0)
Urinary tract infection	1 (4.3)	1 (4.3)	0 (0.0)
Blood alkaline phosphatase increased	1 (4.3)	1 (4.3)	0 (0.0)
Lipase increased	1 (4.3)	0 (0.0)	1 (4.3)
Hypophosphatemia	1 (4.3)	1 (4.3)	0 (0.0)
Interstitial lung disease	1 (4.3)	0 (0.0)	1 (4.3)
Hypertension	1 (4.3)	1 (4.3)	0 (0.0)

patients pretreated with mogamulizumab. Patients who did not respond to their last previous treatment were not included, thus the efficacy of lenalidomide in patients with refractory ATLL was not evaluated. In that study, the median PFS was 3.8 months.¹⁷ In the present tucidinostat study, five refractory ATLL patients received tucidinostat, and two patients were observed with SD, but there was no responder. The median PFS observed in this study appeared to be shorter than in mogamulizumab and lenalidomide studies in which refractory patients were excluded. It is likely that the extent of advanced disease of the study cohort and the limitation of sample sizes attributed to the difference in observed efficacy.

In conclusion, tucidinostat monotherapy showed clinically meaningful antitumor activity for patients with R/R aggressive ATLL, with an acceptable and manageable safety profile. Tucidinostat targets different pathways than current treatments, thus it could further expand the number of available treatment options and improve outcomes for patients with R/R aggressive ATLL.

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DISCLOSURE

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