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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *Lancet Oncol* 2020; published online Oct 6. http://dx.doi.org/10.1016/S1470-2045(20)30441-1.

Online Supplement

Supplemental Methods

EZH2 Mutation Testing

Central testing of EZH2 mutation status was most often performed on biopsy tissue from the lymph node (>80%). Other biopsies sources included liver, posterior chest wall, retroperitoneal mass, pelvic mass, and other locations. No bone marrow biopsies were recorded as the tissue source for EZH2 testing. Most EZH2 testing was performed on formalin fixed paraffin embedded (FFPE) tissue obtained at diagnosis and the most common biopsy method was resection/excisional biopsy, although needle biopsies were performed in some patients.

Central EZH2 testing was evaluated at the designated study laboratory testing sites using the cobas® EZH2 Mutation Test (Roche Molecular Systems, Pleasanton, CA, USA). The cobas® EZH2 Mutation Test (Roche Sequencing Solutions) is a multiplexed real-time PCR-based assay that detects gain-of-function human EZH2 mutations in the SET domain that catalytically activate this lysine methyltransferase. The hotspot mutations detected by the cobas® assay are Y646F, Y646N, Y646S, Y646H, Y646C, A682G, A692V. Formalin-fixed paraffin-embedded (FFPE) tumour tissue sections (5 micron thickness) were provided, typically mounted on slides. The majority of the FFPE tumour tissue samples used were biopsied within 1 year of cobas testing. The tissue samples were deparaffinized and scraped into tubes for DNA extraction. In cases where tumour content was <10%, macrodissection was done following deparaffinization. DNA was isolated from tumour tissue extract and quantitated using a Nanodrop UV-Vis Spectrophotometer. The DNA stock concentration from the samples must be ≥2 ng/µL to perform the cobas® EZH2 Mutation Test. Three amplification/detection replicates are run per sample using a total of 50-ng input DNA for each replicate. The 7 mutant EZH2 variants were configured into 3 separate PCR amplification reactions. PCR amplification, product detection, and analysis were conducted on the cobas z480 analyzer. Mutant EZH2 products are detected with oligonucleotide probes labeled with various fluorescent dyes (eg, FAM, HEX, CY5.5, JA270). The variant allele detection limit per test is 1–2%.

Definition of transformed follicular lymphoma

Histologic transformation refers to the evolution of a clinically indolent follicular lymphoma to a clinically aggressive lymphoma (e.g., diffuse large B cell lymphoma [DLBCL]) defined as those lymphomas in which survival of the untreated patient is measured in months. Histologic transformation of follicular lymphoma occurs at a rate of approximately 1–2% per year and is associated with rapid progression of lymphadenopathy, infiltration of extranodal sites, development of systemic symptoms, elevated serum lactate dehydrogenase, hypercalcemia, and often a poor prognosis. As noted, these patients were enrolled in the follicular lymphoma cohorts of this study based upon their initial diagnosis and, therefore, analysed in the intent-to-treat population, regardless of the transformation noted at the time of study enrolment. This approach was considered acceptable when the United States Food and Drug administration was reviewing data on the efficacy and safety of tazemetostat in follicular lymphoma.

Exploratory outcomes definitions

Overall survival: Defined as the time (in months) from the date of the first dose of study drug until the date of death from any cause.

Disease control rate: Defined at the specified time point (i.e., month 12, month 18, and month 24) as the percentage of patients who achieve either confirmed complete response or partial response of any duration or who have stable disease lasting at least the number of month indicated from the start of study drug.

Time to first response: Defined as the time (in months) from the date of the first dose of study drug until the date of first response (complete or partial response, whichever is first recorded).

See protocol in appendix (starting on p. 18) for additional information on exploratory endpoints.

Reference

1. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;**25:** 579–86.

Table S1 Study investigators

Site	Country	Principal investigator	Number of patients enrolled
CHU Lille Hopital Claude Huriez Service des maladies du sang, Lille	France	Franck Morschhauser	18
Service d'Hématologie, Centre Hospitalier Lyon Sud, Lyon	France	Gilles Salles	10
Centre Henri Becquerel, Service hematologie, Rouen	France	Herve Tilly	7
Catherine Lewis Centre, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London	UK	Aristeidis Chaidos	5
Beatson West of Scotland Cancer Centre, Glasgow	UK	Pamela McKay	5
Institut de cancérologie gustave Roussy, Villejuif	France	Vincent Ribrag	4
Memorial Sloan Cancer Center, New York	US	Connie Batlevi	4
University of Michigan, Comprehensive Cancer, Ann Arbor	US	Tycel Phillips	4
Andrew Love Cancer Centre and University Hospital Geelong, Geelong	Australia	Phillip Campbell	4
Jewish General Hospital, Montreal, Quebec	Canada	Sarit Assoulin	4
Institut d'hématologie de Basse Normandy	France	Gandhi Damaj	3
Institut Bergonié, Service d'Hématologie, Bordeaux	France	Anna Schmitt	3
Cancer Research UK Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester	UK	John Radford	3
Peter MacCallum Cancer Centre, Victoria	Australia	Michael Dickinson	3
Monash Medical Centre, Victoria	Australia	Stephen Opat	3
Malopolskie Centrum Medyczne, Kraków	Poland	Wojceich Jurczak	3
Examen Sp z o.o. 60-192 UL Barwicka, Poznań	Poland	Maciej Kazmierczak	3
CHU Hôtel Dieu, Service d'Hématologie Clinique, Nantes	France	Steven Le Gouill	2
Hôpital Henri Mondor, Unité Hémopathies Lymphoïdes, Créteil	France	Corinne Haioun	2
Cancer Research UK Clinical Centre, Somers Cancer Research Building, Southampton	UK	Peter Johnson	2
Institute of Hematology and Medical Oncology, Bologna	Italy	Pier Luigi Zinzani	2
Institut Paoli Calmettes, Service hematologie Clinique, Marseille	France	Reda Bouabdallah	1
Centrum Onkologii Ziemi Lubelskiej im św. Jana z Dukli Oddział Hematologiczny, Lublin	Poland	Krzysztof Giannopoulos	1
Princess Margaret Cancer Centre, Division of Medical Oncology & Hematology, Toronto	Canada	Michael Crump	1
Virginia Cancer Specialists, P.C., Fairfax	US	Gregory Orloff	1
Sansum Clinic, Santa Barbara and Solvang	US	Daniel Greenwald	1

Table S2 Dose adjustment of tazemetostat

Treatment-Related Toxicity[a]	During Therapy	Approximate Dose Adjustment[b]
Grade 1		
Any occurrence	Continue tazemetostat	Maintain dose level
Grade 2[c]		
First occurrence	Interrupt tazemetostat until resolved to grade ≤1 or baseline level[b]	Maintain dose level
Second occurrence (same or new toxicity)		Reduce dose to 75% of starting dose
Third occurrence (same or new toxicity)		Reduce dose to 50% of starting dose
Fourth occurrence (same or new toxicity)		Discuss with Medical Monitor
Grade 3, excluding neutropenia		
First occurrence	Interrupt tazemetostat until resolved to grade ≤1 or baseline level[b]	Reduce dose to 75% of starting dose
Second occurrence (same or new toxicity)		Reduce dose to 50% of starting dose
Third occurrence (same or new toxicity)	Discontinue tazemetostat	Not applicable
Grade 3 neutropenia (ANC <1–0·5 × 10^9/L)		
ANC ≥0·75 × 10^9/L		
First occurrence	Continue tazemetostat	Maintain dose level
<0·75 × 10^9/L		
First occurrence	Interrupt tazemetostat until resolved to ANC ≥0·75 × 10^9/L	Reduce dose to 75% of starting dose
Second occurrence		Reduce dose to 50% of starting dose
Third occurrence	Discontinue tazemetostat	Not applicable
Grade 4[d]		
Any occurrence	Discontinue tazemetostat	Not applicable

[a]Excluding alopecia and inadequately treated nausea, vomiting, or diarrhoea. [b]A delay of tazemetostat for >28 days due to any toxicity must have been discussed with the sponsor before treatment could have been resumed.
[c]Excluding grade 2 anaemia, as these patients were allowed to continue tazemetostat at the current dose level.
[d]Excluding grade 4 hematologic toxicities <72 hours in duration. ANC=absolute neutrophil count.

Table S3 IRC-assessed efficacy outcomes in clinically relevant subgroups by EZH2 mutation status (intent-to-treat population)

	POD24		Double-Refractory[d]		Refractory to Rituximab[e]	
Endpoint	**MT EZH2 (n=19)**	**WT EZH2 (n=32)**	**MT EZH2 (n=9)**	**WT EZH2 (n=15)**	**MT EZH2 (n=22)**	**WT EZH2 (n=32)**
Objective response rate[a], no. (%) [95% CI[b]]	12 (63) [38·4 to 83·7]	8 (25) [11·5 to 43·4]	7 (78) [40·0 to 97·2]	4 (27) [7·8 to 55·1]	13 (59) [36·4 to 79·3]	10 (31) [16·1 to 50·0]
Best overall response, no. (%)						
Complete response	2 (11)	1 (3)	2 (22)	0	2 (9)	1 (3)
Partial response	10 (53)	7 (22)	5 (56)	4 (27)	11 (50)	9 (28)
Stable disease	7 (37)	11 (34)	1 (11)	4 (27)	8 (36)	8 (25)
Progressive disease	0	9 (28)	1 (11)	5 (33)	1 (5)	10 (31)
NE or unknown	0	4 (13)	0	2 (13)	0	4 (13)
Duration of response						
Responders, no.	12	8	7	4	13	10
Median, months [95% CI[c]]	6·6 [2·1 to NE]	13·0 [0·5 to NE]	6·1 [2·1 to NE]	6·1 [3·4 to NE]	7·3 [2·9 to 12·0]	7·4 [1·0 to NE]
PFS						
Events, no.	10	18	6	11	17	21
Median, months [95% CI[c]]	13·8 [7·3 to NE]	5·8 [2·0 to 16·7]	8·4 [1·3 to NE]	3·7 [1·8 to 11·1]	10·9 [5·5 to 11·9]	5·6 [1·9 to 13·8]

[a]Objective response rate includes patients with complete or partial response. [b]By Clopper–Pearson exact method. [c]By Brookmeyer and Crowley method. [d]Refractory to rituximab (as monotherapy or as part of a combination therapy) and a chemotherapy induction regimen containing ≥1 alkylating agent or purine nucleoside antagonist and relapsed within 6 months. [e]Refractory to either rituximab monotherapy or rituximab-containing therapy or progressive disease within 6 months of completion of rituximab-containing therapy. CI=confidence interval. IRC=independent radiology committee. MT=mutant. NE=not estimable. PFS=progression-free survival. POD24=progression of disease or relapse within 24 months of diagnosis or the start of frontline treatment with immunochemotherapy. WT=wild-type.

Table S4 IRC-assessed objective response rate in additional subgroups

Subgroup	MT EZH2			WT EZH2		
	n	**Objective response rate[a], no. (%) [95% CI[b]]**	**Duration of response, median, months [95% CI[c]]**	**N**	**Objective response rate[a], no. (%) [95% CI[b]]**	**Duration of response, median, months [95% CI[c]]**
Lines of prior therapy						
≤2	24	18 (75) [53·3–90·2]	20·3 [5·0–NE]	17	9 (53) [27·8–77·0]	11·1 [0·5–14·7]
>2	21	13 (62) [38·4–81·9]	8·3 [3·7–NE]	37	10 (27) [13·8–44·1]	19·3 [3·4–NE]
Refractory to treatment						
Yes	33	21 (64) [45·1–79·6]	8·3 [3·7–NE]	42	12 (29) [15·7–44·6]	7·4 [3·4–19·3]
No	12	10 (83) [51·6–97·9]	11·3 [6·5–NE]	12	7 (58) [27·7–84·8]	14·7 [0·5–NE]
Prior radiotherapy						
Yes	13	8 (62) [31·6–86·1]	7·5 [2·1–20·3]	12	5 (42) [15·2–72·3]	7·4 [0·5–NE]
No	32	23 (72) [53·3–86·3]	11·3 [6·5–NE]	42	14 (33) [19·6–49·5]	14·7 [5·6–NE]
Tumour burden (bulky disease)						
Yes	3	2 (67) [9·4–99·2]	12·0 [NE–NE]	2	0 (0) [0·0–84·2]	12·0 [NE–NE]
No	33	24 (73) [54·5–86·7]	8·3 [5·0–NE]	46	17 (37) [23·2–52·5]	13·0 [4·8–NE]
Gender						
Male	19	13 (68) [43·4–87·4]	11·1 [2·1–NE]	34	9 (26) [12·9–44·4]	13.0 [0.5–NE]
Female	26	18 (69) [48·2–85·7]	8·3 [6·5–NE]	20	10 (50) [27·2–72·8]	11.1 [1.0–NE]
Age						
<65 years	25	18 (72) [50·6–87·9]	8·3 [3.7–12.0]	32	9 (28) [13·7–46·7]	14.7 [4.8–NE]
≥65 years	20	13 (65) [40·8–84·6]	NE [2·9–NE]	22	10 (45) [24·4–67·8]	11.1 [0.5–NE]
Time from last therapy to first dose						
≤1 month	5	3 (60) [14·7–94·7]	NE [2·1–NE]	3	0 (0) [0·0–70·8]	NE [2·1–NE]
>1 month	40	28 (70) [53·5–83·4]	10·9 [7·2–20·3]	51	19 (37) [24·1–51·9]	13·0 [5·6–NE]
Region						
Europe	29	20 (69) [49·2–84·7]	11·3 [5·0–NE]	47	18 (38) [24·5–53·6]	5·6 [0·5–13·0]
North America	12	7 (58) [27·7–84·8]	8·3 [2·0–NE]	2	0 (0) [0·0–84·2]	8·3 [2.0–NE]
Rest of the world	4	4 (100) [39·8–100]	NE [8·3–NE]	5	1 (20) [0·5–71·6]	5·7 [NE–NE]
GELF						
Yes	31	21 (68) [48·6–83·3]	8·3 [3·7–NE]	40	11 (28) [14·6–43·9]	7·4 [1·0–14·7]
No	14	10 (71) [41·9–91·6]	11·3 [2·0–NE]	14	8 (57) [28·9–82·3]	NE [4·8–NE]

[a]Objective response rate includes patients with complete or partial response. [b]By Clopper–Pearson exact method.
[c]By Brookmeyer and Crowley method. CI=confidence interval. GELF=Groupe d'Etude des Lymphomes Folliculaires. IRC=independent radiology committee. MT=mutant. NE=not estimable. WT=wild-type.

Table S5 IRC-assessed progression-free survival in additional subgroups

Subgroup	MT EZH2			WT EZH2		
	n	**PFS events, no.**	**PFS, median months [95% CI[a]]**	**n**	**PFS events, no.**	**PFS, median months [95% CI[a]]**
Lines of prior therapy						
≤2	24	10	19·2 (10·9–NE)	17	11	14·3 (3·3–16·7)
>2	21	15	11·2 (5·4–16·3)	37	20	5·8 (2·0–21·0)
Refractory to treatment						
Yes	33	19	11·1 (8·3–22·1)	42	24	8·2 (2·3–13·8)
No	12	6	19·2 (8·3–NE)	12	7	14·6 (3·7–NE)
Prior radiotherapy						
Yes	13	8	11·2 (8·1–22·0)	12	9	7·6 (1·0–21·0)
No	32	17	14·8 (8·3–22·1)	42	22	11·1 (3·7–16·6)
Tumour burden (bulky disease)						
Yes	3	1	13·8 (NE–NE)	2	1	8·2 (NE–NE)
No	33	20	11·2 (8·3–22·0)	46	27	11·1 (3·3–16·6)
Gender						
Male	19	10	14·8 (7·3–NE)	34	20	5·4 (1·9–11·1)
Female	26	15	11·9 (8·4–22·0)	20	11	14·3 (5·6–27·6)
Age						
<65 years	25	18	13·8 (8·3–19·2)	32	17	11·1 (2·0–16·6)
≥65 years	20	7	11·9 (8·3–NE)	22	14	11·1 (3·7–16·7)
Time from last therapy to first dose						
≤1 month	5	2	NE (1·3–NE)	3	2	3·2 (0·7–5·8)
>1 month	40	23	13·8 (10·7–19·2)	51	29	11·1 (3·7–16·6)
Region						
Europe	29	15	13·8 (10·9–22·1)	47	27	11·1 (3·7–16·6)
North America	12	9	8·4 (3·6–16·3)	2	1	1·0 (NE–NE)
Rest of the world	4	1	NE (19·2–NE)	5	3	14·3 (2·3–NE)
GELF						
Yes	31	18	11.1 (8.3–19.2)	40	26	5·6 (3·0–11·1)
No	14	7	16.3 (8.3–NE)	14	5	NE (13·8–NE)

[a]By Brookmeyer and Crowley method. GELF=Groupe d'Etude des Lymphomes Folliculaires. CI=confidence interval. IRC=independent radiology committee. MT=mutant. NE=not estimable. PFS=progression-free survival. WT=wild-type.

Table S6 Treatment emergent adverse events (TEAEs) including treatment-related TEAEs leading to study drug discontinuation

Treatment emergent adverse events leading to drug discontinuation in one patient[a]
Prolonged QT on electrocardiogram
Acute myeloid leukaemia
Chronic kidney disease
Oral fungal infection[b]
Oral herpes[b]
Pneumonia[b]
Decreased weight[b]
Myelodysplastic syndrome[b]
Thrombocytopenia[b]
Dyaesthesia[b]
Dysgeusia[b]
Hypoaesthesia[b]

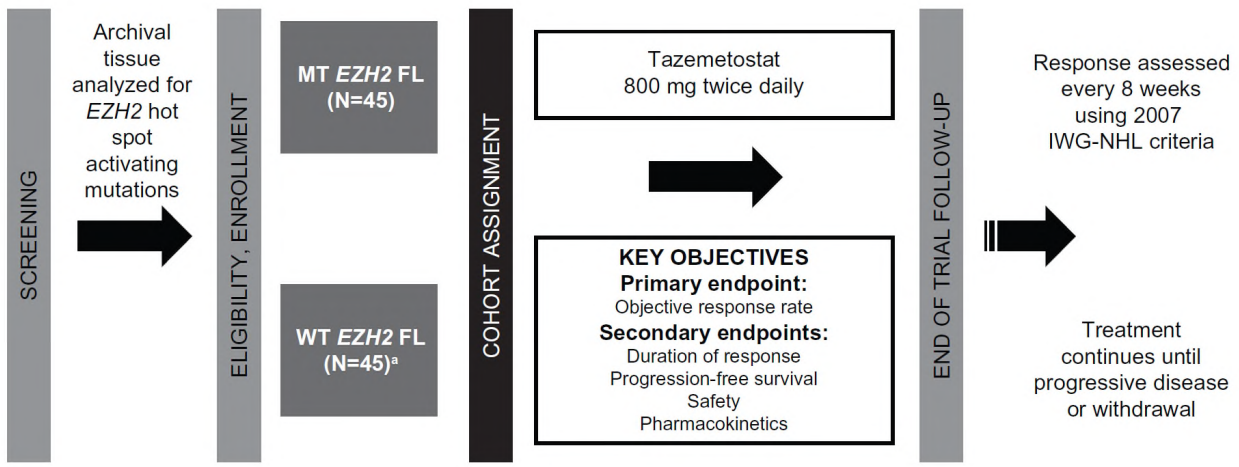
[a]Patients may have experienced more than one TEAE leading to study drug discontinuation. All TEAEs leading to discontinuation occurred in only one patient. [b]TEAE was considered treatment-related.

Table S7 Summary of second primary malignancies

Sex/Age[a]	Diagnosis	Time of Onset, Months[b]	Prior Anticancer Treatment
Male/61	MDS/MPN	15·3	Vincristine, doxorubicin, cyclophosphamide, methotrexate, rituximab, gemcitabine, idelalisib, 1x radiotherapy, 2x stem-cell transplant
Male/68	AML	25·8	2 systemic regimens of chlorambucil, cyclophosphamide, doxorubicin, rituximab, vincristine

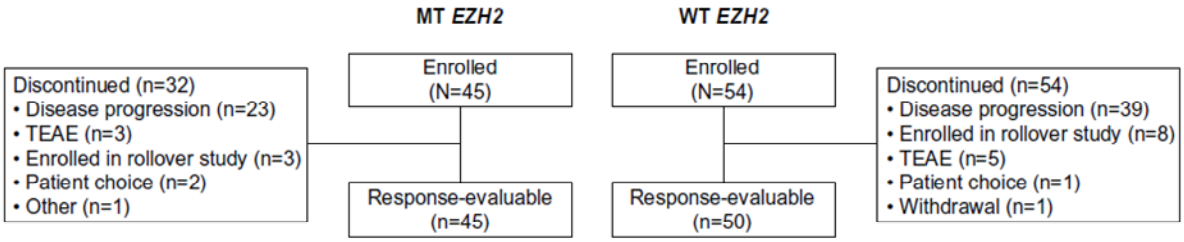
[a]Age at initial study entry. [b]Relative to first dose of tazemetostat. MDS=myelodysplastic syndrome. MPN=myeloproliferative neoplasm. AML=acute myeloid leukaemia.

Figure S1 Study design



[a]Planned enrollment was at least 45 patients; actual enrollment was 54 patients. MT=mutant. FL=follicular lymphoma. WT=wild-type. IWG-NHL=International Working Group response criteria for non-Hodgkin lymphoma.

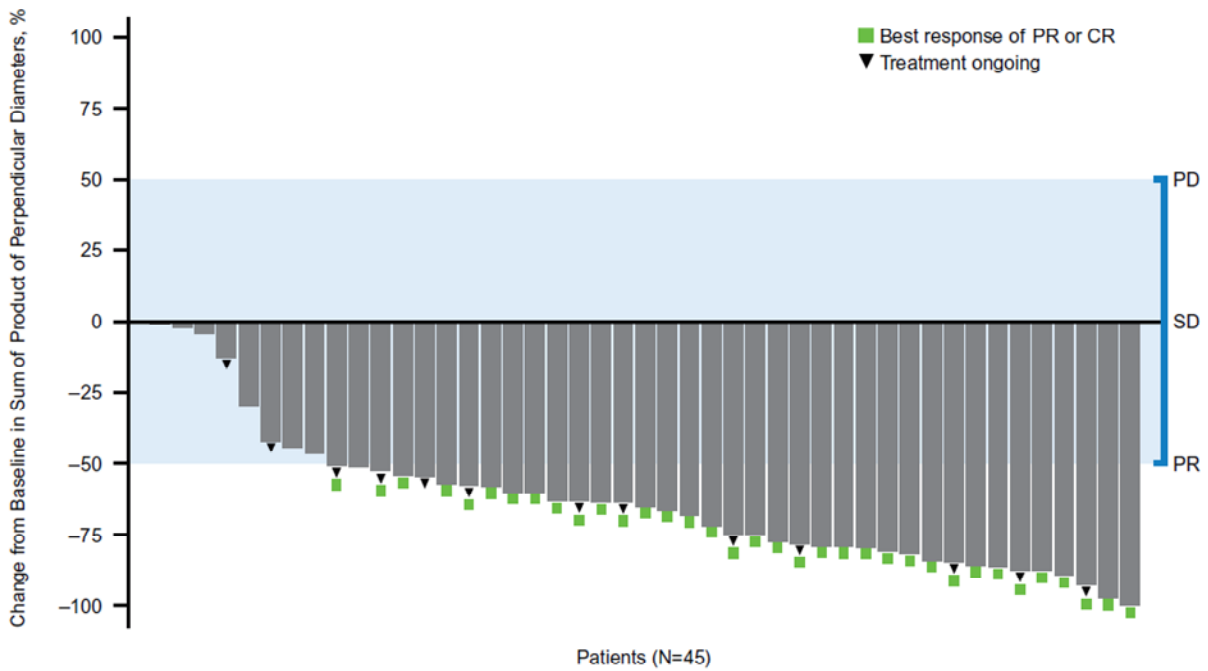
Figure S2 Patient disposition



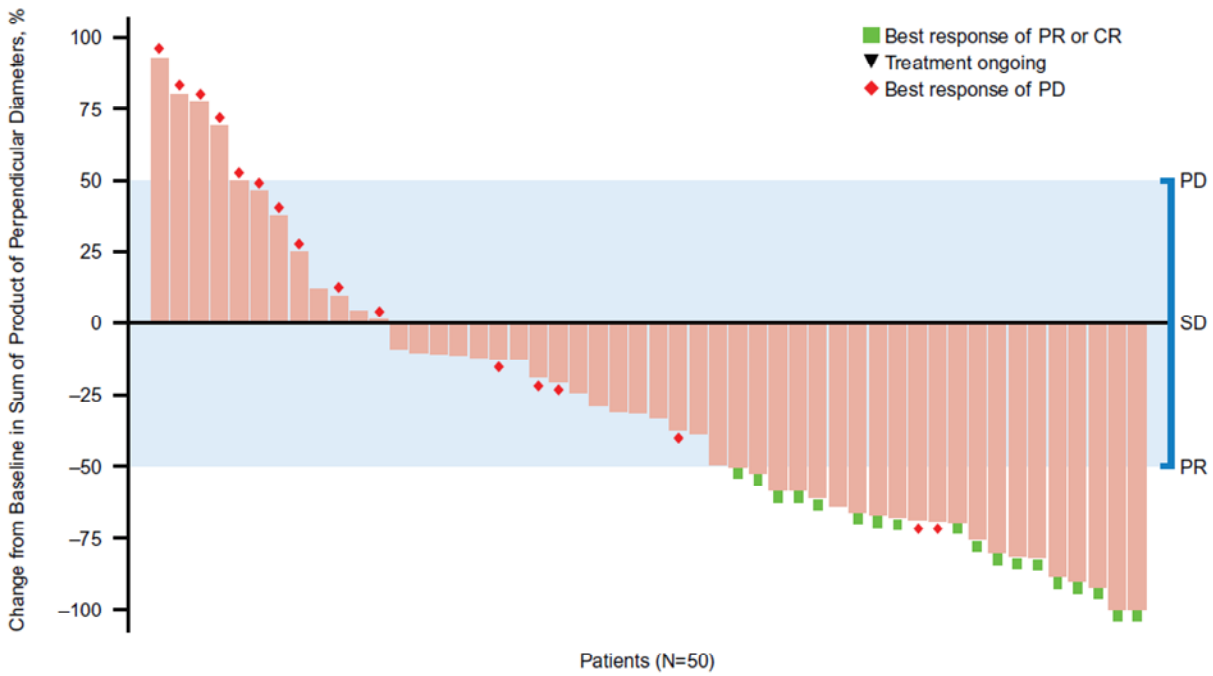
Tumour responses were not estimable, missing, or unknown in 4 patients in the WT EZH2 cohort. MT=mutant. WT=wild-type. TEAE=treatment-emergent adverse event.

Figure S3 Investigator-assessed tumour change from baseline in FL patients with (A) MT and (B) WT EZH2

A.



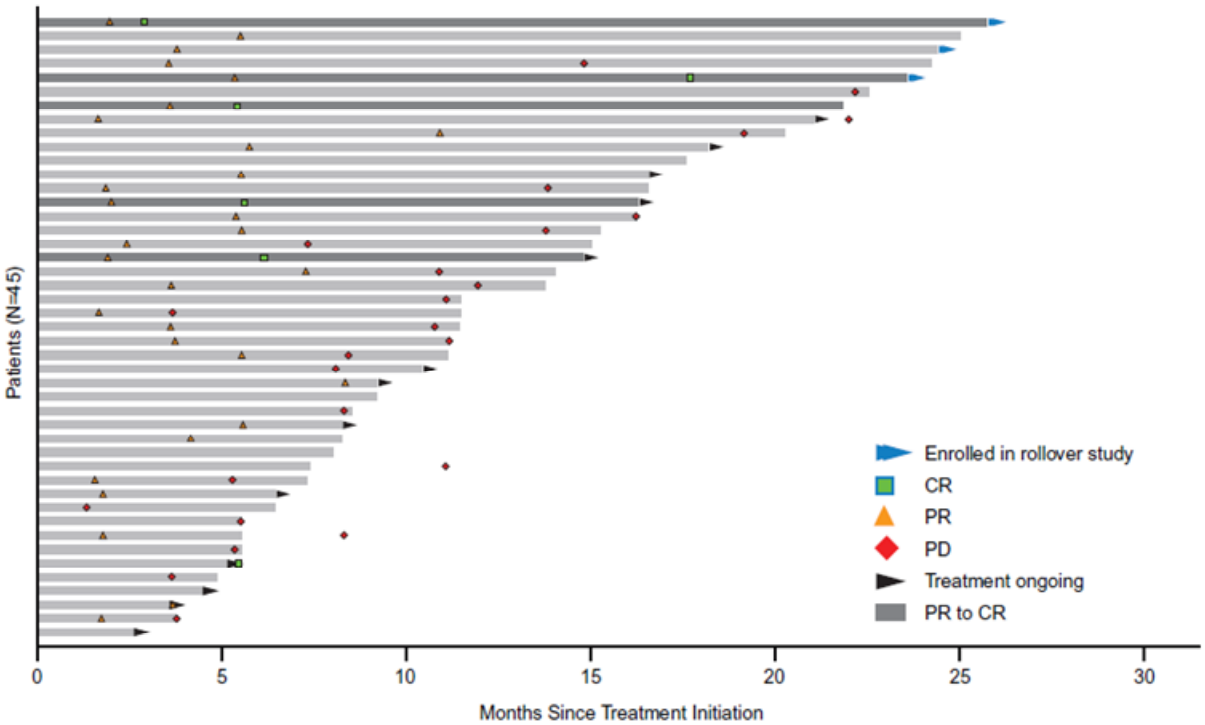
B.



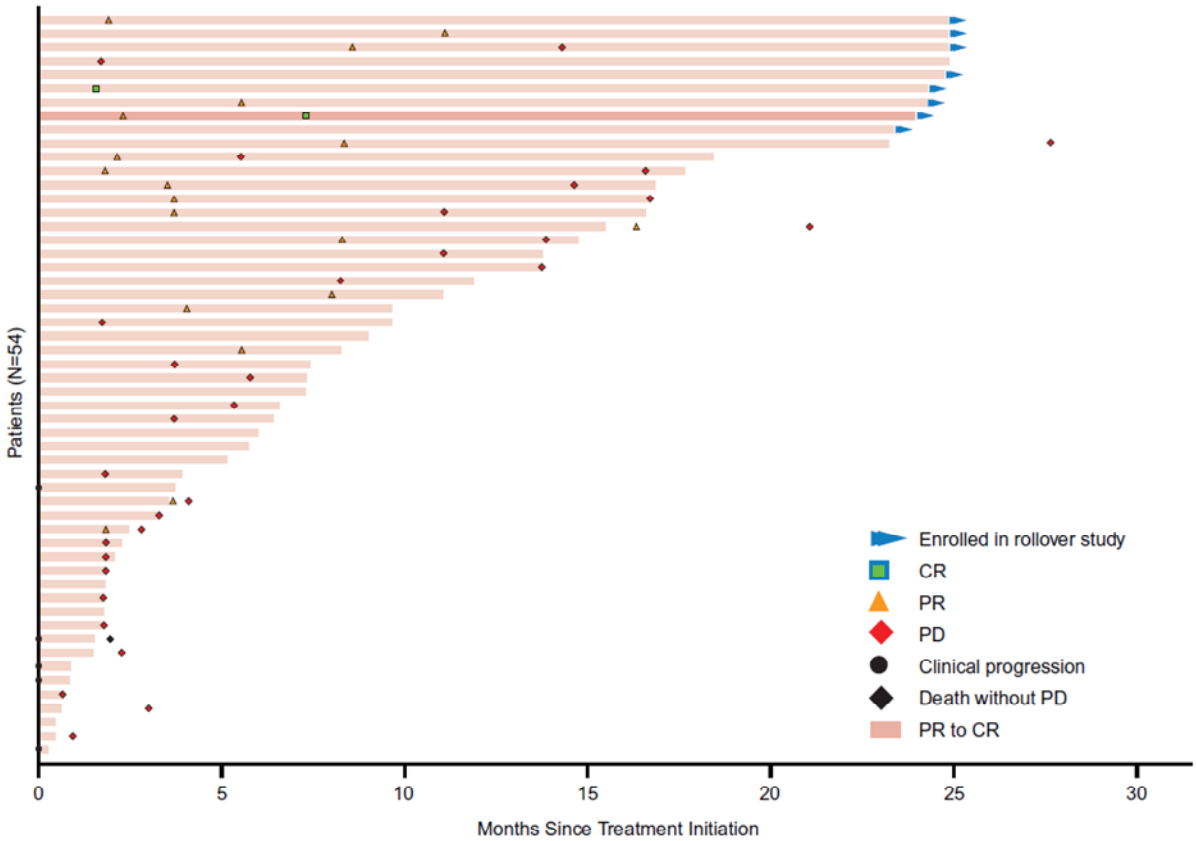
Tumour responses were not estimable, missing, or unknown in 4 patients in the WT EZH2 cohort. FL=follicular lymphoma. MT=mutant. WT=wild-type. PR=partial response. CR=complete response. SD=stable disease.

Figure S4 IRC-assessed tumour response over time for FL patients with (A) MT and (B) WT EZH2

A.



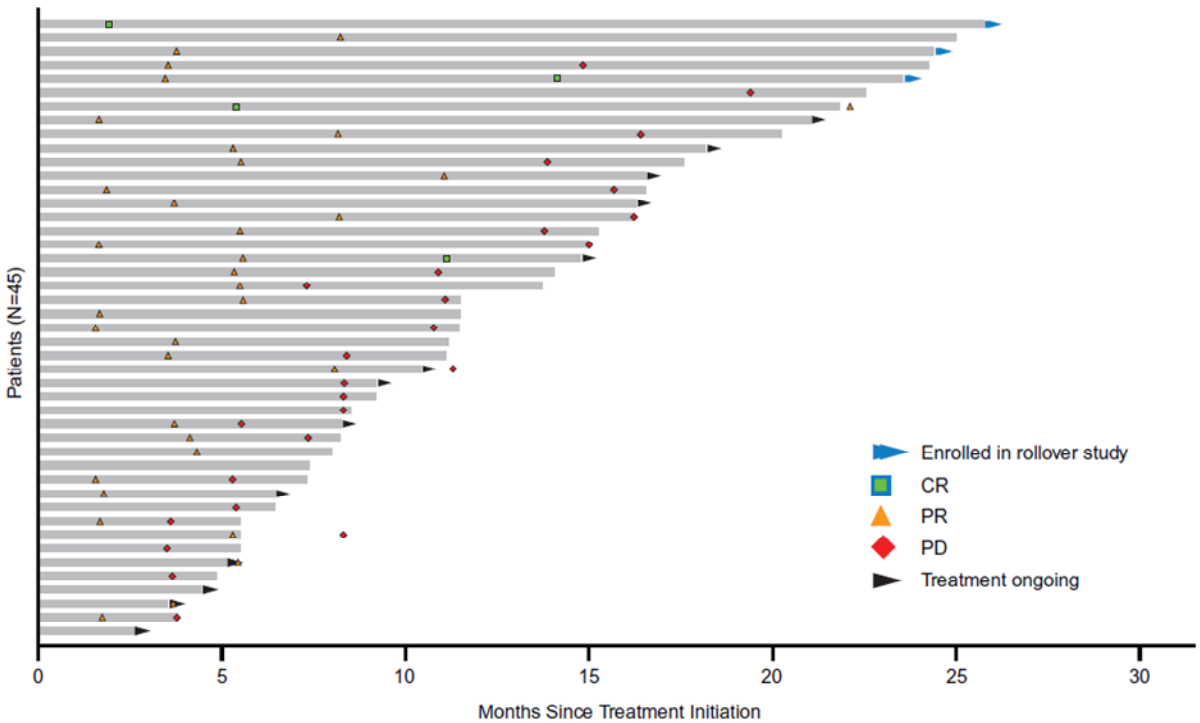
B.



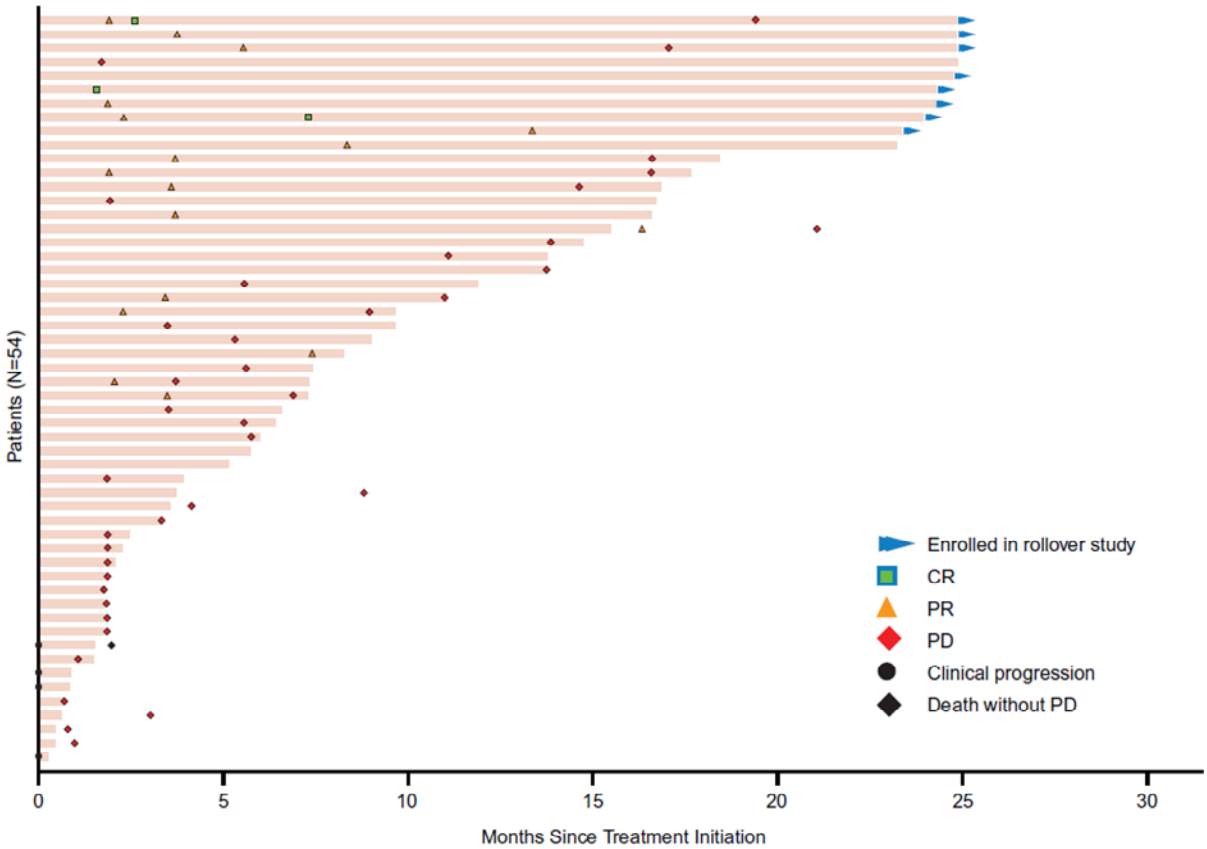
Tumour responses were not estimable, missing, or unknown in 5 patients in the WT EZH2 cohort. IRC=independent radiology committee. FL=follicular lymphoma. MT=mutant. WT=wild-type. CR=complete response. PR=partial response. PD=progressive disease.

Figure S5 Investigator-assessed tumour response over time for FL patients with (A) MT and (B) WT EZH2

A.



B.



Tumour responses were not estimable, missing, or unknown in 4 patients in the WT EZH2 cohort. FL=follicular lymphoma. MT=mutant. WT=wild-type. CR=complete response. PR=partial response. PD=progressive disease.

SPONSOR PROTOCOL APPROVAL PAGE

Protocol Title: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B Cell Lymphoma

Protocol Number: E7438-G000-101

Approved by:

INVESTIGATOR AGREEMENT PAGE

Protocol Title: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B Cell Lymphomas

Protocol Number: E-7438-G000-101

By signature below,
I agree to comply with the contents of this protocol and to conduct this study in compliance with Good Clinical Practices (GCP) and all applicable requirements.

I acknowledge that I am responsible for the overall study conduct and that I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information and training throughout the conduct of the study.

I have read and agree to the following Confidentiality Statement:

Confidentiality Statement: This protocol and any related documents from Epizyme, Inc., contain privileged information that is confidential and may not be disclosed unless such disclosure is required by federal laws or regulations. In any event, persons to whom the information is disclosed must be informed that it is privileged and/or confidential and may not be further disclosed by them. Information from this study may not be reproduced in any form without the written permission of Epizyme, Inc.

Principal Investigator:

Name: _____

Title: _____

Signature: _____ **Date:** _____

Name/Address of Institution: _____

_____

CLINICAL STUDY PROTOCOL

Protocol Number:	E7438-G000-101
Study Protocol Title:	An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B Cell Lymphomas
Sponsor:	Epizyme, Inc. 400 Technology Square – 4th Floor Cambridge, Massachusetts 02139 USA
Investigational Product Name:	Tazemetostat (formerly EPZ-6438 and E7438)
Indication:	Relapsed or progressive diffuse large B cell or follicular lymphoma
Phase:	1/2
Approval Date:	Original protocol: 01 Nov 2012 Amendment 01: 11 Feb 2013 Amendment 02: 24 Apr 2013 Amendment 03: 19 Jun 2013 Amendment 04: 22 Oct 2013 Amendment 05: 24 Feb 2014 Amendment 06: 29 Aug 2014 Amendment 06.1: 14 Oct 2014 Amendment 07: 19 Feb 2015 Amendment 07.1: 21 May 2015 Amendment 08: 15 Sep 2015 *Amendment 08.1 (US only): 03 Nov 2015* Amendment 09: 15 Apr 2016 *Amendment 09.1 (US only): 15 Apr 2016* Amendment 10: 21 Nov 2016 *Amendment 10.1 (US only): 21 Nov 2016* *Amendment 11.2 (Canada only): 08 Nov 2018*
EudraCT Number:	2012-004083-21
IND Number:	124025
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Epizyme (the Sponsor). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

1 CLINICAL PROTOCOL SYNOPSIS

Compound Name

Tazemetostat (formerly known as EPZ-6438 and E7438)

Name of Active Ingredient

N-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-yl)methyl]-5-[ethyl(tetrahydro-2*H*-pyran-4-yl)amino]-4-methyl-4'-(morpholin-4-ylmethyl)biphenyl-3-carboxamide hydrobromide

Study Protocol Title

An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B Cell Lymphomas

Sites

Phase 1: 2 sites (Institut Bergonie [IB] and Institut Gustave Roussy [IGR] sites in France only)
Phase 2: Up to 50 sites

Study Period and Phase of Development

Phase 1: First subject in 2Q2013; Last subject in 4Q2015. Enrollment closed.

Phase 2: First subject in 3Q2015; Last subject in 4Q2019

Objectives

Primary Objectives

Phase 1

- To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of tazemetostat as a single agent administered orally twice daily (BID), continuously in 28-day cycles, in subjects with advanced solid tumors or with relapsed and/or refractory B cell lymphomas

Phase 2

- To determine the objective response rate (ORR; complete response + partial response [CR + PR]) of tazemetostat in subjects with enhancer of zeste homolog 2 (EZH2) gene mutation positive or negative (wild-type) with histologically-confirmed diffuse large B cell lymphoma (DLBCL) or follicular lymphomas (FL), with relapsed or refractory disease

Secondary Objectives

Phase 1

- To assess the effect of a high-fat meal on the bioavailability of tazemetostat
- To assess the effect of tazemetostat on exposure of midazolam, a cytochrome P450 (CYP)3A4 substrate
- To assess the preliminary activity of tazemetostat

Phase 2

- To assess the effect of tazemetostat on progression-free survival (PFS)
- To assess the effect of tazemetostat on duration of response (DOR)

All Phases and Cohorts

- To assess the safety and tolerability of tazemetostat monotherapy in
- To assess the pharmacokinetic (PK) profile of tazemetostat

Exploratory Objectives

All Phases and Cohorts

- To explore the PK and pharmacodynamic (PD) relationship of tazemetostat
- To identify and investigate biomarkers and their correlation with biological activity for tazemetostat
- To explore the effects of tazemetostat on histone H3K27 methylation, target gene expression, and phenotypic markers including those for differentiation, apoptosis, cell proliferation, and changes in the tumor microenvironment
- To explore the role of DNA sequence variability on absorption, metabolism, excretion, and susceptibility to adverse events of tazemetostat
- To explore the effect of tazemetostat on overall survival

Study Design

Overall Design:

This is a multicenter, open-label, Phase 1/2 study that will be conducted in 2 parts. The Phase 1 part (dose escalation and expansion parts have completed enrollment) is comprised of dose escalation and expansion parts to establish the MTD and/or RP2D when tazemetostat is given BID orally on a continuous basis in subjects with histologically- and/or cytologically-confirmed advanced or metastatic solid tumors or B cell lymphomas that have progressed after treatment with approved therapies or for which there are no standard therapies available. Additionally, in separate cohorts in Phase 1, the effect of food on the bioavailability of tazemetostat will be evaluated as well as the drug-drug interaction (DDI) potential as evaluated by the effect of tazemetostat on the PK of midazolam, a CYP3A4 substrate. The effect of food on bioavailability cohort was initiated after safety of the 200 mg tazemetostat dose (highest available tablet dosage strength) was evaluated. The DDI potential cohort was initiated at the RP2D of 800 mg BID. The Food Effect (FE) and DDI cohorts were performed once the dose escalation was completed. The Phase 2 part was initiated once the MTD and/or RP2D was established. Phase 2 will enroll subjects with DLBCL (Cohorts 1-3) and FL (Cohorts 4 and 5) for the determination of efficacy and safety of tazemetostat (Cohorts 1-5) and of tazemetostat monotherapy in determined by centrally confirmed histology, cell of origin (COO), and EZH2 mutation status as shown in the schematic below.

Study Scheme

Phase 1

Subjects with advanced solid tumors or B cell lymphomas →

Food Effect Substudy
(13 subjects enrolled)
- Randomized to either fasted or fed tazemetostat treatment
- 200 mg single dose on Day -8 and Day -1
- Tazemetostat 400 mg BID beginning on Day 1

Dose Escalation tazemetostat single agent →

DDI Substudy
(13 subjects enrolled)
- Midazolam single dose on Day -1 and 15
- Tazemetostat (fasted) MTD/RP2D BID beginning on Day 1

→

Phase 2
Subjects with B cell lymphomas
Tazemetostat Monotherapy Cohorts
- Cohort 1: DLBCL (GCB subtype) EZH2 mutation positive (- enrollment closed)
- Cohort 2: DLBCL (GCB subtype) EZH2 wild-type (enrollment closed)
- Cohort 3: DLBCL non-GCB subtype (enrollment closed) Note: Upon cohort closure, up to 5 DLBCL non-GCB EZH2 mutation positive subjects can be enrolled in Cohort 1
- Cohort 4: FL (Grades 1 to 3) EZH2 mutation positive (up to 45 subjects)
- Cohort 5: FL (Grades 1 to 3) EZH2 wild-type (enrollment closed)

BID = twice daily, DDI = drug-drug interaction, DLBCL = diffuse large B cell lymphoma, EZH2 = enhancer of zeste- homolog 2, FL = follicular lymphoma, GCB = germinal-center B-cell-like, MTD = maximum tolerated dose, RP2D = recommended Phase 2 dose

Number of Subjects

Phase 1 (IB and IGR sites in France only):

Dose Escalation (closed to enrollment)

Thirty-eight subjects with advanced solid tumors or B cell lymphomas were enrolled.

Food Effect and Drug-Drug Interaction (closed to enrollment):

Thirteen evaluable subjects with advanced solid tumors or B cell lymphomas were enrolled in each FE and DDI cohort (for a total of 26 subjects).

Phase 2:

Up to 45 subjects will be enrolled in Cohort 4 FL (Grades 1-3) EZH2 mutation positive. All other cohorts have completed enrollment. Approximately 420 subjects will be enrolled in the entire study.

Sample Size Rationale

For Phase 1, the sample size of 6 to 45 subjects is considered adequate for the purposes of selecting a dose. Per Food and Drug Administration (FDA) guidance, 12 subjects are considered adequate to evaluate food effect. The sample size for the DDI cohort was not based on statistical considerations.

For Phase 2, the original study design planned enrollment of up to 30 subjects in each cohort. The initial assessment of efficacy was to be conducted within each cohort when 10 subjects had been enrolled (Stage 1). For each DLBCL cohort, if zero responders (with CR or PR) out of the initial 10 subjects was observed, further enrollment in the cohort was to be terminated for futility. This rule was based on the underlying assumption that the response rate is 30% and there is a 2.8% probability of observing no responders among 10 subjects. For each FL cohort, if 1 or zero responders (CR or PR) out of the initial 10 subjects was observed, further enrollment in the cohort was to be terminated for futility. This rule was based on the underlying assumption that the response rate is 40% and there is a 4.6% probability of observing ≤ 1 responder among 10 subjects. Subsequent to the futility analysis in the DLBCL cohorts, the Data Monitoring Committee (DMC) endorsed a study design change to a modified 2-stage Green-Dahlberg design. The resulting expanded sample size is as follows:

	DLBCL GCB EZH2 Mutant	DLBCL GCB EZH2 Wild-Type	DLBCL non-GCB	FL EZH2 Mutant	FL EZH2 Wild-Type
Stage 1	10	10	10	10	10
Stage 2	50	50	50	35	35
Total	60	60	60	45	45

Abbreviations: DLBCL = diffuse large B cell lymphoma, EZH2 = enhancer of zeste- homolog 2, FL = follicular lymphoma, GCB = germinal-center B-cell-like

Inclusion Criteria

All Subjects:

1. Phase 1: Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Phase 2: ECOG performance status of 0 to 2 (Appendix 1).
2. Life expectancy ≥ 3 months before starting tazemetostat.
3. Subjects with a history of hepatitis B or C are eligible on the condition that subjects have adequate liver function as defined by Inclusion Criterion #6 and are hepatitis B surface antigen negative and/or have undetectable hepatitis C virus (HCV) RNA.
4. Adequate renal function defined as calculated creatinine clearance ≥ 40 mL/min per the Cockcroft and Gault formula (Appendix 2) or local institutional standard formula.
5. Adequate bone marrow function:
   a. Absolute neutrophil count (ANC) ≥ 750/mm^3 (≥ 0.75 × 10^9/L)
      - Without growth factor support (filgrastim or pegfilgrastim) for at least 14 days
   b. Platelets ≥ 75,000/mm^3 (≥ 75 × 10^9/L)
      - Evaluated after at least 7 days since last platelet transfusion
   c. Hemoglobin ≥ 9.0 g/dL
      - May receive transfusion
6. Adequate liver function:
   a. Total bilirubin ≤ 1.5 × the upper limit of normal (ULN) except for unconjugated hyperbilirubinemia of Gilbert's syndrome
   b. Alkaline phosphatase (ALP) (in the absence of bone disease), alanine aminotransferase (ALT),

and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if subject has liver metastases)

7. Time between prior anticancer therapy and first dose of tazemetostat as below:
   - Cytotoxic chemotherapy – At least 21 days
   - Non-cytotoxic chemotherapy (eg, small molecule inhibitor) – At least 14 days
   - Nitrosoureas – At least 6 weeks
   - Monoclonal antibody(ies) – At least 28 days
   - Radiotherapy
     - At least 14 days from local site radiation therapy;
     - At least 6 weeks from prior radioisotope therapy;
     - At least 12 weeks from 50% pelvic or total body irradiation
   - High-dose therapy with autologous hematopoietic cell infusion – At least 60 days
   - High-dose therapy with allogeneic transplant – At least 90 days (if graft versus host disease [GVHD] is present, must be < Grade 2) and on no prohibited medications, per Exclusion Criterion #3)
     - **NOTE:** Starting at Cycle 1 Day 1, subjects may receive no more than 10 mg of prednisone daily (or equivalent corticosteroid,) when used for treatment of lymphoma-related symptoms, with the intent to taper by the end of Cycle 1.
8. Males or females aged ≥ 18 years at the time of informed consent (Phase 2). Males and females aged ≥16 years of age at time of informed consent (Phase 1).
9. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. All females will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutively amenorrheic, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). Females of childbearing potential must not have had unprotected sexual intercourse within 30 days prior to study entry and must agree to use a highly effective method of contraception, from the last menstrual period prior to randomization, during Treatment Cycles, and for 30 days after the final dose of study drug, and have a male partner who uses a condom. Highly effective contraception includes:
   a. Double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.
   b. Placement of an intrauterine device.
   c. Established hormonal contraceptive methods: oral, injectable, or implant. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation.

   Female subjects exempt from this requirement are subjects who practice total abstinence or have a male partner who is vasectomized. If currently abstinent, the subject must agree to use a highly effective method of contraception as described above if they become sexually active during the Treatment Cycles, and for 30 days after study drug discontinuation.
10. Male subjects must have had either a successful vasectomy **OR** they and their female partner must meet the criteria above (ie, not of childbearing potential **OR** practicing highly effective

contraception and use a condom throughout the study period and for 30 days after study drug discontinuation).

11. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.

Phase 1 only (IGR and IB sites in France only):

12. Histologically- and/or cytologically-confirmed advanced or metastatic solid tumor or B cell lymphomas that have progressed after treatment with approved therapies or for which there are no standard therapies available.

Phase 2:

13. Subjects must satisfy all of the following criteria:
    a. Have histologically-confirmed DLBCL (including primary mediastinal B cell lymphoma), with relapsed or refractory disease following at least 2 lines of prior standard therapy, including alkylator/anthracycline (unless anthracycline–based chemotherapy is contraindicated)/anti-CD20-based therapy (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] or equivalent) AND must be considered unable to benefit from intensification treatment with autologous hematopoietic stem cell transplantation (ASCT), as defined by meeting at least 1 of the following criteria:
       - Relapsed following, or refractory to, previous ASCT
       - Did not achieve at least a partial response to a standard salvage regimen (eg, rituximab, ifosfamide, carboplatin, and etoposide phosphate [R-ICE] or rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP])
       - Ineligible for intensification treatment due to age or significant comorbidity
       - Ineligible for intensification treatment due to failure to mobilize an acceptable number of hematopoietic stem cells
       - Refused intensification treatment and/or ASCT

       or

    b. Have histologically-confirmed FL, all grades. Subjects may have relapsed/refractory disease following at least 2 standard prior systemic treatment regimens where at least 1 anti-CD20-based regimen was used. Subjects with prior radiotherapy will be included; however, radiotherapy alone will not be considered a separate systemic treatment regimen.
    c. Have provided sufficient archival tumor tissue that has been successfully tested for EZH2 mutation status and cell of origin (DLBCL only) at study specific laboratories allowing for allocation into an open cohort.
    d. Have measurable disease as defined by International Working Group-Non-Hodgkin's Lymphoma (IWG-NHL [Cheson, 2007]).

Exclusion Criteria

All Subjects:

1. Prior exposure to tazemetostat or other inhibitor(s) of EZH2.
2. Subjects with known leptomeningeal metastases or brain metastases or history of previously treated brain metastases.
3. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE 4.03 criteria) and any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS).

   NOTE: Bone marrow aspirate/biopsy will be conducted following abnormal peripheral blood smear morphology assessment conducted by central laboratory. Cytogenetic testing and DNA sequencing will be conducted following an abnormal result of bone marrow aspirate/biopsy.
4. Has a prior history of T-LBL/T-ALL.

5. Subjects taking medications that are known potent CYP3A4 inducers/inhibitors (including St. John's wort) (see Section 7.3.4.3 and http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm; http://medicine.iupui.edu/clinpharm/ddis/).
6. Subjects unwilling to exclude Seville oranges, grapefruit juice, and grapefruit from their diet.
7. Any prior treatment-related (ie, chemotherapy, immunotherapy, radiotherapy), clinically significant toxicities have not resolved to ≤ Grade 1 per CTCAE version 4.03, or prior treatment-related toxicities are clinically unstable and clinically significant at time of enrollment.
8. Major surgery within 4 weeks before the first dose of study drug.
    - **NOTE**: Minor surgery (eg, minor biopsy of extracranial site, central venous catheter placement, shunt revision) is permitted within 3 weeks prior to enrollment.
9. Inability to take oral medication, or malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, or vomiting) that might impair the bioavailability of tazemetostat.
10. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug; or cardiac ventricular arrhythmia (Appendix 3).
11. Prolongation of corrected QT interval using Fridericia's formula (QTcF) to > 480 msec.
12. Venous thrombosis or pulmonary embolism within the last 3 months before starting tazemetostat.
13. Active infection requiring systemic therapy.
14. Known hypersensitivity to any component of tazemetostat.
15. Immunocompromised subjects, including subjects known to be infected with human immunodeficiency virus (HIV).
16. Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the subject's participation in this study.
17. Females who are pregnant or breastfeeding.
18. Subjects who have undergone a solid organ transplant.

Phase 2 only:

19. Subjects with noncutaneous malignancies other than B cell lymphomas.
    - **Exception:** Subjects with another malignancy who have been disease-free for 5 years, or subjects with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible.

Study Drugs

Study Drug: EPZ-6438

Tazemetostat is available as tablets in strengths of 100 mg (Phase 1 only) and 200 mg and supplied in white high-density polyethylene bottles.

Dosage and Administration of EPZ-6438:

Tazemetostat is administered orally with or without food. The doses being administered in each part of the study are as follows:

Phase 1 Dose Escalation **(closed to enrollment)** – Five dose levels were explored: 100 mg BID, 200 mg BID, 400 mg BID, 800 mg BID and 1600 mg BID starting on Cycle 1 Day 1.

Phase 1 Food Effect **(closed to enrollment)** – A single 200 mg dose administered on Day -8 and Day -1. Starting on Cycle 1 Day 1 400 mg BID is administered.

Phase 1 Drug-Drug Interaction **(closed to enrollment)** – Midazolam 2 mg is given orally on Day -1 and Day 15. Starting on Cycle 1 Day 1, tazemetostat 800 mg BID is administered.

Phase 2 – 800 mg BID is administered starting on Cycle 1 Day 1.

Duration of Treatment

The Treatment Phase for the Phase 1 Dose Escalation part will last for 1 cycle. In the Extension Phase, subjects may remain on study until they have disease progression, development of unacceptable toxicity that leads to tazemetostat treatment withdrawal, or withdrawal of consent.

Food Effect and DDI cohorts were initiated as part of the Phase 1 study after safety of the 200 mg tazemetostat dose (highest available tablet dosage strength) was evaluated, and at the RP2D of 800 mg BID, respectively. The Treatment Phase for both cohorts will last until the end of Cycle 1.

Subjects will continue to receive study treatment per study design until disease progression, development of unacceptable toxicity that leads to study treatment withdrawal, or withdrawal of consent. Investigators who note subjects with disease progression who are receiving continued clinical benefit without clinical deterioration should contact the Medical Monitor to discuss the assessment of risk/benefit of keeping the subject on study.

Rollover Study: All subjects in Phase 1 who remain on tazemetostat for 9 months or longer, and are eligible to continue receiving tazemetostat, will transfer to a Rollover Study for monitoring and continued study drug at the Investigator's and the Medical Monitor's discretion. All subjects in Phase 2 who remain on tazemetostat for 24 months or longer, and are eligible to continue receiving tazemetostat, also will transfer to a Rollover Study for monitoring and continued access to study drug at the Investigator's and the Medical Monitor's discretion.

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LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
^{18}FDG-PET	^{18}fluorodeoxyglucose-positron emission tomography
ABC	Activated B-cell-like
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	Autologous hematopoietic stem cell transplantation
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from zero extrapolated to infinity
AUC_{0-12}	Area under the concentration-time curve from zero time to 12 hours
AUC_{0-24}	Area under the concentration-time curve from zero time to 24 hours
β-hCG	Beta-human chorionic gonadotropin
BID	Twice daily
BP	Blood pressure
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Confidence interval
C_{max}	Maximum drug concentration
CL	Total body clearance
CLr	Renal clearance
CNS	Central nervous system
COO	Cell of origin
COP	CHOP without doxorubicin
CR	Complete response
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLBCL	Diffuse large B cell lymphoma
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
EZH2	Enhancer of zeste homolog 2
EU	European union
FDA	Food and Drug Administration
fe	Fraction excreted
FE	Food effect
FFPE	Formalin fixed paraffin embedded
FL	Follicular lymphoma
GCB	Germinal-center B-cell-like

Abbreviation	Term
GCP	Good Clinical Practice(s)
GVHD	Graft versus host disease
H3K27	Histone H3 lysine 27
H3K27me3	Trimethylated state of histone H3 lysine 27
HAT	Histone acetyltransferase
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HMT	Histone methyltransferase
HR	Heart rate
IB	Institut Bergonie (when referring to study site in France) Investigator's Brochure (when referring to document)
IC_{90}	90% of the maximal inhibition
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IGR	Institut gustave roussy
IHC	Immunohistochemistry
IRB	Institutional review board
IV	Intravenous
IWG-NHL	International working group-non-Hodgkin's lymphoma
LNH	Low/normal/high classification
LVEF	Left ventricular ejection fraction
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPN	Myeloproliferative neoplasm
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple-gated acquisition
NE	Not evaluable
NHL	Non-Hodgkin lymphoma
NYHA	New York heart association
ORR	Objective response rate
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s) or progressive disease
PET	Positron-emission tomography
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic(s)/pharmacodynamic(s)
PMBCL	Primary mediastinal B cell lymphoma
PR	Partial response
PT	Preferred term
QT	The time interval from the beginning of the cardiac QRS complex to the end of the T wave
QTc	Corrected QT interval
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
R	Accumulation ratio
R-CHOP	Rituximab plus CHOP
R-DHAP	Rituximab, dexamethasone, cytarabine, and cisplatin
RECIST	Response Evaluation Criteria in Solid Tumors
R-ICE	Rituximab, ifosfamide, carboplatin, and etoposide phosphate

Abbreviation	Term
RP2D	Recommended Phase 2 dose
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SmPC	Summary of Product Characteristics
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Elimination half-life
tazemetostat (EPZ-6438 and E7438)	Investigational study drug: *N*-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-yl)methyl]-5-[ethyl(tetrahydro-2*H*-pyran-4-yl)amino]-4-methyl-4'-(morpholin-4-ylmethyl)biphenyl-3-carboxamide hydrobromide
T-ALL	T-cell acute lymphoblastic leukemia
T-LBL	T-cell lymphoblastic lymphoma
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach maximum concentration (following drug administration)
ULN	Upper limit of normal
US/USA	United States/United States of America
UTX	Ubiquitously transcribed tetratricopeptide repeat, X chromosome
UV	Ultraviolet
V_d	Volume of distribution

4 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Epizyme (the Sponsor) at up to 5 investigational sites in the European Union (EU) for the Phase 1 part of the study. Investigational sites for Phase 2 are being identified globally.

The name of the Sponsor's medical monitor, along with the telephone and fax numbers of the other contact persons at the Sponsor and, if applicable, any contract research organization (CRO), will be listed in the Investigator File provided to each site.

5 INTRODUCTION

Tazemetostat is a selective small molecule inhibitor of the histone lysine methyltransferase enhancer of zeste homolog 2 (EZH2). Posttranslational modifications of core histone proteins of chromatin play an important role in controlling the fidelity of gene transcription patterns in cells. Paramount among these transcription-controlling modifications is methylation events at lysine and arginine residues, catalyzed by histone methyltransferases (HMTs). Genetic alterations in a number of HMTs have been identified in human cancers where they are purported to play a causal role in malignancies. Of note, non-Hodgkin lymphoma (NHL) shows a high propensity in mutations in chromatin modifying enzymes, including HMTs (EZH2, MLL2), histone demethylases (for instance ubiquitously transcribed tetratricopeptide repeat, X chromosome, UTX) and histone acetyltransferases (HATs), perturbing the state of chromatin leading to aberrant gene expression (Morin, 2011). EZH2 is the catalytic subunit of the multi-protein HMT complex known as polycomb repressive complex 2, which is responsible for mono-, di-, and tri-methylation of histone H3 lysine 27 (H3K27); hypertrimethylation of H3K27 is known to silence tumor suppressor genes and thus to be tumorigenic. MLL2, in contrast, methylates H3K4, a histone modification associated with actively transcribed chromatin (Milne, 2005). Loci of genes bivalently modified at H3K27 and H3K4 are poised for rapid expression regulation in either direction (Voigt, 2013), and perturbation of the correct methylation balance can lead to cancer (Béguelin, 2013). Multiple mechanisms have been shown to lead to hypertrimethylation of H3K27 in cancer, including mutation, amplification and overexpression of EZH2, and inactivating mutations of the H3K27 demethylase UTX. Somatic mutations within the EZH2 gene on 3 hotspots (Y646. A682, and A692 [NM_001203247]) are present in follicular and diffuse large B cell lymphoma (FL, DLBCL) and lead to high levels of H3K27 trimethylation (H3K27me3) in these lymphomas. Those mutations of EZH2, therefore, have been proposed to be required for the development and maintenance of the mutation-bearing lymphomas. Inhibition of EZH2 leads to reduction in H3K27me3 and cell death in lymphoma cell lines bearing the mutation. In addition, loss of function of MLL2 and HATs may generate abnormal methylation states of H3K27, potentially leading to a dependency on EZH2. In nonclinical models, inhibition of EZH2 leads to reduction in H3K27me3 in all lymphoma cell lines irrespective of their EZH2

mutation status. While cells with wild-type EZH2 are growth inhibited with EZH2 inhibition in vitro, only mutant bearing cells undergo cell death in culture (Béguelin, 2013; Knutson, 2014).

Changes to the tumor microenvironment, for instance those affecting antitumor immunity, are increasingly recognized as an important mechanism in lymphomagenesis, affecting all types of NHL (Scott, 2014). Epigenetic therapy has been suggested to release repression of molecules important for immune recognition on tumor cells (Wrangle, 2013), and EZH2 inhibition may induce similar effects. In addition, loss of EZH2 has been described as affecting T helper cell plasticity (Tumes, 2013) and is proposed to inhibit the function of regulatory T cells (Arvey, 2014; DuPage, 2015; Yang, 2015), suggesting that EZH2 inhibition may contribute to enhancing antitumor immunity.

In summary, the available nonclinical data suggest that EZH2 mutant lymphomas should show the highest sensitivity to EZH2 inhibition, but wild-type cases could also be affected through tumor cell autonomous mechanisms (mutations in MLL2, HATs, UTX, etc.) and/or effects of EZH2 inhibitors on the tumor microenvironment.

Diffuse large B cell lymphoma (DLBCL) and FL are the 2 most common lymphoid malignancies with annual incidences of 3.8 and 2.2/100,000, respectively, in Europe (Sant, 2010) and 6.9 and 3.7/100,000, respectively, in the United States (US) (National Cancer Institute 2014). For both DLBCL and advanced FL, chemoimmunotherapy with rituximab has substantially improved long-term disease control (Dreyling, 2014; Tilley, 2012). There are 3 histologically-indistinguishable molecular subtypes of DLBCL: the activated B-cell-like (ABC) subtype, the germinal-center B-cell-like (GCB) subtype, and the primary mediastinal B cell lymphoma (PMBCL) subtype. These subtypes differ in terms of gene expression and are believed to originate in B cells at different stages of differentiation. In addition, the process of malignant transformation differs for each subtype, resulting in distinctive patterns of genetic abnormality. Clinical presentation and responsiveness to targeted therapies also vary across the subtypes (Foon, 2012).

Gene expression in GCB lymphomas is characteristic for germinal-center B cells, with deletion of the tumor suppressor gene PTEN and p53 mutations being specific to GCB lymphomas. Genetic abnormalities that are characteristic for ABC DLBCL include deletion of the INK4α/ARF tumor suppressor locus on chromosome 9 and amplification of the 9-Mb region on chromosome 19. Loss of these tumor suppressors impedes the action of chemotherapy and may contribute to the poor prognosis associated with this subtype. PMBCL may present with distinct clinical features, with disease thought to originate in the thymus, and often confined to the mediastinum. Gene expression profiling may provide additional information on characteristics of PMBCL such as deletion of SOCS1, a suppressor of JAK signaling, and gene profiling has identified similarities between PMBCL and classical Hodgkin's lymphoma (Foon, 2012;

Rosenwald, 2003). FL is thought to arise from germinal center B cells, and the majority of subjects have a t(14:18) translocation at the site of the BCL-2 oncogene and 1 of the 3 immunoglobulin genes. However, BCL-2 expression alone is not considered sufficient for FL development and other genetic mechanisms or host factors, such as epigenetic abnormalities, are considered required. FL is graded based on the proportion of centroblasts in the follicle with Grade 3b often being BCL-2 negative and displaying histological similarities to DLBCL. An integral part of the natural history of FL is progression to a higher-grade histologic subtype such as DLBCL.

Of note, in the Phase 1 Dose Escalation part of the present study, objective responses have been observed in subjects with both EZH2 wild-type and mutant NHL. In addition, objective responses have been noted in subjects with both GCB and non-GCB cell of origin (COO), determined by immunohistochemistry (IHC), including 1 subject with a classical clinical presentation of PMBCL. Based on these findings, the design of the Phase 2 part of this study has been modified to include a new cohort to evaluate the activity of tazemetostat in subjects with the non-GCB DLBCL subtype (inclusive of subjects with PMBCL), in addition to the previously described cohorts for mutation-bearing and non-mutation-bearing GCB DLBCL.

5.1 Investigational Product

Tazemetostat is under investigation as a treatment for subjects with relapsed or refractory DLBCL or FL for the Phase 2 portion of the protocol.

5.1.1 Tazemetostat

Active ingredient: *N*-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-yl)methyl]-5-[ethyl(tetrahydro-2*H*-pyran-4-yl)amino]-4-methyl-4'-(morpholin-4-ylmethyl)biphenyl-3-carboxamide hydrobromide

5.1.1.1 Therapeutic Pathway or Mechanism of Action

Tazemetostat inhibits EZH2, both wild-type and mutation-bearing, with nanomolar affinity. The compound shows 36-fold selectivity over the closest family member, EZH1, and greater than 4500-fold selectivity over other HMTs. It selectively inhibits intracellular histone H3K27 methylation in a concentration and time-dependent manner. In cells harboring the EZH2 Y646 or A682 mutations, inhibition of EZH2 results in concentration and time dependent inhibition of histone H3K27 methylation with subsequent cell killing. EPZ-6438 demonstrates antitumor activity against several NHLs carrying the EZH2 Y646 or A682 mutations in mouse xenograft studies.

5.1.1.2 Nonclinical Experience with Tazemetostat

[redacted]nical [redacted] No incidences of abnormal bone formation have been observed in the ongoing clinical study. Female subjects of reproductive age will provide blood and urine samples for pregnancy testing at screening. All subjects must agree to use a reliable birth control method during the study, and for 30 days after the last tazemetostat dose, and additionally will be actively monitored for signs or symptoms of abnormal bone formation.

5.1.1.3 Clinical Experience with Tazemetostat

This clinical study (Phase 1/2) is the first-in-human study with tazemetostat. The study parts and dose levels of the Phase 1 study are: Dose Escalation at 100 mg BID, Dose Escalation at 200 mg BID, Dose Escalation at 400 mg BID, Dose Escalation at 800 mg BID, Dose Escalation at 1600 mg BID, Dose Expansion at 800 mg BID, Dose Expansion at 1600 mg BID, Food Effect (FE) at 400 mg BID, and Drug-Drug Interaction (DDI) at 800 mg BID. The Phase 1 dose escalation and expansion parts have been completed and the recommended Phase 2 dose (RP2D) was defined as 800 mg BID. The Phase 1 part also determined the relationship between exposure and H3K27me3 reduction in skin, and provided a preliminary assessment of activity.

As of 07 November 2015, 58 subjects were enrolled into the study (dose escalation, dose expansion, food effect, and drug-drug interaction), including 21 NHL subjects (14 DLBCL, 6 follicular lymphoma [FL], and 1 marginal zone lymphoma [MZL]). Adverse events (AE) occurring in ≥ 10% of the 58 subjects regardless of attribution were asthenia, anorexia, thrombocytopenia, nausea, diarrhea, and vomiting. There were 4 Grade ≥ 3 related AEs:

thrombocytopenia, neutropenia, hypertension, and transaminase elevation. The median age of the NHL subjects enrolled was 63 years (range: 24-84) and 71% of subjects were male. Among the 16 response-evaluable NHL subjects, objective responses were seen in 5/10 DLBCL, 3/5 FL and 1/1 MZL subjects.

As of 19 August 2016, 106 subjects were enrolled to the 5 monotherapy cohorts in the Phase 2 portion of the study. The safety profile of subjects in Phase 2 was generally consistent with that observed for subjects in Phase 1. [redacted] Based on the review of safety and efficacy data, the DMC concluded on 6 September 2016 that futility hurdles had been surpassed in all 5 monotherapy cohorts and no safety issues preclude the continued enrollment of study subjects.

Further information on clinical efficacy and safety can be found in the tazemetostat Investigator's Brochure (IB), Version 8.0.

5.1.1.4 Common Serious Adverse Events Expected to Occur in the Study Population Even in the Absence of Study Drug Exposure

Lymphomatous meningitis, superior vena cava syndrome, compression syndromes, spinal cord compression, and pathologic fractures are known to occur in this study population.

5.2 Study Rationale

The proposed clinical study is a multicenter, open-label, Phase 1/2 study that will be conducted in 2 parts.

The Phase 1 part (Institut Bergonie [IB] and Institut Gustave Roussy [IGR] sites in France only) will comprise dose escalation and establishment of the maximum tolerated dose (MTD) and/or RP2D when tazemetostat is given BID orally on a continuous basis in subjects with histologically- and/or cytologically-confirmed advanced or metastatic solid tumors or B cell lymphomas that have progressed after treatment with approved therapies or for which there are no standard therapies available. Additionally, in separate cohorts in Phase 1, the effect of food on the bioavailability of tazemetostat will be evaluated as well as the DDI potential as evaluated by the effect of tazemetostat on the pharmacokinetics (PK) of midazolam, a cytochrome P450 (CYP)3A4 substrate. The effect of food on bioavailability will be initiated at 200 mg tazemetostat dose (highest available tablet dosage strength). DDI potential will be initiated at 800 mg BID (RP2D). The FE and DDI cohorts may be performed in parallel and may subsequently continue in parallel with Phase 2.

The Phase 2 part will be initiated at a recommended dose of 800 mg BID. Based upon both the in vitro responses to tazemetostat of both EZH2 wild-type and mutant DLBCL cell lines and Phase 1 objective responses seen to date (Knutson, 2014a; Ribrag, 2015). Phase 2 will enroll subjects with DLBCL (Cohorts 1-3) or FL (Cohorts 4 and 5) for the determination of efficacy and safety of tazemetostat monotherapy (Cohorts 1-5) and of tazemetostat in 5 separate cohorts determined by centrally confirmed histology, COO, and EZH2 mutation status.

5.2.1 Rationale for Dosage Selection

5.2.1.1 Tazemetostat

The first-in-human dose selected for tazemetostat is 100 mg BID or 200 mg daily. [redacted]

Twice-daily administration of tazemetostat was selected based on the nonclinical studies in nude and severe combined immunodeficiency mice xenograft models, wherein BID dosing resulted in maximal tumor growth inhibition and sustained inhibition of intratumoral H3K27me3.

In a nonclinical study, the tazemetostat mean bioavailability in the fed state was roughly 5-fold lower than that in fasted state in cynomolgus monkeys. Thus, this study was originally designed to administer tazemetostat in the fasted state, defined as no food for 2 hours before and after study drug ingestion. The effect of food on tazemetostat bioavailability in humans was explored in the Phase 1 part of this study to inform tazemetostat dosing in the Phase 2 part.

Tazemetostat is metabolized primarily by CYP3A4. Tazemetostat was also shown to be a time-dependent CYP3A4 inhibitor and a CYP3A4 inducer. To assess the effect of tazemetostat coadministration on drugs metabolized by CYP3A4, a DDI cohort with midazolam, a probe CYP3A4 substrate, is included in this study. Assessment of the effect of tazemetostat on exposure to midazolam and its metabolites will be used to guide coadministration of tazemetostat with drugs metabolized by CYP3A4.

Tazemetostat was initially supplied as an oral suspension. Tazemetostat was subsequently made available as tablets in strengths of 50, 100, and 200 mg and supplied in white high-density polyethylene (HDPE) bottles. The first cohort (100 mg BID) included 3 subjects dosed with tazemetostat suspension and 3 subjects dosed with the tazemetostat tablet formulation. Tablet strengths of 200 mg will be made available during the Phase 2 part of the study.

Inclusion of subjects 16 years of age and older in Phase 1 (FE and DDI cohorts only):

PK modeling has been conducted using a GastroPlus PBPKPlus module that is integrated with age-related population data for body weight, height, body mass index, and bioelectrical

impedance resistance measured at 50 KHz for humans from the US population 0 to 85 years of age. Using tazemetostat concentration-time data from the completed Phase 1 Dose Escalation/Expansion part of the current study, the predicted mean steady-state AUC and steady-state maximum drug concentration (C_{max}) values were 4900 ng•h/mL and 1500 ng/mL, respectively, for subjects 12 to 18 years of age after administration of 800 mg BID. These predicted PK exposure values are within the range of observed values in subjects after administration of 800 or 1600 mg BID. The 1600 mg BID dose was tolerated without an MTD being reached.

5.2.2 Rationale for Phase 2 Dose

Oral tazemetostat doses of 100 mg to 1600 mg BID were investigated in the Dose Escalation part of this study. As of 09-Jul. 2015, 45 subjects with advanced or metastatic solid tumors or B cell lymphomas had been included in the Phase 1 Dose Escalation part of the study. Clinical activity of tazemetostat was observed at dose levels of 100, 200, and 800 mg BID, including objective responses observed in 9 of 15 evaluable subjects with B cell lymphoma who have had tumor assessments while on study drug. Objective responses were observed in 5/9 DLBCL, 3/5 FL, and 1/1 MZL subjects. An MTD was not established with tazemetostat doses of up to 1600 mg BID.

Inhibition of H3K27Me3 in skin was utilized as a measure of target engagement. A relationship between tazemetostat AUC on Day 15 and inhibition of H3K27 methylation in skin was observed in the Dose Escalation part of Study E7438-G000-101. Results of preliminary pharmacokinetic/pharmacodynamic (PK/PD) modelling predicted that a tazemetostat Day 15 AUC of approximately 4000 ng•h/mL will result in 90% of the maximal inhibition (IC_{90}) of H3K27Me3 in the skin. The mean tazemetostat area under the concentration-time curve from zero time to 12 hours (AUC_{0-12}) on Day 15 in the 800 mg BID cohort (n = 13) was 3670 ng•h/mL, which is similar to the predicted IC_{90}.

The safety, tolerability, clinical activity, PK, and pharmacodynamic (PD) assessments from the subjects treated in the Dose Escalation part of the study were used to select the RP2D. The greatest number of objective responses was observed in the 800 mg BID cohort during the Dose Escalation part of the study. Administration of 800 mg tazemetostat BID also resulted in a mean AUC_{0-12} similar to the AUC predicted to result in 90% of the maximal inhibition of H3K27Me3 in skin. Therefore, the RP2D of 800 mg BID was selected. This RP2D has been endorsed by the investigators and an independent Data Monitoring Committee (DMC). [redacted]

Table 1 Geometric Mean [(%CV), (range)] for Preliminary Tazemetostat Pharmacokinetic Parameters after Administration Fasted or Immediately After a High-Fat Breakfast in Study E7438-G000-101 (n = 11)

Meal State	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng*h/mL)	t_{max}[a] (h)
Fed	232 (107) (65.7 – 752)	1080 (85.3) (317.7 – 3070)	4.0 (1.0 – 6.0)
Fasted	322 (130) (59.6 – 1470)	1140 (135) (179.3 – 6251)	1.0 (0.5 – 6.0)

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from zero extrapolated to infinity, C_{max} = maximum drug concentration, CV = coefficient of variation, n = number of subjects, t_{max} = time to reach maximum concentration (following drug administration)

a t_{max} presented as median (range)

Administration of tazemetostat with a high-fat meal decreased geometric mean area under the concentration-time curve from zero extrapolated to infinity ($AUC_{0-\infty}$) and C_{max} values approximately 6% and 28%, respectively, relative to administration in the fasted state. However, for both C_{max} and $AUC_{0-\infty}$, all values observed after administration of tazemetostat following a high-fat meal were within the range of values observed after administration in the fasted state. Administration of tazemetostat with a high-fat meal also resulted in a 4-fold increase in median time to reach maximum concentration (following drug administration) (t_{max}) relative to administration in the fasted state. The relationship between tazemetostat AUC on Day 15 and inhibition of H3K27 methylation in skin observed in the Dose Escalation part of Study E7438-G000-101 indicates that target inhibition is related to AUC. The decrease in systemic exposure as measured by $AUC_{0-\infty}$ is not clinically significant, and therefore, tazemetostat can be taken without regards to meals.

Further information on the rationale for the RP2D can be found in the tazemetostat IB, Version 8.0.

6 STUDY OBJECTIVES

6.1 Primary Objectives

The primary objectives of this study are:

Phase 1

- To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of tazemetostat as a single agent administered orally twice daily (BID), continuously in 28-day cycles in subjects with advanced solid tumors or with relapsed and/or refractory B cell lymphomas

Phase 2

- To determine the objective response rate (ORR; complete response + partial response [CR + PR]) of tazemetostat in subjects with enhancer of zeste homolog 2 (EZH2) gene mutation positive or negative (wild-type) with histologically-confirmed diffuse large B cell lymphoma (DLBCL) or follicular lymphomas (FL)

6.2 Secondary Objectives

The secondary objectives of this study are:

Phase 1

- To assess the effect of a high-fat meal on the bioavailability of tazemetostat
- To assess the effect of tazemetostat on exposure of midazolam, a cytochrome P450 (CYP)3A4 substrate
- To assess the preliminary activity of tazemetostat

Phase 2

- To assess the effect of EPZ-6438 on progression-free survival (PFS)
- To assess the effect of EPZ-6438 on duration of response (DOR)

All Phases and Cohorts

- To assess the safety and tolerability of EPZ-6438 administered BID orally, continuously in 28-day cycles
- To assess the pharmacokinetic (PK) profile of tazemetostat

6.3 Exploratory Objectives

The exploratory objectives of this study are:

All Phases and Cohorts

- To explore the PK and pharmacodynamic (PD) relationship of tazemetostat
- To identify and investigate biomarkers and their correlation with biological activity for tazemetostat
- To explore the effects of tazemetostat on histone H3K27 methylation, target gene expression, and phenotypic markers including those for differentiation, apoptosis, and cell proliferation, and changes in the tumor microenvironment
- To explore the role of DNA sequence variability on absorption, metabolism, excretion and susceptibility to adverse events of tazemetostat
- To explore the effect of tazemetostat on overall survival

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

This is a multicenter, open-label, Phase 1/2 study that will be conducted in 2 parts (see Section 7.3.2). The Phase 1 part (dose escalation and expansion parts have completed enrollment) comprised of dose escalation and expansion to establish the MTD and/or RP2D when tazemetostat is given BID orally on a continuous basis in subjects with histologically- and/or cytologically-confirmed advanced or metastatic solid tumors or B cell lymphomas that have progressed after treatment with approved therapies or for which there are no standard therapies available. Additionally, in separate cohorts in Phase 1 (IB and IGR sites in France only), the effect of food on the bioavailability of tazemetostat will be evaluated as well as the DDI potential as evaluated by the effect of tazemetostat on the pharmacokinetics of midazolam, a CYP3A4 substrate. The effect of food on bioavailability was initiated after safety of the 200 mg tazemetostat dose (highest available tablet dosage strength) was evaluated. The DDI potential cohort was initiated at the RP2D of 800 mg BID. The FE and DDI cohorts were performed once the dose escalation was completed. The Phase 2 part was initiated once the MTD and/or RP2D was established. Phase 2 will enroll subjects with DLBCL (Cohorts 1-3) and FL (Cohorts 4 and 5) for the determination of efficacy and safety of tazemetostat monotherapy (Cohorts 1-5) in five separate cohorts as determined by centrally confirmed histology, COO, and EZH2 mutation status as described below:

- **Subjects with histologically-confirmed DLBCL (including PMBCL and transformed FL) (all enrollment of these Cohorts is closed)**
    - DLBCL Cohort 1: Subjects with GCB subtype and the following EZH2 mutations: Y646F, Y646N, Y646S, Y646H, Y646C, A682G, and/or A692V
    - DLBCL Cohort 2: Subjects with GCB subtype and EZH2 wild-type
    - DLBCL Cohort 3: Subjects with non-GCB subtype (including PMBCL)

or

- **Subjects with histologically-confirmed FL, all grades**
    - FL Cohort 4: Subjects with the following EZH2 mutations: Y646F, Y646N, Y646S, Y646H, Y646C, A682G, and/or A692V
    - FL Cohort 5: Subjects with EZH2 wild-type (enrollment closed)

Subjects will be required to undergo EZH2 mutation testing of their tumor tissue. An EZH2 mutation result will be determined at designated study laboratory testing sites using a cobas® EZH2 Mutation Test (under development, Roche Molecular Systems, Inc.), which is a real-time allele-specific polymerase chain reaction (PCR) test to detect the following mutations within

codons Y646, A682, and A692 of the EZH2 gene in formalin fixed paraffin embedded (FFPE) NHL tumor tissue specimens: Y646F, Y646N, Y646S, Y646H, Y646C, A682G, and/or A692V; results for codons Y646S, Y646H, and Y646C are not reported individually (grouped as Y646X). For the purposes of this protocol, the term “wild-type” refers to the absence of detection of the above-specified mutations. Subjects with tumors that are wild-type for EZH2 will be enrolled in the EZH2 wild-type cohort. The EZH2 mutation test is intended to be used as an Investigational Use Only assay.

COO status will be determined for DLBCL subjects by the Hans method (Hans, 2004) using available tumor tissue at designated study laboratory testing sites. Further details of EZH2 mutation and COO testing are provided in the Laboratory Manual.

The tumor tissue EZH2/COO testing can be performed prior to other screening procedures, for example, during wash-out of the second line anticancer therapy, after the subject is consented for the prescreening testing.

This study will be conducted in 3 phases: a Pretreatment Phase, a Treatment Phase, and an Extension Phase. The Pretreatment Phase consists of Screening and Baseline Visits (see Table 8 and Table 9).

The Treatment Phase for the Phase 1 Dose Escalation and Expansion parts last for 1 cycle. Subjects were enrolled using a dose-escalation algorithm (3+3 subjects per dose level) to identify the MTD and/or RP2D.

Each 28-day period will be considered 1 treatment cycle. PK sampling will be performed on every subject and samples will be collected predose and at protocol-defined intervals as described in the Schedule of Visits and Procedures (see Table 8 and Table 9).

The treatment cycle will begin with the first dose of study drug administration and continue for 1 cycle (28 days [4 weeks]). Treatment may continue in the Extension Phase with Cycle 2 and beyond until completion of the Off-Treatment Visit (30 days after the last study drug administration).

The enrollment for the Phase 1 part of the study commenced in June 2013. Using a standard 3+3 design and increasing in 100% increments, enrollment of 5 dose cohorts of 3 to 6 subjects was completed with tazemetostat at 100, 200, 400, 800, and 1600 mg BID, with 1 dose-limiting toxicity (DLT) reported at 1600 mg BID. As of 07-Nov. 2014, the maximum delivered dose was 1600 mg BID, and hence, an MTD had not been reached. The RP2D was therefore 800 mg BID because of the safety, PK, biological activity, and responses at this dose.

Dose escalation (complete): Dose escalation proceeded in 100% increments in subsequent cohorts unless 1 Grade ≥ 2 nonhematological toxicity during Cycle 1 was assessed as related to

the study drug in 2 or more subjects at a dose level. For dose escalation purposes, toxicities assigned as DLTs during the first cycle were assessed (see Table 4). After completion of Cycle 1 in each cohort, all available safety data were reviewed jointly by the Sponsor and the investigators and the decision to proceed to the next dose cohort was made. If 0 of 3 or 1 of 6 subjects demonstrated DLT(s), then enrollment proceeded to the next dose level. If 1 DLT was reported for the first 3 (or 4) subjects, the cohort expanded to a total of 6 subjects. If 2 subjects in any cohort demonstrate DLT(s) during Cycle 1, enrollment into that cohort stopped and a dose reduction took place. In the first and second cohorts only, the first subject in each dose level must have completed at least 2 weeks of treatment during Cycle 1 without experiencing any DLTs before additional subjects were treated at that dose level. A dose-escalation meeting occurred when 3 evaluable subjects (for DLTs) completed 1 cycle of treatment. If a fourth subject in this cohort experienced a DLT after a decision had been made to escalate to the next dose level, then this dose cohort (of the fourth subject) was expanded to a total of 6 subjects. Any subject initiated at a higher dose level continued to receive the same dose. If 2 subjects in the expanded cohort experience a DLT(s), a dose reduction took place. Additionally, any subject being treated at a higher dose level had the dose reduced to below the dose level that exceeded the tolerable dose level. The highest dose level below the dose level that exceeds a tolerable dose level (ie, results in ≥ 2 of 6 subjects with DLTs was considered the MTD of Phase 1 and was used to determine the RP2D). Dose escalation continued until the MTD is reached, or up to a maximum feasible dose of 1600 mg BID, whichever comes first. If no DLTs are observed, the RP2D was determined based on safety, tolerability, activity, PK, and PD assessments. Two dose cohorts were expanded up to 12 subjects each in the Dose Expansion part.

In the Extension Phase of the Dose Escalation and Expansion parts, subjects may remain on study until disease progression, development of unacceptable toxicity that leads to tazemetostat treatment withdrawal, or withdrawal of consent. Investigators who note subjects with disease progression who are receiving continued clinical benefit without clinical deterioration should contact the Medical Monitor to discuss the assessment of risk/benefit of keeping the subject on study.

Food Effect and DDI cohorts were initiated as part of the Phase 1 study after safety of the 200 mg tazemetostat dose (highest available tablet dosage strength) was evaluated, and at the RP2D of 800 mg BID, respectively. The Treatment Phase for both cohorts will last until the end of Cycle 1. In the Extension Phase, subjects may remain on study until disease progression, development of unacceptable toxicity that leads to tazemetostat treatment withdrawal, or withdrawal of consent.

Randomization will be used in the Phase 1 FE cohort in this study.

The Phase 2 study was initiated after a minimum of 6 subjects complete dosing at the RP2D. The RP2D has been determined as 800 mg BID. The Phase 2 proof-of-concept part of the study will enroll subjects with B cell lymphoma for the determination of efficacy and safety of EPZ-6438 in 5 separate cohorts determined by centrally confirmed histology, COO, and EZH2 mutation status. The Treatment Phase in Phase 2 will end when the last subject completes assessments following a minimum of 6 cycles or discontinues treatment due to disease progression, development of unacceptable toxicity that leads to tazemetostat treatment withdrawal, or withdrawal of consent.

In the Extension Phase in both the Phase 1 and Phase 2, subjects will continue to receive study drug until disease progression, development of unacceptable toxicity that leads to study treatment withdrawal, or withdrawal of consent. An Off-Treatment Visit will occur up to 30 days after final administration of study drug, or initiation of a new anticancer treatment, whichever occurs earlier, after which subjects will enter the Follow-up Period.

During the Follow-up Period, survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent.

Rollover Study: All subjects in Phase 1 who receive tazemetostat for 9 months or longer, and are eligible to continue receiving tazemetostat, will transfer to a Rollover Study for monitoring and continued study drug at the Investigator's and the Medical Monitor's discretion. All subjects in Phase 2 who remain on tazemetostat for 24 months or longer, and are eligible to continue receiving tazemetostat, also will transfer to a Rollover Study for monitoring and continued study drug at the Investigator's and the Medical Monitor's discretion.

This study will include PD assessments of the effects of tazemetostat in a variety of matrices, including plasma, PBMCs, skin, bone marrow, and malignant tissue as appropriate, which may help confirm the mechanism of action of tazemetostat, predict responses, and guide further development and optimize use of tazemetostat. See Section 7.4.1.6 for further information on PD assessments.

An overview of the study design is presented in Table 2.

Table 2 Study Design for E7438-G000-101

Phase 1

Subjects with advanced solid tumors or B cell lymphomas

Dose Escalation tazemetostat single agent

→ **Food Effect Substudy**
(13 subjects enrolled)
- Randomized to either fasted or fed tazemetostat treatment
- 200 mg single dose on Day -8 and Day -1
- Tazemetostat 400 mg BID beginning on Day 1

→ **DDI Substudy**
(13 subjects enrolled)
- Midazolam single dose on Day -1 and 15
- Tazemetostat (fasted) MTD/RP2D BID beginning on Day 1

→ **Phase 2**
Subjects with B cell lymphomas
Tazemetostat Monotherapy Cohorts
- Cohort 1: DLBCL (GCB subtype) EZH2 mutation positive (enrollment closed)
- Cohort 2: DLBCL (GCB subtype) EZH2 wild-type (enrollment closed)
- Cohort 3: DLBCL non-GCB subtype (enrollment closed)
  Note: Upon cohort closure, up to 5 DLBCL non-GCB EZH2 mutation positive subjects can be enrolled in Cohort 1
- Cohort 4: FL (Grades 1 to 3) EZH2 mutation positive (up to 45 subjects)
- Cohort 5: FL (Grades 1 to 3) EZH2 wild-type (up to 45 subjects) (enrollment closed)

BID = twice daily, DDI = drug-drug interaction, DLBCL = diffuse large B cell lymphoma, EZH2 = enhancer of zeste homolog 2, GCB = germinal-center B-cell-like, FL = follicular lymphoma, MTD = maximum tolerated dose, RP2D = recommended Phase 2 dose

The end of study is defined as last subject last follow-up visit or the last subject transferred to the Rollover Study (EZH-501).

7.2 Selection of Study Population

Approximately 420 subjects will be enrolled in the entire study. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

In Phase 1, a total of 64 subjects with advanced solid tumors or B cell lymphomas were enrolled. Two dose levels were expanded (to 14 subjects at 800 mg BID and 12 subjects at 1600 mg BID) to support the determination/confirmation of the RP2D per joint decision of the Sponsor and the investigators.

Thirteen evaluable subjects with advanced solid tumors or B cell lymphomas were enrolled in each FE and DDI cohort (IB and IGR sites in France only). Enrollment is closed for both cohorts.

In Phase 2, approximately 340 subjects with histologically-confirmed DLBCL or FL with relapsed or refractory disease will be enrolled (monotherapy: up to 60 subjects in each of the 3 DLBCL cohorts and up to 45 subjects in each of the 2 FL cohorts).

7.2.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

All Subjects:

1. Phase 1: Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
   Phase 2: Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Appendix 1).
2. Life expectancy ≥ 3 months before starting tazemetostat.
3. Subjects with a history of hepatitis B or C are eligible on the condition that subjects have adequate liver function as defined by Inclusion Criterion #6 and are hepatitis B surface antigen negative and/or have undetectable HCV RNA.
4. Adequate renal function defined as calculated creatinine clearance ≥ 40 mL/min per the Cockcroft and Gault formula (Appendix 2) or local institutional standard formula.
5. Adequate bone marrow function:
   a. Absolute neutrophil count (ANC) ≥ 750/mm^3 (≥ 0.75 × 10^9/L)
      - Without growth factor support (filgrastim or pegfilgrastim) for at least 14 days
   b. Platelets ≥ 75,000/mm^3 (≥ 75 × 10^9/L)
      - Evaluated after at least 7 days since last platelet transfusion
   c. Hemoglobin ≥ 9.0 g/dL
      - May receive transfusion
6. Adequate liver function:
   a. Total bilirubin ≤ 1.5 × the upper limit of normal (ULN) except for unconjugated hyperbilirubinemia of Gilbert's syndrome
   b. Alkaline phosphatase (ALP) (in the absence of bone disease), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 ×

ULN if subject has liver metastases)

7. Time between prior anticancer therapy and first dose of tazemetostat as below:
    - Cytotoxic chemotherapy – At least 21 days
    - Non-cytotoxic chemotherapy (eg small molecule inhibitor) – At least 14 days
    - Nitrosoureas – At least 6 weeks
    - Monoclonal antibody(ies) – At least 28 days
    - Radiotherapy
        - At least 14 days from local site radiation therapy;
        - At least 6 weeks from prior radioisotope therapy;
        - At least 12 weeks from 50% pelvic or total body irradiation
    - High-dose therapy with autologous hematopoietic cell infusion – At least 60 days
    - High-dose therapy with allogeneic transplant – At least 90 days (if graft versus host disease [GVHD] is present, must be < Grade 2) and on no prohibited medications, per Exclusion Criterion #3)
    - **NOTE:** Starting at Cycle 1 Day 1, subjects may receive no more than 10 mg of prednisone daily (or equivalent corticosteroid) when used for treatment of lymphoma related symptoms, with the intent to taper by the end of Cycle 1.
8. Males or females aged ≥ 18 years at the time of informed consent (Phase 2). Males or females aged ≥ 16 years at the time of informed consent (Phase 1).
9. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. All females will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutively amenorrheic, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). Females of childbearing potential must not have had unprotected sexual intercourse within 30 days prior to study entry and must agree to use a highly effective method of contraception, from the last menstrual period prior to randomization, during Treatment Cycles, and for 30 days after the final dose of study drug, and have a male partner who uses a condom. Highly effective contraception includes:

a. Double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

b. Placement of an intrauterine device.

c. Established hormonal contraceptive methods: oral, injectable, or implant. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation.

Female subjects exempt from this requirement are subjects who practice total abstinence or have a male partner who is vasectomized. If currently abstinent, the subject must agree to use a highly effective method of contraception as described above if they become sexually active during the Treatment Cycles, and for 30 days after study drug discontinuation.

10. Male subjects must have had either a successful vasectomy **OR** they and their female partner must meet the criteria above (ie, not of childbearing potential **OR** practicing highly effective contraception and use a condom throughout the study period and for 30 days after study drug discontinuation).

11. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.

Phase 1 only (IB and IGR sites in France only):

12. Histologically- and/or cytologically-confirmed advanced or metastatic solid tumor or B cell lymphomas that has progressed after treatment with approved therapies or for which there are no standard therapies available.

Phase 2:

13. Subjects must satisfy all of the following criteria:

    a. Have histologically-confirmed DLBCL (including primary mediastinal B cell lymphoma), with relapsed or refractory disease following at least 2 lines of prior standard therapy, including alkylator/anthracycline (unless anthracycline –based chemotherapy is contraindicated)/ anti-CD20-based therapy (R-CHOP or equivalent) AND must be considered unable to benefit from intensification treatment with autologous hematopoietic stem cell transplantation (ASCT), as defined by meeting at least 1 of the following criteria:

        - Relapsed following, or refractory to, previous ASCT

- Did not achieve at least a partial response to a standard salvage regimen (eg, rituximab, ifosfamide, carboplatin, and etoposide phosphate [R-ICE] or rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP])
- Ineligible for intensification treatment due to age or significant comorbidity
- Ineligible for intensification treatment due to failure to mobilize an acceptable number of hematopoietic stem cells
- Refused intensification treatment and/or ASCT

or

b. Have histologically-confirmed FL, all grades. Subjects may have relapsed/refractory disease following at least 2 standard prior systemic treatment regimens where at least 1 anti-CD20-based regimen was used. Subjects with prior radiotherapy will be included; however, radiotherapy alone will not be considered a systemic treatment regimen.

c. Have provided sufficient archival tumor tissue that has been successfully tested for EZH2 mutation status and cell of origin (DLBCL only) at study specific laboratories allowing for allocation into an open cohort.

d. Have measurable disease as defined by International Working Group-Non-Hodgkin's Lymphoma (IWG-NHL [Cheson, 2007]).

7.2.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

All Subjects:

1. Prior exposure to tazemetostat or other inhibitor(s) of EZH2.
2. Subjects with known leptomeningeal metastases or brain metastases or history of previously treated brain metastases.
3. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE 4.03 criteria) and any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS).

   NOTE: Bone marrow aspirate/biopsy will be conducted following abnormal peripheral blood smear morphology assessment conducted by local laboratory. Cytogenetic testing and DNA sequencing will be conducted following an abnormal bone marrow aspirate/biopsy result.
4. Has a prior history of T-Cell lymphoblastic lymphoma (T-LBL) or T-Cell lymphoblastic leukemia (T-ALL).
5. Subjects taking medications that are known potent CYP3A4 inducers/inhibitors (including St. John's wort) (see Section 7.3.4.3 and

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm; http://medicine.iupui.edu/clinpharm/ddis/).

6. Subjects unwilling to exclude Seville oranges, grapefruit juice, and grapefruit from their diet.
7. Any prior treatment-related (ie, chemotherapy, immunotherapy, radiotherapy) clinically significant toxicities have not resolved to ≤ Grade 1 per CTCAE version 4.03, or prior treatment-related toxicities are clinically unstable and clinically significant at time of enrollment.
8. Major surgery within 4 weeks before the first dose of study drug.
    - **NOTE**: Minor surgery (eg, minor biopsy of extracranial site, central venous catheter placement, shunt revision) is permitted within 3 weeks prior to enrollment.
9. Inability to take oral medication, or malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, or vomiting) that might impair the bioavailability of tazemetostat.
10. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug; or cardiac ventricular arrhythmia (Appendix 3).
11. Prolongation of corrected QT interval using Fridericia's formula (QTcF) to > 480 msec.
12. Venous thrombosis or pulmonary embolism within the last 3 months before starting tazemetostat.
13. Active infection requiring systemic therapy.
14. Known hypersensitivity to any component of tazemetostat,
15. Immunocompromised subjects, including subjects known to be infected with human immunodeficiency virus (HIV).
16. Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the subject's participation in this study.
17. Females who are pregnant or breastfeeding.
18. Subjects who have undergone a solid organ transplant.

Phase 2 only:

19. Subjects with noncutaneous malignancies other than B cell lymphomas.
    - **Exception:** Subjects with another malignancy who have been disease-free for 5 years, or

subjects with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible.

7.3 Treatments

7.3.1 Identity of Investigational Product

Tazemetostat is available as tablets in strengths of 100 (Phase 1 only) and 200 mg and supplied in white HDPE bottles.

7.3.1.1 Chemical Name, Structural Formula of Tazemetostat

Test drug code: EPZ-6438 (for free base)

International non-proprietary name (INN) name: tazemetostat

Chemical name: *N*-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-yl)methyl]-5-[ethyl(tetrahydro-2*H*-pyran-4-yl)amino]-4-methyl-4'-(morpholin-4-ylmethyl)biphenyl-3-carboxamide hydrobromide

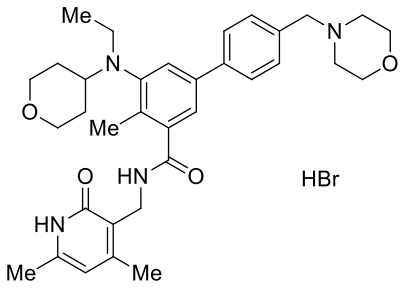
Molecular formula: $C_{34}H_{45}BrN_4O_4$ (Hydrobromide salt)

$C_{34}H_{44}N_4O_4$ (Free base)

Molecular weight: 653.65 (Hydrobromide salt)

572.74 (Free base)

Structural formula:



7.3.1.2 Labeling for Study Drug

Tazemetostat will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

7.3.1.3 Storage Conditions

Tablets: Tazemetostat tablets will be stored in accordance with the labeled storage conditions. See pharmacy manual.

7.3.2 Treatments Administered

Tazemetostat will be administered orally in Phase 1 and Phase 2.

Midazolam will only be administered in the Phase 1 DDI cohort and will be administered orally according to the Summary of Product Characteristics (SmPC).

Phase 1 Dose Escalation and Expansion (closed to enrollment): In the Phase 1 Dose Escalation and Expansion parts, 38 subjects with advanced solid tumors or B cell lymphomas were given tazemetostat orally, starting at 100 mg BID (200 mg total daily dose) continuously starting Cycle 1 Day 1 in 28-day cycles. Dose escalation proceeded in 100% increments in subsequent cohorts unless 1 Grade ≥ 2 nonhematological toxicity during Cycle 1 was assessed as related to the study drug in 2 or more subjects at a dose level until the MTD and/or RP2D was established. Tazemetostat can be taken with or without food.

Phase 1 Food Effect (IB and IGR sites in France only, closed to enrollment): In the Phase 1 FE cohort, 13 subjects with advanced solid tumors or B cell lymphomas were randomized to receive the tazemetostat 200 mg as a single oral dose on Day -8 after fasting for 8 hours before dosing and immediately after consuming a high-fat breakfast (see Appendix 6). For 7 subjects, 200 mg was dosed as a single dose on Day -8 after fasting for 8 hours before tazemetostat dosing, and for 6 subjects, 200 mg was dosed immediately after consuming a high-fat breakfast. Because tazemetostat was to be taken in a fasting state, subjects were required to record the time at which they ate food. Following a 7-day wash-out period subjects crossed over to receive the second tazemetostat 200 mg single oral dose on Day -1. Subjects were instructed to consume the high-fat breakfast within a 30-minute period before study drug administration. Each 28-day period was considered 1 treatment cycle.

If a subject did not consume the full breakfast (when appropriate) and complete all PK assessments, this subject was replaced to ensure that there were 6 subjects in each sequence (fed/fasted and fasted/fed) with all PK assessments.

Beginning on Day 1 of Cycle 1, tazemetostat 400 mg was administered BID for 28-day cycles and could be taken with or without food.

Phase 1 CYP3A4 DDI with Midazolam (IB and IGR sites in France only, closed to enrollment): In the Phase 1 DDI cohort, 13 subjects with advanced solid tumors or B cell lymphoma were enrolled for a DDI study with midazolam to determine the effect of tazemetostat on CYP3A4. Subjects received 800 mg tazemetostat BID, continuously starting on Day 1.

Subjects received a single oral dose of midazolam on Day -1 and Day 15. Subjects fasted 2 hours before and 1 hour after tazemetostat dosing. Once the DDI evaluation was completed in Cycle 1 (after Day 15), continuous dosing of tazemetostat 800 mg BID continued, and tazemetostat was taken with or without food.

Midazolam: Midazolam was administered only in the Phase 1 CYP3A4 DDI cohort of the study. A single 2-mg dose of midazolam was administered orally on Days -1 and Day 15, according to the instructions contained in the SmPC. On Day 15, midazolam was administered concurrently with tazemetostat administration.

Phase 2: Subjects with B cell lymphoma will be administered 800 mg BID of tazemetostat. Tazemetostat will be dosed BID beginning on Cycle 1 Day 1 for continuous 28-day cycles, with or without food.

Each dose of tazemetostat should not be given any earlier than 8 hours after the previous dose or 8 hours before the next dose. If a tazemetostat dose is missed (ie, not taken within 4 hours after the scheduled dosing time), that dose should not be made up and the subject should resume dose administration with the next scheduled dose. If a subject vomits within 30 minutes of study treatment dose administration, anti-emetics should be given and a second dose of study treatment should be administered.

Study treatment in Phase 2 will continue until disease progression, development of unacceptable toxicity, or withdrawal of consent. Subjects may be permitted to continue study treatment if they meet the IWG-NHL (Cheson, 2007) criteria for PD as well as the following criteria:

- Absence of symptoms and signs (including worsening of laboratory values, eg, new or worsening hypercalcemia) that indicate unequivocal PD
- No decline in ECOG performance status
- Absence of tumor growth at critical anatomical sites (eg, leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

At the time of apparent PD per the IWG 2007, subjects for whom approved treatment exists must provide written consent to acknowledge their choice to continue to receive study treatment.

Subjects whose radiographic PD is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the Investigator if they have evidence of clinical benefit and continue to meet the above criteria. Investigators who note subjects with disease progression who are receiving continued clinical benefit without clinical deterioration should contact the Medical Monitor to discuss the assessment of risk/benefit of keeping the subject on study.

7.3.2.1 Dose-Limiting Toxicity

Dose-limiting toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE v4.03 [Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, 2009], see Appendix 5) and are defined in Table 3. Final determination of whether a subject was counted as having experienced a DLT for dose escalation purposes or MTD and/or RP2D confirmation purposes, and whether the dose escalation proceeded in 100% increments, was made jointly by the Sponsor and the investigators.

Table 3 Dose-Limiting Toxicities

Toxicity Category	Toxicity/CTCAE Grade
Hematological	• Grade 4 neutropenia for ≥ 7 days or Grade 3 neutropenia with fever (> 38.5 °C in axilla) • Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or lasting > 7 days
Other Nonhematological Toxicity	• Grade 3 fatigue, or a 2-point decline in Eastern Cooperative Oncology Group (ECOG) performance status that persists for > 7 days • Grade 3 aspartate transaminase ([AST], also referred to as serum glutamic oxaloacetic transaminase [SGOT]) or Grade 3 alanine aminotransferase ([ALT], also referred to as serum glutamic pyruvic transaminase [SGPT]) elevation of > 7 days or Grade 4 AST or ALT of any duration • ≥ Grade 2 neurotoxicity or cardiotoxicity • Grade 2 hypersensitivity reaction • Nausea, vomiting, or diarrhea that persists at Grade 3 or 4 despite maximal medical therapy • Any Grade 3 or higher nonhematological laboratory abnormalities that require hospitalization

CTCAE = Common Terminology Criteria for Adverse Events

The MTD and/or RP2D was determined based on the incidence of DLTs in Cycle 1, although toxicities occurring during subsequent cycles were also reviewed. If serious toxicities were observed at this dose level in later cycles, a reduction of the MTD and/or RP2D was to be considered.

For subjects who required a dose interruption due to tazemetostat-related toxicity during Cycle 1 in the Dose Escalation part of the study, the treatment was re-started once the toxicity resolved to Grade ≤ 1 or baseline. Treatment was according to the criteria listed below:

- If the observed toxicity was determined to be a DLT according to Table 3, the subject resumed treatment at the next lower dose level.

- If the observed toxicity was not considered to be a DLT according to Table 3, the subject resumed treatment as described in the Dose Reduction and Interruption Instructions in Table 4.

All available safety, PK and PD data were reviewed to decide whether to explore intermediate dose and/or alternative dose regimens. As PK were observed to be linear, the dosing schedule and dose escalation scheme was not modified during the dose escalation part of the study. Treatment will continue until disease progression, development of unacceptable toxicity, or withdrawal of consent.

An independent DMC was established to review available safety data supporting the MTD and/or RP2D once a minimum of 6 subjects at the MTD or highest feasible dose complete 1 cycle of treatment in Dose Escalation. The DMC reviewed safety data including, but not limited to, AEs, serious adverse events (SAEs), laboratory parameters, investigational product dosing records, treatment delays or reductions, and treatment discontinuation due to toxicity. One DLT was observed at the dose level of 1600 mg BID; thus, the protocol-defined MTD was not reached. Based on evaluation of safety, tolerability, activity, PK, and PD assessments from the 24 subjects treated in the Dose Escalation part of the study, an RP2D of 800 mg BID has been determined. The RP2D has been endorsed by the investigators and a DMC.

7.3.2.2 Criteria for Retreatment, Temporary Discontinuation of Treatment, Dose Reduction, and Resumption of Treatment

Tazemetostat dose reductions and interruptions will be allowed in Phase 1 and Phase 2; however, an interruption in the administration of tazemetostat for more than **14 days** must be discussed with the Medical Monitor before treatment can be resumed.

Toxicity will be managed by concomitant medication (as appropriate), treatment interruption, dose reduction, and treatment discontinuation, or a combination of these. During treatment with tazemetostat, dose interruption and reduction for subjects who experience tazemetostat-related toxicity will be in accordance with the Dose Reduction and Interruption Instructions in Table 4. If a case of adult T-LBL/T-ALL occurs, enrollment will be suspended and the risk:benefit of the drug will be assessed by the Tazemetostat Safety Committee and will be communicated to all Health Authorities and Ethics Committees. For any MDS/AML or other myeloid malignancies like MPN, tazemetostat will be held, and after discussion with the Investigator, tazemetostat dose will be modified or discontinued.

For subjects who require dose interruption due to tazemetostat-related toxicity in Phase 1 or in Phase 2, the treatment may re-start once the toxicity has been resolved to Grade ≤ 1 or baseline according to the Dose Reduction and Interruption Instructions in Table 4.

For continuation of treatment for Cycle 2 and beyond, subjects must meet the following retreatment criteria:

- Platelet count must be $\geq 75 \times 10^9$/L
- ANC must be $\geq 0.75 \times 10^9$/L, and
- Any Grade 3 or higher toxicity must have resolved to Grade 1 or baseline, unless otherwise noted.

Table 4 Tazemetostat Dose Reduction and Interruption Instructions

	During Therapy	Approximate Dose Adjustment[b]
Grade 1		
All occurrences	Continue tazemetostat	Maintain dose level
Grade 2[c]		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Maintain dose level
2nd occurrence (same or new toxicity)		Restart at 600 mg BID
3rd occurrence (same or new toxicity)		Restart at 400 mg BID
4th occurrence (same or new toxicity)		Discuss with medical monitor
Grade 3[c] not including neutropenia and thrombocytopenia		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 600 mg BID
2nd occurrence (same or new toxicity)		Restart at 400 mg BID
3rd occurrence (same or new toxicity)	Discontinue tazemetostat	Not applicable
Grade 3 Neutropenia (ANC: < 1 – 0.5 × 10^9/L)		
ANC < 0.75×10^9/L 1st occurrence	Interrupt tazemetostat until resolved to ANC ≥ 0.75×10^9/L	Restart at 600 mg BID
2nd occurrence		Restart at 400 mg BID
3rd occurrence	Discontinue tazemetostat	Not applicable
Grade 3 Thrombocytopenia		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 600 mg BID
2nd occurrence		Restart at 400mg BID
3rd occurrence	Discontinue tazemetostat	Not applicable
Grade 4		
Any occurrence	Interrupt study drug until resolved to Grade 2 or less	Discuss with medical monitor

ANC = absolute neutrophil count, BID = twice daily

a Excluding alopecia and nausea, vomiting or diarrhea not receiving adequate treatment.

b An interruption of tazemetostat for more than 14 days due to any toxicity must be discussed with the Sponsor before treatment can be resumed.

c Excluding Grade 2 and 3 anemia: Subjects are allowed to continue tazemetostat at their current dose level with transfusion per investigator discretion.

7.3.3 Method of Assigning Subjects to Treatment Groups

For the Phase 1 Dose Escalation part, subjects with advanced solid tumors or B cell lymphoma were enrolled using a dose-escalation algorithm (3+3 subjects per dose level) to identify the MTD and/or RP2D. Food Effect cohort subjects with advanced solid tumors or B cell lymphoma were randomized to 1 of 2 treatment sequences (either fed/fasted or fasted/fed) according to a randomization scheme. Subjects will be enrolled sequentially in the Dose Escalation component and DDI cohort.

For Phase 2, DLBCL subjects will be allocated into cohorts (Cohorts 1-3)prior to tazemetostat dosing based on the results of the EZH2 mutation and COO testing. FL subjects will be allocated into cohorts (Cohorts 4 and 5) prior to tazemetostat dosing based on the results of EZH2 mutation testing. The tumor tissue EZH2/COO testing can be performed prior to other screening procedures, for example, during wash-out of the second line anticancer therapy, after the subject is consented for the prescreening testing.

7.3.4 Prior and Concomitant Therapy

Prior and concomitant medications include all prescription and nonprescription medications, vitamins, herbals, and transfusions.

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug will be recorded. In the Phase 1 part of the study any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study drug will be recorded. In the Phase 2 part of the study any concomitant therapy administered to the subject during the course of the study (starting at the date of first dose of study drug) until 30 days after the final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded.

7.3.4.1 Permitted and Concomitant Medication

Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with tazemetostat may be continued during the study.

Subjects may receive prednisone (or equivalent corticosteroid) for systemic or local symptom control prior to and while on study. Starting at Cycle 1 Day 1 however, subjects may receive no more than 10 mg of prednisone daily (or equivalent corticosteroid) when used for treatment of lymphoma related symptoms, with the intent to taper by the end of Cycle 1.

Treatment of complications or AEs or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs, etc.) may be given at the discretion of the Investigator, unless it is expected to interfere with the evaluation of

(or to interact with) tazemetostat. The Investigator will record any AE on the AE case report form (CRF) for which the concomitant medication/therapy was administered.

Over the counter medications, nutritional supplements, vitamins, and herbal preparations are permitted under physician recommendation only. Aspirin, nonsteroidal anti-inflammatory drugs, and low-molecular-weight heparin or prophylactic doses of heparin are permissible but should be used with caution. Granulocyte colony-stimulating factor or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines.

7.3.4.2 Permitted Radiation Therapy

Palliative radiotherapy may be given for the control of pain or for other reasons (ie, bronchial obstruction, ulcerating skin lesions) with no curative intent. The irradiated area should be as small as possible and should never involve more than 10% of the bone marrow in any given 4-week period for distribution of active bone marrow). The irradiated area cannot be used as a parameter for response assessment. Treatment with tazemetostat should be delayed in subjects receiving palliative radiotherapy after discussion with the Medical Monitor. In addition, other palliative procedures intended for symptom control and concurrent dose interruptions may be permitted after discussion with the Medical Monitor. These procedures will be limited to non-target lesions only.

7.3.4.3 Prohibited Concomitant Therapies and Drugs

Subjects must not receive other antitumor therapies while on study. Prohibited medications during this study are any other experimental or unapproved drugs, other anticancer therapies unless otherwise stated, and known potent CYP3A4 inhibitors and inducers within 14 days prior to the first dose of tazemetostat and for the duration of the study. Medications that are strong inhibitors and strong inducers include, but are not limited to those listed in Table 5.

Table 5 Medications that are Potent Inhibitors and Inducers of CYP3A4

CYP Enzymes	Strong Inducers	Strong Inhibitors
CYP3A	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, elaprevir, telithromycin, voriconazole

Please refer to the following websites for a comprehensive list of these medications or contact the Medical Monitor for additional questions:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

http://medicine.iupui.edu/clinpharm/ddis/

7.3.4.4 Concomitant Medications to be used with Caution

Substrates of P-gp, CYP3A, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 should be used with caution. Medications that are substrates of CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 and have a narrow therapeutic range should be avoided if possible. Medications that are substrates of CYP2C8, CYP2C9, CYP2C19, CYP3A, and CYP2D6 and have a narrow therapeutic range include, but are not limited to, those listed in Table 6.

NOTE: A listing of CYP substrates can be found using the following link: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Table 6 Medications that are CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 Substrates that have a Narrow Therapeutic Range

CYP Enzymes	Substrates with Narrow Therapeutic Range
CYP2C8	Paclitaxel
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus
CYP2D6	Thioridazine

Please refer to the following websites for a list of these medications or contact the medical monitor for additional questions:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

If subjects receive any of the prohibited antitumor medications, this will be judged as evidence of disease progression, and study drug will be discontinued. These subjects should complete all off-treatment assessments and be followed for survival in the Follow-up Period.

7.3.5 Prohibitions and Restrictions during Study Period

Grapefruit and grapefruit juice-containing products and Seville oranges are not permitted for 1 week before dosing and throughout the study.

Phototoxic Potential: [redacted] prolonged exposure to sunlight should be avoided during treatment. In addition, subjects should take other measures to avoid ultraviolet (UV) exposure such as wearing sun screen and sun glasses, wearing protective clothing, and avoiding tanning beds. Refer to the tazemetostat IB for details.

7.3.6 Treatment Compliance

Compliance for doses taken outside of the clinic may be assessed by a count of the capsules returned to the study trial site by the subject and review of doses taken with the subject. This will be recorded in the source documents, which may include the use of a subject medication diary per institutional practice.

7.3.7 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the Investigator until the following documentation has been received by the Sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page signed and dated by the Investigator
- Written proof of approval of the protocol, the informed consent form(s) (ICFs), and any other information provided to the subjects by the Institutional Review Board or Independent Ethics Committee (IRB/IEC) for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required) and the Import License (if required)
- An investigator-signed and dated Form Food and Drug Administration (FDA) 1572, a signed and dated curriculum vitae for the principal investigator (PI) including a copy of the PI's current medical license (required in the US) or medical registration number on curriculum vitae
- Financial Disclosure Form for the PI listed on Form FDA 1572

- A signed and dated clinical trials agreement.

The Investigator and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following the Sponsor's instructions and adherence to Good Clinical Practice (GCP) guidelines as well as local and regional requirements.

Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled in the study. An accurate and timely record of the receipt of all clinical supplies, dispensing of study drug to the subject, collection and reconciliation of used and unused supplies that are either returned by the subject or shipped to the site but not used, subsequent return of unused study drug to the Sponsor or designated central or local depot, and (where applicable) destruction of study drug at the site must be maintained. This includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) study drug dispensing/return reconciliation log, (c) study drug accountability log, (d) all shipping service receipts, (e) documentation of drug returned to the Sponsor, and (f) certificates of destruction for any destruction that occurs at site. All forms will be provided by the Sponsor. Any comparable forms that the investigational site wishes to use must be approved by the Sponsor.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor or a representative of any national health authority. All used and unused study drugs, including empty containers, are to be returned to the Investigator by the subject and ultimately to the Sponsor's designated contractor or depot by the conclusion of the study, unless approval is given by the Sponsor for destruction of supplies and containers at the investigational site. Upon completion of drug accountability and reconciliation procedures by investigational site personnel and documentation procedures by the Sponsor's personnel, study drug that is to be returned to the Sponsor's approved contract vendor must be boxed and sealed and shipped back to the Sponsor's approved contract vendor following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the Sponsor's specified location by sponsor representatives.

Drug accountability will be reviewed during investigational site visits and at the completion of the study.

7.4 Study Assessments

7.4.1 Assessments

7.4.1.1 Screening Assessments and Demography

Demographic information will be collected at the Screening Visit. Standard demography parameters include age, gender, and race/ethnicity (recorded in accordance with prevailing

regulations). The Screening Visit will occur in the period specified in Table 8 and Table 9. The purpose of the Screening Period is to obtain informed consent and establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 8.2.1.

7.4.1.2 Medical History and Physical Examinations

Medical and surgical histories will be obtained during the Pretreatment Phase, along with a record of prior and concomitant medications. Significant findings before the start of study drug will be recorded on the Medical History and Current Medical Conditions CRF. A standard-of-care clinical examination for lymphoma, including assessment of B symptoms, will also be performed at the Screening Visit and at all disease assessments.

Physical examinations (comprehensive or symptom-directed) will be performed as specified in the Schedule of Visits and Procedures (Table 8 and Table 9). Documentation of the physical examination will be included in the source documentation at the investigational site. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AE CRF.

Phase 2

EZH2 Mutation Status and Confirmation of Cell of Origin

Sufficient tumor tissue must be available for central testing of EZH2 mutation status for all subjects at screening and COO status (for DLBCL subjects) at Screening. An EZH2 mutation result will be determined at designated study laboratory testing sites using the **cobas®** EZH2 Mutation Test, which is a real time allele-specific PCR test to detect the following mutations within codons Y646, A682, and A692 of the EZH2 gene in FFPE NHL tumor tissue specimens: Y646F, Y646N, Y646S, Y646H, Y646C, A682G, and/or A692V; results for codons Y646S, Y646H, and Y646C are not reported individually (grouped as Y646X). For the purposes of this protocol, the term “wild-type” refers to the absence of detection of the above-specified mutations and assigned to the appropriate cohort. The EZH2 mutation test is intended to be used as an Investigational Use Only assay.

COO will be determined for **DLBCL** subjects using the Hans method [Hans 2004] at designated study laboratory testing sites. Further details of EZH2 mutation and COO testing will be provided in the Laboratory Manual.

Collection details will be presented in the Laboratory Manual. For additional details, see Table 9.

7.4.1.3 Tumor Assessments

Solid tumors: Tumor assessment will be performed based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1 [Eisenhauer, 2009]); see Appendix 4. Investigator-determined response assessments at each assessment time point will be entered onto the appropriate CRF.

B cell lymphoma: Tumor assessments will be performed based upon IWG-NHL (Cheson, 2007) criteria at each assessment time point and entered onto the appropriate CRF. Investigator-determined response assessments at each assessment time point will be entered onto the appropriate CRF. For the Phase 2 part of the study, scans will be performed according to guidelines provided by the imaging core laboratory designated for this study (see Imaging Manual). All tumor assessment scans will be sent, as soon as they have been performed, to the imaging core laboratory for quality assessment and archival for potential independent imaging review.

For additional tumor assessment details, see the Schedules of Procedures and Assessments (Table 8 and Table 9).

During the **Screening Period:**

All subjects: Computed tomography (CT) scans of the chest; and CT or magnetic resonance imaging (MRI) scans of the brain, abdomen, pelvis, and other known sites of disease (as well as photographs of skin lesions that will be followed as target and nontarget lesions), will be performed at Screening. Standard of care scans performed within 28 days before Cycle 1 Day 1 using the protocol-specified parameters may be used as screening assessments.

Solid tumor only: Bone scans will be performed as clinically indicated.

NHL only: An ^{18}fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) scan will be performed (NHL only). A bone marrow biopsy (including IHC) will be performed for all subjects with FL and if clinically indicated in subjects with DLBCL if these have not been performed within 42 days (an approval is needed from the Sponsor's Medical Monitor if the window has been beyond 42 days) of Cycle 1 Day 1.

During the **Treatment Phase:**

All subjects: CT scans of the chest, and CT or MRI of the brain (if clinically indicated), abdomen, pelvis, and other known sites of disease will be performed every 8 weeks (starting from Cycle 1 Day 1 of continuous tazemetostat dosing), or sooner if clinically indicated. If local regulatory authorities mandate less frequent imaging, minimum frequency must be every 12 weeks. Tumor assessments will be carried out every 8 weeks (or sooner, if clinically indicated) during treatment cycles in both the Treatment Phase and the Extension Phase. For

subjects who remain on study drug for 24 weeks or more, radiologic disease assessments will be performed every 12 weeks.

Solid tumor only: Possible PR and CR (according to RECIST 1.1 criteria) must be confirmed at least 4 weeks after the initial response assessment.

NHL only: At the first notation of possible PR and CR, a whole body ^{18}FDG-PET scan should be performed. At the first notation of CR, a repeat bone marrow biopsy will be performed if lymphoma involvement in the bone marrow was reported at Screening. Repeat bone marrow biopsies will be performed if clinically indicated (if progressive disease or relapse is suspected).

All Subjects: The CT scan should be a diagnostic quality spiral or multidetector CT with oral and iodinated intravenous (IV) contrast, and the MRI scan should be performed with IV gadolinium chelate. Scans of the neck, abdomen, pelvis, and other areas of the body may be performed with MRI instead of CT, but evaluation of the chest must be done with CT. If iodinated IV contrast is contraindicated, the chest evaluation should be done with noncontrast CT, and the abdomen and pelvis evaluation should be performed using either CT with oral contrast (without IV contrast) or MRI with gadolinium chelate IV contrast (the latter is preferred). Spiral/multidetector CT should be performed with a 5-mm contiguous slice reconstruction algorithm. If body MRI scans are performed, contiguous slices of 5 mm are also recommended.

The same imaging modality and image-acquisition protocol (including use or nonuse of IV contrast) should be used consistently across all time points to allow consistent comparison of lesions. Low-dose noncontrast CT transmission scans from a positron emission tomography-CT (PET-CT) combination scanner are not acceptable. Ultrasound should not be used for radiographic tumor assessment. A chest x-ray or skeletal x-ray that clearly demonstrates a new metastatic lesion may be used to document progression in lieu of the CT or MRI scans.

Brain scans should be performed by MRI pre- and post-contrast enhancement or CT with contrast enhancement, with 5-mm contiguous slices recommended (maximum inter-slice gap of 1 mm on MRI).

Solid tumor subjects only: The recommended bone scan technique is ^{99}m-technetium methylene polyphosphonate (ie, methylene diphosphonate or hydroxymethylene diphosphonate scintigraphy or whole body-bone MRI, or ^{18}F-sodium fluoride PET. The same methodology and scan acquisition techniques used at Screening should be used throughout the study to ensure comparability. If a bone lesion is to be followed as a nontarget lesion (RECIST 1.1 criteria), it is preferable that this be performed using CT or MRI. For bone nontarget lesions that can be followed only on bone scans, a time point response other than not evaluable (NE) will be

allowed despite an individual lesion assessment of NE for weeks when bone scans are not required.

Whole body ^{18}FDG-PET scans should be performed using institutional guidelines for Phase 1 and according to the imaging core laboratory guidelines for the Phase 2 part.

If subcutaneous masses or nodes are palpable (eg, bulky) and are assessable by both clinical and radiographic techniques, the radiographic (CT or MRI) technique should be used for the assessment of target and nontarget lesions.

Assessments are to be performed at the site by appropriately qualified personnel and results of the site interpretation are to be recorded on the appropriate CRFs.

7.4.1.4 Exploratory Assessments

Overall survival

Overall survival is the duration measured from the date of first dose until the date of death from any cause. Survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent. Anti-cancer therapies and AESI information will also be collected at this time.

7.4.1.5 Pharmacokinetic Assessments

Phase 1: Blood samples for PK analyses will be collected during Cycle 1 Day 1 and Day 15 in the Phase 1 Dose Escalation part, on Day -8 and Day -1 of the FE cohort, Day -1 and Day 15 of the DDI cohort, and Cycles 1 and 2 in the Phase 1 FE and DDI cohorts.

Urine samples for PK analyses will be collected during the Phase 1 Dose Escalation part only during Cycle 1.

Phase 2: Sparse PK blood samples will be collected during Cycle 1 and Cycle 2 of the Phase 2 study until sample size needed for population PK analysis has been met.

Refer to Laboratory Manual and see Table 8 and Table 9 for additional details.

7.4.1.6 Biomarker and Pharmacogenomic Assessments

Biomarker discovery and validation may be performed through all phases of this clinical study. The goal of these studies is to assay biomarkers in blood, normal, and malignant tissue to confirm the mechanism of action of tazemetostat and discover biomarkers that may predict response to tazemetostat.

Phase 1 Dose Escalation and Food Effect Cohort (Closed to Enrollment)

Blood samples and skin punch biopsies (Dose Escalation only: closed), will be obtained predose and at various specified times postdose and may be assessed for molecular changes associated

with exposure to tazemetostat, such as changes in histone methylation, gene expression (protein and/or mRNA), or other markers with the potential to confirm the mechanism of action of tazemetostat (PD biomarker). Results will be correlated with PK and safety data.

Archival, FFPE tumor tissue from all enrolled subjects will also be collected (if available) for assessment of EZH2 mutation status, for confirmation of COO in DLBCL cohorts, and for exploratory response biomarker analysis. Biomarker assays for analysis of markers identified in nonclinical studies and/or the scientific literature may include DNA mutation assessment, gene-expression profiling, proteomics, or IHC analysis. Results may be correlated with efficacy data.

During the FE cohort, paired tumor biopsies or bone marrow samples (for FL cases) may be obtained, with appropriate subject consent, to examine tumor tissue for molecular evidence of the downstream consequences of EZH2 inhibition (see below under Phase 2).

For details regarding the Phase 1 PD analyses, see Schedule of Visits and Procedures (Table 8) and the Laboratory Manual.

Phase 2

Blood samples will be obtained predose and at various specified times postdose and assessed for molecular changes induced by exposure to tazemetostat, such as changes in histone methylation, gene expression (protein and/or mRNA), or other markers with the potential to elucidate or confirm the mechanism of action of tazemetostat.

Paired tumor biopsies and/or bone marrow (FL cohorts) may be obtained, with appropriate subject consent, to examine tumor tissue for molecular evidence of the downstream consequences of EZH2 inhibition using relevant PD biomarkers such as H3K27 methylation status or others as assayed by appropriate methodologies. The aim is to obtain paired tumor tissue from a minimum of 4-6 subjects from each of the planned cohorts in Phase 2, FE, and Dose Expansion cohorts. Depending on tissue availability, assessment of the drug's effect on both tumor and stromal cells is planned, as changes in 1 or both tissue types may predict tumor response. Lymphoma cell-specific markers can include, but are not limited to, differentiation markers, markers of immune cell recognition, and markers of proliferation and apoptosis. The general tumor/stromal architecture will be examined to study the drug's effects on the interaction of lymphoma cells with the tumor microenvironment. Specific markers can include, but are not limited to, the presence and activation state of regulatory T cells, the Th1/Th2 profile of intra-tumoral T helper cells, and expression of programmed death receptor 1 (PD1) and programmed death ligands (PDL1 and PDL2) on tumor and T cells. Refer to Section 7.4.1.7 for biopsy schedules. A plasma sample for cell-free nucleic acid analysis (circulating tumor DNA) will be obtained predose and at various time points as specified in the Schedule of Visits and Procedures (Phase 2 only). Cell-free nucleic acid isolated from blood plasma samples may be used to

explore tumor genetic alterations, including mutations observed in archival tumor samples, mutations that may emerge with drug treatment, and candidate biomarkers of response to tazemetostat.

Archival, FFPE tumor tissue from all enrolled subjects must be collected for prospective assessment of EZH2 mutation status, for confirmation of COO in DLBCL cohorts. Additional exploratory response biomarker analysis may be performed retrospectively. Gene-expression profiling, proteomics, DNA mutation analysis, or IHC analysis may be performed, based on the amount of tumor tissue available, for analysis of markers identified in preclinical studies and/or the scientific literature. Gene expression profiling may be performed and correlated with PK, PD, or safety data.

An EZH2 mutation result will be determined at designated study laboratory testing sites using the **cobas**® EZH2 Mutation Test, which is a real time allele-specific PCR test to detect mutations within codons Y646, A682, and A692 of the EZH2 gene in FFPE NHL tumor tissue specimens: Y646F, Y646N, Y646S, Y646H, Y646C, A682G, and/or A692V; results for Y646S, Y646H, and Y646C are not reported individually (grouped as Y646X). The EZH2 mutation test is an Investigational Use Only assay.

COO will be determined for DLBCL subjects using the Hans method (Hans, 2004) at designated laboratory testing sites. Further details of EZH2 mutation and COO testing will be provided in the Laboratory Manual.

Applicable to both Phase 1 and Phase 2

Plasma samples from subjects receiving tazemetostat may undergo global proteomic and enzyme-linked immunosorbent assay-based analyses and multiplex bead-based immunoassay in an effort to identify protein markers.

Genomic DNA samples may be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion or the development of AEs. Variation in tazemetostat exposure or AEs may be evaluated by correlation of single-nucleotide polymorphisms with PK, safety, or PD data. Collection of Genomic DNA will cease when sample size has been met.

Data obtained will be used only for research, to assist in developing safer and more effective treatments, and will not be used to change the diagnosis of the subject or alter the therapy of the subject. Biomarker specimens and any DNA, RNA, protein, or metabolites derived from the collected specimens may be stored for up to 15 years to assist in any research (eg, scientific questions related to tazemetostat, solid tumors, or B cell lymphoma) as well as for potential use in diagnostic development.

For additional information, see Appendix 7. Details of pharmacogenomic and biomarker sampling and analysis will be provided in the Laboratory Manual.

PHARMACODYNAMIC ASSESSMENTS

Blood samples, skin punch biopsies (for Dose Escalation only: closed), and optional tumor biopsies for PD assessments will be obtained predose and at various time points as specified in the Schedule of Visits and Procedures. Refer to Laboratory Manual and see Table 8 and Table 9 for additional details.

Pharmacokinetic/Pharmacodynamic Assessments

The PK/PD relationship between exposure to tazemetostat and histone methylation will be explored graphically and any emergent relationship will be followed by model-based PK/PD analysis.

PK/PD relationships will be assessed for exploratory biomarkers, safety, and preliminary efficacy.

PK/PD analysis may be performed to correlate best overall response with tazemetostat exposure.

The total volume of blood to be drawn per period or cycle can be found in the Laboratory Manual provided separately. Instructions for the processing, storage, and shipment of samples will be provided in a separate Laboratory Manual.

7.4.1.7 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE v4.03 [Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, 2009], see Appendix 5) (for both increasing and decreasing severity), and SAEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; and periodic measurement of vital signs, echocardiograms/ multiple-gated acquisition (MUGA) scans, electrocardiograms (ECGs), and physical examinations. Additionally, QT interval corrected for heart rate using Fridericia's formula (QTcF) will be evaluated.

For details, refer to the Schedule of Visits and Procedures (Table 8 and Table 9).

LABORATORY MEASUREMENTS

The clinical laboratory parameters that will be measured are detailed in Table 7.

Phase 1 only: Clinical laboratory tests will be performed by a central laboratory. All blood samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern or to guide clinical dosing, a local laboratory may be used in addition to a central laboratory. If central laboratory results are not available

within the necessary time frame to allow the subject to be enrolled, local laboratories may be used to perform laboratory tests to qualify subjects for entry into the study. Urinalysis may be performed at the investigational site by dipstick or sent to the central laboratory.

For the Phase 2 part of the study clinical laboratory tests will be performed locally.

The Schedules of Visits and Procedures (Table 8 and Table 9) show the visits at which blood and urine will be collected for clinical laboratory tests. A Laboratory Manual will be provided to detail handling, processing, and shipping procedures.

All hematology, blood chemistry (including pregnancy test, where applicable) samples are to be obtained before study drug administration and results reviewed before administration/dispensing of study drug at the beginning of each cycle. For the management of clinically significant laboratory abnormalities, refer to the Dose Reduction and Interruption Instructions for tazemetostat in Section 7.3.2.2 (Table 4).

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 7.4.4.2) and the CRF Completion guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the AE CRF.

For laboratory abnormalities meeting criteria as SAEs (Section 7.4.4.2), the study site must send the SAE report including the laboratory report to the Sponsor using the SAE fax number or email address provided in the Investigator File.

Table 7 Clinical Laboratory Tests

Category	Parameters
Hematology	• hematocrit, hemoglobin, red blood cell count (RBC), platelet count, white blood cell count (WBC) with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils) • Peripheral blood smear morphology assessment (If peripheral blood smear morphology is abnormal, then conduct bone marrow aspirate with cytogenic testing to closely monitor subjects with cytogenic abnormalities known to be associated with myelodysplastic syndrome (MDS) 9del 5q, chr 7, abn, etc.) and gene mutations associated with myeloproliferative neoplasm (MPN) (eg, JAK2 V617F, etc.)
Chemistry	
Electrolytes	• bicarbonate, chloride, potassium, sodium
Liver function	• alkaline phosphatase (ALP), alanine aminotransferase (ALT [or serum glutamic pyruvic transaminase (SGPT)]), aspartate aminotransferase (AST [or serum glutamic oxaloacetic transaminase (SGOT)]), conjugated (direct) bilirubin[a], total bilirubin
Renal function	• blood urea or blood urea nitrogen (BUN), creatinine
Other	• albumin, amylase, calcium, cholesterol, , creatine phosphokinase (CPK), glucose, International Normalized Ratio (INR), lactate dehydrogenase (LDH), phosphorous, total protein, triglycerides, uric acid

a. The collection of conjugated bilirubin and globulin is not standard of care test across all institutions. Conjugated bilirubin should be collected whenever possible or if clinically indicated. Globulin is no longer required.

VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital signs and body weight (kg) will be collected at the visits designated in the Schedule of Visits and Procedures (Table 8 and Table 9) by a validated method. Vital sign measurements include blood pressure ([BP], systolic BP, diastolic BP), heart rate (HR, beats per minute), and body temperature (°C). Height will be measured at the Screening Visit only. Blood pressure and HR will be collected after subjects have been sitting for 5 minutes.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

ECOG Performance Status

An ECOG performance status should be done at each visit as designated in the Schedule of Visits and Procedures (Table 8 and Table 9).

Physical Examinations

Comprehensive physical examinations and symptomatic physical examinations will be performed as designated in the Schedule of Visits and Procedures (Table 8 and Table 9). Documentation of the physical examination will be included in the source documentation at the investigational site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the AE CRF.

A comprehensive physical examination will include evaluation of the head, eyes, ears, nose, throat, neck, heart, chest, lungs, abdomen, extremities, skin, and neurological status.

Symptom directed physical examination will include health status assessed by a brief evaluation of the head, eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination.

Electrocardiograms

Electrocardiograms will be complete, standardized, 12-lead recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format as designated in the Schedule of Visits and Procedures (Table 8 and Table 9). In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes before the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (Section 7.4.4.3) and the CRF instructions. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AE CRF.

For ECG abnormalities meeting criteria as SAEs (Section 7.4.6), the study site must send the SAE report including the ECG report to the number indicated in the Investigator File using the SAE reporting form.

7.4.1.8 Other Assessments

Pregnancy Test

A serum β-hCG test and/or urine β-hCG test will be performed at Screening for all women of child bearing potential. A urine or serum pregnancy test will be performed before the first tazemetostat dose and prior to dosing on Day 1 of each cycle. For the serum β-hCG test, a 6-mL sample of blood will be taken at designated time points on the Schedule of Visits and Procedures (Table 8 and Table 9).

Paired Tumor Biopsies

Paired tumor biopsies (Phase 2 cohorts, Dose-Escalation cohorts, and FE cohort) and/or bone marrow biopsies (Phase 2 FL cohorts) may be obtained, with appropriate subject consent, from 4 to 6 subjects per cohort to examine tumor tissue for molecular evidence of the downstream consequences of EZH2 inhibition using relevant PD biomarkers assayed by appropriate methodologies. Paired tumor tissue will be obtained from the pool of subjects recruited to the Expansion Cohorts, FE cohort, and Phase 2 part. Tissue sample collection, for PD assessments will occur at the designated time point on the Schedule of Visits and Procedures (Table 9). Subjects should have the biopsy before administration of the first dose of tazemetostat and the second biopsy at Cycle 2 Day 1.

Tumor Biopsy at Disease Progression

Tumor biopsy is requested, where medically feasible, at disease progression in subjects who achieve a PR or better with tazemetostat.

Bone Marrow Biopsy with IHC

A bone marrow biopsy (including IHC) will be performed for all subjects with FL and in subjects with DLBCL if clinically indicated or if subject has history of bone marrow involvement if these have not been performed within 42 days (an approval is needed from the Sponsor's medical monitor if the window has been beyond 42 days) of Cycle 1 Day 1. At the first notation of CR, a repeat bone marrow biopsy should be performed if lymphoma involvement in the bone marrow was reported at Screening. For further details, see Table 9.

Peripheral Blood Smear / Bone Marrow Biopsy

If peripheral blood smear morphology assessment is confirmed to be abnormal, the subject will be required to undergo bone marrow aspirate/biopsy for cytogenetic testing to closely monitor subjects with cytogenetic abnormalities known to be associated with MDS (9del 5q, chr 7, abn, etc.) and sequencing of genes known to be mutated in MPN (eg, JAK2 V617F, etc.) If abnormal results, pause tazemetostat and after discussion with the Investigator modify the dose or discontinue the drug.

Optional Chest Ultrasound

An optional chest ultrasound may be performed at screening and every 8 weeks at the Investigator's discretion to monitor for early signs of T-LBL/T-ALL.

Annual Assessments

Annual assessments will be conducted to review AESIs, PK, and tumor response. A 3 mL blood sample will be required for annual PK assessments.

7.4.1.9 Safety Monitoring

Completed: Final determination of whether a subject should be counted as having experienced a DLT for dose escalation purposes or MTD and/or RP2D confirmation purposes, and whether the dose escalation will proceed in 100% increments or smaller, will be made jointly by the Sponsor and investigators. For additional details, see Section 7.3.2.1.

Completed: An independent DMC was established to review available safety data supporting the MTD and/or RP2D once a minimum of 6 subjects at the MTD or highest feasible dose complete 1 cycle in Dose Escalation. The DMC reviewed safety data including, but not limited to, AEs, SAEs, laboratory parameters, investigational product dosing records, treatment delays or reductions, and treatment discontinuation due to toxicity. Based on all data reviews, the Sponsor and the DMC concurred on the dose for Phase 2.

During Phase 2, in order to adequately monitor safety, data will be reviewed regularly by an independent DMC. The DMC Chair, in consultation with the Sponsor, will be responsible for determining the type and frequency of any additional DMC data review meetings. The DMC will review safety data including, but not limited to, AEs, SAEs, laboratory parameters, investigational product dosing records, treatment delays or reductions, and treatment discontinuations due to toxicity. Any treatment-related death will also trigger review by the DMC. The DMC will determine whether it is safe to proceed.

A full description of the membership and roles and responsibilities of the DMC will be provided in the DMC charter, and its end of Phase 1 assessment report will be transmitted to the approving Ethics Committees and Competent Authorities for this study.

7.4.2 Schedule of Procedures/Assessments

Phase 1 Schedule of Visits and Procedures for assessments are presented in Table 8.

Phase 2 Schedule of Visits and Procedures for assessments are presented in Table 9.

7.4.2.1 Description of Assessment Schedule

Potential subjects will undergo a screening assessment within 28 days before the start of the study to evaluate their eligibility for the study. Before any procedures or assessments are performed, the nature of the study and the potential risks associated with the trial will be explained to all subject candidates, and written informed consent will be obtained. Once informed consent has been obtained, study procedures and evaluations will be performed.

The tumor tissue EZH2/COO testing can be performed prior to other screening procedures, for example, during wash-out of the second line anticancer therapy, after the subject is consented for the prescreening testing.

Efforts should be made to conduct study visits on the day scheduled (± 3 days). Clinical laboratory assessments (Table 7) may be conducted anytime within 72 hours before the scheduled visit, unless otherwise specified in the Schedule of Visits and Procedures. Whenever possible, subjects should be evaluated at approximately the same time of the day (eg, morning or afternoon) at each visit, and reasonable efforts should be made to conduct all evaluations in the same test order at each visit. Subjects on the Phase 1 part of the study who have completed at least 6 cycles of study drug and are considered clinically stable may, after prior agreement with the study medical monitor, have Day 15 assessments in additional cycles consisting of telephone contact to site and local clinical laboratory assessments. For the details of procedures, assessments, and timing of procedures and assessments that are to be conducted at each visit and cycle(s), refer to the Schedule of Visits and Procedures.

Table 8 Schedule of Visits and Procedures: Phase 1 Tazemetostat (All visits starting at Cycle 2 Day 1 can have a +/- 3 Day Window)

Phase	Pretreatment		DDI only	Treatment		Extension		Extension	Off-Treatment[a]	Follow-up[b]
Period	Screening[c]	Baseline[c]		Cycle 1		Cycle 2 - 6		Cycle 7 and Beyond[d]		
Day	-28 to -4	-3 to -1	-1	1	15	1	15	1		
Procedures/Assessments										
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Medical history	X	X								
Prior and concomitant medications				Throughout study						
Comprehensive physical examination	X								X	
Symptom directed physical examination		X		X	X	X	X	X		
Pregnancy test[e]	X	X				X		X		
Body weight	X	X		X	X	X	X	X	X	
Height	X									
Vital signs[f]	X	X		X	X	X	X	X	X	
ECOG performance status	X	X				X		X	X	
12-lead ECGs[g]	X	X		X		X	X	X	X	
Hematology	X	X		X	X	X	X	X	X	
Blood chemistry	X	X		X	X	X	X	X	X	
Genomic DNA[j]		X								
PK blood samples[k]			X		X	X[k]				
PD blood samples[l]				X	X	X[l]				
Paired tumor biopsy[m]		X				X				
Archival tumor block or slides[n]		X								
Tumor assessments: CT (MRI)[o]	X			Tumor assessments must be performed every 8 weeks up to week 24				Tumor assessments performed every 12 weeks	X	
Bone scans (solid tumor as indicated)	X			X						
^{18}FDG-PET Scan (NHL)[p]	X			Repeat PET at PR or CR						
Bone Marrow Biopsy	X									

Table 8 Schedule of Visits and Procedures: Phase 1 Tazemetostat (All visits starting at Cycle 2 Day 1 can have a +/- 3 Day Window)

Phase	Pretreatment		DDI only	Treatment		Extension		Extension	Off-Treatment[a]	Follow-up[b]
Period	Screening[c]	Baseline[c]		Cycle 1		Cycle 2 - 6		Cycle 7 and Beyond[d]		
Day	-28 to -4	-3 to -1	-1	1	15	1	15	1		
Procedures/Assessments										
(NHL if indicated)[q]										
CT or MRI of the brain[r]	Brain scans should be performed if clinically indicated both NHL and solid tumor.									
AEs/SAEs				Throughout study						
Tazemetostat administration[s]				Continuous 28-day cycle of tazemetostat twice daily. Tazemetostat can be taken with or without food.						
Midazolam administration (DDI only)[t]			X		X					
Survival status and subsequent anticancer therapy									X	X

AE = adverse event, BM = bone marrow, β-hCG = beta-human chorionic gonadotropin, BP = blood pressure, CR = complete response, CT = computed tomography, DDI = drug-drug interaction, DNA = deoxyribonucleic acid, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, ^{18}FDG-PET = ^{18}fluorodeoxyglucose-positron emission tomography, HR = heart rate, IV = intravenous, MRI = magnetic resonance imaging, NHL = non-Hodgkin lymphoma, PD = pharmacodynamic, PK = pharmacokinetic, PR = partial response, SAE = serious adverse event

Note: All table footnotes are presented on the following 2 pages.

PHASE 1 IS COMPLETED

Off-treatment assessment may occur at time of treatment discontinuation or up to 30 days after the final dose of study drug. AE and concomitant medication data must be collected for 30 days after the final dose of study drug, or until the start of new therapy. This may occur prior to 30 days if new therapy is started within 30 days of last dose of study drug.

b Survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent. Information on all anticancer therapies will be collected (the Sponsor may choose to stop the collection of therapies after the first anticancer treatment following tazemetostat). This may be done by telephone contact.

c The Screening Period extends from Day -28 to Day -4, except for signing of the informed consent form, which may be up to 8 weeks before the first dose of study drug. The baseline assessments may be performed from Day -3 to Day -2 (before the first dose of tazemetostat). The screening assessments (except tumor assessment) must be performed within 28 days before the first dose of study drug and may be used as baseline assessments if performed within 72 hours of the first dose of study drug. Tumor assessment must occur within 28 days of CT or MRI or photographs and within 42 days of bone scans (if a bone scan is appropriate for a tumor type).

d Starting at Cycle 7, a Day 15 visit is not required. On Day 15 of each cycle, subjects will have hematology and blood chemistry samples drawn at a local laboratory and telephone contact with the site to review AEs.

e A serum pregnancy test (β-hCG) will be performed at Screening for all women of childbearing potential. A urine or serum pregnancy test will be performed predose on Day 1 of each cycle.

f Vital signs include BP, HR, and body temperature. BP and HR will be collected after the subject has been sitting for 5 minutes.

g 12-Lead ECGs will be collected at the following time points: Screening (single) and Baseline (single unless abnormalities are observed or if clinically indicated, then in triplicate at 2-minute intervals); Day 1 of all cycles (before and after morning dose of study drug administration); at Day 15 from Cycle 2 until Cycle 6; and at Off-Treatment Visit. In case of any alteration, or if clinically necessary, an echocardiogram and/or cardiac enzymes should be performed.

i [Procedure no longer being performed.]

j Genomic DNA samples will be collected predose during Screening or Baseline. If it cannot be collected at the designated time point, it may be collected at a time point after baseline.

k Blood samples for PK analysis in the DDI cohort will be collected in Cycle 1 on Days -1 and 15 at Predose (0 hours), 0.5, 1, 2, 4, 6, 8, 10, and 12 and 24 hours postdose; and on Cycle 2 Day 1 Predose (0 hours), 0.5 to 2 hours, and 3 to 6 hours postdose.

l Blood samples for PD analysis will be collected at the following time points: Predose (0 hours) on Cycle 1 Days 1 and 15; and Predose (0 hours) on Cycle 2 Day 1. Blood samples should be collected on the day after Day 28 of Cycle 1, irrespective of the start of Cycle 2.

m Paired tumor biopsies and/or bone marrow biopsies may be obtained, with appropriate subject consent, from at least 4 to 6 subjects per cohort to examine tissue target inhibition, relevant PD biomarkers, and potential markers of response. Subjects will have the biopsy before administration of the first dose of tazemetostat and on Cycle 2 Day 1.

n Subjects will have collection of archived, tumor-biopsy sections for identification of predictive biomarkers unless no such material is available.

o Tumor assessments include CT scan of the chest, CT or MRI of abdomen, pelvis, and other known sites of disease or newly suspected disease (as well as photographs of skin lesions that will be followed as target and nontarget lesions) and should be performed at Screening and every 8 weeks (starting from Cycle 1 Day 1 through Cycle 6 and every 12 weeks from Cycle 7 and beyond), and as clinically indicated. Subjects with B Cell Lymphoma should be assessed for B symptoms at these time points. See Section 7.4.1.3. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be performed without IV contrast.

p Subjects with B Cell Lymphoma should have ^{18}FDG-PET Scan at Screening and at the first notation of possible PR or CR.

q Subjects with B Cell Lymphoma should have a BM biopsy at Screening (unless performed within 42 days of Cycle 1 Day 1) and at first notation of CR if there was lymphoma involvement of BM at Screening. If a BM biopsy sample was provided for PD sample at Screening, subsequent BM biopsy samples will be requested for PD assessment.

r CT or MRI of the brain should be performed if clinically indicated. The same methodology and scan acquisition techniques used at Screening should be used throughout the study to ensure comparability.

s On visit days, subjects should not take study drug before evaluations are performed.

t A single oral dose of midazolam 2 mg will be given on Day -1 and Day 15 for subjects in the DDI cohort of the study only. See Section 7.3.2 for additional details.

Table 9 Schedule of Visits and Procedures: Phase 2 (All Visits Starting at Cycle 1 Day 15 have ± 3-Day Window)

Period	Screening[a]	Cycles 1 and 2		Cycle 3 and Beyond		Off-Treatment[b]	Follow-up[c]
Day	-28 to -1	1 (± 3 days)	15 (± 3 days)	1 (± 3 days)	15[d] (± 3 days)		
Procedures/Assessments							
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history	X						
Prior and concomitant medications	Throughout study						
Comprehensive physical examination	X					X	
Symptom directed physical exam		X	X	X			
Pregnancy test[e]	X	X		X		X	
Body weight	X	X	X	X		X	
Height	X						
Vital signs[f]	X	X	X	X		X	
ECOG performance status	X	X		X		X	
12-lead ECGs[g]	X	X		X		X	
Hematology[u]	X	X	X	X	X	X	
Blood chemistry	X	X	X	X	X	X	
Genomic DNA[h, t]							
PK blood samples[i, t, w]		X[i]	X[i]				
PD blood samples[j]		X[j]	X[j]				
PD blood sample for nucleic acid[k]		X		X		X	

Table 9 Schedule of Visits and Procedures: Phase 2 (All Visits Starting at Cycle 1 Day 15 have ± 3-Day Window)

Period	Screening[a]	Cycles 1 and 2		Cycle 3 and Beyond		Off-Treatment[b]	Follow-up[c]
Day	**-28 to -1**	**1 (± 3 days)**	**15 (± 3 days)**	**1 (± 3 days)**	**15[d] (± 3 days)**		
Procedures/Assessments							
Sufficient tumor tissue available[l]	X						
Optional Paired tumor biopsies[m]		X					
Tumor biopsy at DP[n]						X	
Tumor assessments: CT (MRI), and assessments of B symptoms[o,w]	X	Radiologic tumor assessments (IWG-NHL [Cheson, 2007] criteria) **must be performed every 8 weeks during Cycles 2-6, and every 12 weeks starting at Cycle 7 and beyond**				X	X
Optional chest ultrasound[v]	X	Every 8 weeks while subject is receiving study drug					
CT or MRI of the brain[p]	Brain scans should be performed if clinically indicated.						
Bone marrow biopsy (with IHC)[q]	X	At first notation of CR if bone marrow involvement at Screening, and if clinically indicated (eg, suspicion of relapse or progressive disease)					
^{18}FDG-PET scan[r]	X	Performed at first notation of possible PR or CR					
AEs/SAEs[w]	Throughout study treatment and off-treatment periods						
Tazemetostat administration[s]		Continuous 28-day cycle of tazemetostat twice daily. Tazemetostat can be taken with or without food.					
Survival status and subsequent anticancer therapy						X	X

AE = adverse event, β-hCG = beta-human chorionic gonadotropin, BP = blood pressure, CR = complete response, CT = computed tomography, DLBCL = diffuse large B cell lymphoma, DNA = deoxyribonucleic acid, DP = disease progression, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EZH2 = enhancer of zeste homolog 2, ^{18}FDG-PET = ^{18}fluorodeoxyglucose-positron emission tomography, FL = follicular lymphoma, HR = heart rate, IHC = immunohistochemistry, IWG-NHL = International Working Group-Non-Hodgkin's Lymphoma, MRI = magnetic resonance imaging, PD = pharmacodynamic, PK = pharmacokinetic, SAE = serious adverse event

a. The Screening Period extends from Day -28 to Day -14, except for signing of the informed consent form, which may be up to 8 weeks before the first dose of study drug. Screening laboratory assessments may be used as Day 1 assessments if performed within 72 hours of the first dose of study treatment, however subjects must continue to meet eligibility criteria prior to first dose of tazemetostat on Cycle 1 Day 1. The screening assessments (except tumor assessment) must be performed within 28 days before the first dose of study drug.

b. Off-treatment assessment may occur at time of treatment discontinuation (eg, at the visit at which the decision to discontinue treatment occurs) or up to 30

days after the final dose of study drug. AE and concomitant medication data must be collected for 30 days after the final dose of study drug, or until the start of new therapy. This may occur prior to 30 days if new therapy is started within 30 days of last dose of study drug. If subject is unable to return to the clinic for assessment of AEs this may be done by telephone.

c. Survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent. Information on all subsequent anticancer therapies and AESIs will be collected throughout the survival follow up. This may be done by telephone contact.

d. Starting at Cycle 3, a Day 15 laboratory assessments are not required, but the telephone contact is still required. Laboratory assessments are to be performed as medically needed and can be either at the clinic or at a local laboratory. Any abnormal laboratory test result collected at Day 15, Cycle 3 and beyond will only need to be entered into the clinical database if they are associated to an AE. These results will be reported as an unscheduled visit.

e. A serum pregnancy test (β-hCG) will be performed at Screening for all women of childbearing potential. A urine or serum pregnancy test will be performed predose on Day 1 of each cycle starting at Cycle 2.

f. Vital signs include BP, HR and body temperature. BP and HR will be collected after the subject has been sitting for 5 minutes.

g. 12-Lead ECGs will be collected at the following time points: Screening (triplicate), Cycles 1 and 2 Day 1 (predose and 0.5 – 2 hours post dose immediately before PK sample), Day 1 of all subsequent cycles (before the morning dose of study drug administration), and at the Off-Treatment Visit. In case of any alteration or if clinically necessary, additional ECGs, an echocardiogram, and/or testing of cardiac enzymes should be performed.

h. Genomic DNA samples will be collected predose at Screening. If it cannot be collected at the designated time point, it may be collected at a time point prior to first dose.

i. Blood samples for PK analysis will be collected in Cycle 1 on Day 1 at 0.5 to 2 hours and 3 to 6 hours and Day 15 at predose (0 hours), 0.5 to 2 hours, and 3 to 6 hours; and Cycle 2 on Day 1 at predose (0 hours), 0.5 to 2 hours, and 3 to 6 hours. Blood samples should be collected on the day after Day 28 of Cycle 1, irrespective of start of Cycle 2.

j. Blood samples for PD analysis will be collected at the following time points: Predose (0 hours) on Cycle 1 Days 1 and 15; and Predose (0 h) on Cycle 2 Day 1. Blood samples should be collected on the day after Day 28 of Cycle 1, irrespective of the start of Cycle 2.

k. Blood samples for nucleic acid analysis will be collected at the following time points: Predose (0 hours) on Cycle 1 Day 1, and Day 1 of every other cycle, and at the off-treatment visit.

l. Subjects will have collection of archived, tumor-biopsy sections for central testing of EZH2 mutation status (all subjects) and confirmation of cell of origin for DLBCL subjects.

m. Paired tumor biopsies (DLBCL cohorts) and/or bone marrow biopsies (FL cohorts) are optional and may be obtained, with appropriate subject consent, from at least 4 to 6 subjects per cohort to examine tissue target inhibition, relevant PD biomarkers, and potential markers of response. Subjects should have the biopsy before administration of the first dose of tazemetostat and the second biopsy on Cycle 2 Day 1. If sufficient tumor exists from archival, this could be considered the predose sample.

n. Tumor biopsy is to be requested, where medically feasible, at disease progression in subjects who achieve a PR or better with tazemetostat.

o. Tumor assessments include CT scan of the chest, CT or MRI of the abdomen, pelvis, and other areas of known disease or newly suspected disease and should be performed between Day -28 and Day -1 and every 8 weeks, irrespective of treatment delays, during Cycles 1 to 6, and every 12 weeks during Cycle 7 and beyond. If local regulatory authorities mandate less frequent imaging, minimum frequency must be every 12 weeks. For countries where CT scan of the chest, CT or MRI of abdomen, pelvis and other areas of known or newly suspected disease are part of Standard Of Care Assessment (SoC), the scan will be performed as per SoC schedule and evaluation of the result will be performed and reported as per the Protocol. The same parameters as the screening scans

should be used. A standard-of-care clinical examination for lymphoma, including assessment of B symptoms, will also be performed at each visit.

p. CT or MRI of the brain should be performed if clinically indicated.

q. A bone marrow biopsy (including IHC) will be performed between Day -28 and Day -1 for all subjects with FL and in subjects with DLBCL if clinically indicated or if subject has history of bone marrow involvement if these have not been performed within 42 days (an approval is needed from the Sponsor's medical monitor if the window has been beyond 42 days) of Cycle 1 Day 1. At the first notation of CR, a repeat bone marrow biopsy should be performed if lymphoma involvement in the bone marrow was reported at Screening.

r. ^{18}FDG-PET scan should be performed at Screening and at the first notation of possible PR or CR.

s. On visit days when PK samples are collected, study drug(s) should be administered in clinic.

t. Effective 16 May 2018, the sample size for population PK and genomic DNA analysis has been met and additional samples are no longer being collected. However, PK samples still need to be collected during annual assessments (see footnote w).

u. At screening, a peripheral blood smear will be collected along with normal hematology testing and assessed for abnormal morphology. If results are abnormal then the patient will be required to undergo a bone marrow aspirate/biopsy conducted by the central laboratory. If morphology is abnormal, then cytogenetic testing will be conducted to closely monitor patients with cytogenetic testing and DNA sequencing for abnormalities known to be associated with MDS (eg, del 5q, chr 7 abn) and MPN (e.g. JAK2 V617F).

v. An optional chest ultrasound may be performed at the Investigator's discretion to monitor for early signs of T-LBL/T-ALL.

w. Annual assessments will be conducted to review AESIs, PK and tumor response.

OFF-TREATMENT PROCEDURES

Off-treatment assessment may occur at time of treatment discontinuation or up to 30 days after the final dose of study drug or initiation of subsequent anticancer therapy. Adverse event and concomitant medication data must be collected for 30 days after the final dose of study drug, or until the start of new therapy. All subjects will be asked to return to the sites for discontinuation or off-treatment assessments, if possible. If a clinic visit is not feasible, follow up information may be obtained via telephone or written correspondence. This may occur prior to 30 days if new therapy is started within 30 days of last dose of study drug.

If a subject fails to appear for a scheduled study visit, the Investigator will make every attempt to contact the subject and determine the reason(s) for the missed visit as completely and accurately as possible. Subjects will only be judged as lost to follow-up if they cannot be reached after 3 documented attempts by the site to contact them (1 week apart).

Whenever possible, the following assessments should be performed within 30 days after subjects have received the final dose of study drug:

PHASE 1

- Comprehensive physical examination
- Body weight
- Vital signs (BP, HR, body temperature)
- ECOG performance status (Appendix 1)
- 12-lead ECGs
- Bone marrow biopsy, if clinically indicated
- Collect blood samples for hematology and blood chemistry analysis (see Table 7 for the tests to be performed)
- Tumor assessments: RECIST 1.1 criteria for solid tumors (Appendix 4) or IWG-NHL (Cheson, 2007) for B cell lymphoma
- Record AEs and SAEs
- Survival status and subsequent anticancer therapy

For details, refer to the Schedule of Visits and Procedures (Table 8 and Table 9).

PHASE 2

- Comprehensive physical examination
- Body weight
- Vital signs (BP, HR, body temperature)
- ECOG performance status (Appendix 1)
- 12-lead ECGs
- Collect blood samples for hematology and blood chemistry analysis (see Table 7 for the tests to be performed)
- Bone marrow biopsy for all FL subjects and if clinically indicated in DLBCL subjects with history of bone marrow involvement
- Tumor assessments: IWG-NHL (Cheson, 2007) criteria
- Record AEs and SAEs
- Survival status subsequent anticancer therapy and AESI

For details, refer to the Schedule of Visits and Procedures (Table 8 and Table 9).

SURVIVAL STATUS AND SUBSEQUENT ANTICANCER THERAPY

Survival status will be collected on all subjects every 12 weeks, unless they withdraw consent. Information about all subsequent anticancer therapies and AESI after study drug discontinuation will be collected (the Sponsor may choose to stop the collection of therapies after the first post study drug discontinuation anticancer treatment).

TUMOR ASSESSMENTS DURING THE FOLLOW-UP PERIOD

Where possible, for subjects who discontinue study drug for reasons other than disease progression, scans performed during the post study drug discontinuation follow-up period should be performed on the same schedule and using the same imaging modality as defined in the study protocol.

7.4.2.2 Total Volume of Blood

The total volume of blood drawn per period or cycle can be found in the Laboratory Manual provided separately. Additional samples may be taken at the discretion of the Investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

7.4.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of solid tumors and hematological malignancies. The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, radiologic studies, and assessment of AEs, are standard International Conference on Harmonisation (ICH) GCP evaluations to ensure subject safety. The use of IWG-NHL (Cheson, 2007) for B cell lymphoma and RECIST 1.1 for solid tumor assessment and are widely accepted (Cheson, 2007; Eisenhauer, 2009).

7.4.4 Adverse Events and Serious Adverse Events, Pregnancy, and Other Events of Interest

7.4.4.1 Adverse Events and Other Events of Interest

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the investigational product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

In the Phase 1 part of the study all AEs, regardless of the relationship to the study drug or procedure, should be collected beginning from the time the subject signs the study consent. In the Phase 2 part of the study all AEs, regardless of the relationship to the study drug or procedure should be collected beginning from the time of first dose of the investigational product.

Worsening of a pretreatment event, after initiation of investigational product, must be recorded as a new AE. For example, if a subject experiences mild intermittent dyspepsia prior to dosing tazemetostat, but the dyspepsia becomes severe or more frequent after the first dose of tazemetostat, a new AE of worsening or more frequent dyspepsia (with the appropriate date of onset and severity) should be recorded in the eCRF.

“Lack of efficacy” or “failure of an expected pharmacological action” *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from “lack of efficacy” will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

All AEs will be collected for 30 days after the final dose of study drug, or until the start of subsequent anticancer therapy, whichever happens first. If subject is unable to return to the clinic for assessment of AEs this may be done by telephone.

Disease progression is a study endpoint and should be captured on the eCRF as reason for discontinuation. Signs and symptoms of the cancer progression clearly related to the progression of the disease are entered as an adverse event on the eCRF and clearly marked as related to disease progression. If these AEs meet the criteria of serious and are clearly marked as disease progression, they will not be reportable to regulatory authorities. The criteria for identifying AEs are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from study drug.
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline.

7.4.4.2 Laboratory Abnormalities

An abnormal laboratory test result may be considered as an AE if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not.

A laboratory result should be considered by the Investigator to be an AE if it:

- Results in the withdrawal of study drug.
- Results in withholding of study drug pending some investigational outcome.
- Results in the initiation of an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia).
- Results in any out-of-range laboratory value that, in the Investigator's judgment, fulfills the definition of an AE with regard to the subject's medical profile.

- Increases in severity compared to baseline by ≥ 2 CTCAE grades (see Appendix 5), with the exception of lymphocytes, albumin, cholesterol, glucose, and phosphate. For these tests, a change of ≥ 2 grades will be evaluated by the Investigator to determine if they are of clinical significance and, if so, will be considered AEs.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the AE CRF.

It is the responsibility of the Investigator to review all laboratory findings in all subjects and determine if they constitute AEs. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

7.4.4.3 Other Safety Assessment Abnormalities

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is > 450 ms and there is an increase of > 60 ms from baseline. Any ECG abnormality that the Investigator considers as an AE should be reported as such.

7.4.4.4 Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v4.03 (Appendix 5). Investigators will collect all CTCAE grades for AEs (for both increasing and decreasing severity). All AEs reported using CTCAE classification and graded as 4 or 5 are to be considered serious. Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to the study drug. In the event that an AE is not covered by the CTCAE, the assessment of severity will be determined by using the CTCAE general guidelines.

Grade 1 = Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 = Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3 = Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4 = Life-threatening consequences: urgent intervention indicated.

Grade 5 = Death related to AE.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an event (as in "mild," "moderate," or "severe"). See Section 7.4.4.8 for the definition of an SAE.

7.4.4.5 Assessing Relationship to Study Drug

A qualified investigator must make the determination of relationship to tazemetostat for each AE or SAE. The Investigator should decide whether, in his or her medical judgment there is a reasonable possibility that the event may have been caused by tazemetostat.

Items to be considered when assessing the relationship of an AE to the study drug are:

- Temporal relationship of the onset of the event to the initiation of the study drug
- The course of the event, considering especially the effect of discontinuation of study drug or reintroduction of study drug, as applicable
- Whether the event is known to be associated with the study drug or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study drug-related factors which are known to be associated with the occurrence of the event.

7.4.4.6 Classification of Causality

Not Related: A causal relationship between the study drug and the AE is not a reasonable possibility.

Related: A causal relationship between the study drug and the AE is a reasonable possibility. The Investigator must further qualify the degree of certainty as "possible" or "probable."

7.4.4.7 Outcome Categorization

Outcome of an AE/SAE may be classified as resolved, resolved with sequelae, unresolved or death.

All treatment-related AEs/SAEs will be followed to resolution (the subject's health has returned to his/her baseline status or all variables have returned to normal), or until an outcome is reached, stabilization occurs (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained, regardless of whether the subject is still

participating in the study. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

7.4.4.8 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, but when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent 1 of the outcomes in the definition of an SAE listed above should also be considered serious SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

The following hospitalizations are not considered to be SAEs because there is no “AE” (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

- Death, hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer or for evaluation of suspected disease progression. Note: Disease progression is a study endpoint and should be captured in the CRF as per the guidelines for disease progression.
- An emergency room visit lasting longer than 24 hours but not resulting in hospitalization

Note: Disease progression is a study endpoint and should not be reported as an SAE term. However, AEs (eg, dyspnea) that meet seriousness criteria, although associated with disease progression, should be reported as SAE.

7.4.4.9 Adverse Events of Special Interest

The following AESIs have been identified, requiring mitigation steps and monitoring to minimize the risk for the occurrence of these events.

7.4.4.9.1 T-LBL/T-ALL

Lymphoblastic lymphomas are considered thymus-derived malignancies that have not yet completed T-cell maturations. Approximately 90% of lymphoblastic lymphomas are the T-cell phenotype and typically occur in young adults and adolescents, accounting for 29% of pediatric and 2% of adult NHL with a median age at diagnosis of 25 years (Lai, 2013; Cortelazzo, 2017; Lones, 2007). T-LBL is morphologically and immunophenotypically indistinct from T-ALL, with both diseases arising from precursor lymphoid cells of the T-cell lineage (Portell, 2012; Patel, 2014). Despite the similarities of the 2 diseases, significant yet unknown characteristics lead to differences in clinical presentations (Burkhardt, 2009). Initial clinical manifestation of both adult and pediatric T-LBL includes a mediastinal mass or lymphadenopathy with <25% bone marrow blasts. Adult T-LBL patients tend to have less thymic disease and greater lymph node disease and bone marrow involvement (Baleydier, 2008; Swerdlow, 2008; Campo, 2011). In contrast, T-ALL cases predominantly present with bone marrow and peripheral blood disease, and >25% bone marrow blasts (Swerdlow, 2008; Campo, 2011).

On 06 April 2018, an event of T-LBL was observed in a subject on study EZH-102. This event was reported to regulatory authorities as a 7-day SUSAR on 13 April 2018 (Case number 2018USEPZ64380299).

Following this report, Epizyme conducted a comprehensive evaluation, including:

- Review of literature and available preclinical/clinical data to better understand event of T-LBL.
- Review of the literature and available preclinical/clinical data to better understand the risk of MDS/AML and myeloid malignancies, and other solid tumor malignancies.

- Assessment of safety, pharmacokinetics (PK) at various doses tested, benefit and risk across tumor types in adults and children.
- Consultation with well recognized external experts in T-cell lymphoma and pediatric/adult oncology.

Based on this evaluation, we continue to believe that tazemetostat is a clinically active drug and has the potential to benefit both adult and pediatric patients across different tumor types where there are unmet medical needs. [redacted]

T-LBL Case

[redacted]

The SUSAR of T-LBL resulted in the Sponsor initiating a temporary global halt in enrollment for the pediatric study EZH-102. In addition, this event led to a partial clinical hold (PCH) on new subject enrollment for tazemetostat by the U.S. (FDA), France (ANSM), and Germany (BfArM) across all studies of the Tazemetostat Development Program. For further details, see the Investigator's Brochure, version 8.0. In the event of suspicion of T-LBL/T-ALL or related concerns, please refer to Section 7.3.2.2 for evaluation and dose adjustments.

Heightened surveillance will be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of T-LBL/T-ALL so that tazemetostat may be discontinued in the subject and treatment can be initiated for these malignancies. If a case of adult T-LBL/T-ALL occurs, enrollment will be suspended and the risk:benefit of the drug will be assessed by the Tazemetostat Safety Committee and will be communicated to all Health Authorities and Ethics Committees.

7.4.4.9.2 MDS/AML/MPN

As of the May 01 2018 data cut, [redacted] cases of MDS/AML/MPN have been reported. [redacted] For all [redacted] cases, the causality assessment was confounded by the subject's prior treatment history or the presence of the disease before starting tazemetostat. For a summary of these [redacted] cases please refer to the Investigator's Brochure, Version 8.0. In the event of suspicion of these malignancies or related concerns, please refer to Section 7.3.2.2 for evaluation and dose adjustments. Heightened surveillance will be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of any MDS/AML and other myeloid malignancies like MPN. For any MDS/AML or other myeloid malignancies like MPN, tazemetostat will be held, and after discussion with the Investigator, tazemetostat will be modified or discontinued.

7.4.4.9.3 Tazemetostat Safety Committee

A safety monitoring committee composed of internal and external medical experts will review all AESI cases, including T-LBL/acute lymphoblastic leukemia (ALL), MDS/acute myeloid leukemia (AML) and other myeloid malignancies like MPN (both related and unrelated), and other solid tumor malignancies. Cases will be evaluated for suspected relationship to tazemetostat and adjudicated by the experts. Recommendations for next steps per the risk management plan will be communicated to the CMO.

OTHER IDENTIFIED RISKS

Further events of interest include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error; and any treatment-emergent significant laboratory abnormality. Laboratory abnormalities are not to be reported as AESIs; laboratory abnormalities should be reported as standard AEs or SAEs if the seriousness criteria are met. These events of interest are to be captured using the SAE procedures but are to

be considered as SAEs only if they met 1 of the above criteria. All AEs associated with events of interest are to be reported on the CRF whether or not they meet the criteria for SAEs.

7.4.5 Completion/Discontinuation of Subjects

The Investigator may permanently discontinue treating a subject with study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to permanently discontinue study drug or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. The Study Disposition Treatment CRF page will be completed indicating the primary reason for discontinuation from treatment and the study drug discontinuation procedures indicated in the Schedule of Visits and Procedures will be completed (if possible).

If a subject discontinues study drug, the subject will have an Off-Treatment Visit with protocol-specified procedures and enter the Survival Follow-up Period unless the subject or parent/guardian withdraws consent or is lost to follow-up.

The Investigator should confirm whether a subject or parent/guardian will permanently discontinue study drug but agree to continue protocol-specified procedures at the Treatment Visit and Survival Follow-Up or whether the subject or parent/guardian will withdraw consent. If consent is withdrawn, the Investigator will promptly explain to the subject involved that the subject will be withdrawn from the study and provide appropriate medical treatment and other necessary measures for the subject. If a subject or parent/guardian withdraws consent, the date will be documented in the source documents.

A subject who has ceased to return for visits will be followed up by mail, phone, or other means as much as possible to gather information such as the reason for failure to return and the status of treatment compliance, presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded in the CRF.

A subject removed from the study for any reason may not be replaced, except if a subject is discontinued before completing the Treatment Phase, an additional subject should be enrolled in the Phase 1 Dose Escalation part, FE cohort, and DDI cohort in this study.

7.4.6 Reporting of Serious Adverse Events

All serious adverse events, irrespective of their relationship to study drug, must be reported as soon as possible, but no later than 24 hours from when the Investigator becomes aware of the event.

Deaths and life-threatening events should be reported immediately. The immediate report should be followed-up within 1 business day of report via CRF into the clinical database or with a completed SAE form in case of no access to clinical database.

It is very important that the SAE is processed as completely as possible at the time of the initial report. This includes the Investigator's assessment of causality.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the Investigator's assessment of causality, this should also be noted on the follow-up SAE form.

The detailed contact information for reporting of SAEs is provided in the Investigator File.

Serious adverse events, regardless of causality assessment, must be collected over the same time period as stated above for AEs through the last visit and for 30 days after last dose following study drug discontinuation.

All SAEs must be followed to resolution, or if resolution is unlikely, to stabilization.

Any SAE judged by the Investigator to be related to the study drug should be reported to the Sponsor regardless of the length of time that has passed since study completion.

For urgent safety issues, please ensure that all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator File.

The Investigator should notify his/her IRB/IEC of the occurrence of the SAE, in writing, in accordance with local requirements. A copy of this communication must be forwarded to the Sponsor or CRO monitor and filed in the Trial Master File.

7.4.6.1 Reporting of Adverse Events of Special Interest

All potential and identified AESIs, irrespective of their relationship to study drug, must be reported as soon as possible, but no later than 24 hours from when the Investigator becomes aware of the event.

All potential and identified AESIs must be discussed with the Medical Monitor.

7.4.6.2 Reporting of Pregnancy

Any pregnancy where the estimated date of conception occurs either before the last visit or within 30 days of the last study drug or any exposure to study drug through breastfeeding during study drug or within 30 days of last study drug must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study drug.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events Section 7.4.6).

Pregnancies or exposure to study drug through breastfeeding must be reported as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the pregnancy.

The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File.

The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but not later than 1 business day from the date the Investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

7.4.6.3 Reporting of Other Events of Interest

Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with an overdose should be captured on the AE CRF. Adverse events associated with overdose, misuse, abuse, or medication error should be reported using the procedures detailed in Reporting of Serious Adverse Events (Section 7.4.6) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the AE CRF.

7.4.6.4 Expedited Reporting

The Sponsor must inform investigators or, as regionally required, the head of the medical institution and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that investigational sites provide complete SAE information in the manner described above.

7.4.6.5 Regulatory Reporting of Adverse Events

Adverse events will be reported by the Sponsor or a third party acting on behalf of the Sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with the European Clinical Trial Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions (SUSARs) will be reported as required to the Competent Authorities of all involved European member states.

7.4.7 Confirmation of Medical Care by Another Physician

The Investigator will instruct the subject to inform beforehand when the subject is going to receive medical care by another physician. At each visit, the Investigator will ask the subject whether the subject has done so since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the Investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

7.5 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating practices, working practice documents, and applicable regulations and guidelines. Site visit audits will be made periodically by the Sponsor's or CRO's qualified compliance auditing team, which is an independent function from the study conduct team.

7.5.1 Data Management

Data required by the protocol will be collected on a CRF and entered into a validated Electronic Data Capture clinical database that is compliant with all regulatory requirements. Data collected on the CRF must follow the instructions described in the CRF Completion Guidelines.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRF. The Investigator or designee as identified on Form FDA 1572 must sign the CRF to attest to its accuracy, authenticity, and completeness.

The completed, original CRF is the sole property of Epizyme and should not be made available in any form to third parties without written permission from Epizyme, except for authorized representatives of Epizyme or appropriate regulatory authorities.

The Data Management Plan defines and documents the procedures necessary to ensure data quality. These activities must be followed to ensure data are properly entered, validated, coded, integrated, reconciled, and reviewed.

7.5.2 Database Quality Assurance

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the investigational site. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

7.5.3 Bioanalytical Data Management and Quality Control

Samples will be shipped according to the Laboratory Manual. Tazemetostat will be quantified using a validated liquid chromatography/mass spectrometry/mass spectrometry method. Before the analysis of study samples, the assay sensitivity, specificity, linearity, and reproducibility will be documented. Details on the analytical methodology, the method of validation, and the analytical within-study quality control procedures will be included in the clinical study report for this protocol.

7.6 Statistical Methods

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released, a snapshot of the database is obtained and released, and randomization codes have been released for the Phase 1 FE cohort. Phase 1 (Dose Escalation and Cohort Expansion), FE, and DDI cohorts may be analyzed separately upon completion (ie, at an earlier time point) from the Phase 2 analysis. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

7.6.1 Statistical and Analytical Plans

The statistical analyses described in this section will be performed as further outlined in the SAP, which will be finalized before database lock and included in the clinical study report for this protocol.

Subjects are analyzed according to their initial dose level, with the exception of subjects in the FE cohort:

- Subjects in the FE cohort who took only 200 mg doses and withdrew before Cycle 1 Day 1 will be included in the 200 mg BID dosing level for analysis.
- Subjects in the FE cohort who completed both single 200 mg doses and started the 400 mg BID dosing level on Cycle 1 Day 1 will be included in the 400 mg BID dosing level for analysis.

7.6.1.1 Definitions of Analysis Sets

The per protocol analysis sets will be defined as follows:

- **Full Analysis Set** will include all subjects who received at least 1 dose of study drug. This will be the primary analysis set for efficacy evaluations, as well as for demographic and baseline characteristics.
- **Safety Analysis Set** will include all subjects who received at least 1 dose of the study drug and have at least 1 post-baseline safety evaluation. This will be the analysis set for all safety evaluations, except for the DLT analysis.
- **Dose-Limiting Toxicity (DLT) Analysis Set** will include all subjects in the Safety Analysis Set who:
    - Experience a DLT during Cycle 1 as defined in Section 7.3.2
      or
    - Are not removed from Cycle 1 for reasons other than toxicity.

- **Pharmacokinetic (PK) Analysis Set** will include all subjects who have received at least 1 dose of tazemetostat and have at least 1 evaluable plasma concentration.
- **Food Effect Analysis Set** will include all subjects for whom a full PK profile of tazemetostat is available after study drug administration in both the fed and fasted state and who consumed the prescribed breakfast before treatment in the "fed" state.
- **Drug-Drug Interaction Analysis Set** will include all subjects for whom a full PK profile of midazolam is available after midazolam administration.
- **Pharmacodynamic (PD) Analysis Set** will include all subjects who have received at least 1 dose of study drug and have evaluable PD data.
- **Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis Set** will consist of all subjects in the Safety Analysis Set that also have evaluable serum PK and PD pretreatment assessment and at least 1 post treatment assessment.

The SAP will outline which analysis sets are to be used for the Phase 1 part, FE cohort, and DDI cohort and Phase 2 analyses.

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be summarized and listed. For continuous demographic/baseline variables including age, weight, and vital signs, results will be summarized and presented as N, mean, standard deviation, median, and minimum and maximum values. For categorical variables such as race/ethnicity, the number and percentage of subjects will be used.

PRIOR AND CONCOMITANT MEDICATIONS

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class.

7.6.1.2 Efficacy Analyses

The efficacy endpoints in Phase 1 will be summarized and listed for each subject by the study part and initial dose level based upon the Full Analysis Set. No formal statistical comparison will be performed.

PHASE 2 PRIMARY EFFICACY ANALYSES

In Phase 2, the evaluation of the ORR (CR + PR) in subjects with B cell lymphomas will be based on IWG-NHL (Cheson, 2007) response criteria.

ORR will be presented with corresponding 2-sided Clopper–Pearson exact 95% confidence intervals (CIs). For each cohort, this analysis will be performed on the Full Analysis Set.

PHASE 2 SECONDARY EFFICACY ANALYSES

PFS is defined as the time from the date of first dose to the date of first documentation of relapse, disease progression, or date of death, whichever occurs first. PFS will be estimated using Kaplan-Meier method. If there are a sufficient number of PFS events (ie, relapses, progressions or deaths), median PFS, first and third quartiles and 2-sided 95% CIs, will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982) for each cohort. Figures and listings of PFS will also be provided.

For each subject with a CR or PR, DOR is defined as time from the first date of response (CR or PR, whichever is first recorded) to recurrence, objectively documented disease progression, or death, whichever occurs first. If there are a sufficient number of responders who subsequently progress or die due to any cause, the median DOR, first and third quartiles, will be calculated from the Kaplan-Meier estimates for each cohort. The associated 2-sided 95% CIs will be estimated using the Brookmeyer-Crowley method for each cohort. A listing of DOR will be provided.

ALL PHASES EXPLORATORY EFFICACY ANALYSES

Overall survival is the duration measured from the date of first dose until the date of death from any cause. The Kaplan-Meier estimate of the median survival time, first and third quartiles will be presented with 2-sided 95% CIs for each cohort.

7.6.1.3 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Analyses

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Pharmacokinetic

Phase 1

Plasma and urine concentrations of tazemetostat will be tabulated and summarized by dose level, day, and time. Tazemetostat PK parameters will be derived from plasma concentrations by noncompartmental analysis using actual times.

Minimally, the following PK parameters will be calculated:

- Maximum drug concentration (C_{max})
- Time to reach maximum concentration (following drug administration) (t_{max})
- Area under the concentration time curve (AUC)

If data permit:

- Elimination half-life ($t_{1/2}$)
- Total body clearance (CL)
- Volume of distribution (Vd)
- Renal clearance (CLr)
- Accumulation ratio (R)
- Fraction excreted (fe)

PK parameters (eg, C_{max}, AUC) for tablet and suspension formulations will be compared within a dose cohort that comprises subjects receiving both tazemetostat formulations to assess the relative performance of each formulation.

Pharmacokinetic parameters for midazolam and its metabolites, 1-OH-midazolam and 4-OH midazolam, and 4β-hydroxycholesterol will be derived from plasma concentrations by noncompartmental analysis using actual times. Minimally, the following PK parameters will be calculated: C_{max}, t_{max}, and AUC. The effect of tazemetostat on AUC and C_{max} of midazolam and its metabolites will be evaluated using a mixed linear model of logarithmically transformed values of the primary PK parameters. Ratios of geometric means and associated 2-sided 90% CIs will be presented. Similar analyses will be conducted for the effect of food on the AUC and C_{max} of tazemetostat (fed/fasted comparison).

Phase 1 and Phase 2

Combined PK data from Phase 1 and Phase 2 will be subjected to population PK analysis. The PK model will be parameterized for clearance and volume(s) and exposure parameters such as C_{max} and AUC will be derived.

Pharmacodynamic

H3K27 trimethylation levels as measured in skin punch biopsies (Phase 1 Dose Escalation only) and tumor, bone marrow, and PBMCs using appropriate methodologies may be explored and summarized by dose for each time point. The effect of tazemetostat therapy on cytogenetic changes, changes in histone methylation or other soluble, tissue, genetic, and imaging biomarkers may be explored and summarized using descriptive statistics.

The percentage change in the sum of the diameters of tumor target lesions based on investigator assessment may be summarized and correlated with tazemetostat exposure and PD markers.

Pharmacokinetic/Pharmacodynamic Analyses:

PK/PD relationships between exposure to tazemetostat and histone methylation status; exposure and exploratory biomarkers of safety; and exposure and best overall response will be explored graphically. Any emergent relationship might be followed by model-based PK/PD analysis.

Biomarker and Pharmacogenomics Analyses:

Details of the biomarker and pharmacogenomics data analysis plan will be defined and reported separately.

BIOANALYTICAL METHODS

Plasma and urine concentrations of tazemetostat will be determined using a validated assay. If appropriate, assay of plasma and urine samples for any metabolites of tazemetostat may be explored in the future.

Plasma concentrations of midazolam and its metabolites, 1-OH-midazolam and 4-OH-midazolam, and 4β-hydroxycholesterol will be determined using a validated assay.

7.6.1.4 Safety Analyses

All safety analyses, unless otherwise specified, will be performed on the Safety Analysis Set. ECG findings and the incidence of AEs and SAEs will be summarized. Laboratory test results, vital signs, bromide levels (bromide monitoring will not be prospectively conducted in the FE and DDI cohorts in Phase 1 or Phase 2), and echocardiograms/MUGA scans (LVEFs), and their changes from baseline, will be summarized using descriptive statistics. Abnormal values will be flagged.

The effects of tazemetostat on cardiovascular repolarization will be evaluated via 12-hour, 12-lead continuous Holter/ECG monitoring on Day -1, and on Cycle 1 Day 1 (ie, amounting to a total of 24 hours continuous cardiac Holter monitoring around first dose administration on Cycle 1 Day 1) and Day 15 in the Dose Escalation part of the study only. Individual ECGs will be extracted in triplicate from the Holter recordings at specified time points and will be evaluated by a central laboratory. QT intervals will be measured from Lead II and will be corrected for HR (QTc) using Fridericia's (QTcF) correction factors. The primary QTc parameter will be QTcF. Secondary parameters (QT interval corrected for heart rate using Bazett’s formula [QTcB], QT, QRS, and HR) and waveforms (T waves) will be evaluated.

EXTENT OF EXPOSURE

The number of cycles/days on treatment, quantity of study drug administered, and the number of subjects requiring dose reductions, treatment interruption, and treatment discontinuation due to AEs will be summarized.

ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 15.1 or higher) lower level term closest to the verbatim term. The linked preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that

- Emerges during treatment, having been absent at Pretreatment (Baseline)
- Reemerges during treatment, having been present at Pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment-emergent and had a start date within the earlier of 30 days following study drug discontinuation or initiation of subsequent anticancer therapy (Section 7.4.4.1) will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Treatment-emergent AEs will be summarized by treatment group. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity by highest CTCAE grade.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (possibly related, probably related, and not related).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

The number (percentage) of subjects in the DLT Analysis Set with TEAEs designated as DLTs in the CRF will be summarized by MedDRA SOC and PT for each treatment group in the Dose Escalation and Expansion parts.

Laboratory Values

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 7.4.1.7 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 7.4.1.7 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Vital Signs

Descriptive statistics for vital signs parameters (ie, diastolic and systolic BP, HR, RR, and body temperature) body weight, and changes from baseline will be presented by visit and treatment group.

Electrocardiogram Results

Electrocardiogram assessments will be performed as specified in the Schedule of Assessments (Table 8 and Table 9). Time-matched, central-read ECGs will be performed to evaluate RR, PR, QRS, QT intervals, and QTc at various time points throughout the study. All 12-lead ECG and Holter-ECG data will be listed, and changes will be summarized by dose group, for each cohort using descriptive statistics. The number and percentage of subjects with abnormal ECG findings at each visit will be reported for each dosing cohort. Descriptive statistics will be used to present the abnormal ECG findings overall. Results will be tabulated and listed in the study report.

MUGA SCANS AND ECHOCARDIOGRAMS

MUGA scans and echocardiogram results will be evaluated on an individual basis by subject. Abnormal readings will be identified as those outside (above or below) the reference range. MUGA scans and echocardiogram findings will be summarized.

OTHER SPECIAL TESTS

SERUM BROMIDE LEVELS

Clinical laboratory values will be evaluated for each laboratory parameter by subject. Abnormal laboratory values will be identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the clinical study report for this protocol. Serum bromide monitoring will not be prospectively conducted in the FE and DDI cohorts in Phase 1 or Phase 2.

ELECTROCARDIOGRAM HOLTER MONITORING

The effects of tazemetostat on cardiovascular repolarization will be evaluated via 12-hour, 12-lead continuous Holter ECG monitoring in Cycle 1, Day 1 and Day 15 of the Dose Escalation part of the study. Individual ECGs will be extracted in triplicate from the Holter recordings at specified time points and will be evaluated by a central laboratory. QT intervals will be measured from Lead II and will be corrected for heart rate (QTc) using Fridericia's (QTcF) correction factors. The primary QTc parameter will be QTcF. Secondary parameters (QTcB, QT, QRS, and HR) and waveforms (T-waves) will be evaluated.

SKIN PUNCH BIOPSY

Skin punch biopsy results will be evaluated on an individual basis by subject. Abnormal readings will be identified as those outside (above or below) the reference range. Skin punch biopsy findings will be summarized.

PAIRED TUMOR BIOPSIES

Paired tumor biopsy explorative analysis will be evaluated on an individual basis by subject. Paired tumor biopsy results will be summarized.

BONE MARROW BIOPSY

Bone marrow biopsy results will be evaluated on an individual basis by subject. Abnormal readings will be identified as those outside (above or below) the reference range. Bone marrow biopsy findings will be summarized.

BONE MARROW BIOPSY (WITH IMMUNOHISTOCHEMISTRY)

Bone marrow biopsy (with IHC) results will be evaluated on an individual basis by subject. Abnormal readings will be identified as those outside (above or below) the reference range. Bone marrow biopsy (with IHC) findings will be summarized.

7.6.2 Determination of Sample Size

For Phase 1, the sample size of 6 to 45 subjects is considered adequate for the purposes of selecting a dose. Per FDA guidance, 12 subjects are considered adequate to evaluate food effect. The sample size for the DDI cohort was not based on statistical considerations. A total of 64 subjects were enrolled in Phase 1.

For Phase 2, the original study design planned enrollment of up to 30 subjects enrolled in each cohort. The initial assessment of efficacy was to be conducted within each cohort when 10 subjects had been enrolled (stage 1). For each DLBCL cohort, if zero responders (with CR or PR) out of the initial 10 subjects was observed, further enrollment in the cohort was to be terminated for futility. This rule was based on the underlying assumption that the response rate is 30% and there is a 2.8% probability of observing no responders among 10 subjects. For each FL cohort, if 1 or zero responders (CR or PR) out of the initial 10 subjects was observed, further enrollment in the cohort was to be terminated for futility. This rule was based on the underlying assumption that the response rate is 40% and there is a 4.6% probability of observing ≤ 1 responder among 10 subjects. Subsequent to the futility analysis in the DLBCL cohorts, the DMC supported a study design change to a modified 2-stage Green-Dahlberg design for each cohort. The resulting expanded sample size is shown in Table 10.

Table 10 2-Stage Green Dahlberg Design

	DLBCL GCB EZH2 Mutant				DLBCL GCB EZH2 Wild-Type	DLBCL non-GCB	FL EZH2 Mutant	FL EZH2 Wild-Type
Ho: CR + PR	≤15%	≤15%	≤15%	≤20%	≤20%			
Ha: CR + PR	≥30%	≥30%	≥30%	≥40%	≥40%			
Stage 1 futility n	10	10	10	10	10			
Stage 1 rejection of treatment	0[a]	0[a]	0[a]	1[b,c]	1[b,c]			
Stage 2 total n	60	60	60	45	45			
Stage 2 rejection of treatment	14	14	14	13	13			
Ho = Null Hypothesis, Ha = Alternative Hypothesis, n = sample size Approximate alpha=0.025 and power =0.80								

Abbreviations: CR = complete response, DLBCL = diffuse large B cell lymphoma, EZH2 = enhancer of zeste homolog 2, FL = follicular lymphoma, GCB = germinal-center B-cell-like, Ha = Alternative Hypothesis, Ho = Null Hypothesis, n = sample size, PR = partial response

Note: Approximate alpha=0.025 and power =0.80

a. Stage 1 futility analysis has been conducted. Enrollment will continue to 60 subjects in each of the DLBCL arms and 45 subjects in each of the FL arms.
b. Includes subjects treated at the dose found to be tolerable during the initial safety run-in assessment.
c. The interim analysis planned at the end of stage 1 may occur sooner if the stage 1 rejection criterion is surpassed before all 35 subjects are treated and have completed at least the Week 24 assessment. In this scenario, the total sample size (stage 1 + stage 2) would still remain unchanged at 70 subjects.

To avoid disruptions in the study, enrollment and treatment of subjects will not be halted in order to conduct the futility analysis. If every cohort completes enrollment of stage 2, a total of 340 subjects will be enrolled in Phase 2.

For the purpose of calculating an expanded cohort size, a modified 2-stage Green-Dahlberg design was used where the stage 1 futility sample size was set to the original protocol design sample size of 10 subjects per cohort and the stage 1 rejection criteria were set to the original protocol defined rejection criteria (0 for the DLBCL cohorts and 1 for the FL cohorts).

For the DLBCL Cohorts (futility analysis completed):

- The probability of early stopping under the null hypothesis is 0.197.
- The probability of stopping under the alternative hypothesis is 0.028.

For the FL Cohorts (futility analysis completed):

- The probability of early stopping under the null hypothesis is 0.376.
- The probability of stopping under the alternative hypothesis is 0.046.

7.6.3 Interim Analyses

Phase 1 Dose Escalation data will be summarized and reported. All available safety and PK data will be evaluated before Phase 2 initiation.

At the end of the FE and DDI cohorts, the data may be analyzed. The results of these analyses will inform Phase 2 dosing.

There will be an interim analysis for futility in each cohort in Phase 2. While evaluating the response for the stage 1 subjects in each cohort, the enrollment and treatment of subsequent subjects will be continued. Timing, sample size, and rejection criteria for the stage 1 futility interim of each cohort are described in Section 7.6.2.

If enrollment in any cohort is terminated for futility, the final reporting for that cohort will be based on all subject data in the database.

7.6.4 Other Statistical/Analytical Issues

Not applicable.

7.6.5 Procedure for Revising the Statistical Analysis Plan

If the planned analysis needs to be revised after the study starts, the Sponsor will determine how the revision impacts the study and determine how the revision should be implemented. The details of the revision will be documented and described in the SAP and the clinical study report.

8 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

8.1 Changes to the Protocol

The protocol, ICF, and appropriate related documents must be reviewed and approved by an IRB or IEC constituted and functioning in accordance with ICH E6, Section 3, and any local regulations, ie, Code of Federal Regulations, Title 21 CFR Part 56. Any protocol amendment and/or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associates [CRAs] or change of telephone number[s]). Documentation of IRB/IEC compliance with ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB/IEC Chairman must be sent to the PI (if regionally required, the heads of the medical institutions) with a copy to the Sponsor before study start and the release of any study drug to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the Investigator (if regionally required, the heads of the medical institutions) will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to the IRB/IEC annually (or as required) by the Investigator or sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The Investigator(s) or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (if regionally required, the heads of the medical institutions) of any reportable AEs per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

8.2 Ethical Conduct of the Study

This study will be conducted in accordance with the standard operating practices of the Sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- In accordance to the principle of World Medical Association Declaration of Helsinki, 2008

- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- US 21CFR, including parts 50 and 56 concerning Informed Patient Consent and IRB regulations, and applicable sections of US 21CFR Part 312
- European Clinical Trial Directive 2005/28/EC, for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states
- In accordance with Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- And other applicable regulatory authorities

8.2.1 Subject Information and Consent

As part of administering the ICF, the Investigator must explain to each subject (or guardian/legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an informed consent at the Screening Visit before any study-specific procedures being performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC and sponsor-approved written informed consent must be prepared in accordance with ICH E 6, Section 4, and all applicable local regulations (eg, Code of

Federal Regulations, Title 21, CFR Part 50) and provided to the Sponsor. Each subject must sign an approved informed consent before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the Sponsor and kept on file, according to local procedure, at the study center.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

8.3 Administrative Procedures

8.3.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRB/IEC of all investigational sites and, in some countries, by the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Sponsor's appropriate study team member must be notified promptly and the IRB/IEC for the site must be informed immediately. Per 21 CFR 312.30, a protocol change intended to eliminate an immediate hazard may be implemented immediately, provided FDA is subsequently notified by protocol amendment.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC (if regionally required, the heads of the medical institutions) must be kept informed of such changes. In these cases, the Sponsor will send a letter to the IRB/IEC (if regionally required, the heads of the medical institutions) detailing such changes.

8.3.2 Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

8.3.3 Monitoring Procedures

The Sponsor's or CRO's CRA will maintain contact with the Investigator and designated staff by telephone, and/or letter, and/or email between study visits. Monitoring visits to each investigational site will be conducted by the assigned CRA as described in the monitoring plan. The Investigator (if regionally required, the heads of the medical institutions) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCPs and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to the study protocol and data accuracy in accordance with federal regulations (or local regulations). All records at the investigational site are subject to inspection by the FDA or local regulatory agency.

In accordance with ICH E6, Section 6.10, source documents include but are not limited to the following:

- Clinic, office, hospital charts
- Copies or transcribed healthcare provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IVRS/IWRS, x-rays, and other imaging reports: eg, sonograms, CT scans, MRIs, nuclear medicine scans, ECGs, rhythm strips, electroencephalograms, polysomnographs, and pulmonary function tests (regardless of how these images are stored, including microfiche and photographic negatives)
- Pain, quality of life, medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs: eg, urine pregnancy test result documentation
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRB/IEC
- CRF components: eg, questionnaires that are completed directly by subjects and serve as their own source

8.3.4 Recording of Data

A CRF is required for each subject and must be completed by qualified and authorized personnel. Only data required by the protocol for the purposes of the study should be reported on the CRF. All data on the CRF must reflect the corresponding source document. Any corrections to entries made on the CRF must be documented in a valid audit trail.

8.3.5 Identification of Source Data

The following items in the CRF will be handled as source data:

- Study drug compliance (eg, the reason for dose increase/reduction)
- Discontinuation information
- Sampling date and time for the drug concentration
- Sampling date and time for the clinical laboratory test
- Comments and other information on AEs (eg, severity, relationship to study drug, outcome)

8.3.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the Investigator (if regionally required, the heads of the medical institutions) has the responsibility to retain all study documents, including but not limited to the protocol, copies of CRFs, the IB, regulatory agency registration documents (eg, FDA 1572 form), ICFs, and IRB/IEC correspondence. The investigational site should plan to retain study documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least until 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period or, should the Investigator retire or relocate, the Investigator (or if regionally required, the heads of the medical institutions) contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

8.3.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the Sponsor’s Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the Sponsor’s standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may also wish to conduct an

inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator must inform the Sponsor immediately that this request has been made.

8.3.8 Handling of Study Drug

All study drug will be supplied to the PI (or a designated pharmacist) by the Sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug label. The Investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. Once study drug has been received by the investigational site, the assigned CRA will review these documents along with all other study conduct documents at appropriate intervals during investigational site visits.

All drug supplies are to be used only for this protocol and not for any other purpose. The Investigator (or a designated pharmacist) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the Sponsor. At the conclusion of the study and as appropriate during the course of the study, the Investigator (or a designated pharmacist) will either return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the Sponsor's designated contractor or, where approval is given by the Sponsor, will destroy supplies and containers at the investigational site.

8.3.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor in advance of submission. The review is aimed at protecting the Sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results or other information, generated or created in relation to the study shall be set out in the agreement between each investigator (or if regionally required, the heads of the medical institutions) and the CRO or the Sponsor, as appropriate.

8.3.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this

study will be utilized in any written work, including publications, without the written consent of the Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the Sponsor and the Investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and the Sponsor (provided by the Sponsor).

8.3.11 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or for any other reason at any time. If the study is prematurely terminated or suspended, the Sponsor will promptly inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, the Investigator should inform the institution where applicable, and the Investigator/institution should promptly inform the Sponsor and the IRB/IEC, and should provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

8.3.12 Subject Insurance and Indemnity

The Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study.

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APPENDIX 1 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Scale	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG = Eastern Cooperative Oncology Group.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

APPENDIX 2 COCKCROFT AND GAULT FORMULA

$$\text{Male} \quad \frac{(140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} = \text{XX mL/min}$$

$$\text{Female} \quad \frac{(140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} = \text{XX mL/min} \times 0.85$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

For serum creatinine measured in μmol/L:

$$\text{Male} \quad \frac{(140\text{-age}) \times \text{weight (kg)} \times 1.23}{\text{Creatinine (μmol/L)}}$$

$$\text{Female} \quad \frac{(140\text{-age}) \times \text{weight (kg)} \times 1.23 \times 0.85}{\text{Creatinine (μmol/L)}}$$

APPENDIX 3 NEW YORK HEART ASSOCIATION CARDIAC DISEASE CLASSIFICATION

The New York Heart Association (NYHA) Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for cardiac subjects. Based on NYHA definitions, subjects are to be classified as follows:

Class	**NYHA Status**
Class I:	Subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II:	Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III:	Subjects with marked limitation of activity; they are comfortable only at rest.
Class IV:	Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

NYHA = New York Heart Association.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. NY: Little Brown;1994. p. 253-6.

APPENDIX 4 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

Tumor response assessments in this clinical trial will utilize Response Evaluation Criteria in Solid Tumors (RECIST 1.1) based on the following 2009 article: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

The modifications to RECIST 1.1 to be implemented in this trial are: 1) chest x-rays may not be used to follow disease; only CT scans may be used to follow chest disease, and 2) the minimum duration of stable disease (or non-CR/non-PD for subjects with nontarget lesions only) is 7 weeks following the date of first dose of study drug.

The Eisenhauer article, published in the *European Journal of Cancer*, is available online at: http://linkinghub.elsevier.com/retrieve/pii/S0959804908008733.

APPENDIX 5 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 4.03 published 28 May 2009) provides descriptive terminology to be used for adverse event (AE) reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE 4.03 have been correlated with single-concept Medical Dictionary for Regulatory Activities (MedDRA) terms.

For details regarding CTCAE v4.03, refer to Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [published 28 May 2009; v4.03: 14 June 2010], available from: http://ctep.cancer.gov/protocolDevelopment/electronic_ applications /docs/ctcaev4.pdf.

For details regarding MedDRA, refer to the MedDRA website at: http://www.meddramsso.com.

APPENDIX 6 STANDARD HIGH-FAT BREAKFAST

Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate and fat, and has comparable meal volume and viscosity.

Item	Amount	Calories	Protein (g)	Fat (g)	Carbohydrate (g)
Eggs (fried)	2	191	14	15	-
Bacon (strip)	2	96	3.6	8.8	0.4
Toast (slice)	2	136	4	-	30
Butter (pat)	2	90	-	10	-
Hash browned potatoes	4 oz (100 g)	156	2	10	15
Whole milk	8 oz (200 mL)	170	8	10	12
Total		841	31.6	53.8	57.4

As recommended by FDA Guidance: Guidance for industry. Food-effect in bioavailability and fed bioequivalence studies, p. 1-9. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Rockville, MD, USA, 2002.

APPENDIX 7 PHARMACOGENOMICS/PHARMACODYNAMICS

Subjects enrolled in this clinical study will have samples collected for pharmacogenomic and biomarker analysis. The aim of the analysis is to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

Collection of the samples for pharmacogenomic analysis will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for pharmacogenomic and biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws. If regionally required, subjects' consent form for collection of samples in which DNA will be analyzed will be prepared separately from the informed consent form for study participation. In these regions, subjects who do not consent to DNA sample collection can be enrolled without collection of these samples.

SAMPLE COLLECTION AND HANDLING

The samples will be collected according to the study flow chart and laboratory manual.

SECURITY OF THE SAMPLES, USE OF THE SAMPLES, RETENTION OF THE SAMPLES

Sample processing, including DNA extraction and genotyping, sequencing or other analysis will be performed by a laboratory under the direction of the Sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol by the Sponsor. Laboratories contracted to perform the analysis on behalf of the Sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The Sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a Health Authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not

possible to prospectively define every avenue of future testing, all samples collected will be single- or double-coded (according to the ICH15 guidelines) in order to maintain subject privacy.

RIGHT TO WITHDRAW

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples, if they can still be identified (not anonymized). Once samples have been anonymized, it will not be possible to identify which samples have come from a particular individual. Therefore, it will not be possible to destroy subject samples after anonymization. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

SUBJECT PRIVACY AND RETURN OF DATA

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. Samples that are processed for analysis (DNA extracted) may be double-coded. Double-coding involves removing the initial code and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded (the first code being the subject number) as long as the initial tube does not carry any personal identifiers or the random code assigned by the central laboratory or biorepository. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

Sample anonymization may occur by destruction of the "key." Once the "key" is destroyed, it will not be possible to trace the pharmacogenomics assay results back to an individual. The Sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The Sponsor and its representatives and agents may share anonymized data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the Sponsor
- Independent ethics committees or institutional review boards that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report that can include part or all of the anonymized data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the planned analysis, it will not be possible to return individual data to subjects participating in the pharmacogenomics analysis.

9.8. Changes in the Conduct of the Study or Planned Analyses

9.8.1. Changes in the Conduct of the Study

The original study protocol was approved on 01 November 2012. The study protocol was subsequently amended 11 times (Table 12). No subjects in the phase 2 part of the study were enrolled under Amendments 1 through 6. Subjects were enrolled under each subsequent amendment as follows:

- Amendment 7: 70 subjects
- Amendment 8: 59 subjects
- Amendment 9: 87 subjects
- Amendment 10: 108 subjects
- Amendment 11: 0 subjects

The original protocol and all amendments up to Amendment 6 are provided in the phase 1 CSR for Study E7438-G000-101. Protocol Amendments 7 through 11 are located in Appendix 16.1.1. The key changes implemented across all amendments are summarized in Table 12.

Table 12: Summary of E7438-G000-101 Protocol Changes

Amendment Number **Date** **Affected Sites**	**Key Modifications**
Amendment 1.0 dated 11 February 2013 (All Sites)	• Added survival follow-up every 12 weeks, unless the subject withdrew consent. • Added a warning of possible phototoxicity during prolonged exposure to sunlight based on available nonclinical data • Added additional assessments to be performed at the Day 1 of Cycles 1 through 6 and/or Off Treatment visit, including ECOG performance status, hematology, chemistry, urinalysis, blood sample for pharmacodynamics • Added that safety data review and decisions on DLTs/dose escalation was done jointly by the Sponsor and Investigators • Clarified the period of relevant exposure for contraception language and what constitutes highly effective methods • Added an exclusion criterion for subjects with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency, since sorbitol was in the final tazemetostat formulation • Clarified language regarding time to event analyses (starting point) for phase 2 Stages 1 and 2 • Added language requiring follow-up tumor assessments for subjects who went off treatment without progression • Clarified language that bone marrow aspirate/biopsy was required if it had not been conducted within 42 days before first dose. • Clarified the baseline criteria for entry into extension study.
Amendment 2.0 dated 24 April 2013 (All Sites)	• Revised the tazemetostat powder for oral suspension containers
Amendment 3.0 dated 19 June 2013 (All Sites)	• Corrected an error in the dose escalation language; text modified to state that 0 of 3 or 1 of 6 subjects could experience a DLT for the cohort to be expanded • Data Monitoring Committee was added for phase 2

Amendment Number **Date** **Affected Sites**	**Key Modifications**

	• Tablet formulation information was added, including maximum daily tablet dose and information on storage, packaging, and administration
	  • Subjects were to continue on the formulation they began receiving at study treatment initiation
	  • When the tablet formulation was released, an additional 3 subjects were to be enrolled in the ongoing cohort and dosed with tazemetostat tablets
	  • Subjects in subsequent cohorts in the escalation were to receive tazemetostat tablets if determined to be safe with acceptable PK in the preceding cohort
	• Add details on preparation of the oral suspension
	• Biomarker and pharmacogenomic studies were corrected from serum to plasma specimens
	• Clarified the pharmacokinetics will be compared for oral suspension and tablet formulations
	• It was clarified that disease progression is not an AE

Amendment 4.0 dated 22 October 2013 (All Sites)	• Added language allowing the FE and DDI studies to be performed in parallel • Removed the restriction on the maximum daily tablet dose of 1000 mg based on available nonclinical data • Indicated that once the tablet formulation was available, all new subjects were to be administered tablets
Amendment 5.0 dated 24 February 2014 (All Sites)	• Allowed for a fourth subject to be enrolled in a dose-escalation cohort(s) to ensure 3 evaluable subjects, and clarified language around cohort expansion if the fourth subject had a DLT • As no DLTs were reported in the first 2 dose-escalation cohorts; the required 2-week waiting period between the first and second subjects in a cohort was removed • Clarified the timing of the administration of study treatment and the washout period relative to the high-fat breakfast in the FE cohort • Clarified blood sample collection for PK/PD assessments, bone marrow aspirate/biopsy samples, and skin punch biopsies. • Clarified the composition of the dose escalation and/or MTD expansion cohort used for decision-making for the RP2D • Added an end-of-cohort dose escalation meeting

Amendment Number **Date** **Affected Sites**	**Key Modifications**
Amendment 6.0 dated 29 August 2014 (All Sites)	• Modified the phase 2 part of the study to include 4 separate cohorts of subjects: DLBCL WT and MT and FL WT and MT. The design allowed up to 30 subjects in each cohort with early in-stream stopping criteria defined based on response evaluation of the first 10 subject in each cohort. • Modified inclusion/exclusion criteria accordingly to accommodate study design changes o Criteria for adequate bone marrow function were revised o Corticosteroid use was clarified and broadened to include standard-of-care regimens o Exclusion added for ABC subtype DLBCL • Mandated availability of tissue for central confirmation of EZH2 mutation status for all subjects and for COO determination for DLBCL subjects • Included the term "recommended phase 2 dose (RP2D)" and introduced a maximum feasible dose of 1600 mg BID • Clarified that up to 2 cohorts may be expanded during dose escalation to inform the safety profile of the study treatment and/or the selection of the MTD/ RP2D • Added optional paired biopsy in a subset of subjects to inform the selection of the RP2D • Clarified the dose for the FE substudy (200 mg)
Amendment 6.1 dated 14 October 2014 (All Sites)	• Adapted dose modifications in line with less conservative requirements for bone marrow function per advice from external experts in the field
Amendment 7.0 dated 19 February 2015 (All Sites)	• The Dose Escalation Phase had been completed and the RP2D was determined as 800 mg twice daily. Provided the rationale for the RP2D. • Based on demonstration of clinical activity in subjects with non-GCB subtype in the phase 1 part, a cohort of non-GCB subtype was included in phase 2 and revised sample size estimate accordingly. • Added details of on specific testing methods for EZH2 mutation and COO for the phase 2 part of the study. • Revised inclusion criteria for the phase 2 population to require that subjects have relapsed/refractory disease following at least 2 standard prior treatment regimens and have no curative options with other available therapy or those therapies are contraindicated. • Objectives modified to remove clinical benefit rate, which is not a recognized efficacy measure in NHL, and to add DOR, which has more clinical and regulatory relevance. Included an additional exploratory objective measurement of OS to be in line with existing protocol language on survival follow-up. • Eligibility: o Revised measurement of renal function (calculation using Cockcroft and Gault formula only). o Clarified the adequate liver function inclusion criterion refers to total bilirubin, since the exception cited was specific only to unconjugated bilirubin. o Specific screening for presence of leptomeningeal metastases or brain metastases in asymptomatic subjects without history of central nervous system involvement was not necessary as this is a rare event in the study population. The exclusion criteria were updated to be consistent with the imaging requirements. o Exclusion for ABC subtype of DLBCL was removed. o Symptomatic venous thromboembolism (VTE) added as an exclusion as a precautionary measure per IDMC recommendation, since 2 subjects in the

Amendment Number Date Affected Sites	Key Modifications
	phase 1 part experienced pulmonary emboli. The events were not considered related to tazemetostat by the Investigator, and both subjects had established risk factors for VTE. • Permitted clinically stable subjects who had completed 6 cycles of therapy to have Day 15 assessment by telephone contact and local laboratory assessments. • Following feedback from Regulatory Authorities (FDA, CDRH and CDER), subjects were no longer required to provide fresh tumor biopsies for the purpose of participation in this study. • Modified the dose of tazemetostat to be used for the FE substudy to 400 mg • Requirement for monitoring of serum bromide was removed from the study based on results from the phase 1 part showing no subject had serum bromide levels above the lower limit of detection at any point. • Requirement for skin punch biopsies was removed. • Safety data from the phase 1 part showed no reported AEs of phototoxicity or rash. The text was amended to reflect the presence of these safety data. • Findings from 13-week rat studies showed the development of secondary lymphoma and bone changes with tazemetostat exposure. While the relevance of these findings was unknown in humans, information on these events of special interest was added to include special reporting requirements. • The statistical methodology was simplified to reflect appropriate flexibility for the analyses based on the emerging data. New text allowed for separate analysis of phase 1, FE, and DDI substudies prior to phase 2 data becoming available. • Provided additional clarity that any dose interruption of over 28 days for any reason was to be discussed with the Medical Monitor • Stated the dose of tazemetostat in the DDI substudy as 800 mg. • Added collection of anticancer therapies administered after tazemetostat.
Amendment 7.1 dated 21 May 2015 (All Sites)	• Protocol amended to allow for enrollment of subjects ≥16 years of age in the FE and DDI substudies. • Justification for dose administered to subjects ≥16 years of age to the Phase 1 portion of the study
Amendment 8.0 dated 15 September 2015 (All Sites)	• Updated the protocol due to acquisition of the clinical development for tazemetostat by Epizyme from Eisai in March 2015 • Simplified the protocol based on completion of phase 1 (dose escalation and expansion and food effect) • Removed fasting restriction based on results of the FE study and included the tazemetostat could be administered with or without food. • Eligibility criteria: o Expanded ECOG performance status inclusion to 0 to 2 o Defined laboratory criteria for hepatitis B and C infection o Added criteria surrounding required hematology laboratory parameters o Defined length of time from various prior anticancer therapies and start of study treatment o Clarified that one of the prior treatment for R/R FL was radiation therapy if given for treatment not palliation o Removed restriction for concomitant medications that are substrates of CYP2C8, 2C9, and 2C19 and provided guidance for taking these medications o Clarified that subjects must be 3 months from any deep vein thrombosis including pulmonary embolism o Eliminated restrictions of antacid/proton pump inhibitor use, as preliminary PK data from phase 1 showed no meaningful effect on tazemetostat exposure

Amendment Number **Date** **Affected Sites**	**Key Modifications**
	○ Removed exclusion for subjects with fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency at the phase 2 portion utilizes an oral formulation that does not contain sucralose ○ Clarified restrictions surrounding history of previous malignancy ○ Due to concomitant medication(s), possible organ dysfunction and unknown risk of tazemetostat in this population, subjects who hade undergone a solid organ transplant were excluded • Added that subjects who complete study-required assessments may participate in a rollover study • Updated dose modifications section: ○ Provided instruction around continued dosing, modification, and interruption ○ Added section to establish parameters that must be met prior to starting the next cycle of study treatment ○ Added that discussion with the Medical Monitor was required for Grade 4 toxicity and for study treatment interruption lasting longer than 14 days ○ Neutropenia was included as a Grade 4 toxicity that required interruption of study treatment dosing • No longer required in-clinic visits on Day 15 after Cycle 2, only a telephone contact was required; subjects were to have hematology and blood chemistry samples drawn at local laboratory. • Changed radiologic tumor assessment to every 12 weeks after Cycle 6 to minimize radiation exposure and more accurately reflect standard of care • Changed screening brain MRI to "only if clinically indicated" • Added that all scans were to be submitted to the imaging core laboratory for quality assessment and archiving for potential independent review. • Added the FDG-PET should be conducted at first indication of CR or PR and that a repeat bone marrow biopsy should be performed at first indication of CR for subjects with bone marrow involvement at screening. • Modified physical exam to a symptom-directed exam during treatment period. • Clarified that AEs and concomitant medications should be collected for 30 days after treatment discontinuation unless a new cancer therapy was started • Clarified the analyses to be conducted for PFS, DOR, and OS
Amendment 8.1 dated 03 November 2015 (US Only)	• Original US submission of the protocol; does not allow for enrollment of FL subjects
Amendment 9, dated 15 April 2016 (Ex-US Sites) Amendment 9.1, dated 15 April 2016 (US Only)	• Following futility analysis on the DLBCL cohorts, the IDMC endorsed a study design change to a modified 2-stage Green-Dahlberg. Additional information added on the expanded sample size and statistical assumptions. • Eligibility criteria: ○ Allowance for subjects with long term but non-clinically significant toxicity from prior therapy to be enrolled ○ Removed requirement for left ventricular ejection fraction (LVEF) measurement ○ Modified timing related to stop date of prior therapies • Assessment of respiratory rate, urinalysis, and multigated acquisition (MUGA) scan/echocardiogram were removed • Added information about rollover study • Absolute neutrophil count (ANC) requirement for continuation of treatment for Cycle 2 and beyond was modified to $\geq 0.75 \times 10^9$/L to match eligibility criterion • A tumor biopsy was requested, where medically feasible, at the time of disease progression in subjects who achieved a PR or better.

Amendment Number **Date** **Affected Sites**	**Key Modifications**
Amendment 9.2 dated 19 September 2016 (Germany only)	• Clarified that SAEs related to disease progression should be reported as serious events. • Clarified that scans conducted as part of standard of care can be performed as per the SOC schedule but assessments should be performed per protocol.
Amendment 10 dated 21 November 2016 (Global: all but US, Canada and UK) Amendment 10.1 dated 21 November 2016 (US only)** Amendment 10.2 dated 28 February 2017 (UK) **The U.S. and global protocols were aligned on 18 January 2017	• Added an additional cohort to phase 2 to test tazemetostat in combination with prednisolone in subjects with DLBCL. Enhanced activity was observed when tazemetostat was combined with prednisolone in DLBCL cell lines containing either wild-type or mutant EZH2, and in mice bearing an EZH2-mutant lymphoma xenograft. • Added an option for non-GCB mutation subjects to enter Cohort 1 when Cohort 3 was full. This change was made based on the observation that EZH2 mutations have been identified in the non-GCB cohorts and those subjects have benefited from tazemetostat treatment. • Added that study treatment may continue upon initial disease progression if the subject meets certain criteria because there was a subject in the study who initially progressed but later achieved a PR • The US-specific amendment allowed for the inclusion of FL subjects in the US; this amendment was not implemented as the US and global protocols were aligned on 18 January 2017** • The UK-specific amendment modified the language for the new cohort to clarify use of high-dose prednisolone (removing the monotherapy vs combination therapy terminology)
Amendment 11 dated 24 September 2018 (ex-UK and ex-Canada) Amendment 11.1 dated 07 November 2018 (UK only) Amendment 11.2 dated 08 November 2018 (Canada only)	• Added new AESI, T-LBL/T-ALL, and MDS, based on updated clinical data, and the risk mitigation and monitoring required for these events. o Added language to advise Investigators to discontinue tazemetostat treatment in the event of T-LBL/T-ALL. Tazemetostat is to be held in the event of a case of MDS; pending discussion between the Investigator and the Medical Monitor, treatment may be modified or discontinued. o Added new exclusion criteria to exclude subjects with thrombocytopenia, neutropenia, or anemia and prior history of myeloid malignancies, including MDS o Addition of new exclusion criteria for subjects with T-LBL or T-ALL o Added an optional chest ultrasound to be performed at screening and at every 8 weeks to monitor for early signs of T-LBL o Added the requirement to assess blood smear morphology and perform a bone marrow aspirate with cytogenetic testing if the blood smear morphology was abnormal to monitor subjects with cytogenetic abnormalities known to be associated with MDS o Added an annual blood draw for assessment of AESI, PK, and tumor response to align with updated clinical data and subsequent risk management o Modified dose modification criteria to remove first occurrence and continuation of tazemetostat treatment language under Grade 3 neutropenia and treatment reduction and interruption instructions for Grade 3 thrombocytopenia o Added language describing a new tazemetostat safety committee that would review and adjudicate all AESI cases for a suspected relationship to tazemetostat • Added language for subjects who had disease progression that are also receiving clinical benefit to discuss the risk/benefit of keeping the subject on study with the Medical Monitor

Amendment Number Date Affected Sites	Key Modifications
	• Changed inclusion criteria to clarify that subjects with histologically confirmed FL should have at least 2 standard lines of systemic therapy prior to study enrollment. Subjects who had previously received radiotherapy were allowed; however, radiotherapy alone was not considered a separate systemic treatment regimen. • Clarified language for bone marrow biopsies to be performed for subjects with FL and in subjects with DLBCL if clinically indicated, or if the subject had history of bone marrow involvement. Additionally, bone marrow biopsies were to be performed at the first indication of CR • Starting Cycle 3, Day 15 laboratory assessments were no longer required; assessments were performed as medically necessary

9.8.2. Changes to the Planned Analysis

The major changes from the analyses planned in the protocol and Version 2 of the SAP are summarized below; complete details are outlined that document in Appendix 16.1.9.

- Based on a request from the FDA, the analyses conducted on the primary and secondary efficacy endpoints were based on IRC review. Analyses were also included based on Investigator assessments.
- The primary population for efficacy analysis was subjects with FL enrolled in Cohorts 4 and 5 as of the data cutoff date of 24 May 2019. At that time, 99 subjects had been enrolled in these cohorts.

The following changes were made after finalization of the SAP:

- The summary tabulation for parameters not graded by CTCAE, shifts from baseline to worst post-baseline value that was <0.25 × LLN or >2.5 × ULN was not produced; data listings were included.
- The Investigator overall interpretation of ECGs was not tabulated.
- A listing of echocardiogram/multigated acquisition scans was not produced. This will be included in the final CSR.

Epizyme, Inc

STATISTICAL ANALYSIS PLAN

An Open-Label, Multicenter, Phase 1/2 Study of Tazemetostat (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B Cell Lymphomas and Tazemetostat in Combination With Prednisolone in Subjects With Diffuse Large B Cell Lymphoma

Protocol E7438-G000-101

SAP Version:	Date of Statistical Analysis Plan:
Version 2.0	4 September 2019

SIGNATURE PAGE

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Table of Contents

LIST OF ABBREVIATIONS

Abbreviation	Full Term
^{18}FDG-PET	^{18}fluorodeoxyglucose-positron emission tomography
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
COO	Cell of origin
CR	Complete Response
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DLBCL	Diffuse Large B-Cell Lymphoma
DMC	Data Monitoring Committee
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EZH2	Enhancer of zeste homolog 2

FL	Follicular Lymphoma
GCB	Germinal-Center B-cell-like
GELF	Groupe d'Etude des Lymphomas Folliculaires
HMT	Histone Methyl Transferase
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IRC	Independent Review Committee
ITT	Intent-to-Treat
IWG	International Work Group
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple gated acquisition
NHL	Non-Hodgkin Lymphoma
ORR	Objective Response Rate
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PT	Preferred term
QTc	Corrected QT interval
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's

	formula
PFS	Progression-free survival
PK	Pharmacokinetics
POD24	Progression or relapse within 24 months of diagnosis
PR	Partial Response
RP2D	Recommend Phase 2 Dose
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SI	Système International
SOC	System organ class

1 INTRODUCTION

The clinical study, E7438-G000-101, is a Phase 1/2, open-label, multicenter study of tazemetostat. The Phase 1 portion is comprised of dose escalation and expansion parts to establish the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) when tazemetostat is given twice daily (BID) orally on a continuous basis in subjects with histologically and/or cytologically confirmed advanced or metastatic solid tumors or B cell lymphomas that have progressed after treatment with approved therapies or for which there are no standard therapies available. Additionally, in the Phase 1 portion of the study, which is completed, the effect of food on the bioavailability of tazemetostat was evaluated as well as the drug-drug interaction potential as evaluated by the effect of tazemetostat on the pharmacokinetics (PK) of midazolam, a cytochrome P450 (CYP) 3A4 substrate. Phase 2 enrolls subjects with Diffuse Large B-Cell Lymphoma (DLBCL) and Follicular Lymphoma (FL) for the determination of efficacy and safety of tazemetostat monotherapy and of tazemetostat in combination with prednisolone.

This statistical analysis plan (SAP) describes the planned analyses to be included in the Clinical Study Report for the Phase 2 portion of Protocol E7438-G000-101. The efficacy analyses described in this SAP will be performed for the FL cohorts of WT and MT only. Only the first 45 MT enrolled subjects per agreement with the Regulatory agency will be included in this analysis. Additional, patients beyond initial protocol-defined 45 EZH2 MT patients in cohort 4 will be included in subsequent analysis and datasets for the clinical study reports.

This SAP is based on Amendment 11.0 of the protocol, dated 24 September 2018. The analyses will also include safety analysis of all Phase 2 subjects, with the exception of the FL MT cohort, which will only include the first 45 subjects enrolled. Any changes made to the planned analyses after this document has been finalized will be noted in the interim clinical study report. This SAP was written in accordance with International Council on Harmonisation (ICH) Guideline E9.

Analyses of the Phase 2 PK, pharmacodynamics, biomarker, and pharmacogenomics data will not be covered in this SAP.

2 STUDY SUMMARY

2.1 STUDY OBJECTIVES

2.1.1 Primary Objective

- For the Phase 2 portion of the study, the primary objective is to determine the objective response rate (ORR; complete response + partial response [CR +

PR]) of tazemetostat in subjects with enhancer of zeste homolog 2 (EZH2) gene mutation positive or negative (wild-type) with histologically confirmed DLBCL or FL with relapsed or refractory disease and the ORR of tazemetostat in combination with prednisolone in subjects with EZH2 wild-type DLBCL. ORR will be assessed by the International Working Group-Non-Hodgkin's Lymphoma (IWG-NHL; Cheson 2007) criteria.

2.1.2 Secondary Objectives

For the Phase 2 portion of the study, the secondary objectives are as follows:

- To assess the effect of tazemetostat monotherapy and tazemetostat in combination with prednisolone on progression-free survival (PFS) based on IWG-NHL (Cheson 2007) criteria (this SAP covers PFS in the FL cohorts only);
- To assess the effect of tazemetostat monotherapy and tazemetostat in combination with prednisolone on duration of response (DOR) based on IWG-NHL (Cheson 2007) criteria (this SAP covers DOR in the FL cohorts only);
- To assess the safety and tolerability of tazemetostat monotherapy and tazemetostat in combination with prednisolone;
- To assess the PK profile of tazemetostat monotherapy and tazemetostat in combination with prednisolone (covered in a separate SAP).

2.1.3 Exploratory Objectives

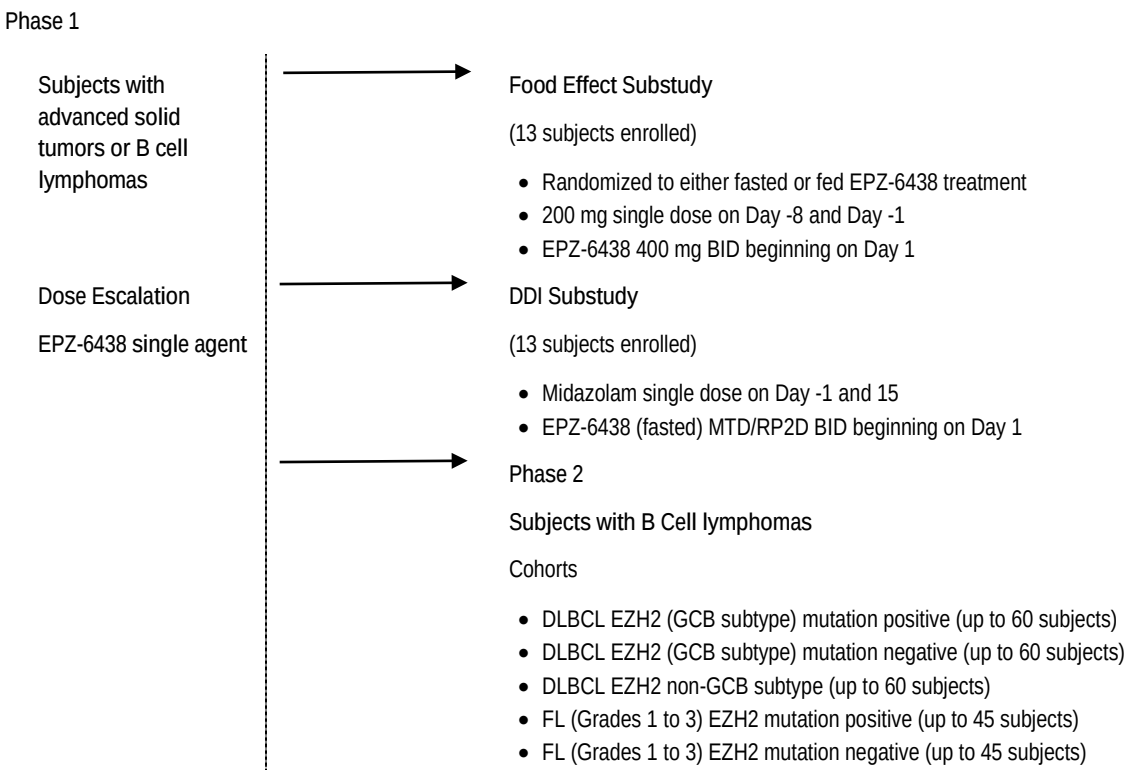
For the Phase 2 portion of the study, the exploratory objectives of the study are as follows:

- To explore the effect of tazemetostat monotherapy and tazemetostat in combination with prednisolone on overall survival (this SAP covers overall survival in the FL cohorts only)
- To explore the PK and pharmacodynamic relationship of tazemetostat (covered in a separate SAP)
- To identify and investigate biomarkers and their correlation with biological activity for tazemetostat (covered in a separate SAP)
- To explore the effects of tazemetostat on histone H3K27 methylation, target gene expression, and phenotypic markers including those for differentiation, apoptosis, cell proliferation, and changes in the tumor microenvironment (covered in a separate SAP)
- To explore the role of DNA sequence variability on absorption, metabolism, excretion and susceptibility to adverse events of tazemetostat (covered in a separate SAP)

2.2 STUDY DESIGN

The overall study design for both Phases 1 and 2 is displayed in Figure 1.

Figure 1 Schematic of the Study Design



Phase 2 of the study is an open-label, multicenter study of tazemetostat that enrolls subjects with DLBCL (Cohorts 1-3 and 6) and FL (Cohorts 4 and 5) for the determination of efficacy and safety of tazemetostat monotherapy (Cohorts 1-5) and of tazemetostat in combination with prednisolone (Cohort 6) with placement determined by centrally confirmed histology, cell of origin, and EZH2 mutation status as shown below.

Table 1 Phase 2 Cohorts

Cohort	Treatment	Description	Planned Enrollment
1	Tazemetostat Monotherapy	DLBCL (GCB subtype) EZH2 mutation positive	60
2	Tazemetostat Monotherapy	DLBCL (GCB subtype) EZH2 wild-type	60
3	Tazemetostat Monotherapy	DLBCL non-GCB subtype	60
4	Tazemetostat Monotherapy	FL (Grades 1 to 3) EZH2 mutation positive	45
5	Tazemetostat Monotherapy	FL (Grades 1 to 3) EZH2 wild-type	45
6	Tazemetostat/Prednisolone Combination	DLBCL GCB or non-GCB subtype EZH2 wild-type	70

DLBCL = diffuse large B cell lymphoma, EZH2 = enhancer of zeste- homolog 2, FL = follicular lymphoma, GCB = germinal-center B-cell-like

2.2.1 Number of Patients

Approximately 340 subjects were planned to be enrolled in the Phase 2 portion of the study with 60 subjects planned for each of the 3 DLBCL monotherapy cohorts, 45 for each of the 2 FL cohorts, and 70 for DLBCL combination therapy cohort.

2.2.2 Sample Size Determination

The original study design planned enrollment of up to 30 subjects enrolled in each monotherapy Cohort for Phase 2. The initial assessment of efficacy was to be conducted within each cohort when 10 subjects had been enrolled (stage 1). For each DLBCL cohort, if zero responders (with CR or PR) out of the initial 10 subjects was observed, further enrollment in the cohort was to be terminated for futility. This rule was based on the underlying assumption that the response rate is 30% and there is a 2.8% probability of observing no responders among 10 subjects. For each FL cohort, if 1 or zero responders (CR or PR) out of the initial 10 subjects was observed, further enrollment in the cohort was to be terminated for futility. This rule was based on the underlying assumption that the response rate is 40% and there is a 4.6% probability of

observing ≤ 1 responder among 10 subjects. Subsequent to the futility analysis in the DLBCL cohorts, the Data Monitoring Committee (DMC) supported a study design change to a modified 2-stage Green-Dahlberg design [Green, 1992] for each cohort.

Up to 70 subjects with DLBCL (GCB or non-GCB, EZH2 wild-type) was to be enrolled in an additional combination therapy cohort (tazemetostat and prednisolone). A 2-stage Green-Dahlberg design was used to terminate enrollment for futility.

For the purpose of calculating an expanded cohort size, a modified 2-stage Green-Dahlberg design was used where the stage 1 futility sample size was set to the original protocol design sample size of 10 subjects per cohort (for Cohorts 1-5) and the stage 1 rejection criteria was set to the original protocol defined rejection criteria (0 for the DLBCL cohorts and 1 for the FL cohorts). Final sample sizes are displayed in Table 2.

For the DLBCL Monotherapy Cohorts (futility analysis completed):

- The probability of early stopping under the null hypothesis is 0.197.
- The probability of stopping under the alternative hypothesis is 0.028.

For the FL Monotherapy Cohorts (futility analysis completed):

- The probability of early stopping under the null hypothesis is 0.376.
- The probability of stopping under the alternative hypothesis is 0.046.

A 2-stage Green-Dahlberg design was used to assess futility in the DLBCL combination therapy cohort. The stage 1 rejection criterion is 6 or fewer responders (CR + PR).

- The probability of early stopping under the null hypothesis is 0.433.
- The probability of stopping under the alternative hypothesis is 0.017.

Table 2 2-Stage Green Dahlberg Design

	Monotherapy					Combination therapy
	DLBCL GCB EZH2 Mutant	**DLBCL GCB EZH2 Wild-Type**	**DLBCL non-GCB**	**FL EZH2 Mutant**	**FL EZH2 Wild-Type**	**DLBCL EZH2 Wild-Type**
Ho: CR + PR	≤15%	≤15%	≤15%	≤20%	≤20%	≤20%
Ha: CR + PR	≥30%	≥30%	≥30%	≥40%	≥40%	≥35%
Stage 1						
n	10	10	10	10	10	35[a]
ORR events for declaring rejection of treatment	0	0	0	≤1	≤1	≤6
Stage 2						
Total n	60	60	60	45	45	70
ORR events for declaring rejection of treatment at end of Stage 2	≤14	≤14	≤14	≤13	≤13	≤19

CR = complete response, DLBCL = diffuse large B cell lymphoma, EZH2 = enhancer of zeste homolog 2, FL = follicular lymphoma, GCB = germinal-center B-cell-like, Ha = Alternative Hypothesis, Ho = Null Hypothesis, n = sample size, PR = partial response
Note: Approximate alpha=0.025 and power =0.80

2.2.3 Randomization and Blinding Procedures

The Phase 2 portion of the study was not randomized and includes no blinding.

2.2.4 Data Monitoring Committee

An independent Phase 2 DMC performed futility analysis during three DMC meetings. The stopping boundaries detailed in Table 2 were utilized by the DMC to assess the futility of the study. Details governing the independent DMC review are covered in a separate Charter and DMC Reporting Plan.

2.2.5 Efficacy Assessments

Tumor assessments were performed based upon IWG-NHL (Cheson, 2007) criteria at each assessment time point and entered onto the appropriate CRF page. Investigator determined response assessments at each assessment time point was also entered onto the appropriate CRF page. Scans were performed according to guidelines provided by the imaging core laboratory designated for this study. All tumor assessment scans were sent, as soon as they had been performed, to the imaging core laboratory for quality assessment and an Independent Review Committee (IRC) provided an independent response assessment.

During Screening:

Computed tomography (CT) scans of the chest, and CT or magnetic resonance imaging (MRI) scans of the brain, abdomen, pelvis, and other known sites of disease (as well as photographs of skin lesions that were to be followed as target and nontarget lesions), were performed at Screening. Standard of care scans performed within 28 days before Cycle 1 Day 1 using the protocol-specified parameters could have been used as screening assessments. An ^{18}fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) scan was performed. A bone marrow biopsy (including IHC) was to be performed for all subjects with FL and if clinically indicated in subjects with DLBCL, if they were not performed within 42 days of Cycle 1 Day 1.

During the Treatment Phase:

CT scans of the chest, and CT or MRI of the brain (if clinically indicated), abdomen, pelvis, and other known sites of disease were to be performed every 8 weeks (starting from Cycle 1 Day 1 of continuous tazemetostat dosing), or sooner if clinically indicated. If local regulatory authorities mandate less frequent imaging, maximum frequency would be every 12 weeks. Tumor assessments was to be carried out every 8 weeks (or sooner, if clinically indicated) during treatment cycles in the Treatment Phase. For subjects who remain on study drug for 24 weeks or more, radiologic disease assessments were to be performed every 12 weeks. At the first indication of

possible PR and CR, a whole body ^{18}FDG-PET scan was to be performed. At the first indication of CR, a repeat bone marrow biopsy was to be performed if lymphoma involvement in the bone marrow was reported at Screening. Repeat bone marrow biopsies were to be performed if clinically indicated (if progressive disease or relapse is suspected).

After the treatment phase, subjects were to be followed for overall survival every 12 weeks unless they withdraw consent.

2.2.6 Safety Assessments

Safety assessments consisted of monitoring and recording all AEs, regular laboratory evaluation for hematology, blood chemistry, and urine values; and periodic measurement of vital signs, echocardiograms/ multiple gated acquisition (MUGA) scans, electrocardiograms (ECGs), and physical examinations.

For details, refer to the Schedule of Visits and Procedures in appendix 1.

2.2.6.1 Laboratory Measurements

For the Phase 2 part of the study, clinical laboratory tests were performed locally. Blood samples were to be collected for clinical laboratory tests at Screening, Day 1 and 15 of every cycle, and the End of Treatment visit. All hematology, blood chemistry (including pregnancy test, where applicable) samples were to be obtained before study drug administration and results reviewed before administration/dispensing of study drug at the beginning of each cycle. If a laboratory abnormality met the criteria to qualify as an AE as described in the protocol and the CRF Completion guidelines, the AE corresponding to the laboratory abnormality was to be recorded on the AE CRF page.

2.2.6.2 Vital Signs and Weight Measurements

Vital signs and body weight (kg) were to be collected at Screening, Day 1 and 15 of Cycles 1 and 2, Day 1 of every cycle starting with Cycle 3, and the End of Treatment visit. Vital sign measurements included systolic and diastolic blood pressure (BP, mmHg), heart rate (HR, beats per minute), and body temperature (°C). Height was to be measured at the Screening visit only. Blood pressure and HR were to be collected after subjects have been sitting for 5 minutes.

2.2.6.3 ECOG Performance Status

An Eastern Cooperative Oncology Group (ECOG) performance status was to be done at Screening, Day 1 of every cycle, and the End of Treatment visit.

2.2.6.4 Physical Examinations

Comprehensive physical examinations were to be performed at Screening and the End of Treatment visit, and symptomatic physical examinations were to be performed on Day 1 and 15 of Cycles 1 and 2 and Day 1 of every cycle starting with Cycle 3. Documentation of the physical examination was to be included in the source documentation at the investigational site. Only changes from screening physical examination findings that meet the definition of an AE were to be recorded on the AE CRF.

2.2.6.5 Electrocardiograms

Electrocardiograms were to be complete, standardized, 12-lead recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format at Screening, Day 1 of every cycle, and the End of Treatment visit. In addition to a rhythm strip, a minimum of 3 full complexes were to be recorded from each lead simultaneously. Subjects were to be in the recumbent position for a period of 5 minutes before the ECG.

If an ECG abnormality met the criteria to qualify as an AE as described in the study protocol and the CRF Completion guidelines, the AE corresponding to the ECG abnormality was to be recorded on the AE CRF page.

2.2.6.6 MUGA Scans and Echocardiograms

MUGA scan or an echocardiogram were to be performed at baseline and as clinically indicated.

2.2.7 Other Assessments

2.2.7.1 Pregnancy Test

A serum β-hCG test and/or urine β-hCG test was to be performed at Screening for all women of child bearing potential. A urine or serum pregnancy test was to be performed before the first tazemetostat dose and prior to dosing on Day 1 of each cycle.

2.2.7.2 Tumor Biopsy at Disease Progression

Tumor biopsy was requested, where medically feasible, at disease progression in subjects who achieved a PR or better with tazemetostat.

2.2.7.3 Bone Marrow Biopsy with IHC

A bone marrow biopsy (including IHC) was to be performed for all subjects with FL and in subjects with DLBCL if clinically indicated or if subject has a history of bone marrow involvement, if these have not been performed within 42 days (an approval is

needed from the Sponsor's medical monitor if the window has been beyond 42 days) of Cycle 1 Day 1. At the first notation of CR, a repeat bone marrow biopsy was to be performed if lymphoma involvement in the bone marrow was reported at Screening.

2.2.7.4 Peripheral Blood Smear/ Bone Marrow Biopsy

If peripheral blood smear morphology assessment was confirmed to be abnormal, the subject was required to undergo bone marrow aspirate/biopsy for cytogenetic/genetic testing to closely monitor the cytogenetic/genetic abnormalities known to be associated with MDS (9del 5q, chr 7, abn,etc.) and MPN (e.g. JAK2 V617F, etc.). If results were abnormal, treatment with tazemetostat was to be paused and after discussion with the Investigator, the dose was to be modified or the drug discontinued.

2.2.7.5 Optional Chest Ultrasound

An optional chest ultrasound could have been performed at screening and every 8 weeks at the Investigator's discretion to monitor for early signs of T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia (T-LBL/T-ALL).

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

All statistical analyses will be performed using SAS® Version 9.4 or higher.

3.1.2 Reporting of Numerical Values

All clinical study data will be presented in patient data listings. Descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum) will be calculated for continuous variables.

Frequencies and percentages will be presented by treatment group for categorical and ordinal variables. If there are missing values, the number and percent missing will be presented.

Time-to-event statistics will include the 25th percentile, median, and 75th percentile, provided they are estimable. Two-sided 95% CIs, will be estimated using the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982)

Means, medians, and confidence intervals will be reported to one decimal place more than the data reported on the CRF or by the laboratory/vendor. Standard deviation

will be reported to two decimal places more than the data reported. Minimum and maximum will be reported to the same number of decimal places as the data reported. P-values will be reported to 3 decimal places.

Start of study treatment will use the date of first dose of tazemetostat for cohorts 1-5 and the first dose of tazemetostat or prednisolone for cohort 6.

3.1.3 Study Day

Study Day will be calculated as follows:

- Assessment date ≥ first dose date: Study Day = (date – first dose date) + 1
- Assessment date < first dose date: Study Day = (date – first dose date)

Study Day will appear as missing in the listings if the assessment date is partial.

3.1.4 Baseline Value and Change from Baseline

Baseline is defined as the last non-missing (including unscheduled) assessment prior to the first dose of study drug. Unless the collection time or label indicates otherwise, assessments performed on the same day as the first dose of study drug will be considered as performed prior to treatment. AEs and medications with a start date on the date of first dose of study drug will be considered to have occurred after the start of treatment.

Change from baseline will be calculated by subtracting the baseline value from the post-dose value for each subject (i.e., post dose – baseline). Percent change from baseline will be calculated by dividing the change value by the baseline value and multiplying the result by 100% (i.e., [{post dose value – baseline} / baseline] x 100).

3.1.5 Analysis Visits

For by-visit summaries, nominal visits will be presented (i.e. visit windowing will not be applied). Unscheduled measurements will not be included in by-visit table summaries but will contribute to worst-case values table summaries. Listings will include both scheduled and unscheduled data.

3.1.6 Handling of Missing/Incomplete Values

Unless otherwise explicitly specified, missing data will not be imputed; observed data will be used in the analyses.

3.1.7 Adjustments for Multiplicity

There will be no adjustments for multiplicity.

3.2 Analysis Populations and Subgroups

3.2.1 Definition of Analysis Populations

The Enrolled population will consist of all subjects who sign informed consent and were entered into the electronic case report form (eCRF) for the study and were not screen failed. The Enrolled population will be used for summaries of analysis populations, inclusion and exclusion protocol deviations.

The Intent-to-Treat (ITT) population will include all subjects who receive at least one dose of study treatment. The ITT population will be used for summarizing subject disposition, demographic and baseline characteristics and will be used for the efficacy analysis.

The Safety population will include all subjects who received at least one dose of study drug and have at least 1 post-baseline safety evaluation. The Safety population will be used for all safety analyses.

3.2.2 Definition of Subgroups

Refractory definitions.

Treatment refractory:

- No objective response to prior treatment or PD within 6 months of last dose of prior therapy

Rituximab refractory:

- No objective response to either rituximab monotherapy or rituximab-containing therapy (e.g., R-CHOP)

  OR

- Progressive disease (loss of CR/PR) within 6 months of completion of R-containing therapy.
    - Patient received at least 4 doses of rituximab for monotherapy or 5 cycles of R+chemo

Double refractory:

- No objective response to any rituximab-containing therapy (monotherapy or in combination with chemotherapy)

  AND

- Relapsed within 6 months or refractory to any alkylator-based chemotherapy

    - These can be given at the same time. For example, a patient who was relapsed within 6 months orrefractory to R-CHOP would be considered “double refractory”

- **Early Relapse patients: (POD24)** Defined as disease progression within 2 years of first-line treatment.
    - Defined from the start date of first line systemic therapy

Presentations of efficacy analyses will be repeated for the following groups of subjects:

- Treatment refractory
- Rituximab refractory
- Double refractory
- POD24
- Age group (<65 or >= 65)
- Prior radiation (Yes or No)
- Tumor burden (bulky disease [i.e., tumor ≥ 10 cm in longest diameter (as checked by the Investigator on the eCRF)]) (Yes or No)
- Gender (Male or Female)
- Lines of prior therapy (<=2 or >2)
- Time from last prior anticancer therapy to first dose (≤ 1 month or > 1 month)
- Region: North America/Europe/Rest of the World
- GELF (Yes or No) (See Section 3.6.2 for GELF definition)

3.3 Efficacy Endpoints

3.3.1 Primary Efficacy Endpoint

- Objective response rate based on IWG-NHL

3.3.2 Secondary Efficacy Endpoints

- Duration of response based on IWG-NHL

- Progression-free survival based on IWG-NHL

3.3.3 Exploratory Efficacy Endpoints

- Overall survival
- Disease control rate
- Time to first response
- Time to first subsequent therapy

3.4 Safety Analyses

- Adverse events
- Laboratory test results
- Vital signs
- Physical exams
- Electrocardiograms
- MUGA scans and echocardiograms

3.5 Subject Disposition and Evaluability

3.5.1 Subject Disposition

Subject disposition, including reasons for treatment withdrawal and status at last contact, will be summarized and listed based on the ITT population. The number of subjects in each analysis population will be summarized based on the Enrolled population.

3.5.2 Major Protocol Deviations

Major protocol deviations will be listed for the ITT population. Predefined categories of major protocol deviations will include:

- Violation of inclusion/exclusion criteria
- Prohibited medications, as defined in section 7.3.4.3 of the protocol, while on tazemetostat (inclusive of the first and last days of treatment)
- Failure to follow the radiological imaging procedures and schedule identified for the study which results in more than 1 unevaluable response assessment.

Additional categories may be added during the course of the study but will be determined prior to the database lock.

3.6 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be presented for the ITT population by FL (WT, MT and overall), by DLBCL, and by combined DLBCL and FL.

3.6.1 Demographics

Descriptive statistics will be provided for age (years) at screening, along with percentages for <65 and >= 65 years. Frequencies and percentages will be tabulated for gender, race, ethnicity and region (North America/Europe/Rest of the World).

3.6.2 Baseline Characteristics

The following baseline disease characteristics will be summarized:

- ECOG status (0, 1, or 2)
- Location of primary tumor at diagnosis
- Sum of target lesion diameters at baseline
- Presence of lymph node target lesions at baseline (Yes, No)
- Presence of non-lymph node target lesions at baseline (Yes, No)
- Presence of non-target lesions at baseline (Yes, No)
- Bulky disease (yes or no)
- Any prior combination therapy (yes or no)
- Any prior monotherapy (yes or no)
- Number of prior therapies (categorical by 1, 2, >=3 and descriptive statistics)
- Refractory to rituximab chemotherapy regimen
- Refractory to last therapy (i.e., no objective response or PD after response within 6 months of completion of last therapy)
- Last therapy contains an alkylating agent and is refractory (i.e., no objective response or PD after response within 6 months of completion of therapy)
- POD24 status (yes or no)
- Double refractory status (yes or no)

- FL staging (stage I, II, III and IV)
- Myelosuppression (yes or no) (anemia, neutropenia or thrombocytopenia of grade ≥ 1 based on baseline laboratory data)
- Prior radiation
- Prior stem cell transplant, including type of transplant (a subject with both allogenic and autologous stem cell transplants will be categorized as allogenic)
- Groupe d'Etude des Lymphomas Folliculaires (GELF) criteria (yes or no) GELF is defined as meeting at least one of the following criteria:
    - A target lesion > 7 cm in diameter
    - 3 nodal target lesions > 3 cm diameter each
    - B symptoms at baseline
    - Serum LDH greater than normal
    - Hbg = 10 gm/dl or less
    - Neutrophil count 1500 /mm3 or less
    - Platelets 100,000 /microliter or less

For the calculation of progression date and last date of prior therapy for refractory definitions, partial progression dates and end of therapy dates will be imputed as July 1 of the year when only a year is recorded and as the 15th of the month when only a month and year are recorded. If this imputation yields a date of last progression after the informed consent date, then the partial date of last progression will be imputed as January 1 of the year when only a year is provided and the 1st of the month when only a month and year are provided. Other combinations of missing date elements will be treated as missing values.

3.7 Medical and Surgical History

All relevant medical history conditions will be coded using the Medical Dictionary of Regulatory Activities (MedDRA, Version 18.1) and will be classified by MedDRA system organ class (SOC) and preferred term (PT). Medical history conditions will be tabulated by SOC and PT. Surgical history will be summarized by the MedDRA high-level group term (HLGT) and PT. Listings will include start date and stop date or notation of ongoing for conditions continuing into treatment.

3.8 Prior and Concomitant Medications

Medications will be coded using World Health Organization (WHO) Drug Dictionary (version March 2015). Medications will be summarized and listed by Anatomical Therapeutic Chemical (ATC) level 4 and PT for the ITT population.

3.8.1 Previous Anticancer Therapies

Previous anticancer therapy and radiotherapy will be summarized and listed for the ITT population. The summary for previous anticancer therapies will include:

- Number of regimens (1, 2, 3, 4, or more than 4 prior regimens)
- Therapy setting (Neoadjuvant, Adjuvant, Therapeutic for Advanced/Metastatic Disease, Consolidation, Maintenance, or Unknown); a subject may be counted in multiple categories
- Incidence of prior anticancer therapies by WHO Drug ATC level 4 and PT

The summary for the previous radiotherapy will include:

- Number of prior courses (0, 1, or 2 or more courses)
- Major sites of prior radiotherapy (subdivisions of those sites will be listed); A subject may be counted in multiple categories
- Progression at the site of the most recent radiotherapy (Yes, No, Not Evaluated)

The summary for prior hematopoietic stem cell transplantation will include:

- Incidence of prior hematopoietic stem cell transplantation
- Type of hematopoietic stem cell transplantation (autologous, allogenic)

3.8.2 Other Prior and Concomitant Medications

Medications will be summarized and listed for the ITT population. Summary tables will include incidence (number and percentage) of subjects receiving any medication and incidence of specific medications by WHO Drug ATC level 4 and PT.

Prior and concomitant medications will be summarized and listed separately. Prohibited medications, as defined in Section 7.3.4.3 of the protocol, will be identified with a '*' in the listing.

Prior and concomitant medications will be defined as follows:

- Prior medications will include medications which started and stopped prior to the first dose of study drug.

- Concomitant medications will include medications taken any time from the start of the first dose of study drug through 30 days following end of study drug administration or until the start of a subsequent anticancer therapy, whichever is earlier. Medications that started prior to the first dose of study drug but continued into treatment are considered both concomitant and prior.

For partial start dates, assume the earliest possible date (i.e., missing day will be set to the first day of the month and missing month will be set to January). For partial end dates, assume the latest possible date (i.e., missing day will be set to the last day of the month and missing month will be set to December). A completely missing start date will be assumed to have started prior to the first dose, and a completely missing end date will be assumed to have ended after the first dose.

3.9 Study Drug Exposure and Compliance

Study drug exposure and compliance will be summarized and listed for the Safety population.

3.9.1 Exposure to Study Treatment

The following summaries of study drug exposure will be presented:

- Duration of exposure (weeks) = [(last dose date of tazemetostat – first dose date of tazemetostat) + 1]/7. Except for the first and last dose dates, this calculation is not adjusted for periods where dosing is interrupted or dose is recorded as 0.
- Total number of cycles of study drug categorized as follows:
  - Cycle 1 (Days 1-28; weeks 1-4)
  - Cycle 2 (Days 29-56; weeks 5-8)
  - Cycle 3 (Days 57-84; weeks 9-12)
  - Cycle 4 (Days 85-112; weeks 13-16)
  - Cycle 5 (Days 113-140; weeks 17-20)
  - Cycle 6 (Days 141-168; weeks 21-24)
  - Cycle 7 (Days 169-196; weeks 25-28)
  - Cycle 8 or more (Day 197 and beyond; week 29 and beyond)
- Total amount of study drug taken (mg)

- Average dose intensity (mg BID/day) where the average dose intensity (mg BID/day) = total amount of study drug taken (mg) / [2 * duration of exposure (days)]
- Numbers of subjects requiring dose reductions, treatment interruption or treatment discontinuation in response to AEs (based on action taken for reported AEs).

Duration of exposure for prednisolone exposure (cohort 6) will be summarized similarly.

3.9.2 Study Drug Compliance

The following summaries of study drug compliance will be presented:

- Percentage of study drug taken = 100% * Average dose intensity (mg BID/day) / 800 mg BID/day.
- Category of percentage of study drug taken (using categories ≥ 90%, 80% to < 90%, 70% to < 80%, and < 70%).

3.10 Efficacy Analyses

All efficacy analyses will be performed only for the FL subject and will be summarized by cohort (WT and MT subjects – only the first 45 subjects per agreement with the Regulatory agency) and overall for the ITT population. The primary analysis of the primary and secondary endpoints will be performed using the IRC response assessments. The investigator response assessments will be analyzed as supportive evidence.

The analyses of the primary and secondary endpoints by IRC and investigator will be repeated for the subgroups defined in Section 3.2.2.

No statistical hypothesis testing for comparison between cohorts will be performed. The issue of statistical multiplicity will not apply to this study, therefore, all analyses will be conducted at the nominal 2-sided alpha 0.05 significance level.

3.10.1 Primary Efficacy Endpoint

Objective response rate (ORR; complete response or partial response [CR or PR])) from the IRC review will be summarized and listed for patients with FL in the ITT population. Evaluation of response for the subjects with FL will be based on IWG-NHL (Cheson, 2007) response criteria.

ORR is defined as the percentage of subjects achieving a CR or PR out of the total number of subjects included in the analysis population. The CR or PR must occur

prior to PD and the start of any subsequent anticancer therapy. Subjects with not evaluable, unknown or missing best response will be handled as non-responders; i.e. they will be included in the denominator when calculating the ORR.

The summaries of ORR will include number and percentage of subjects in each best overall response (BOR) category: Complete response (CR), Partial response (PR), Stable disease (SD), Progressive disease (PD), and Not Evaluable, Missing, or Unknown.

ORR will also be presented with corresponding 2-sided Clopper–Pearson exact 95% confidence intervals (CIs) for each FL cohort and overall.

A plot of the maximum percent tumor reduction from baseline in target lesions for each subject will be provided by cohort. Each plot will be color coded for best overall response.

Forest plots will present the ORR and 95% CI by subgroups.

3.10.2 Secondary Efficacy Endpoints

3.10.2.1 Duration of Response

For each subject with a response, duration of response (DOR) is defined as the time (in months) from the date of first response (CR or PR, whichever is first recorded) to objectively documented disease progression according to the IRC review or death whichever comes first. For patients with a response and no subsequent objectively documented disease progression according to the IRC review or death, censoring rules for DOR will be same as for those PFS as detailed in Table 3. The number (%) of subjects with events and censored, as well the reason for censoring will be provided. DOR will be estimated using the Kaplan-Meier method. Median DOR, first and third quartiles and the associated 2-sided 95% CIs will be estimated using the Brookmeyer-Crowley method will be presented for each FL cohort and overall. Figures displaying Kaplan-Meier curves of DOR by FL cohort will be provided. Kaplan-Meier estimates and 95% CIs will be presented at 6, 12 and 18 months. Forest plots will present the median DOR and 95% CI by subgroups. In addition, the number and percentage of subjects with duration of response ≥ 6, ≥ 12, and ≥ 18 months will be presented. A listing of DOR will be provided.

3.10.2.2 Progression-Free Survival

PFS is defined as the time from the date of first dose of study drug to the date of first documentation of disease progression, or death, whichever occurs first and will be presented based on IRC assessments. Subjects that do not die or progress on study

will be censored at the last adequate assessment. Subjects who do not die on study and who do not have a baseline tumor assessment or at least one post-baseline tumor assessment will be censored at the first treatment day. Subjects who begin a new cancer therapy before documented progression will be censored at the date of the last adequate tumor assessment prior to the new cancer therapy, and subjects who progress or die immediately after one missed tumor assessment will be censored at the last adequate assessment prior to the missed assessment (See Table 3 for full details on PFS censoring). Then number (%) of subjects with events and censored, as well as the reason for censoring will be provided. PFS will be estimated using the Kaplan-Meier method. Median PFS, first and third quartiles and 2-sided 95% CIs, will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982) for each FL cohort and overall. Figures displaying Kaplan-Meier curves of PFS by FL cohort will be provided. Kaplan-Meier estimates and 95% CIs will be presented at 6, 12, 18, and 24 months. Forest plots will present the median PFS and 95% CI by subgroups. A listing of PFS will also be provided.

Table 3 Assignments for Progression and Censoring Dates for DOR and PFS Analysis

Situation	Date of Event (PD/Death) or Censoring	Outcome: Event (PD/Death) or Censored
No *(or inadequate)* baseline tumor assessments and the subject has not died	Date of Study Day 1	Censored
No post-baseline assessments and the subject has not died	Date of Study Day 1	Censored
No post-baseline disease assessments and death occurred prior to the first planned assessment	Date of death	Event
Progression documented between scheduled visits	Date of assessment of progression[1]	Event
No progression (or death) and no new anticancer treatment documented	Date of last 'adequate' assessment of response[2]	Censored

Situation	Date of Event (PD/Death) or Censoring	Outcome: Event (PD/Death) or Censored
New anticancer treatment started during study treatment and prior to documented disease progression or death).[3]	Date of last 'adequate' assessment of response[2] on or prior to starting anti-cancer therapy	Censored
New anticancer treatment started after study treatment end and prior to documented disease progression or death).[3]	Date of last 'adequate' assessment of response[2] on or prior to starting anti-cancer therapy	Censored
Death between two planned assessment visits	Date of death	Event
Death or progression after two missed visit (with 2 week window)	Date of last 'adequate' assessment of response[2] prior to missed assessments	Censored
Alive and without documented disease progression	Date of last 'adequate' assessment of response[2]	Censored
No documented disease progression or death and rolled over into Study 501	Date of last 'adequate' assessment of response[2]	Censored

[1] The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non-target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)

[2] An adequate assessment is defined as a radiological assessment where CR, PR, or SD was determined.

[3] If PD and subsequent anti-cancer therapy occur on the same day assume the progression was documented first, e.g., outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of Study Day 1.

3.10.3 Concordance

Concordance of the investigator and IRC assessments for BOR, ORR, and DCR will be summarized by FL cohorts and for all FL subjects.

3.10.4 Exploratory Efficacy Endpoints

3.10.4.1 Overall Survival (OS)

Overall survival is the duration (in months) measured from the date of first dose of study drug until the date of death from any cause. Subjects who do not die will be censored at the time of the last contact. The Kaplan-Meier estimate of the 25th percentile, median, and 75th percentile, of survival times will be presented with the corresponding 2-sided 95% CIs for each of the FL cohorts and overall.

Figures displaying Kaplan-Meier curves of overall survival by FL cohort and overall will be provided.

The analyses for OS will be repeated for the subgroups defined in Section 3.2.2.

Forest plots will present the median OS time and 95% CI by subgroups.

3.10.4.2 Disease Control Rate (DCR)

DCR at the specified time point (month 12, month 18, and month 24) is defined as the percentage of subjects who achieve either confirmed CR or PR of any duration or who have SD lasting at least the number of month indicated from the start of study drug, according to the IWG-NHL (Cheson, 2007). Subjects with a best response of unknown/non-evaluable response will be handled as not achieving disease control, i.e., they will be included in the denominator when calculating the percentage. Subjects with a time point response of unknown/non-evaluable response on or before the specified time point will still be classified as having disease control as long as there is a response of CR, PR, or SD on or after the specified time point. Disease control rate will be analyzed and summarized in the same manner as ORR. Forest plots will present DCR and 95% CI by subgroups.

3.10.4.3 Time to First Response

For each subject with a response, the time to first response (months) is defined as time from the date of the first dose of study drug until the date of first response (CR or PR, whichever is first recorded). Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented for time to first response.

3.10.4.4 Time to First Subsequent Therapy (TFST)

TFST is defined as the time from the date of first dose of study drug to the date of start of the first subsequent anticancer therapy and will be summarized only for patients who started subsequent anticancer. Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented for TFST

3.11 Safety Analysis

Safety analyses will be performed on the Safety population by FL (WT, MT and overall), by DLBCL and by combined FL and DLBCL.

3.11.1 Adverse Events

The AE verbatim description (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Adverse events will be coded to the MedDRA lower level term closest to the verbatim term, the associated preferred term (PT) and primary system organ class (SOC). AEs will be graded by severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A treatment-emergent AE (TEAE) is defined as an AE that:

- Emerges during treatment, having been absent at Baseline
- Reemerges during treatment, having been present at Baseline but stopped before treatment, or
- Worsens in severity during treatment relative to baseline, when the AE is continuous.

If there are missing or partial AE start and/or end dates that prevent the AE as being classified as a TEAE, the following imputation rules will be applied:

1. If partial start date imputed to earliest possible date (i.e., missing day set to the first day of the month and missing month set to January) is on or after first dose date, then classify as a TEAE.
2. If partial start date imputed to latest possible date (i.e., missing day set to the last day of the month and missing month set to December) is before first dose date, then classify as not a TEAE.
3. If partial stop date imputed to latest possible date (i.e., missing day set to the last day of the month and missing month set to December) is before first dose date, then classify as not a TEAE.
4. Otherwise, assume the event was a TEAE.

Only those AEs that are treatment-emergent and had a start date within the earlier of 30 days following study drug discontinuation or initiation of subsequent anticancer therapy will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Each summary table will include the incidence (number and percentage) of subjects reporting any TEAE, as well as, by SOC and PT. A subject will be counted once within an SOC, even if the subject experienced more than one TEAE within a specific SOC (likewise for PT).

Investigator assessed causality to study drug will be categorized as "not related," "possibly related," or "probably related". For summary purposes, treatment-related TEAEs will include events with relationship to study drug classified as "possibly related" or "probably related". A TEAE with a missing causality will be classified as "possibly related" to study drug. A subject will be counted once at the strongest causality within a SOC and/or PT.

Deaths due to progressive disease were not to be recorded in the AE CRF page for the study. Thus, fatal AEs (i.e., Grade 5 events) will be not be included in TEAE summaries but will be summarized in the summary of deaths.

Events with a missing grade will not be summarized in "by grade" tables. In "by grade" tables, events will be summarized by Grade 3, Grade 4 and Grade 3 or 4. A subject will be counted once at the worst severity grade within a SOC and/or PT.

Adverse events of special interest (AESI) include T-LBL/T-ALL and MDS/AML/MPN and will be assessed by Sponsor pre-defined MedDRA PTs.

AEs will be summarized with a separate table for each of the following:

- TEAEs
- TEAEs of grade 3 or 4
- Treatment-related TEAEs
- Treatment-related TEAEs of grade 3 or 4
- TEAEs leading to dose interruption
- TEAEs leading to dose reduction
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal from study

- Serious adverse events (SAEs)
- Treatment-related SAEs
- AESIs

Deaths

- Summary and listing of subjects who died ≤30 days after last dose of study drug
  - Any AE (by MedDRA preferred Term)
  - Any treatment related TEAE
  - Progressive Disease
  - Disease under Study
  - Unknown/Other causes
- Summary and listing of subjects who died ≤ 30 days after last dose of study drug with treatment-related TEAEs
- Summary and listing of subjects who died > 30 days after the last dose of study drug with treatment-related AEs

Listings of all AEs, SAEs, AESIs, and TEAEs leading to discontinuation of study drug.

3.11.2 Clinical Laboratory Evaluation

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters, the actual value and the change from baseline to each post baseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit using descriptive statistics. The summaries will include all laboratory parameters included in

Table 4.

In addition, creatinine clearance will be calculated by the Cockcroft-Gault formula. For males the creatinine clearance in mL/min will be calculated as (140-age) × weight (kg)/[serum creatinine (mg/dL) × 72]. For females, the creatinine clearance in

mL/min will be calculated as 0.85 × (140-age) × weight (kg)/[serum creatinine (mg/dL) × 72].

Laboratory values that are reported as 'below the detectable limit' of an assay will be analyzed as half the detectable limit when required for analysis purposes but listed as originally reported. The following summaries will be provided for laboratory data:

- For parameters graded by NCI CTCAE, shift from baseline grade to worst post-baseline grade based on NCI CTCAE v4.03). For laboratory tests with both low and high values, summaries will be provided separately.
- For parameters not graded by NCI CTCAE, shift from baseline to worst post-baseline value that is < 0.25 x LLN or > 2.5 x ULN.

For subjects with a post-baseline parameter that is grade 3 or higher (per NCI CTCAE), all values for that parameter will be listed. Similarly, for parameters not gradable by NCI CTCAE for subjects with a post-baseline parameter value that is < 0.25 x LLN or > 2.5 x ULN, all values for that parameter will be listed.

Table 4 Laboratory Parameters

Category	Parameter
Hematology	• Hematocrit • Hemoglobin • Red blood cell count (RBC) • Platelet count • White blood cell count (WBC) • Differentials (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	• Bicarbonate • Chloride • Potassium • Sodium
Liver Function	• Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Total bilirubin
Renal Function	• Blood urea or blood urea nitrogen (BUN) • Creatinine
Other	• Albumin • Amylase • Calcium • Cholesterol • Creatine phosphokinase (CPK)

	• Glucose • International Normalized Ratio (INR) • Lactate dehydrogenase (LDH) • Phosphorous • Total protein • Triglycerides • Uric acid

3.11.3 Vital Signs and Other Physical Findings

Weight (kg) as well as vital signs for sitting systolic blood pressure (mmHg), sitting diastolic blood pressure (mmHg), sitting heart rate (bpm), sitting respiratory rate (breaths/min), and temperature (^{0}C) will be collected and listed. Summaries of heart rate, temperature, systolic blood pressure, and diastolic blood pressure will be based on markedly abnormal criteria defined below:

Table 5 Marked Abnormal Vital Signs Criteria

Vital Sign	**Markedly Abnormal Criteria**
Heart rate (bpm)	< 60 bpm > 100 bpm
Temperature (^{0}C)	≤ 35 ^{0}C ≥ 38 ^{0}C
Systolic blood pressure (mmHg)	120-139 mmHg, inclusive (CTCAE grade 1) 140–159 mm Hg, inclusive (CTCAE grade 2) ≥ 160 mmHg (CTCAE Grade 3)
Diastolic blood pressure (mmHg)	80–89 mmHg, inclusive (CTCAE grade 1) 90–99 mm Hg, inclusive (CTCAE grade 2) ≥ 100 mmHg (CTCAE grade 3)

Incidence of markedly abnormal worst-case values will be presented. For heart rate and temperature, both high and low values will be presented separately such that subjects can be counted in both categories. Markedly abnormal vital sign values will be flagged as such on a vital signs listing.

3.11.4 ECG

Electrocardiogram assessments will be performed as specified in the Schedule of Assessments. Time-matched, central-read ECGs were performed to evaluate RR, PR, QRS, QT intervals, QTc, QTc Fridercia (QTcF), QTc Bazett (QTcB), and heart rate (HR) at various time points throughout the study. All 12-lead ECG data will be listed, and changes from baseline will be summarized using descriptive statistics. When triplicates are collected, the averages (as calculated by the central ECG vendor) will be used in the summaries. The number and percentage of subjects with abnormal ECG findings at each visit will be reported.

The following summaries will be provided for 12-lead ECG assessments listed above:

- Quantitative 12-lead ECG measurements: values and changes from baseline (and changes from pre dose) by planned visit
- Investigator overall interpretation of the ECG: counts and percentages of subjects for each category
- Quantitative 12-lead ECG: Shift from baseline to worst post-baseline in QTcF status categorized as markedly abnormal or not (defined in the table below)
- Quantitative 12-lead ECG measurements: Counts and percentages of subjects whose worst-case changes from baseline in QTcF measurements meet markedly abnormal criteria (described in the table below).

Table 6 Markedly Abnormal ECG Criteria

QTcF Measure	Markedly Abnormal Criteria
Observed	450–480 msec, inclusive [CTCAE grade 1] 481–500 msec, inclusive [CTCAE grade 2] > 500 msec [CTCAE grade 3 or higher]
Change from Baseline	31–60 msec, inclusive, increase from baseline >60 msec increase from baseline

3.11.5 MUGA Scans and Echocardiograms

The results of MUGA scans and echocardiograms at baseline and post-baseline visits will be listed along with the type of assessment (MUGA or echocardiogram).

3.11.6 Concurrent Nonpharmacological Procedures and Palliative Radiotherapy

Concurrent nonpharmacological anticancer procedures noted during survival follow up and palliative radiotherapy will be summarized and listed.

The number and percentage of subjects with anticancer procedures noted during survival follow up and reason for the procedure (pre-existing condition, AE, or other) will be summarized. The incidence (number and percentage) of subjects undergoing each anticancer procedure will also be summarized by MedDRA HLGT and PT.

The number and percentage of subjects receiving concurrent palliative radiotherapy will be summarized overall and by site of palliative radiotherapy.

3.12 CHANGES TO ANALYSES FROM PROTOCOL

- The primary analysis of the primary and secondary efficacy endpoints is based on the data assessed by IRC, which was requested by regulatory agency. As a result, concordance analysis was added.
- TEAEs with a missing causality will be assumed to be “possibly related” to study drug.
- Time to first response analysis was added.
- Disease control rate added as an exploratory endpoint.
- Time to First Response is added as an exploratory endpoint.
- Time to first subsequent therapy is added as an exploratory endpoint.
- Section 7.6.1.4 of the protocol indicates that laboratory parameters will be summarized descriptively as actual value and change from baseline, as well as, shifts from baseline (based on low, normal, high categorization) at each visit. To allow for more focused presentation of values most likely to represent a safety concern, laboratory parameters will be summarized as shift from the baseline to the worst post-baseline severity (based on National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] severity grades). When an NCI CTCAE category is undefined for a parameter, a multiple of the nearer normal limit will be used.

- The Full Analysis Set is relabeled as the Intent-to-Treat (ITT) population. Other analysis sets are relabeled as the corresponding populations.
- For vital signs, Section 7.6.1.4 of the protocol specifies summarizing the values and change from baseline for each vital sign by visit. The analysis of vital signs specified in the SAP will only present the number of subjects that have markedly abnormal vital signs as defined in Section 3.11.3 of the SAP.
- For ECGs, markedly abnormal definitions have been added to the SAP, and the number of subjects meeting the markedly abnormal criteria will be summarized.
- A summary of concurrent nonpharmacological anticancer procedures and palliative radiotherapy has been added to track other anticancer therapies given after the first dose of study drug for subjects.

4 References

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Green S and Dahlberg S. Planned versus attained design in Phase II Clinical Trials. *Statistics and Medicine.* 1992 Vol II:853-862.

5 Appendix

Appendix 1 Schedule of Visits and Procedures: Phase 2 (All Visits Starting at Cycle 1 Day 15 Have ± 3-Day Window)

Period	**Screening[a]**	**Cycles 1 and 2**		**Cycle 3 and Beyond**		**Off-Treatment[b]**	**Follow-up[c]**
Day	**-28 to -1**	**1 (± 3days)**	**15 (± 3days)**	**1 (± 3days)**	**15[d] (± 3days)**		
Procedures/Assessments							
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history	X						
Prior and concomitant medications	Throughout study						
Comprehensive physical examination	X					X	
Symptom directed physical exam		X	X	X			
Pregnancy test[e]	X	X		X			
Body weight	X	X	X	X		X	
Height	X						
Vital signs[f]	X	X	X	X		X	
ECOG performance status	X	X		X		X	
12-lead ECGs[g]	X	X		X		X	
Hematology	X	X	X	X		X	

Appendix 1 Schedule of Visits and Procedures: Phase 2 (All Visits Starting at Cycle 1 Day 15 Have ± 3-Day Window)

Period	**Screening[a]**	**Cycles 1 and 2**		**Cycle 3 and Beyond**		**Off-Treatment[b]**	**Follow-up[c]**
Day	**-28 to -1**	**1 (± 3days)**	**15 (± 3days)**	**1 (± 3days)**	**15[d] (± 3days)**		
Procedures/Assessments							
Blood chemistry	X	X	X	X	X	X	
Genomic DNA[h]							
PK blood samples[i]		X[i]	X[i]				
PD blood samples[j]		X[j]	X[j]				
PD blood sample for nucleic acid[k]		X		X		X	
Sufficient tumor tissue available[l]	X						
Paired tumor biopsies[m]		X					
Optional tumor biopsy at DP[n]						X	
Tumor assessments: CT (MRI), and assessments of B symptoms[o]	X	Radiologic tumor assessments (IWG-NHL [Cheson 2007] criteria) **must be performed every 8 weeks during Cycles 2-6, and every 12 weeks starting at Cycle 7 and beyond**				X	X
CT or MRI of the brain[p]	Brain scans should be performed if clinically indicated.						
Bone marrow biopsy (with IHC)[q]	X	At first notation of CR if bone marrow involvement at Screening, and if clinically indicated (eg, suspicion of relapse or progressive disease)					
^{18}FDG-PET scan[r]	X	Performed at first notation of possible PR or CR					

Appendix 1 Schedule of Visits and Procedures: Phase 2 (All Visits Starting at Cycle 1 Day 15 Have ± 3-Day Window)

Period	Screening[a]	Cycles 1 and 2		Cycle 3 and Beyond		Off-Treatment[b]	Follow-up[c]
Day	**-28 to -1**	**1 (± 3days)**	**15 (± 3days)**	**1 (± 3days)**	**15[d] (± 3days)**		
Procedures/Assessments							
AEs/SAEs	Throughout study						
EPZ-6438 administration[e]		Continuous 28-day cycle of EPZ-6438 twice daily. EPZ-6438 can be taken with or without food.					
Survival status and subsequent anticancer therapy						X	X

AE = adverse event, β-hCG = beta-human chorionic gonadotropin, BP = blood pressure, CR = complete response, CT = computed tomography, DLBCL = diffuse large B cell lymphoma, DNA = deoxyribonucleic acid, DP = disease progression, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EZH2 = enhancer of zeste homolog 2, ^{18}FDG-PET = ^{18}fluorodeoxyglucose-positron emission tomography, FL = follicular lymphoma, HR = heart rate, IHC = immunohistochemistry, IWG-NHL = International Working Group-Non-Hodgkin's Lymphoma, MRI = magnetic resonance imaging, PD = pharmacodynamic, PK = pharmacokinetic, SAE = serious adverse event.

a. The Screening Period extends from Day -28 to Day -1, except for signing of the informed consent form, which may be up to 8 weeks before the first dose of study drug. Screening laboratory assessments may be used as Day 1 assessments if performed within 72 hours of the first dose of study treatment, however subjects must continue to meet eligibility criteria prior to first dose of tazemetostat on Cycle 1 Day 1. The screening assessments (except tumor assessment) must be performed within 28 days before the first dose of study drug. Tumor assessment must occur within 28 days for CT or MRI or photographs.

b. Off-treatment assessment may occur at time of treatment discontinuation (e.g., at the visit at which the decision to discontinue treatment occurs) or up to 30 days after the final dose of study drug. AE and concomitant medication data must be collected for 30 days after the final dose of study drug, or until the start of new therapy. This may occur prior to 30 days if new therapy is started within 30 days of last dose of study drug. If subject is unable to return to the clinic for assessment of AEs this may be done by telephone.

c. Survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent. Information on all anticancer therapies will be collected (the sponsor may choose to stop the collection of therapies after the first anticancer treatment following EPZ-6438). This may be done by telephone contact.

d. **Starting at Cycle 3, a Day 15 visit is not required**. On Day 15 of each cycle, subjects will have hematology and blood chemistry samples drawn at a local laboratory and telephone contact with the site to review AEs.

e. A serum pregnancy test (β-hCG) will be performed at Screening for all women of childbearing potential. A urine or serum pregnancy test will be performed predose on Day 1 of each cycle starting at Cycle 2.

f. Vital signs include BP, HR and body temperature. BP and HR will be collected after the subject has been sitting for 5 minutes.

g. 12-Lead ECGs will be collected at the following time points: Screening (triplicate), Cycles 1 and 2 Day 1 (predose and **0.5 – 2 hours post dose immediately before PK sample**), Day 1 of all subsequent cycles (before and after morning dose of study drug administration), and at the Off-Treatment Visit. In case of any alteration or if clinically necessary an echocardiogram and/or cardiac enzymes should be performed.

h. Genomic DNA samples will be collected predose at Screening. If it cannot be collected at the designated time point, it may be collected at a time point after baseline.

i. Blood samples for PK analysis will be collected in Cycle 1 on Day 1 at 0.5 to 2 hours and 3 to 6 hours and Day 15 at predose (0 hours), 0.5 to 2 hours, and 3 to 6 hours; and Cycle 2 on Day 1 at predose (0 hours), 0.5 to 2 hours, and 3 to 6 hours. Blood samples should be collected on the day after Day 28 of Cycle 1, irrespective of start of Cycle 2.

j. Blood samples for PD analysis will be collected at the following time points: Predose (0 hours) on Cycle 1 Days 1 and 15; and Predose (0 h) on Cycle 2 Day 1. Blood samples should be collected on the day after Day 28 of Cycle 1, irrespective of the start of Cycle 2.

k. Blood samples for nucleic acid analysis will be collected at the following time points: Predose (0 hours) on Cycle 1 Day 1, and Day 1 of every other cycle, and at the off-treatment visit.

l. Subjects will have collection of archived, tumor-biopsy sections for central testing of EZH2 mutation status (all subjects) and confirmation of cell of origin for DLBCL subjects.

m. Paired tumor biopsies (DLBCL cohorts) and/or bone marrow biopsies (FL cohorts) are optional and may be obtained, with appropriate subject consent, from at least 4 to 6 subjects per cohort to examine tissue target inhibition, relevant PD biomarkers, and potential markers of response. Subjects should have the biopsy before administration of the first dose of EPZ-6438 and the second biopsy at the time of first disease assessment. If sufficient tumor exists from archival, this could be considered the predose sample.

n. Tumor biopsy is to be requested, where medically feasible, at disease progression in subjects who achieve a PR or better with EPZ-6438.

o. Tumor assessments include CT scan of the chest, CT or MRI of the neck, abdomen, pelvis, and other areas of known disease or newly suspected disease and should be performed between Day -28 and Day -14 and every 8 weeks, irrespective of treatment delays, during Cycles 1 to 6, and every 12 weeks during Cycle 7 and beyond. If local regulatory authorities mandate less frequent imaging, minimum frequency must be every 12 weeks. The same parameters as the screening scans should be used. A standard-of-care clinical examination for lymphoma, including assessment of B symptoms, will also be performed at each visit.

p. CT or MRI of the brain should be performed if clinically indicated.

q. A bone marrow biopsy (including IHC) will be performed between Day -28 and Day -4, unless there is a report of bone marrow negative for lymphoma involvement within 42 days before administration of the first dose of study drug. At the first notation of CR, a repeat bone marrow biopsy should be performed if lymphoma involvement in the bone marrow was reported at Screening.

r. ^{18}FDG-PET scan should be performed at Screening and at the first notation of possible PR or CR.

s. On visit days, subjects should not take study drug before evaluations are performed.