Oral HDAC inhibitor tucidinostat in patients with relapsed or refractory peripheral T-cell lymphoma: phase IIb results

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Abstract

Tucidinostat (formerly known as chidamide) is an orally available, novel benzamide class of histone deacetylase (HDAC) inhibitor that selectively blocks class I and class IIb HDAC. This multicenter phase IIb study aimed to investigate the efficacy and safety of tucidinostat, 40 mg twice per week (BIW), in patients with relapsed/refractory (R/R) peripheral T-cell lymphoma (PTCL). The primary endpoint was overall response rate (ORR) assessed by an independent overall efficacy review committee. Between March 2017 and March 2019, 55 patients were treated, and 46 and 55 were evaluated for efficacy and safety, respectively. Twenty-one of 46 patients achieved objective responses with an ORR of 46% (95% confidence interval : 30.9-61.0), including five patients with complete response (CR). Responses were observed across various PTCL subtypes. In angioimmunoblastic T-cell lymphoma, there were two CR and five partial responses (PR) among eight patients, achieving an ORR of 88%. The disease control rate (CR + PR + stable disease) was 72% (33/46). The median progression-free survival, duration of response, and overall survival were 5.6 months, 11.5 months, 22.8 months, respectively. The most common adverse events (AE) (all grades) were thrombocytopenia, neutropenia, leukopenia, anemia, and diarrhea. The grade ≥3 AE emerging in ≥20% of patients included thrombocytopenia (51%), neutropenia (36%), lymphopenia (22%), and leukopenia (20%). Importantly, most of the AE were manageable by supportive care and dose modification. In conclusion, the favorable efficacy and safety profiles indicate that tucidinostat could be a new therapeutic option in patients with R/R PTCL (*clinicaltrials gov. Identifier: NCT02953652*).

Introduction

Peripheral T-cell lymphoma (PTCL) is a rare and heterogeneous disease entity that encompasses nearly 30 distinct subtypes, including PTCL, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large-cell lymphoma (ALCL), most of which show aggressive behavior.[1] First-line treatment with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), or a CHOP-like regimen has been widely utilized.[2,3] Recently, brentuximab vedotin (BV), an antibody–drug conjugate targeting CD30, in combination with cyclophosphamide, doxorubicin, and prednisone has been revealed to be superior to CHOP for patients with CD30-positive PTCL.[4] However, the treatment responses are rarely durable in most PTCL subtypes excluding anaplastic lymphoma kinase (ALK)-positive ALCL, and patients with relapsed/refractory (R/R) PTCL have a dismal outcome,[5] with a median survival after first relapse or progression of less than 6 months.[6,7]

For R/R PTCL, several novel single agents such as a folic acid activation inhibitor (pralatrexate),[8,9] a purine nucleoside phosphorylase inhibitor (forodesine),[10] histone deacetylase (HDAC) inhibitors (belinostat[11] and romidepsin[12,13]), a recombinant cytotoxic fusion protein composed of the diphtheria toxin fragments A and B and human interleukin-2 (E7777),[14] BV,[15] and a humanized anti-CCR4 antibody (mogamulizumab),[16] have been approved or are being developed in various countries. However, the responses of these agents, except for BV in patients with R/R CD30-positive ALCL, are generally not durable. Because there is still no established standard treatment in patients with R/R PTCL, novel therapeutic agents are needed to improve the dismal prognosis.

Epigenetic modification has a strong influence on cell regulation and function, and the treatment targeting epigenetics is becoming an attractive strategy in the field of cancer therapy. One of the key epigenetic processes is the posttranslational modification of histone residues that regulates the accessibility of chromatin, thereby controlling various gene expressions.[17] Essentially, the balance between histone acetyltransferases (HAT) and HDAC is critical to maintain a normal histone acetylation status,[17] and aberrant HDAC activities are associated with the development of various types of cancers.[18] In PTCL, several studies showed that class I HDAC (including HDAC1 and HDAC2) were overexpressed regardless of the subtypes of PTCL,[19-21] and highly expressed HDAC2 exhibited a poorer overall survival rate.[21]

Tucidinostat (formerly known as chidamide) is an orally available, novel benzamide class of HDAC inhibitor that selectively blocks class I (HDAC1, 2 and 3) and class IIb (HDAC10) HDAC.[22] The anti-tumor effects of tucidinostat such as inducing apoptosis and cell cycle arrest have been determined by using cancer cells in various preclinical studies.[23-25] Furthermore, several reports showed that it could also enhance immune cell-mediated tumor cell cytotoxicity *in vitro*[26,27] and *in vivo*.[22] The activities of tucidinostat have also been evaluated in clinical studies[28-30]. In a phase II trial in patients with R/R PTCL, tucidinostat showed an overall response rate of 28%, and was approved in China based on the pivotal trial.[29] However, it is still not available for R/R PTCL in many other countries.

The current phase IIb study was planned to investigate the safety and efficacy of tucidinostat in Japanese and South Korean patients with R/R PTCL (*clinicaltrials gov. Identifier: NCT02953652*). The dose, 40 mg twice per week (BIW), was determined based on the result from the preceding phase I study for Japanese patients with non-Hodgkin lymphoma,[31] which was higher than that approved for patients with PTCL in China (30 mg BIW). The data described herein led to the approval of tucidinostat for R/R PTCL by the Japanese Ministry of Health, Labour and Welfare in 2021.

Methods

Study design

This phase IIb, open-label, non-randomized, single-arm study was conducted in Japan and South Korea to evaluate the safety and efficacy of tucidinostat in patients with R/R PTCL in accordance with Good Clinical Practice, International Council for Harmonization guidelines, applicable drug and data protection laws and regulations, and the Declaration of Helsinki. The study was approved by Ethics Committees at each site and an informed consent was obtained from each patient. Protocol Synopsis is available in the *Online Supplementary Appendix*.

Study population

Patients aged ≥ 20 years with at least one measurable lesion (defined as more than 1.5 cm in greatest dimension) were eligible if they had histologically diagnosed PTCL according to the 2008 World Health Organization classification,[32] history of at least one prior previous systemic chemotherapy.

Study treatment

Tucidinostat was administered orally, 40 mg BIW, until progressive disease (PD) or unacceptable toxicities. A cycle was defined as 28 consecutive days. Tucidinostat was stopped temporarily for ≤2 weeks for the management of adverse events (AE). After recovery of AE, dose reductions were allowed from 40 mg to 30 mg, or from 30 mg to 20 mg. Data cut-off occurred in March 2019 when the last subject completed the cycle 5 day 1 assessment.

Study endpoints and procedures

The primary endpoint was objective response rate (rate of complete response [CR] and partial response [PR]). Secondary endpoints included ORR by disease subtypes, duration of response (DOR), progression-free survival (PFS), overall survival (OS) and safety parameters, AE (using National Cancer Institute Common Toxicity Criteria Version 4.03 and coded with Medical Dictionary for Regulatory Activities version 21.1), laboratory tests and electrocardiograms (ECG).

Based on the disease responsiveness to the most recent therapy, patients were grouped into two subsets: relapsed (patients who had previously achieved CR, unconfirmed CR [CRu], or PR) and refractory (patients who previously had stable disease [SD] or PD). Response was assessed every two cycles according to the computed tomography-based response criteria of the Lugano Classification[33] and the modified Severity Weighted Assessment Tool (mSWAT)[34] for skin lesions if present. The best response by treatment end was selected as an ORR. An Independent Radiology Review (IRR) reviewed all images and an Independent Overall Efficacy Review Committee (IOERC) reviewed all efficacy data including the radiological assessment provided by the IRR, the mSWAT score, and applicable clinical observations. The disease subtype was independently diagnosed by the Central Pathology Review (CPR). The primary analysis was conducted using IOERC assessment results. Safety data were reviewed by a Data Safety Monitoring Board (DSMB).

Analytical plan

The ORR was calculated on the per protocol set (PPS), subjects who met all eligibility criteria and had completed cycle 1 or discontinued tucidinostat during cycle 1 due to clinical PD. Forty patients were required to meet the target ORR of 30% (95% confidence interval [CI]: 15.8-44.2), with a power of 89% to show ORR>10% at 2-sided α of 5%. The default significance level was to be 5%; CI were to be 95%, and all tests were to be 2-sided, unless otherwise specified in the description of the analyses.

Table 1. Baseline patient demographic and clinical characteristics.

Characteristics	Total N=55
Sex, N (%)	
Male	35 (64)
Female	20 (36)
Age (years), median (min, max)	71 (38, 87)
Ethnicity, N (%)	
Japanese	39 (71)
South Korean	16 (29)
ECOG Performance Status, N (%)	
0	28 (51)
1	25 (46)
2	2 (4)
Diagnosis (confirmed by CPR), N (%)	
PTCL	52 (95)
PTCL-NOS	37 (67)
AITL	10 (18)
ALCL, ALK-negative	3 (5)
EATL	2 (4)
Non-PTCL	2 (4)
DLBCL	1 (2)
NLPHL	1 (2)
Unknown	1 (2)
Duration since initial diagnosis in years, median, range	1.339 (0.06-12.88)
PTCL subset, N (%)	
Relapsed (CR, CRu, PR)	32 (58)
Refractory (SD, PD)	23 (42)

AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large-cell lymphoma; ALK: anaplastic lymphoma kinase; CPR: central pathology review; CR: complete response; CRu: unconfirmed complete response; DLBCL: diffuse large B-cell lymphoma; EATL: enteropathy-associated T-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; NLPHL: nodular lymphocyte-predominant Hodgkin lymphoma; PD: progressive disease; PR: partial response; PTCL-NOS: peripheral T-cell lymphoma not otherwise specified; N: number of subjects.

Results

Patients

Between March 2017 and November 2018, 74 patients consented to be screened, and 55 of them were treated with 40 mg of tucidinostat twice per week. Of these, six patients were excluded from the full analysis set (FAS) for efficacy analysis. Among them, four patients did not meet the eligibility criteria, and two patients were not diagnosed as PTCL by the CPR (diffuse large B-cell lymphoma [DLBCL] [n=1] and nodular lymphocyte-predominant Hodgkin lymphoma [n=1]). Because a tumor sample from one patient was not submitted, CPR could not be performed for the patient, and the eligibility criteria was not met. Additionally, three patients were excluded from the PPS because they did not complete one cycle of treatment due to adverse events or withdrawal of consent (*Online Supplementary Figure S1*). Demographics and disease history are shown in Table 1 and previous cancer therapy is shown in Table2.

The most common subtypes were PTCL-NOS (n=37), followed by AITL (n=10). Patients had been treated with a median of two (range, 1-9) prior systemic therapies. The median time from initial PTCL diagnosis was 1.3 years (range, 0.06-12.88). All patients (n=55) had received prior chemotherapy, and 18 patients (33%) had a history of three or more lines of prior systemic therapies. A total of 20 patients (36%) had previously been treated with single agents, including darinaparsin,[35] forodesine, and romidepsin. Six patients (11%) had received radiotherapy.

Six patients (11%) had undergone prior autologous stem cell transplantation (SCT) (1 patient, who was diagnosed as DLBCL by the CPR, was excluded from the PPS). Twenty-three patients (42%) were refractory to their most recent therapies. The median time from the last treatment to the start of tucidinostat was 97 days.

Efficacy

In the PPS population (n=46), the primary endpoint of ORR as assessed by IOERC was 46% (95% CI: 30.9-61.0), with five patients experiencing CR (11%, 5/46) and 16 patients experiencing PR (35%, 16/46). The disease control rate (DCR=CR+PR+SD) was 72% (95% CI: 56.5-84.0). Responses were observed across the more common PTCL subtypes of PTCL-NOS, AITL, ALK-negative ALCL and enteropathy-associated T-cell lymphoma. Of interest, the ORR was relatively higher in patients with AITL (88%, 7/8), including two patients (25%, 2/8) of patients with CR (Table 3). There were no significant differences in the ORR based on sex, Eastern Cooperative Oncology Group (ECOG) performance status, or whether the patients were refractory to their last prior therapies (*Online Supplementary Figure S2*). In the FAS population (n=49), the ORR as assessed by IOERC was 43% (95% CI: 28.8-57.8). This study included a heavily pretreated patient population with about 33% (15/46) of patients in PPS that received three or more lines of prior systemic therapies, and the ORR was 27% (4/15) in these patients. In the PPS population, the objective responses were seen in two of five patients (40%) who received prior autologous SCT and were also seen in two of three (67%), one of three (33%), and two of six (33%) patients who were previously treated with pralatrexate, romidepsin, or forodesine, respectively. A summary of the patients who have a history of prior romidepsin treatment is shown in the *Online Supplementary Table S1*. The median time to response (TTR) was 8.1 weeks (95% CI: 8.0-8.4) in the 21 patients

Table 2. Previous cancer therapy.

Characteristics	Total N=55
Type of previous cancer therapy, N (%)	
Chemotherapy	55 (100)
Other anticancer therapy	16 (29)
Brentuximab vedotin	2 (4)
Darinaparsin	8 (15)
Denileukin Diftitox	2 (4)
Forodesine	6 (11)
Mogamulizumab	1 (2)
Pralatrexate	3 (5)
Rituximab	2 (4)
Romidepsin	4 (7)
Radiotherapy	6 (11)
Autologous stem cell transplantation	6 (11)
Other	2 (4)
N of prior systemic therapies including targeted therapies, median (min, max)	2 (1, 9)
N of regimens received (%)	
1 regimen	20 (36)
2 regimens	17 (31)
3 regimens	8 (15)
4 regimens	5 (9)
5 or more regimens	5 (9)
N of days from end of last immediate previous therapy, median (min, max)	97 (29, 3,861)

N: number.

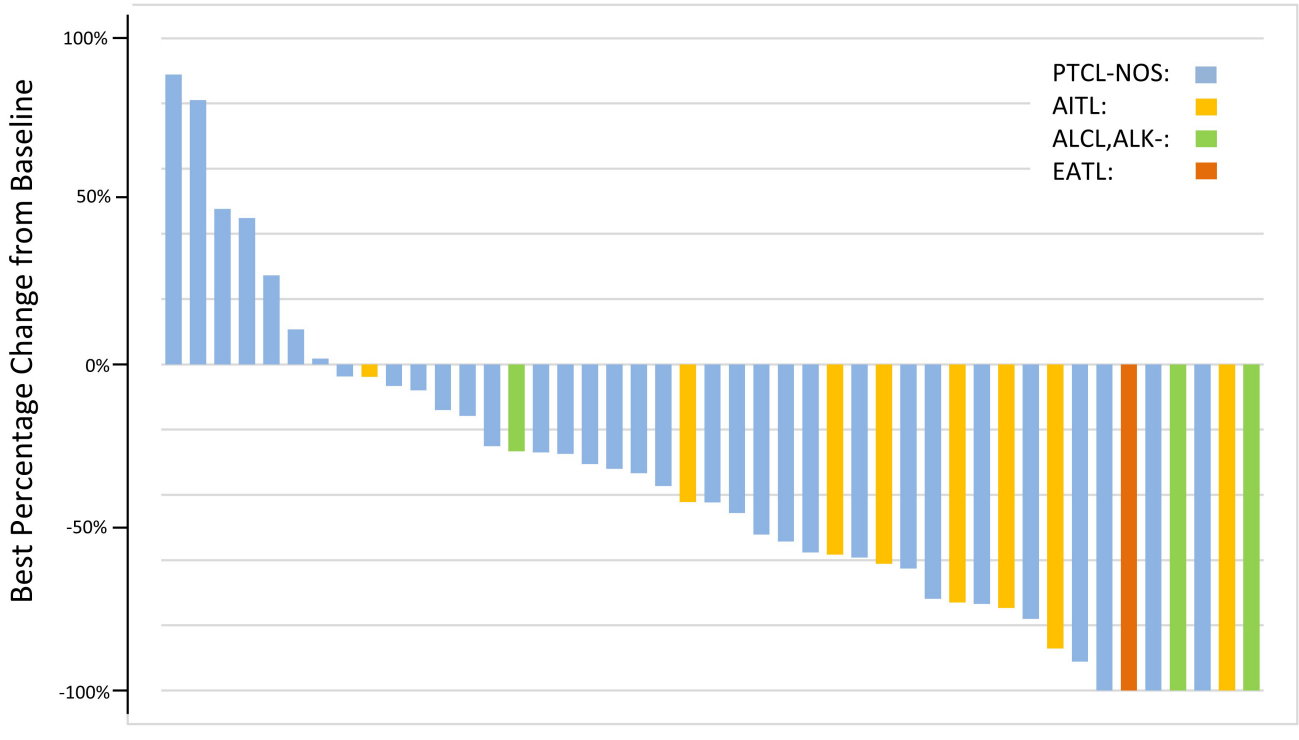

Figure 1. Waterfall plot showing best percentage change from baseline in sum of products of perpendicular diameter of target lesions in 45 patients.

achieving objective responses. Waterfall plot of change from baseline in sum of products of perpendicular diameter of diameters are shown in Figure 1. One patient was excluded from these plots since the patient had no post-baseline data. Thirty-eight patients (84%, 38/45) exhibited a decrease in tumor volume of their target lesions, and all AITL patients (n=8) showed tumor size reduction (Figure 1). For patients assessed as CR or PR, 11 of 21 (52%) patients had a dose interruption and six of 21 (29%) patients had a dose reduction prior to achieving objective responses. In addition, ten of 14 (71%) patients assessed as SD had a dose interruption and reduction (Figure 2). The median dose for these responding patients (CR, PR, and SD) who continued treatment at 4 months (n=14) was 40 mg (range, 20-40). The median treatment duration was 80 days (range, 10-580) and the median time to first dose interruption or dose reduction was 15 days (range, 4-366) or 33 days (range, 11-127), respectively.

At the data cut-off date, with a median follow-up duration of 8.3 month, eight of 55 (15%) patients continued treatment, and 12 patients received tucidinostat more than 6 months (Figure 2). Two of the patients retained the tumor response at 10 months even after discontinuing tucidinostat. The median PFS was 5.6 months (95%

Table 3. Objective response rate assessed by an Independent Overall Efficacy Review Committee (per-protocol set).

		Total N=46	
	Response	**N (%)**	**95% CI**
Objective response	CR or PR	21 (46)	30.9-61.0
Best response	CR	5 (11)	
	PR	16 (35)	
	SD	12 (26)	
	PD	13 (28)	
ORR by PTCL subtype	PTCL-NOS	12/34 (35)	19.7-53.5
	AITL	7/8 (88)	47.3-99.7
	ALCL, ALK-negative	1/3 (33)	0.8-90.6
	EATL	1/1 (100)	2.5-100

N: number of patients; 95% CI: 95% confidence interval; CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease; AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large-cell lymphoma; ALK: anaplastic lymphoma kinase; EATL: enteropathy-associated T-cell lymphoma; PTCL NOS: peripheral T-cell lymphoma not otherwise specified.

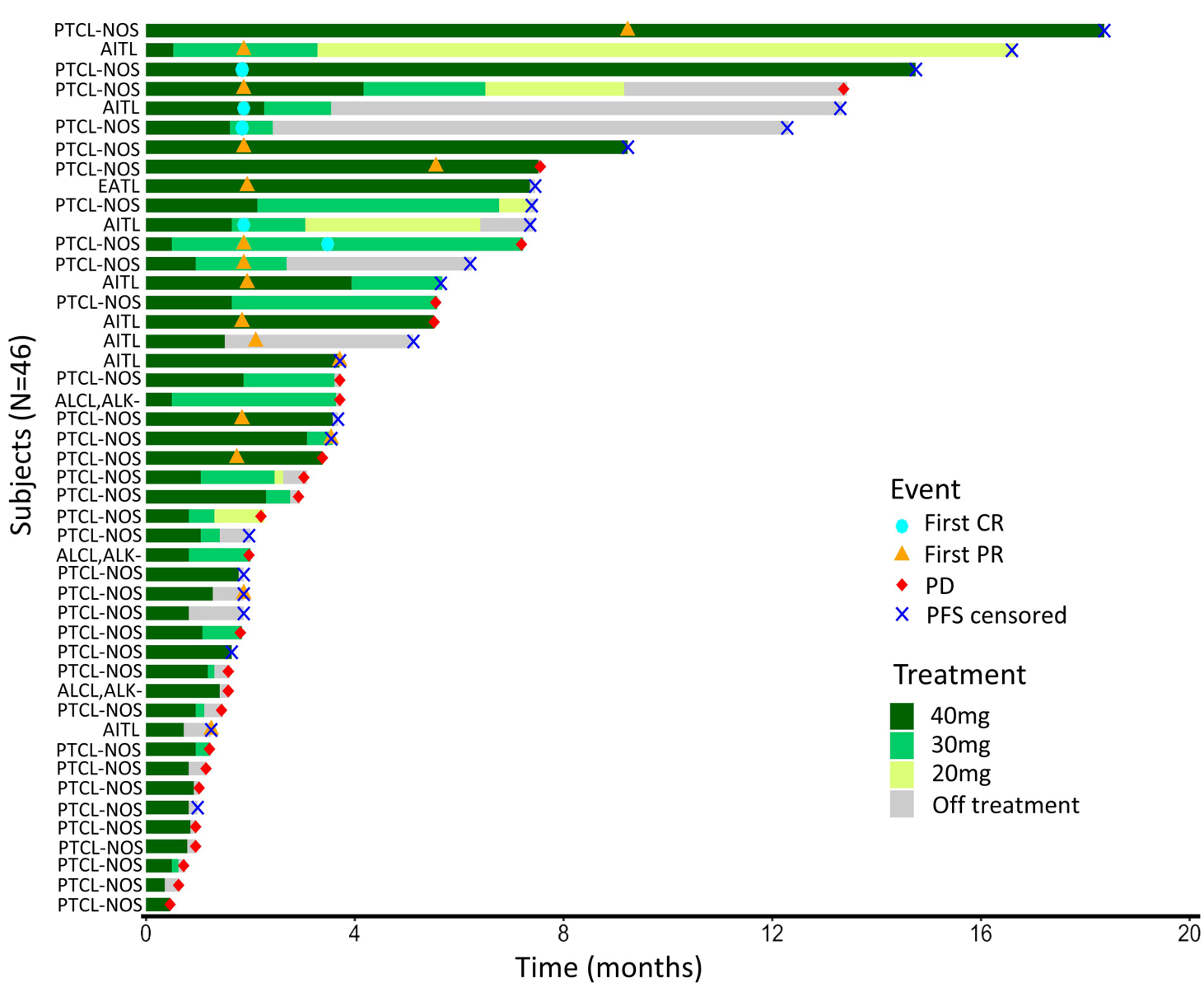

Figure 2. Swimmer plot showing treatment exposure and responses over time by peripheral T-cell lymphoma subtype in 46 pa-

CI: 2.9-13.4) (Figure 3A), and the median DOR was 11.5 months (95% CI: 5.4-not reached [NR]) (Figure 3B). The median OS was 22.8 months (95% CI: 12.6-NR) (Figure 3C).

Safety and tolerability

The safety population included 55 patients. All patients experienced at least one AE, most of which (93%, 51/55) were related to tucidinostat. The most common AE (all grades) were thrombocytopenia, neutropenia, leukopenia, anemia, and diarrhea (Table 4). ECG abnormalities were uncommon, and grade 1 or 2 ECG QTc prolongation was reported in five patients (9%, 5/55). The grade ≥3 AE emerging in ≥20% of patients included thrombocytopenia (51%, 28/55), neutropenia (36%, 20/55), lymphopenia (22%, 12/55), and leukopenia (20%, 11/55) (Table 4). Most of the hematologic AE were manageable by supportive care and dose modification, with nine patients receiving a platelet transfusion and 19 patients receiving granulocyte colony stimulating factor (G-CSF). Fourteen (26%, 14/55) patients had 17 serious AE, 10 of which were related to tucidinostat (febrile neutropenia [in two patients]; pneumonia, aplastic anemia, pneumonitis, *Pneumocystis jirovecii* pneumonia, interstitial lung disease, C-reactive protein increased, hyponatremia, and development of *de novo* PTCL-unspecified [one patient

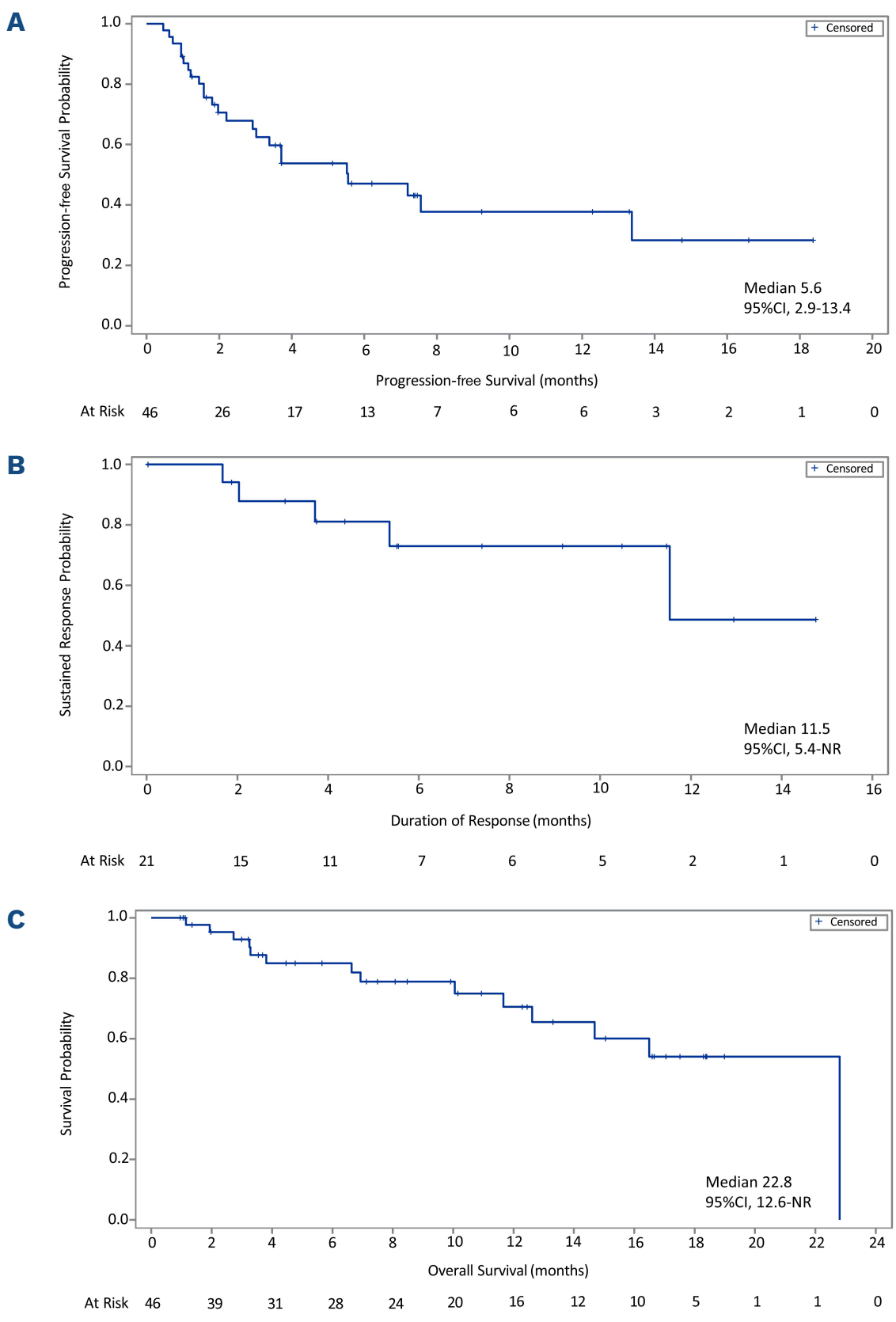

Figure 3. Durability of response to tucidinostat. (A) Kaplan-Meier plot of progression-free survival. (B) Kaplan-Meier plot of duration of response. (C) Kaplan-Meier plot of overall survival.

each]). Infections were reported in 19 patients (35%, 19/55), and those grade ≥3 included pharyngitis, enterocolitis infectious, *Pneumocystis jirovecii* pneumonia, pneumonia, and staphylococcal skin infection (1 patient each). One death from pneumonia was reported in this study, however, this fatal outcome was not judged to be related to tucidinostat, but assessed as being associated with progression of disease.

Dose reduction/interruption of therapy as a result of AE were reported in 40 patients (73%, 40/55) (Table 5), with 26 patients (47%, 26/55) having dose reduction. The major AE leading to drug reduction/interruption were thrombocytopenia (38%, 21/55) and neutropenia (35%, 19/55). Consequently, 18 patients (33%, 18/55) discontinued tucidinostat due to AE, including neutropenia (9%, 5/55), thrombocytopenia (7%, 4/55), lymphopenia (4%, 2/55), and leukopenia (2%, 1/55) (Table 5).

Discussion

Patients with R/R PTCL have dismal outcomes, and there is still high unmet medical need for their treatment options. In this phase IIb study, the treatment with tucidinostat (40 mg BIW) was effective and well tolerated in Japanese and South Korean patients with R/R PTCL with an ORR of 46% (the primary endpoint), including 11% of patients with CR. Furthermore, the efficacy results included a median PFS, DOR, and OS of 5.6 months, 11.5 months, and 22.8 months, respectively.

In the previous Chinese phase II study of 79 patients with R/R PTCL, tucidinostat, 30 mg BIW, showed that the ORR was 28% including 14% with CR/CRu, and the median PFS, DOR, and OS were 2.1 months, 9.9 months, and 21.4 months, respectively.[29] A real-world multicenter monitoring study in 256 Chinese patients with R/R PTCL receiving tucidinostat as a monotherapy, reported an ORR of 39%, a median PFS of 129 days, and a median DOR of 148 days.[36] These differences regarding the efficacy data between our study and the Chinese studies may be due in part to the different doses of this agent and the different patient characteristics. As a matter of fact, the median number of prior systemic therapies in our cohort (2 [range, 1-9]) was fewer than that of the pivotal Chinese study (3 [range, 1-9]), suggesting that patients with favorable features were enrolled in our study. In the present study, the dose of 40

Table 4. Adverse events regardless of causal relationship to tucidinostat observed in ≥10% of patients (n=55).

Adverse event	Any grade, N (%)	Grade ≥3, N (%)
Patients with at least one AE	55 (100)	46 (84)
Thrombocytopenia	46 (84)	28 (51)
Neutropenia	31 (56)	20 (36)
Leukopenia	24 (44)	11 (20)
Anemia	18 (33)	9 (16)
Diarrhea	17 (31)	1 (2)
Lymphopenia	16 (29)	12 (22)
Decreased appetite	13 (24)	2 (4)
Nausea	12 (22)	0 (0)
Pyrexia	11 (20)	0 (0)
Blood alkaline phosphatase increased	8 (15)	1 (2)
Gamma-glutamyltransferase increased	8 (15)	3 (6)
Malaise	8 (15)	0 (0)
Aspartate aminotransferase increased	7 (13)	0 (0)
Cough	6 (11)	0 (0)
Fatigue	6 (11)	0 (0)
Headache	6 (11)	0 (0)
Weight decreased	6 (11)	1 (2)

N: number of subjects; AE: adverse event; anemia: anemia/hemoglobin decreased; leukopenia: leukopenia/white blood cell count decreased; lymphopenia: lymphocyte count decreased/lymphopenia; neutropenia: neutropenia/neutrophil count decreased/granulocytopenia; thrombocytopenia: thrombocytopenia/platelet count decreased.

mg BIW was determined based on the results from the phase I study of Japanese patients with non-Hodgkin lymphoma, in which 40 mg BIW was tolerable and the ORR for the 40 mg cohort was higher than that for the 30 mg cohort.[31]

Several results from the pivotal trials of other HDAC inhibitors in patients with R/R PTCL, have been reported showing the ORR as 26% and 25%-43%, and the PFS as 1.6 months and 4.0-5.6 months for belinostat[11] and romidepsin,[12,13] respectively. It is difficult to make scientific comparisons between our current trial and any individual trials mainly because of the different patient characteristics and limited subject numbers. However, it is likely that the ORR and PFS were similar to those of romidepsin in Japan. Because tucidinostat is orally available, the advantage would be that tucidinostat may be more convenient in the outpatient setting than other intravenous HDAC inhibitors.

In the present study, efficacy was observed regardless of sex, ECOG performance status, or whether the patient was refractory to their last prior therapy. Furthermore, efficacy was seen across all the disease subtypes, and the patients with AITL tended to have a higher ORR of 88% (*Online Supplementary Figure S2*). Given the small numbers of patients in some subgroups, including AITL, this should be interpreted with caution. In accordance with our results, however, treatment with HDAC inhibitors appears to achieve relatively higher response rates in patients with AITL compared to those in their overall PTCL patient population.[11-13,29] The unique activity of HDAC inhibitors for AITL might be explained by the fact that epigenetic dysregulation plays a critical role in AITL pathogenesis. Meanwhile, recent molecular studies revealed that AITL and nodal PTCL with T-follicular helper cell (TFH) phenotype share some of the recurrent genetic alterations in epigenetic regulatory genes, such as *TET2*[37] and *DNMT3A*.[1,38,39] Thus, therapies targeting epigenetic changes, such as HDAC inhibitors and the hypomethylating 5-azacytidine agent, either as monotherapy or in combination setting, are now being developed in these diseases.[40-42]

In this study, a higher dose of tucidinostat, 40 mg BIW was given, compared to that used in the previous studies.[29,36] The most common AE were hematologic abnormalities (thrombocytopenia, neutropenia, leukopenia, anemia, lymphopenia), and gastrointestinal disturbances, which were consistent with previously reported AE with tucidinostat[28,29,36] as well as with other HDAC inhibitors such as belinostat[11] and romidepsin.[12] In addition, the AE reported in our study were manageable by supportive care and dose modifications. Most infections were grade 1 to 2 in severity (29%), and grade ≥3 infections occurred in 6% of

Table 5. Adverse events leading to dose reduction/interruption and/or discontinuation in ≥2 patients (n=55).

Adverse events	AE leading to dose reduction/interruption, N (%)	AE leading to discontinuation, N (%)	*Any grade, N (%)
Patients with at least one AE	40 (73)	18 (33)	55 (100)
Thrombocytopenia	21	4	46
Neutropenia	19	5	31
Decreased appetite	3	0	13
Febrile neutropenia	3	0	3
Leukopenia	2	1	24
Pyrexia	2	0	11
C-reactive protein increased	2	0	3
Hyponatremia	2	0	2
Lymphopenia	0	2	16
Gamma-glutamyltransferase increased	0	2	8
Pneumonitis	0	2	4

N: number of subjects; AE: adverse event; leukopenia: leukopenia/white blood cell count decreased; lymphopenia: lymphocyte count decreased/lymphopenia; neutropenia: neutropenia/neutrophil count decreased/granulocytopenia; thrombocytopenia: thrombocytopenia/platelet count decreased. *All AE regardless of AE leading to dose reduction/Interruption and/or AE leading to discontinuation. Other AE leading to dose reduction/interruption (n=1): angina unstable, bronchitis, vertigo, diarrhea, electrocardiogram QT prolonged, electrocardiogram T wave inversion, nasopharyngitis, nausea, oedema peripheral, peripheral arterial occlusive disease, rash, urticaria. Other AE leading to discontinuation (n=1): blood alkaline phosphatase increased, brain natriuretic peptide increased, dyspnea, interstitial lung disease, peripheral T-cell lymphoma unspecified, pneumocystis jirovecii pneumonia, pneumonia.

patients, which were controllable with antibiotic, antimycotic or antiviral agents.

In the present study, forty patients (73%) had dose reduction or interruption which were frequently observed during cycle 1; however, most of these AE were reversible and all patients could resume treatment with tucidinostat. The main reasons for dose reduction/interruption were hematological toxicities such as thrombocytopenia and neutropenia, and 26 patients (47%) consequently had dose reduction. Eighteen patients (33%) discontinued treatment due to AE, most of which were also related to the hematological toxicities. The incidence of discontinuation was slightly higher compared with that of the Chinese study,[29] possibly because of the higher dose of tucidinostat in this study. However, 29 (53%) patients did not need dose reduction due to AE. In addition, neither unexpected safety signals nor AE leading to death were observed in this study. Therefore, we consider that 40 mg is suitable as the starting dose. However, it is important to note that patients treated with 40 mg of tucidinostat should be carefully monitored, and appropriate dose modification is essential.

There are several limitations in our study, including the small sample size, short follow-up period, and lack of information regarding the efficacy in patients with nodal PTCL with TFH phenotype, as well as biomarkers that could predict the drug response. Therefore, additional research to address these issues is warranted. Moreover, several drug resistance mechanisms to HDAC inhibitors have been reported in hematological malignancies, including drug efflux, chromatin alterations, upregulation of oxidative stress response mechanism, defect, and upregulation in apoptotic pathways.[43,44] Thus, future combination of HDAC inhibitors with other anticancer drugs would be a promising strategy to improve the dismal prognosis of R/R PTCL.[45]

In conclusion, the current study demonstrated the favorable efficacy and safety of tucidinostat in Japanese and South Korean patients with R/R PTCL. Of note, tucidinostat is orally available and thus may be more convenient in the outpatient setting than conventional cytotoxic agents or other novel intravenous agents for R/R PTCL. Together, the favorable efficacy and safety results indicate that tucidinostat is a promising new therapeutic option in patients with R/R PTCL.

Disclosures

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Contributions

SR, WSK, KA, IC, KoI, NT, MY, KuT, JK, JA, MH, YK, HS, TU, DeHY, KjI , KiI, JSK, HGL, HM, HSE, MK, JHL, JSL, WSL, HN, TS, DoHY and SY participated in the study, treated patients, and provided data. SR, MG, HO and KeT were involved in the manuscript development. MG, HO and KeT were involved in the study design, data collection and analysis and data interpretation. All authors were involved in the review of the content and approved the submitted version of the manuscript.

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Data-sharing statement

Individual participant data will not be shared, because informed consent was not obtained for data sharing, and protocols will also not be shared, due to sponsor policy.

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