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

Shinya Rai,[1] Won Seog Kim,[2] Kiyoshi Ando,[3] Ilseung Choi,[4] Koji Izutsu,[5] Norifumi Tsukamoto,[6] Masahiro Yokoyama,[7] Kunihiro Tsukasaki,[8] Junya Kuroda,[9] Jun Ando,[10] Michihiro Hidaka,[11] Youngil Koh,[12] Hirohiko Shibayama,[13] Toshiki Uchida,[14] Deok Hwan Yang,[15] Kenji Ishitsuka,[16] Kenichi Ishizawa,[17] Jin Seok Kim,[18] Hong Ghi Lee,[19] Hironobu Minami,[20] Hyeon Seok Eom,[21] Mitsutoshi Kurosawa,[22] Jae Hoon Lee,[23] Jong Seok Lee,[24] Won Sik Lee,[25] Hirokazu Nagai,[26] Takero Shindo,[27] Dok Hyun Yoon,[28] Shinichiro Yoshida,[29] Mireille Gillings,[30] Hiroshi Onogi[31] and Kensei Tobinai[5]

[1]Kindai University Hospital, Osaka-Sayama, Japan; [2]Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Korea; [3]Tokai University Hospital, Isehara, Japan; [4]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [5]National Cancer Center Hospital, Tokyo, Japan; [6]Gunma University Hospital, Maebashi, Japan; [7]The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [8]International Medical Center, Saitama Medical University, Saitama, Japan; [9]Kyoto Prefectural University of Medicine, Kyoto, Japan; [10]Juntendo University Hospital, Tokyo, Japan; [11]National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan; [12]Seoul National University Hospital, Seoul, Korea; [13]Osaka University Hospital, Suita, Japan; [14]Japanese Red Cross Nagoya Daini Hospital, Nagoya, Japan; [15]Chonnam National University Hwasun Hospital, Jeollanam, Korea; [16]Kagoshima University Hospital, Kagoshima, Japan; [17]Yamagata University Hospital, Yamagata, Japan; [18]Yonsei University College of Medicine, Severance Hospital, Seoul, Korea; [19]Konkuk University Medical Center, Seoul, Korea; [20]Kobe University Graduate School of Medicine and Hospital, Kobe, Japan; [21]National Cancer Center, Gyeonggi, Korea; [22]National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan; [23]Gachon University Gil Medical Center, Incheon, Korea; [24]Seoul National University Bundang Hospital, Gyeonggi, Korea; [25]Inje University Busan Paik Hospital, Busan, Korea; [26]National Hospital Organization Nagoya Medical Center, Nagoya, Japan; [27]Kyoto University Hospital, Kyoto, Japan; [28]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [29]National Hospital Organization Nagasaki Medical Center, Omura, Japan; [30]HUYABIO International, San Diego, CA, USA and [31]Huya Japan GK, Tokyo, Japan

Correspondence: S. Rai
rai@med.kindai.ac.jp

Received: March 25, 2022.
Accepted: September 27, 2022.
Early view: October 6, 2022.

https://doi.org/10.3324/haematol.2022.280996

Supplemental Appendix

Supplemental Protocol Synopsis

<table>
<tr><td>Study Drug:</td><td colspan="2">HBI-8000</td></tr>
<tr><td>Title of Study:</td><td colspan="2">A Phase 2b Open-Label Single Arm Study to Evaluate the Efficacy and Safety of Oral HBI-8000 in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)</td></tr>
<tr><td>Protocol No:</td><td colspan="2">HBI-8000-203</td></tr>
<tr><td>Study site(s):</td><td colspan="2">25 to 35 sites in Japan and 10 to 15 sites in South Korea</td></tr>
<tr><td colspan="2">Study duration: Approximately 60 months</td><td rowspan="2">Phase: 2b</td></tr>
<tr><td colspan="2">Planned study period: 4quarter 2016 (first patient in) to
3quarter 2018 (last patient in)
4quarter 2021 study completion</td></tr>
<tr><td colspan="3">Objectives:
<u>Primary:</u>
• To determine the efficacy of HBI-8000 administered twice a week (BIW) continuously
<u>Secondary</u>:
• To evaluate the safety and tolerability of HBI-8000 administered BIW continuously</td></tr>
<tr><td colspan="3">Endpoints:
<u>Primary</u>:
• Objective response rate (ORR; Complete Response [CR] + Partial Response [PR])
<u>Secondary</u>:
• ORR by disease subtype (see inclusion criteria)
• Median duration of progression-free survival (PFS)
• Median duration of response (DOR)
• Safety
<u>Exploratory:</u>
• Median duration of overall survival (OS)</td></tr>
<tr><td colspan="3">Study Design:
This is a Phase 2b, open-label, non-randomized, single arm study to evaluate the safety, efficacy, and PK of HBI-8000 40 mg BIW in patients with relapsed or refractory PTCL (R/R PTCL). HBI-8000 will be administered orally approximately 30 minutes after any regular meal. The treatment will be continuous, with 3-4 days between dosing. A cycle is defined as 28 days solely for the purpose to schedule assessments required by the study.

Treatment-related adverse events (AEs) will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. In the event of unacceptable toxicities, study drug will be held until recovery and dosing will be resumed at reduced dose level, following protocol guidelines. An unacceptable toxicity is defined as the following:

• Grade 4 afebrile neutropenia > 7 days despite optimal growth factor support
• Grade ≥ 3 febrile neutropenia or neutropenic infection
• Grade ≥ 3 thrombocytopenia with clinically significant bleeding or Grade ≥ 3 thrombocytopenia requiring a platelet transfusion</td></tr>
</table>

<table>
<tr><td colspan="2">

Grade ≥3 nausea, vomiting, diarrhea, or electrolyte imbalances lasting greater than 48 hours despite optimal prophylactic and curative treatment
Grade ≥3 allergic reaction
Grade ≥3 other non-hematologic AEs
Treatment delay >14 days secondary to recovery from study drugs- related AEs

For determination of efficacy, HBI-8000 administration will be continued until disease progression (PD) or unacceptable toxicities are observed despite appropriate dose reduction or treatment interruption.
</td></tr>
<tr><td>Number of patients:</td><td>40 patients evaluable for efficacy with approximately 27 from Japan and 13 from Korea. To ensure meeting this target, an estimated 50 to 60 patients would be enrolled in anticipation that some patients may not complete study treatment.</td></tr>
<tr><td>Entry Criteria:</td><td>Inclusion
1. Histological or cytological diagnosis of the following peripheral T-cell lymphoma (PTCL) subtypes as defined by the WHO classification (2008) may be included:
a. PTCL, NOS
b. Angioimmunoblastic T-cell lymphoma (AITL)
c. Anaplastic large-cell lymphoma (ALCL), ALK^+
d. Anaplastic large-cell lymphoma (ALCL), ALK^-
e. Enteropathy-associated T-cell lymphoma (EATL)
f. Hepatosplenic T-cell lymphoma
g. Subcutaneous panniculitis-like T-cell lymphoma
2. Patients for whom at least 1 measurable lesion is confirmed by the lesion assessment at baseline; An evaluable lesion is defined according to Cheson criteria 2014.
3. Relapsed or refractory disease after receiving ≥1 prior systemic therapy with anti-tumor agent(s) and there is no other standard treatment which can be considered appropriate for patients. Systemic therapy is defined as frontline chemotherapy or immunotherapy administered systemically.
4. Male or female, age 20 years or older
5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2
6. Life expectancy of greater than 3 months
7. Meeting the following baseline laboratory criteria for screening:
a. Absolute Neutrophil Count >1500/μL independent of growth factor support within 7 days
b. Platelets >75,000/μL independent of transfusion within 14 days
c. Hemoglobin >8 g/dL independent of transfusion within 14 days
d. Serum creatinine < 1.5 × ULN
e. Serum aspartate aminotransferase/glutamyl oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/glutamyl pyruvic transaminase (ALT/SGPT) ≤ 3 × ULN
f. Serum Bilirubin ≤ 1.5 × ULN
8. Negative serum pregnancy test for females of childbearing (reproductive) potential. Female patients of child bearing potential must use an effective method of birth control (e.g., hormonal</td></tr>
</table>

	contraceptive, intrauterine device, diaphragm with spermicide or condom with spermicide) during treatment period and 1 month thereafter. Males must use an effective method of birth control (2 barrier methods) during treatment period and 3 months thereafter. Note: Female patients will be considered to be women of childbearing potential unless having undergone permanent contraception or postmenopausal. Postmenopausal is defined as at least 12 months without menses with no other medical reasons (e.g., chemical menopause because of treatment with anti-malignant tumor agents) 9. Signed informed consent **Exclusion** 1. Patients in whom central nervous system lymphoma is recognized during screening (if suspected clinically, imaging study should be performed to confirm) 2. Male patients with QTcF >450 msec at screening, female patients with QTcF >470 msec at screening or patients with congenital long QT syndrome, clinically significant arrhythmia, history of congestive heart failure (New York Heart Association Class III or IV) or acute myocardial infarction within 6 months of starting the study drug 3. Patients with known hypersensitivity to benzamide class of compounds or any of the components of HBI-8000 tablets, and patients with prior exposure of HBI-8000 4. Patients with a history of second malignancy other than disease under study. The exceptions are diseases (excluding diseases listed below) that have been treated with curative intent with no evidence of recurrence in past 5 years. Furthermore, if the second malignancy is one of the following diseases that were treated with curative intent, it is only required that there is no evidence of recurrence in past 2 year. a. Basal cell carcinoma of the skin b. Squamous cell carcinoma of the skin c. Cervical carcinoma in situ d. Carcinoma in situ of the breast e. An incidental histological finding of prostate carcinoma (TNM stage T1a or T1b) f. Early-stage gastric cancer treated with endoscopic mucosal resection or endoscopic submucosal dissection g. Thyroid cancer with differentiated histology (e.g. papillary) treated with curative intent 5. Autologous stem cell transplantation within 12 weeks (84 days) of starting the study drug 6. History of allogeneic stem cell transplantation 7. Organ transplantation recipients except for autologous hematopoietic stem cell transplantation 8. Uncontrolled inter-current infection 9. Hepatitis B surface antigen-positive, or hepatitis C virus antibody positive. In case hepatitis B core antibody and/or hepatitis B surface antibody is positive even if hepatitis B surface antigen-negative, a hepatitis B virus DNA test (real-time polymerase chain reaction

	(PCR) measurement) should be performed and if positive, the patient should be excluded from study 10. Any history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) 11. Uncontrolled diabetes mellitus, hypertension, endocrine disorder, bleeding disorder 12. Major surgery or radiation therapy within 28 days of starting the study drug 13. Receiving investigational agents or anti-cancer therapy, within 28 days, nitrosourea or mitomycin C within 42 days of starting the study drug 14. Receiving antibody therapy for PTCL within 12 weeks of starting the study drug 15. Women who are breastfeeding or women who are not willing to stop breastfeeding during study treatment period and for 30 days after the last dose of study drug 16. Potential for non-compliance or at increased risk based on investigator's judgement
Excluded Prior or Concomitant Medications or Therapy:	The following drugs are prohibited. • Drugs known to produce significant QT prolongation and ventricular dysrhythmias Prohibited from signing informed consent through the EoT assessment • Anti-cancer therapy other than study medication Prohibited during the study and within the following time intervals prior to the first dose of study drug. - 4 weeks for anti-cancer chemotherapy - 6 weeks for nitrosourea and mitomycin C - 12 weeks for anti-cancer monoclonal antibody therapy Corticosteroid prescribed for medical conditions other than lymphoma is not considered as an anti-cancer therapy for this study, for example: chronic obstructive pulmonary disease, allergy, topical steroids for rash.
Treatments:	Study drug is to be taken after any regular meal twice weekly, each dose separated by 3-4 days. Treatment will continue until PD in the absence of unacceptable toxicity.
Efficacy Data:	Response and progression for PTCL will be evaluated according to the revised criteria for response assessment in lymphoma [Cheson 2014]. To be included in final efficacy analyses, the histopathology diagnosis of disease will be verified by Central Pathology Review, and disease response will be confirmed by Independent Radiology and Independent Overall Efficacy Review.
Safety Data:	All patients who receive at least one dose of HBI-8000 will be evaluable for safety. Adverse event severity (grade) will be defined according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Serial ECGs and clinical laboratory tests will be collected to evaluate safety and potential toxicity. Laboratory and other tests, as appropriate to the clinical situation, may be obtained more frequently than stipulated in the schedules of events. All reported AEs will be collected, evaluated and coded using Medical Dictionary for Regulatory Activities (MedDRA).

Statistical Procedures:

Statistical analysis for all safety and efficacy will be primarily descriptive in nature. Categorical variables will be summarized by frequency distributions (number and percentages of patients), continuous variables will be summarized by mean, standard deviation, median, minimum, maximum, and time-to-event variables will be summarized using Kaplan-Meier methods and figures for the estimated median time. A formal statistical analysis plan will be completed prior to database lock and any study-related analyses.

Disease diagnosis including histological subtypes will be confirmed by central pathology review conducted by independent pathologists.

Efficacy should be analyzed using Full analysis set (FAS) and Per protocol set (PPS).

The FAS is defined as Patients meeting all eligibility criteria and having received at least one dose of study medication, and at least one efficacy assessment of disease with either imaging studies or clinical examination after receiving study medication.

The PPS is defined as Patients meeting all eligibility criteria and having completed Cycle 1 treatment or discontinued study treatment during cycle 1 due to clinical PD. It should be noted that the PPS includes subjects who discontinue within Cycle 1 due to clinical PD without imaging studies to assess disease status.

In addition, Patients who are assessed as Non-PTCL by the central pathology review committee should be excluded from the FAS and PPS for efficacy. The non-PTCL subjects will be included in safety analysis for the study.

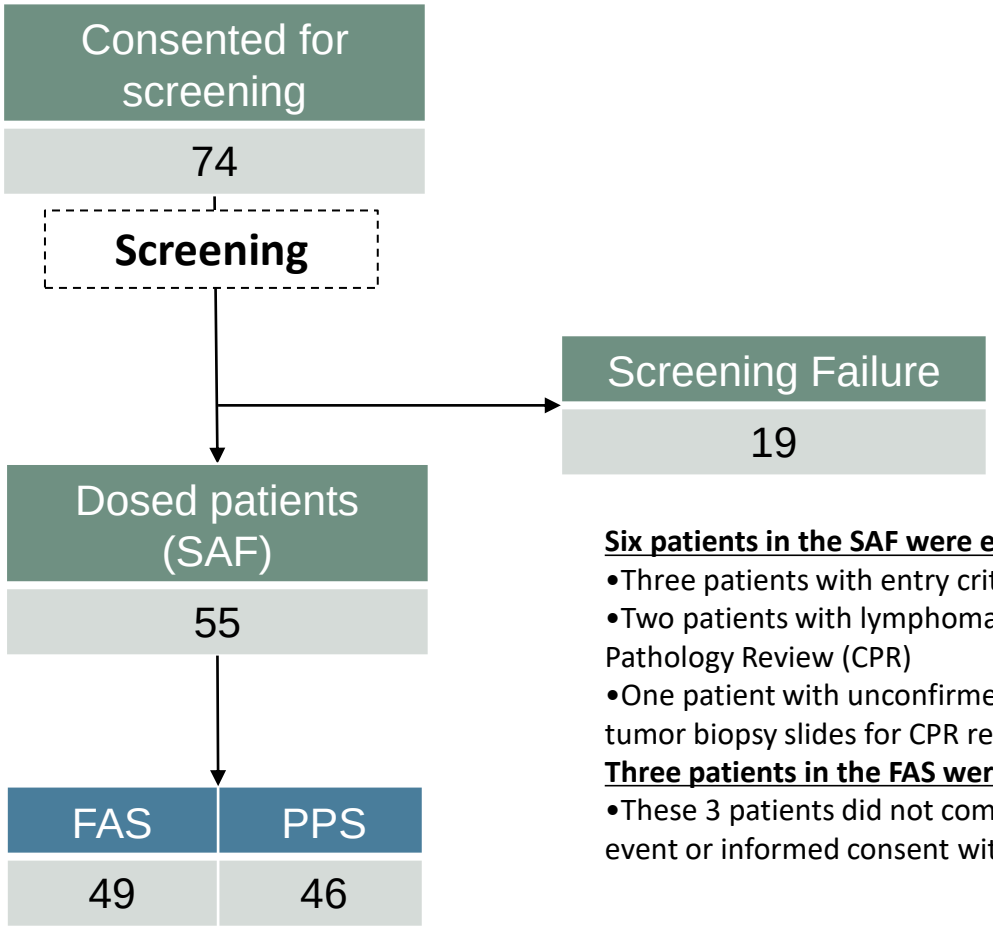
The primary efficacy analysis is conducted in the PPS. The Efficacy analysis using the FAS will be also reported.

It is estimated that 40 evaluable patients are adequate to provide efficacy assessment. Assuming a 30% ORR in this population of 40 evaluable patients, the conclusion would be that there is a 95% chance that the ORR in this protocol population would lie between 15.8% and 44.2%. The power for showing the response rate >10% at 5% two-sided alpha in 40 patients is 89%.

All patients who have received any amount of study medication will be considered as evaluable for safety. Safety data will be summarized with descriptive statistics and frequency tables and will include AEs, hematology, coagulation, serum chemistry, urinalysis, vital signs, and ECG data. Laboratory values will be summarized by numerical value and toxicity grade.

Supplemental Figure

Figure S1. Disposition of patients



Six patients in the SAF were excluded from the FAS.

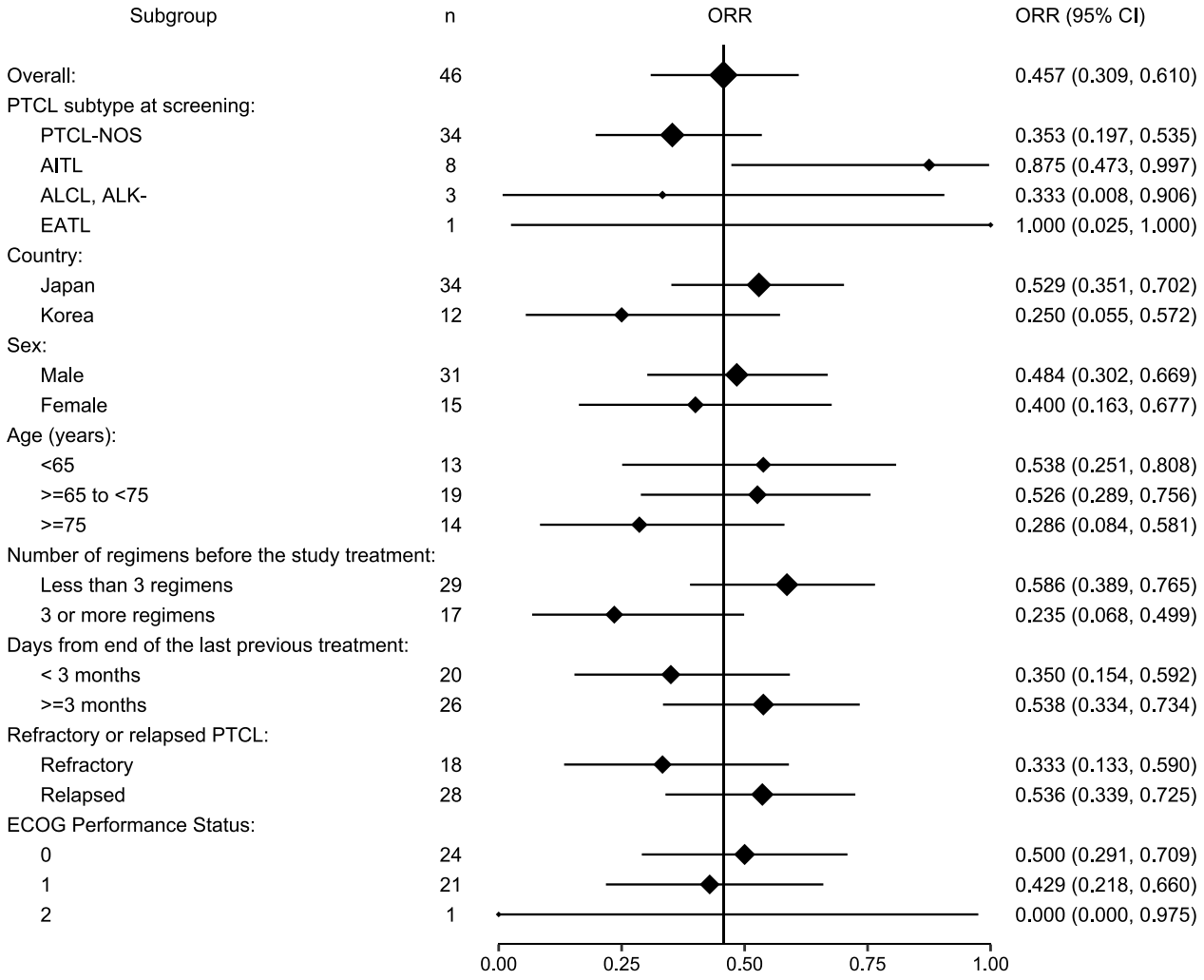
- Three patients with entry criteria violations
- Two patients with lymphoma but not PTCL after Central Pathology Review (CPR)
- One patient with unconfirmed disease due to missing tumor biopsy slides for CPR review

Three patients in the FAS were excluded from the PPS.

- These 3 patients did not complete 1st cycle due to adverse event or informed consent withdrawal

SAF: safety analysis set
FAS: full analysis set
PPS: per protocol set

Figure S2. Forest Plot of Objective Response Rate by Subgroup



Supplemental Table

Table S1. Prior romidepsin treated patients summary

Case	Age	Subtype	N of prior systemic therapies	Autologous stem-cell transplantation	romidepsin treated line	Overall response of romidepsin	Overall response of tucidinostat
1	68	PTCL-NOS	4	No	2	CR	PR
2	65	AITL	3	No	2	CRu	SD, excluded from the PPS
3	78	PTCL-NOS	4	No	2	CR	SD
4	78	PTCL-NOS	5	No	4	PR	PD

N = number,

CR = complete response, CRu = complete response/unconfirmed, PD = progressive disease, PR = partial response, SD = stable disease,

AITL = angioimmunoblastic T-cell lymphoma, PTCL-NOS = peripheral T-cell lymphoma, not otherwise specified,

PPS = per-protocol set