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Phase 1 study of tazemetostat in Japanese patients with relapsed or refractory B-cell lymphoma

Wataru Munakata[1] | Yukari Shirasugi[2] | Kensei Tobinai[1] | Makoto Onizuka[2] | Shinichi Makita[1] | Rikio Suzuki[2] | Dai Maruyama[1] | Hidetsugu Kawai[2] | Koji Izutsu[1] | Tadashi Nakanishi[3] | Sari Shiba[4] | Seichiro Hojo[5] | Kiyoshi Ando[2]

[1]Department of Hematology, National Cancer Center Hospital, Tokyo, Japan

[2]Department of Hematology and Oncology, Tokai University School of Medicine, Isehara, Japan

[3]Department of Clinical Development, Eisai Co., Ltd., Tokyo, Japan

[4]Clinical Pharmacology Science Department, Eisai Co., Ltd., Tokyo, Japan

[5]Clinical Data Science Department, Eisai Co., Ltd., Tokyo, Japan

Correspondence
Wataru Munakata, Department of Hematology, National Cancer Center Hospital, Tokyo, Japan.
Email: wmunakat@ncc.go.jp

Funding information
Eisai

Abstract

Background: Tazemetostat is a selective and orally available inhibitor of enhancer of zeste homolog 2 (EZH2), a histone methyltransferase and epigenetic regulator of cellular differentiation programs. We carried out a phase I study of tazemetostat in Japanese patients with relapsed or refractory B-cell non-Hodgkin-type lymphoma (B-NHL) to evaluate its tolerability, safety, pharmacokinetics, and preliminary antitumor activity.

Methods: Tazemetostat was given orally at a single dose of 800 mg on the first day and 800 mg twice daily (BID: total 1600 mg/d) on following days in a 28-day/cycle manner. Tazemetostat dose-limiting toxicity (DLT) was evaluated up to the end of the first treatment cycle. Archival tumor tissues were analyzed for hotspot *EZH2* mutations.

Results: As of 15 January 2018, seven patients (four follicular lymphoma [FL] and three diffuse large B-cell lymphoma [DLBCL]) were enrolled. The median age was 73 (range, 59-85) years, and the median number of prior chemotherapy regimens was three (range, one to five). No DLT was observed (one patient was not evaluable due to early disease progression). The common treatment-related adverse events (AEs) were thrombocytopenia and dysgeusia (three patients each; 42.9%). No treatment-related serious AEs were observed. The objective response rate was 57% (4/7 patients), including responses in three of four patients with FL and one of three patients with DLBCL. An *EZH2* mutation was detected in one patient with FL responding to treatment.

Conclusions: Tazemetostat at 800 mg BID showed an acceptable safety profile and promising antitumor activity in Japanese patients with relapsed or refractory B-NHL.

Abbreviations: AE, adverse event; AUC, area under the concentration-time curve; BOR, best overall response; CI, confidence interval; COO, cell-of-origin; CR, complete response; CT, computed tomography; CYP3A, cytochrome P450 family 3 subfamily A; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; ECG, electrocardiogram; EZH2, enhancer of zeste homolog 2; FL, follicular lymphoma; GC, germinal center; GCB-DLBCL, germinal center B-cell-like diffuse large B-cell lymphoma; H3K27, lysine 27 on histone 3; IHC, immunohistochemistry; NHL, non-Hodgkin-type lymphoma; ORR, objective response rate; PK, pharmacokinetic; PR, partial response; PRC2, polycomb repressive complex 2; PS, performance status; R-CHOP, combination of several chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine, and prednisone) and rituximab (R); R/R, relapsed or refractory; SAE, serious adverse event; SWI/SNF, switch/sucrose nonfermentable; $t_{1/2}$, terminal elimination phase half-life; TR-AE, treatment-related adverse event.

KEYWORDS
diffuse large B-cell lymphoma, enhancer of zeste homolog 2, follicular lymphoma, phase I study, tazemetostat

1 | INTRODUCTION

The disruption of chromatin modulation has emerged as an important step in oncogenesis, including lymphomagenesis. Mutations in chromatin modifiers, associated with aberrant cell fate decisions, have been reported to frequently occur in a number of tumors.[1–3] Loss-of-function mutations in E1A binding protein P300 (*EP300*), CREB binding protein (*CREBBP*), or lysine methyltransferase 2D (*KMT2D*, also known as *MLL4*) have been shown to occur frequently in B-NHL.[4–6] Enhancer of zest homolog 2 is a histone methyltransferase known to function as the catalytic subunit of PRC2. Briefly, PRC2 is known to methylate H3K27.[7–13] Patients with solid tumors characterized by loss of expression of the SWI/SNF subunits of the SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1, also known as INI1, SNF5, and BAF47) protein have an extremely poor prognosis and lack efficacious treatments. More specifically, *INI1* is a potent tumor suppressor gene and encodes a core component of the SWI/SNF complex that is known to act in opposition to PRC2, the integrated functions of which have been shown to control diverse cellular processes, such as cell differentiation and proliferation.[14,15] Loss of INI1 has been reported to disrupt the function of the SWI/SNF complex, leading to aberrant recruitment of EZH2 to target genes, increased H3K27me3, transcriptional repression of key tumor suppressors, and the upregulation of several oncogenic signaling pathways, including Sonic hedgehog, Wnt/β-catenin, and myc.[15–17] With regard to B-NHL, recurrent gain-of function alterations in *EZH2* have been reported to occur in approximately 21.7% of GCB-DLBCLs and 7%-27% of FLs.[6,18,19] Once GC B-cells complete their affinity maturation, they resume their normal path of plasma cell differentiation.[20] Both GCB-DLBCL and FL have been reported to arise from this inherently tumorigenic GC B-cell phenotype.[21,22] Accordingly, EZH2 was found to be essential for maintaining the GC phenotype and is thus required for the development of pre-B cells to acquire a full spectrum of immunoglobulin recombination.[23] Moreover, EZH2 is known to be highly expressed in GC, and conditional deletion of EZH2 in established GC B-cells results in their failure to form functional GCs.[24,25] Tazemetostat (EPZ-6438, E7438) is an orally administered, highly selective EZH2 inhibitor, and its first-in-human study was undertaken in France.[26] In this study, tazemetostat showed a favorable safety profile and antitumor activity in patients with refractory B-NHL and advanced solid tumors, including epithelioid sarcomas. The recommended dose was set to 800 mg BID. Tazemetostat received accelerated approval by the US FDA in January 2020 for the treatment of adults and adolescents aged 16 years or older with locally advanced or metastatic epithelioid sarcoma not eligible for complete resection, based on the ORR and duration of response observed in the phase II study.[27] With respect to B-NHL, a separate phase II study reported that the ORR of tazemetostat was 69% (95% CI, 53-82; 31 of 45 patients) in the *EZH2* mutant FL cohort and 3% (95% CI, 23-49; 19 of 54 patients) in the *EZH2* WT FL cohort.[28] Based on this study, tazemetostat also received accelerated approval from the FDA in June 2020 for the treatment of adult patients with R/R FL whose tumors are positive for an *EZH2* mutation as detected by an FDA-approved test and who have received at least two prior systemic therapies, as well as for adult patients with R/R FL who have no satisfactory alternative treatment options. Here, we report a phase I study of tazemetostat in Japanese patients with relapsed or refractory B-NHL.

2 | MATERIALS AND METHODS

2.1 | Study design and treatment

This multicenter, single-arm, phase I study (ClinicalTrials.gov identifier: NCT03009344) in Japanese patients with relapsed or refractory B-NHL aimed to evaluate the tolerability, safety, PKs, and preliminary antitumor activity of tazemetostat. In addition, the *EZH2* mutation status in tumors was explored. For this, 800 mg tazemetostat was given orally in a single dose in cycle 0 (4 days) and in continuous doses of 800 mg BID (1600 mg total daily dose) in cycle 1, and later in 28-day cycles. Dose reduction and interruption were allowed in case patients experienced toxicity, such as intolerable grade 2 or more toxicity (except for absolute neutrophil counts of 0.75×10^9/L or higher). Dose reductions were in the order of 600 and 400 mg BID (1200 mg and 800 mg total daily dose, respectively) and were not allowed to increase later. Treatment with tazemetostat continued until disease progression, development of unacceptable toxicity, patient request to discontinue, withdrawal of consent, and other activities and were discussed with the sponsor. Follow-up was carried out until 30 days after the final treatment with tazemetostat.

The selection of initiation dose in this study was based on a phase I/II study of tazemetostat (NCT01897571) undertaken outside of Japan, where the recommended dose of tazemetostat was determined to be 800 mg BID.[26] The tolerability of tazemetostat was determined based on the incidence of DLTs in cycles 0 and 1. If DLTs occurred in two or fewer of six patients, this dosage level was considered tolerable.

2.2 | Patient eligibility

Eligible patients were a minimum of 20 years of age with a histological diagnosis of DLBCL or FL (except for transformed lymphoma), for which no standard therapy existed. Patients must have had previous therapy with systemic chemotherapy or Ab therapy, and measurable

disease detected by a CT scan. Patients also had to have an ECOG-PS of 0 or 1 and life expectancy of at least 3 months, as well as adequate renal, liver, bone marrow, and cardiac function. Patients were not eligible if they had allogeneic stem cell transplantation or prior exposure to an EZH2 inhibitor. Patients were also excluded if they were unable to take oral medication, had malabsorption syndrome, or had venous thrombosis or pulmonary embolism within the past 3 months before study drug administration, complications of hepatic cirrhosis, interstitial pneumonia, or pulmonary fibrosis. Other key exclusion criteria included medication comprising potent or moderate inhibitors/inducers of CYP3A, use of H2 blockers or proton-pump inhibitors, significant cardiovascular impairment, prolongation of QT interval, malignancy other than B-NHL, and pregnancy or lactation. This study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol and its amendments were approved by the Institutional Review Board, and all patients provided written informed consent.

2.3 | Definition of DLT

The following toxicities were regarded as DLTs: (a) grade 4 neutropenia for more than 7 consecutive days or neutropenia requiring hematopoietic growth factors; (b) grade 3 or higher febrile neutropenia; (c) grade 4 thrombocytopenia, grade 3 thrombocytopenia with bleeding, or thrombocytopenia requiring platelet transfusion; (d) grade 4 anemia or anemia requiring erythrocyte transfusion; (e) grade 3 or higher nausea, vomiting, or diarrhea persisting for more than 7 consecutive days despite maximal medical therapy; (f) grade 3 or higher nonhematological laboratory abnormalities with clinical symptoms persisting for more than 7 days; (g) other grade 3 toxicity lasting more than 7 consecutive days or grade 4 nonhematological toxicity of any duration; (h) failure to administer 75% or more of the planned administration number (42 or more of 56 doses) of the study drugs in cycle 1 as a result of treatment-related toxicity.

2.4 | Safety

Safety assessments consisted of monitoring and recording all AEs, including all grading of Common Terminology Criteria for Adverse Events (version 4.03), SAEs, regular laboratory evaluation of hematology, blood chemistry, and urine values, and periodic measurements of vital signs, including 12-lead ECGs, echocardiograms/multigated acquisition scans to assess left ventricular ejection fraction, ECOG-PS, and physical examinations.

2.5 | Pharmacokinetics

Blood samples for PK analyses were collected as follows: predose, and 0.5, 1, 2, 4, 6, 8, 10, and 12 hours (day 1), 24 hours (day 2), 48 hours (day 3), and 72 hours (day 4) postdose in cycle 0; predose in the first administration on cycle 1 day 3 (C1D3) and cycle 1 day 8 (C1D8); predose and 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose in the first administration on cycle 1 day 15 (C1D15); and predose in the first administration on cycle 1 day 22 (C1D22) and cycle 2 day 1 (C2D1). Urine samples for PK analyses of tazemetostat were collected as follows: predose and 0-72 hours postdose in C0D1; and 0-12 hours postdose for the first administration in C1D15. Tazemetostat was given in a fasted state in cycle 0 day 1 (C0D1) and at the first administration of cycle 1 day 15 (C1D15) defined as 2 hours or more before and 2 hours or more after a meal (only water was allowed). The plasma and urine concentrations of tazemetostat and the plasma concentrations of its desethyl metabolite (EPZ-6930) were measured by validated methods using liquid chromatography with tandem mass spectrometry. Pharmacokinetic parameters were calculated using noncompartmental analysis, including C_{max} (maximum plasma concentration), time to C_{max} (t_{max}), and AUC at both first [C0D1] and repeated [C1D15] administrations).

2.6 | Antitumor activity

Tumor assessment was carried out according to the Lugano Classification (CT-based Response).[29] The ORR and BOR were assessed. The CT scans were undertaken within 28 days prior to the initiation of treatment, every 8 weeks (starting at C1D1) during cycle 2-6, every 12 weeks starting at cycle 7 (C7D1) and beyond, and at discontinuation. Bone marrow aspiration or biopsy was carried out at screening for the evaluation of bone marrow infiltration in the tumor. After studying drug administration, bone marrow aspiration or biopsy was carried out if the result of screening was positive or unconfirmed and when required to confirm CR as the best response or if clinically indicated.

2.7 | *EZH2* mutation and COO status

Archival, formalin-fixed tumor tissues from available patients were collected for assessment of the mutational status of the *EZH2* (codons Y646, A682, and A692). The COO status of DLBCL patients was collected as patient characteristics. The COO status of all three patients was identified using the Hans IHC-based algorithm.[30] The frequency of *EZH2* mutation status and COO status were calculated.

2.8 | Statistical analysis

All subjects who completed treatment cycles 0 and 1 without major protocol deviations with at least 75% treatment compliance in cycle 1 were assessed for DLT, in addition to subjects who experienced DLT during cycles 0 and 1. All subjects who received at least one dose of tazemetostat were analyzed for safety, efficacy, and PKs. The BOR was summarized in total or for each disease (DLBCL and FL). The ORR was presented with corresponding two-sided

Clopper-Pearson exact 95% CIs. Statistical analyses were performed using SAS Version 9.2 or later and Phoenix WinNonlin software (version 7.0) for PK analysis.

3 | RESULTS

3.1 | Patient characteristics

This study was carried out between 10 January 2017 and 21 May 2019 at two study sites in Japan. A total of seven patients received at least one dose of the study drug. Two patients were in cycle 29 as of the date of data cut-off, whereas five patients discontinued the study. Dose-limiting toxicities were evaluated in six patients, but one patient was not included, due to disease progression with less than 75% treatment compliance in cycle 1. A summary of patient characteristics is presented in Table 1. The median age was 73.0 years (range, 59-85 years), with four male (57.1%) patients. All patients were Japanese. Baseline ECOG-PS scores of patients were either 0 (five patients; 71.4%) or 1 (two patients; 28.6%).

3.2 | Treatment

The median number of cycles received was 12 (range, 1-29), whereas the median duration of exposure was 11.2 months (range, 0.6-26.4). Of the seven treated patients, one (14.3%) received 100% of their planned starting dosage, five (71.4%) received at least 90% of the dosage, and one (14.3%) patient received at least 70% of the dosage. Tazemetostat treatment was interrupted for three (42.9%) patients. Only one patient (14.3%) received a reduction in the tazemetostat dose, with the time to first dose reduction at 4.9 months.

TABLE 1 Demographics and characteristics of Japanese patients with relapsed or refractory B-cell lymphoma treated with tazemetostat

Characteristic	Patients (n = 7)
Age, years; median (range)	73.0 (59-85)
Sex, male/female	4 (57.1)/3 (42.9)
ECOG performance status, n (%)	
0/1	5 (71.4)/2 (28.6)
Histopathologic subtype, n (%)	
Follicular lymphoma	4 (57.1)[a]
Diffuse large B-cell lymphoma	3 (42.9)[b]
Number of prior chemotherapy treatments, n (%)	
1	3 (42.9)
2	0 (0.0)
≥3	4 (57.1)
Median (range)	3 (1-5)
Auto-HSCT, n (%)	0 (0)

Abbreviation: Auto-HSCT, autologous hematopoietic stem cell transplantation.

[a]One patient with *EZH2* gene mutation.

[b]One patient was germinal center B-cell-like (GCB)-type, whereas two patients were non-GCB type, based on Hans criteria-based diagnosis at the investigator site.

3.3 | Adverse events and DLTs

A summary of treatment-emergent AEs and TR-AEs is shown in Table 2. All seven patients experienced at least one AE, with six (85.7%) patients having at least one TR-AE. Grade 3 or higher AEs occurred in four (57.1%) patients. The common AEs were nasopharyngitis (five patients; 71.4%) and thrombocytopenia, constipation, and dysgeusia (three patients each; 42.9%). Grade 3 AEs reported were thrombocytopenia (two patients; 28.6%) and anemia, leukopenia, neutropenia, lymphopenia, fatigue, increased γ-glutamyltransferase, hypophosphatemia, and squamous cell carcinoma of the tongue (one patient each; 14.3%). Grade 4 AEs were intestinal perforation and increased levels of blood triglycerides (one patient each; 14.3%). The common TR-AEs were thrombocytopenia and dysgeusia (three patients each; 42.9%). No DLTs were observed. None of the patients died or had AEs resulting in death. Serious AEs occurred in two (28.6%) patients, consisting of intestinal perforation and squamous cell carcinoma of the tongue, but both assessed as not related to study drug. One patient (14.3%) experienced grade 2 peripheral neuropathy, leading to drug dose reduction. One patient (14.3%) discontinued the treatment due to squamous cell carcinoma of the tongue, which is not a treatment-related event. One (14.3%) patient experienced an AE leading to dose reduction, whereas four (57.1%) patients experienced AEs leading to dose interruption.

No AEs of T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia or myeloid malignancy, including myelodysplastic syndrome, were reported during the study. No clinically important changes were observed in the mean or median laboratory values, vital signs, or weight over time. Shift analyses revealed no shifts of clinical concern noted in urinalysis parameters and ECG findings. No abnormal QT interval corrected for heart rate using Fridericia's formula values was found.

3.4 | Antitumor activity and EZH2 mutations

In seven treated patients, one (14.3%) had CR, three (42.9%) had PR, one (14.3%) had stable disease, and two (28.6%) had progressive disease as BOR, based on the investigator assessment (Table 3). The ORR was 57.1% (95% CI: 18.4-90.1) with response in one patient with DLBCL (n = 3) and three patients with FL (n = 4). Overall, six (85.7%) patients experienced a reduction of tumor burden (Figure 1). One (14.3%) patient had an *EZH2* mutation, whereas five (71.4%) patients did not. One patient (14.3%) had an unknown *EZH2* mutational status. The COO status of the three patients with DLBCL was GCB type in one patient and non-GCB type in two patients.

TABLE 2 D-limiting toxicity and treatment-emergent adverse events (TEAEs) (≥2 patients) in Japanese patients with relapsed or refractory B-cell lymphoma treated with tazemetostat

	Patients (n = 7)			
	All TEAEs		Treatment-related TEAEs	
TEAEs	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)
Hematologic toxicity				
Thrombocytopenia	3 (42.9)	2 (28.6)	3 (42.9)	2 (28.6)
Anemia	2 (28.6)	1 (14.3)	2 (28.6)	1 (14.3)
Leukopenia	2 (28.6)	1 (14.3)	1 (14.3)	0 (0.0)
Neutropenia	2 (28.6)	1 (14.3)	1 (14.3)	0 (0.0)
Nonhematologic toxicity				
Nasopharyngitis	5 (71.4)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	3 (42.9)	0 (0.0)	1 (14.3)	0 (0.0)
Dysgeusia	3 (42.9)	0 (0.0)	3 (42.9)	0 (0.0)
Blood creatinine increased	2 (28.6)	0 (0.0)	1 (14.3)	0 (0.0)
Dry eye	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)
Dry skin	2 (28.6)	0 (0.0)	2 (28.6)	0 (0.0)
Fatigue	2 (28.6)	1 (14.3)	2 (28.6)	1 (14.3)
Insomnia	2 (28.6)	0 (0.0)	1 (14.3)	0 (0.0)
Muscle spasms	2 (28.6)	0 (0.0)	2 (28.6)	0 (0.0)
Rash	2 (28.6)	0 (0.0)	2 (28.6)	0 (0.0)
Stomatitis	2 (28.6)	0 (0.0)	2 (28.6)	0 (0.0)

TABLE 3 Summary of tumor response in Japanese patients with relapsed or refractory B-cell lymphoma treated with tazemetostat

Response category	DLBCL (n = 3)	FL (n = 4)	Total (n = 7)
Best overall response, n (%)			
Complete response (CR)	1 (33.3)	0 (0.0)	1 (14.3)
Partial response (PR)	0 (0.0)	3 (75.0)	3 (42.9)
Stable disease	0 (0.0)	1 (25.0)	1 (14.3)
Progressive disease	2 (66.7)	0 (0.0)	2 (28.6)
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)
Objective response rate (CR + PR), n (%)	1 (33.3)	3 (75.0)	4 (57.1)
95% CI of objective response rate[a]	(0.8, 90.6)	(19.4, 99.4)	(18.4, 90.1)

Abbreviations: CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

[a]Calculated using Clopper-Pearson's exact method.

3.5 | Pharmacokinetics

The plasma concentration profiles and PK parameters of tazemetostat and its desethyl metabolite EPZ-6930 are shown in Figure 2 and Table 4. After oral administration of 800 mg tazemetostat, tazemetostat was rapidly absorbed. The median t_{max} values for tazemetostat and EPZ-6930 were approximately 2 hours after the C0D1 dosing and approximately 1 hour after the C1D15 dosing. The mean $t_{1/2}$ values of tazemetostat and EPZ-6930 were 7.59 and 8.83 hours, respectively, after C0D1 dosing and 4.59 and 4.91 hours, respectively after C1D15 dosing. The $t_{1/2}$ values were shorter for C1D15 than C0D1, but slopes of decline in mean plasma concentration profiles for tazemetostat and EPZ-6930 were similar up to 12 hours after dosing between C0D1 and C1D15. In addition, the slope of decline in mean plasma concentration profiles for tazemetostat and EPZ-6930 were slower after 12 hours after dosing for C0D1 (Unpublished data in Eisai). No remarkable difference in mean PK profiles was observed between the first dose administration for C1D1 and multiple doses for C1D15. The AUC ratios of EPZ-6930 to tazemetostat were shown to be 141% for C0D1 and 256% for C1D15. Plasma concentrations of tazemetostat reached steady-state after multiple dosing reached steady-state by C1D8 in almost all subjects. The mean urinary excretion of tazemetostat was less than 3% both after C0D1 and C1D15 dosing.

4 | DISCUSSION

In this multicenter, single-arm phase I study of tazemetostat in Japanese patients with relapsed or refractory B-NHL, tazemetostat was given orally at a dose of 800 mg BID and was found to be well tolerated. We did not observe any DLT in six DLTs evaluable patients. In a total of seven patients, the common AEs observed included thrombocytopenia, dysgeusia (43%), anemia, dry skin, fatigue, rash, and stomatitis (29%). No treatment-related SAEs were

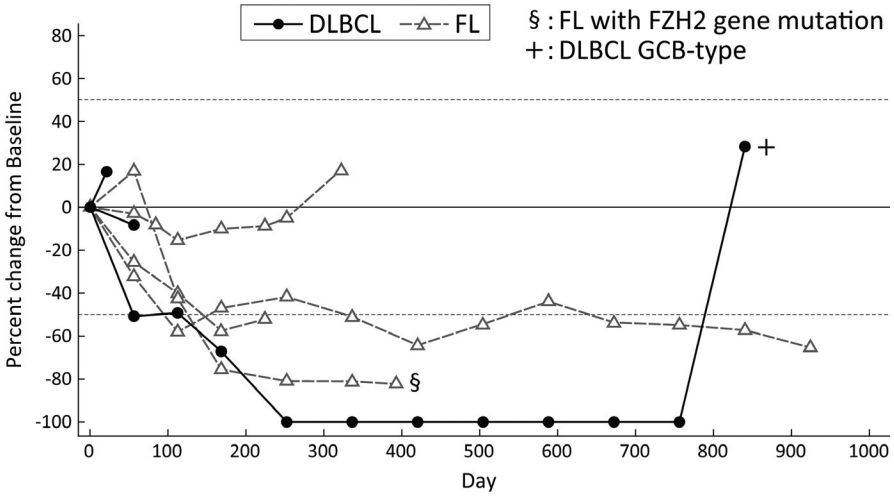

FIGURE 1 Changes in target tumor burden over time in Japanese patients with relapsed or refractory B-cell lymphoma treated with tazemetostat. Black circles indicate diffuse large B-cell lymphoma (DLBCL); gray triangle indicates follicular lymphoma (FL). §Patient with an *EZH2* mutation. +Patient with germinal center B-cell-like (GCB)-type DLBCL

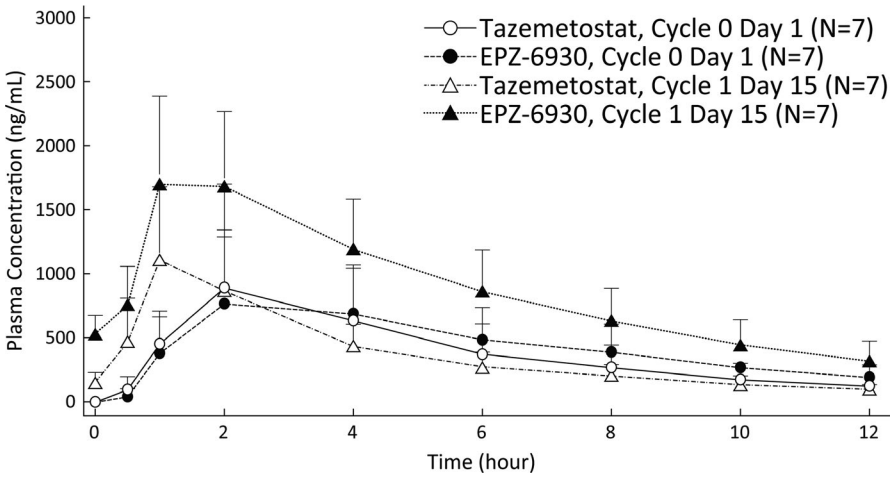

FIGURE 2 Plasma concentration profiles of tazemetostat and its metabolite, EPZ-6930, in Japanese patients with relapsed or refractory B-cell lymphoma. Plasma concentration shown as the mean + SD after single and multiple oral administrations of 800 mg tazemetostat

observed. In the global phase II study, among all 99 patients, common treatment-related grade 3 or higher AEs were thrombocytopenia (3%), neutropenia (3%), and anemia (2%). Treatment-related SAEs were reported in four (4%) of 99 patients. Importantly, there were no treatment-related deaths.[28] There was some difference between safety profiles in the global phase II study and in this phase I study. However, as the number of patients in our present study was limited, the safety profile of tazemetostat in Japanese patients will be confirmed in the next phase II study.

The ORR was 57% (4/7 patients), including response in three of four patients with FL and one of three patients with DLBCL. We observed a gain-of-function mutation in *EZH2* in one patient with FL showing a partial response with a −82.3% maximum change in the sum of the product of the diameters from baseline in the target lesion. In a preclinical study, tazemetostat showed antiproliferative effects, inducing apoptosis, in *EZH2*-mutant and WT cells.[31] It was also reported that treatment of *EZH2*-mutant NHL xenograft-bearing mice with tazemetostat caused dose-dependent tumor growth inhibition, including complete and sustained tumor regression with a correlative decrease in the levels of H3K27Me3 in tumors and selected normal tissues. Another in vitro study showed that treatment with EZH2 inhibitors reduced viability in both EZH2-WT and *EZH2*-mutated lymphoma cell lines; however, viability was much more reduced in the *EZH2*-mutated cells.[25] In a global (ex-Japan) phase II study, it was reported that tazemetostat showed a greater ORR (69% [95% CI 53-82; 31 of 45 patients]) in *EZH2*-mutated patients compared to that in WT patients (35% [23-49; 19 of 54 patients]). In our study, one patient, classified as GCB-DLBCL, showed complete response. The other two patients with DLBCL were identified as non-GCB type by the Hans IHC-based algorithm. Generally, EZH2 is known to be expressed in GC, playing a crucial role in its proliferation and differentiation. Hence, the cellular origin of lymphoma might be important in predicting the efficacy of tazemetostat. Moreover, a BCL2 fusion was observed in most patients with FL and GCB-DLBCL.[32] Interestingly, BCL-2-transduced *EZH2*-mutant mice were shown to exhibit much faster lymphomagenesis than BCL-2 transduced WT mice.[33] The other two patients with FL showed PR, despite the WT *EZH2* status of their lymphomas. In preclinical animal models, tazemetostat showed potent antitumor effects in *EZH2*-mutant NHL xenograft-bearing mice in a dose-dependent manner. However, tazemetostat was also found to induce antitumor effects in *EZH2*-wt lymphoma xenograft models.[31] Immunodeficient SCID mice lacking mature B and T lymphocytes but showing residual

TABLE 4 Summary of plasma pharmacokinetic parameters of tazemetostat and EPZ-6930 after single and multiple doses in Japanese patients with relapsed or refractory B-cell lymphoma treated with tazemetostat

	After single dose Cycle 0 day 1		After multiple doses Cycle 1 day 15	
Pharmacokinetic parameter	**Tazemetostat**	**EPZ-6930**	**Tazemetostat**	**EPZ-6930**
C_{max} (ng/mL)	1150 (787)	948 (556)	1290 (582)	1950 (773)
$C_{ss,min}$ (ng/mL)	–	–	95.1 (37.7)	322 (170)
t_{max} (h)	1.97 (0.95, 4.08)	1.97 (1.12, 4.08)	1.05 (0.88, 2.03)	1.07 (0.88, 2.03)
$AUC_{(0\text{-}12\ h)}$ (ng·h/mL)	4700 (2810)	5280 (2890)	4500 (1570)	10 800 (3600)
$AUC_{(0\text{-}t)}$ (ng·h/mL)	5990 (3460)[a]	7700 (4090)[a]	4490 (1560)[b]	10 800 (3560)[b]
$AUC_{(0\text{-}inf)}$ (ng·h/mL)	6030 (3470)	7730 (4090)	–	–
$t_{1/2}$ (h)	7.59 (1.24)	8.83 (1.43)	4.59 (1.93)	4.91 (2.32)
CL/*F* (L/h)	175 (90.4)	NA	205 (98.6)	NA
V_z/F (L)	1910 (1050)	NA	1580 (1540)	NA
R_{ac} (C_{max})	–	–	1.32 (0.604)	2.59 (1.36)
R_{ac} (AUC)	–	–	1.09 (0.358)	2.58 (1.44)
R_{ss}	–	–	0.849 (0.277)	1.76 (1.07)

Note: Data are shown as the mean (SD) except for t_{max}; for t_{max}, median (minimum, maximum) is shown. The last sampling time point was 72 h after single administration (a) and 12 h after multiple administrations (b). Pharmacokinetic analysis set: N = 7. R_{ac} and R_{ss} values were calculated using these formulas: R_{ac} (AUC) = $AUC_{(0\ -\ 12\ h)}$ on cycle 1 day 15/$AUC_{(0\ -\ 12\ h)}$ on cycle 0 day 1, R_{ac} (C_{max}) = C_{max} on cycle 1 day 15/C_{max} on cycle 0 day 1, and R_{ss} = $AUC_{(0\ -\ 12\ h)}$ on cycle 1 day 15/$AUC_{(0\ -\ inf)}$ on cycle 0 day 1.

Abbreviations: $AUC_{(0\text{-}12\ h)}$, area under the concentration-time curve from zero time to 12 h; $AUC_{(0\text{-}inf)}$, area under the concentration-time curve from zero to infinite; $AUC_{(0\text{-}t)}$, area under the concentration-time curve from zero time to time of last quantifiable concentration; $AUC_{(0\text{-}t)}$ ratio, metabolite to parent area under the concentration-time curve ratio adjusted in molecular weight; CL/*F*, apparent total clearance following oral administration; C_{max}, maximum plasma concentration; $C_{ss,min}$, minimum observed concentration at steady state; NA, not applicable; R_{ac}, accumulation index; R_{ss}, time and concentration dependent accumulation ratio; $t_{1/2}$, terminal elimination phase half-life; t_{max}, time at which the highest drug concentration occurs; V_z/F, apparent volume of distribution at the terminal phase.

immunity, such as natural killer cells, were used in these xenograft models. Recently, it was reported that an *EZH2* mutation was strongly enriched in both MHC-I and MHC-II negative lymphomas, with EZH2 inhibitors significantly restoring the expression of MHC in DLBCL cell lines. It was also reported that EZH2 regulates the expression of CD58, which is involved in tumor evasion in lymphoid malignancies.[34,35] These results suggested that EZH2 might regulate the immune system by modulating the effects of these molecules, and we thus speculated that tazemetostat might show efficacy through this immune regulation in both EZH2-mutant and WT patients.

Tazemetostat has been reported to be mainly metabolized by CYP3A4, and was shown to induce and inhibit the activity of CYP3A4 in vitro (Unpublished data in Eisai). The PK profiles of tazemetostat in Japanese patients were comparable to those of non-Japanese patients previously reported.[26] The mean value of the time- and concentration-dependent accumulation ratio (R_{ss}) was shown to be 0.849, slightly smaller than 1, suggesting that there was no accumulation of tazemetostat and a possible small effect of autoinduction of CYP3A4. We further observed apparent differences in the $t_{1/2}$ values of tazemetostat and EPZ-6930, its demethylated metabolite, between C0D1 and C1D15. We speculated that this was due to the difference in the last blood sampling time points at 72 and 12 hours after dosing for C0D1 and C1D15, respectively. As EPZ-6930 showed weaker inhibitory activity (1/11-1/31) against EZH2 than tazemetostat in preclinical studies and its exposure was larger than that of tazemetostat, we assumed that EPZ-6930 might partially contribute to the observed antitumor activity.

In conclusion, the present phase I study showed that 800 mg BID of tazemetostat showed an acceptable safety profile and promising antitumor activity in Japanese patients with relapsed or refractory B-NHL. However, most patients in this study carried WT *EZH2*. Subsequent studies to evaluate the efficacy and safety of tazemetostat in Japanese patients with B-NHL, especially in patients with *EZH2* mutations, are warranted.

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DISCLOSURE

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ORCID

Wataru Munakata https://orcid.org/0000-0002-4679-0656
Shinichi Makita https://orcid.org/0000-0001-6609-8088
Dai Maruyama https://orcid.org/0000-0003-0654-6920

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