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APPLICATION NUMBER:

213400Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	New Drug Application (NDA)
Application Number(s)	213400
Priority or Standard	Priority
Submit Date(s)	18 December 2019
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PDUFA Goal Date	18 June 2019
Division/Office	DHM2/OOD
Review Completion Date	16 June 2020
Established/Proper Name	Tazemetostat
(Proposed) Trade Name	Tazverik
Pharmacologic Class	Methyltransferase inhibitor
Code name	EPZ-6438, E7438
Applicant	Epizyme, Inc.
Dosage form	Tablets, 200mg
Applicant proposed Dosing Regimen	800 mg orally twice daily
Applicant Proposed Indication(s)/Population(s)	Indicated for the treatment of patients with relapsed or refractory follicular lymphoma who have received at least two prior therapies
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Follicular Lymphoma
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	▪ Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior therapies ▪ Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Follicular Lymphoma
Recommended Dosing Regimen	800 mg orally twice daily

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Reviewers of Multi-Disciplinary Review and Evaluation

Nonclinical Reviewer	Shwu-Luan Lee
Nonclinical Team Leader	Brenda Gehrke
Office of Clinical Pharmacology Reviewer(s)	Ruby Leong
Office of Clinical Pharmacology Team Leader(s)	Ruby Leong
Pharmacometrics Reviewer	Liang Li
Pharmacometrics Team Leader	Lian Mam
Genomics Reviewer	Sarah Dorff
Genomics Team Leader	Rosane Charlab Orbach
Clinical Reviewer	Margret Merino
Clinical Team Leader	Nicholas Richardson
Statistical Reviewer	Xu, Qing
Statistical Team Leader	Yu-te Wu
Cross-Disciplinary Team Leader	Nicholas Richardson
Division Director (OCP)	Brian Booth
Division Director (OOD)	Nicole Gormley
Office Director (or designated signatory authority)	Nicole Gormley

Additional Reviewers of Application

OPQ	Olen Stephens
OPDP	Emily Dvorsky, Susannah O'Donnell
PLT	Rjuth Mayrosh/Barbara Fuller
OSI	Anthony Orencia, Min Lu, Kassa Ayalew
OSE/DEPI	Fang Tian, Richard Swain, Simone Pinheiro
OSE/DMEPA	Nicole Iverson, Hina Mehta
OSE/DRISK	Brad Moriyama, Naomia Boston
OSE/DPV	Michelle Nadeau-Nguyen, Afrouz Nayerama
Associate Director for Safety	Shaily Arora
Associate Director for Labeling	Stacy Shord
Other - CDRH	Fengmin Li, Donna Roscoe
Regulatory Project Managers	Thomas Iype, Felicia Diggs, Neil Vora, Shamika Brooks

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
PLT=Patient Labeling Team
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPV=Division of Pharmacovigilance
CDRH= Center for Device and Radiological Health

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulation
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	Complete Response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CNG	Copy Number Gain
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
EZH2	Enhancer zeste homolog 2
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FL	Follicular Lymphoma
GCP	good clinical practice
GRMP	good review management practice
H3K27	histone 3 lysine 27
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities

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mITT	modified intent to treat
MT	mutant
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
ORR	Overall Response Rate
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	Polymerase chain reaction
PR	Partial Response
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PRC2	Polycomb repressive complex 2
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SNV	single nucleotide variant
SOC	standard of care
TEAE	treatment emergent adverse event
WT	wild type

1 Executive Summary

1.1. Product Introduction

On December 18th, 2019, Epizyme submitted NDA 213400 under 21 CFR 314.50 and section 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act, seeking accelerated approval of tazemetostat tablets (200 mg) for the following proposed indication:

The treatment of patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies.

The Applicant is requesting accelerated approval under Subpart H.

Tazemetostat is an orally administered small molecule inhibitor of the methyltransferase enhancer of zest homolog 2 (EZH2), which plays a role in B cell development via silencing genes responsible for limiting B-cell proliferation and exit from the germinal center. EZH2 is the catalytic subunit of the multi-protein polycomb repressive complex 2 (PRC2) that catalyzes the mono, di, and trimethylation of histone 3 lysine 27 (H3K27). The recommended dose of tazemetostat is 800 mg twice daily (BID), administered continuously in 28-day cycles until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval of tazemetostat for:

- The treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior therapies.
- The treatment of adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

The recommended dose is 800 mg orally twice daily.

This recommendation is based on efficacy findings from two follicular lymphoma cohorts of the E7438-G000-101 study and safety data from a larger B-cell lymphoma population from study E7438-G000-101 that included patients with both follicular lymphoma and diffuse large B-Cell lymphoma (DLBCL). The E7438-G000-101 study is a multicenter, open-label trial that included 99 patients with relapsed or refractory (R/R) follicular lymphoma (FL) who had received at least 2 prior systemic therapies. Patient enrollment was based on EZH2 mutation status. Mutations were identified by local testing and confirmed centrally by the cobas® EZH2 mutation test, which is designed to detect the following mutations: Y646X [S,H,C], Y646F, Y646N, A682G, and

A692V. Of the 99 patients with FL, 45 patients had an EZH2 mutation (EZH2 mutant) and 54 patients did not have one of the identified EZH2 mutations (EZH2 wild-type). Patients received tazemetostat 800 mg orally twice daily until confirmed disease progression or unacceptable toxicity or up to 24 months. Response assessments were performed every 8 weeks through Week 24 and then every 12 weeks. The primary efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) according to the International Working Group Non-Hodgkin Lymphoma (IWG-NHL) criteria (Cheson et al. 2007) as assessed by Independent Review Committee (IRC).

The efficacy of tazemetostat was based upon 95 patients (42 EZH2 mutant, 53 EZH2 wild-type) who had received at least 2 prior systemic therapies.

In cohort 4 (EZH2 mutant FL) of study E7438-G000-101, all 42 patients received prior anti-CD20 therapy, 81% received an anthracycline, 49% were refractory to rituximab, 49% were refractory to their last therapy, and 9% had a prior stem cell transplant. The median number of prior therapies was 2 (range 2 to 11). The ORR per IRC for the 42 patients was 69% (95% CI: 53%, 82%). The median duration of response was 10.9 (7.2, NE) by Kaplan-Meier estimate, with 61% of patients with at least 6 months of response. Thus, the data support the determination that tazemetostat has clinically meaningful activity in patients with relapsed or refractory FL with an EZH2 mutation who have received at least 2 prior systemic therapies.

In cohort 5 (EZH2 wild-type FL) of study E7438-G000-101, all 53 patients received prior anti-CD20 therapy, 91% received an anthracycline, 59% were refractory to rituximab, 41% were refractory to their last therapy, and 39% had a prior stem cell transplant. The median number of prior therapies was 3 (range 2 to 8). The ORR per IRC for the 53 patients was 34% (95% CI: 22%, 48%). The median duration of response was 13 months (5.6, NE) by Kaplan-Meier estimate, with 51% of the patients remaining in response at 6 months.

For patients with relapsed or refractory FL with EZH2 wild-type who have received at least 2 prior therapies, the recommended indication is restricted to patients with no satisfactory alternative treatment options. The ORR of 34% with a lower bound of the confidence interval of 22% provides evidence of uncertainty regarding the clinical benefit of tazemetostat in these patients. Additional considerations include the limited sample size of 53 patients, the prior therapies received were not consistent with the therapies administered in a representative U.S. population, and no U.S. patients were enrolled in this cohort. Further, the efficacy data needs to be taken into consideration in the context of available therapy in the 2nd line setting and beyond. Available therapy includes anti-CD20 therapy (i.e., rituximab and obinutuzumab) as a single agent and in combination, bendamustine monotherapy and in combination, and immunotherapy combinations such as rituximab plus lenalidomide (Table 3). In the 3rd line setting and beyond, consistent with the EZH2 wild-type population enrolled, the ORRs for these approved and available therapies, including single-agent and combinations, range from 57% to 80% with associated durability (Table 5). Therefore, there is residual uncertainty regarding the benefit of tazemetostat in patients with EZH2 wild-type FL who have received at least 2 prior

systemic therapies, which warrants restriction of the indication to a patient population with no satisfactory alternative treatment options where the benefit-risk balance is favorable.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Tazemetostat is an inhibitor of Enhancer zeste homolog 2 (EZH2), a catalytic component of the polycomb repressive complex 2 (PRC2) which plays a role as a negative regulator of genes required to control lymphoid proliferation. Inhibition of EZH2 is proposed to restore normal repression in B-cell proliferation, differentiation, and migration.

Efficacy:

Efficacy of tazemetostat in patients with relapsed or refractory (R/R) follicular lymphoma (FL) is based on the results of two cohorts from a single, multicenter, open-label trial (E7438-G000-101) that included 99 patients with FL who had received at least 2 prior systemic therapies. Patient enrollment was based on EZH2 mutation status. Mutations were identified by local testing and confirmed centrally by the cobas® EZH2 mutation test, which is designed to detect the following mutations: Y646X [S,H,C], Y646F, Y646N, A682G, and A692V. Of the 99 patients with FL, 45 patients had an EZH2 mutation (EZH2 mutant) and 54 patients did not have one of the identified EZH2 mutations (EZH2 wild-type). Patients received tazemetostat 800 mg twice daily continuously until disease progression, unacceptable toxicity or up to 24 months. Tumor response was assessed per Independent Review Committee using the 2007 International Working Group Non-Hodgkin Lymphoma criteria. The efficacy of tazemetostat was based upon 95 patients (42 EZH2 mutant, 53 EZH2 wild-type) who had received at least 2 prior systemic therapies. For patients with EZH2 mutant FL, the overall response rate (ORR) was 69% [95% confidence interval (CI): 53%, 82%] with a median duration of response of 10.9 months. For patients with EZH2 wild-type FL, the ORR was 34% (95% CI: 22%, 48%) with a median duration of response of 13 months. In both FL cohorts, the majority of responses were partial responses.

Safety:

Tazemetostat demonstrated an acceptable safety profile for the intended patient population. The safety profile was supported by analysis of the 99 patients with follicular lymphoma and a combined safety database of 333 patients with B cell malignancies (patients with follicular lymphoma and diffuse large B cell lymphoma) who received tazemetostat 800 mg twice daily. In patients with R/R FL, the median duration of treatment was 11.5 months (range, 2.8 to 26 months) and the most common adverse reactions (≥20% of patients) were fatigue, upper respiratory infection, musculoskeletal pain, nausea and abdominal pain. Hematologic laboratory abnormalities of any grade occurring in ≥ 20% of patients were thrombocytopenia (50%), anemia (50%), and neutropenia (20%). Serious adverse reactions occurred in 30% of patients and no fatal adverse reactions occurred. Dose discontinuations due to any adverse reactions were reported in 8% of patients, most often due to second primary malignancy.

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Second primary malignancies were identified as an event of clinical interest based on preclinical findings, and data from other clinical studies in solid tumors. In the patients with FL, one patient developed acute myeloid leukemia and one developed myelodysplastic syndrome. Both patients had extensive prior chemotherapy and had prolonged exposure to tazemetostat at the time of the diagnosis of the second malignancy.

Benefit-Risk:

Tazemetostat has an overall favorable benefit-risk in patients with relapsed or refractory follicular lymphoma; however, the benefit-risk determination was considered for each FL cohort separately in the context of available therapy to support an accelerated approval. For patients with EZH2 mutant FL, the median number of prior therapies was 2 and 49% were refractory to rituximab. Therefore, the ORR of 69% with associated durability and a tolerable safety profile constitutes a meaningful clinical benefit and a favorable benefit-risk for these patients. For patients with EZH2 wild-type FL, the median number of prior therapies was 3 and 59% were refractory to rituximab. The ORR of 34% (95% CI: 22%, 48%) with associated durability in 53 patients warrants additional consideration in the context of available therapy in the 2nd line setting and beyond. Available therapy includes anti-CD20 therapy (i.e., rituximab and obinutuzumab) as a single agent and in combination, bendamustine monotherapy and in combination, and immunotherapy combinations such as rituximab plus lenalidomide. In the 3rd line setting and beyond, consistent with the EZH2 wild-type FL population enrolled, the ORRs for these therapies, including single-agent and combinations, ranges from 57% to 80% with associated durability. Further, the patients with EZH2 wild-type FL did not receive prior therapies consistent with the therapies administered in a representative U.S. population and no U.S. patients were enrolled in this cohort. Taking into consideration, the ORR of 34% with a lower bound of the confidence interval of 22%, the small sample size, the overall generalizability to the U.S. patient population, and available therapies in a comparable treatment setting, the review team felt that the residual uncertainty regarding the benefit of tazemetostat in these patients warrants restriction of the indication to patients with R/R FL who have no satisfactory alternative treatment options. Therefore, the benefit-risk of tazemetostat is deemed favorable to support accelerated approval under 21 CFR 314.510 Subpart H for the following indications:

- For the treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least two prior systemic therapies.
- For the treatment of adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Follicular Lymphoma (FL) is considered incurable, and relapse is nearly universal. - With successive treatment regimens for relapsed or refractory disease, response rates and response duration tend to diminish. Patients with symptoms continue to receive treatment repeatedly until fatal resistant disease occurs. - Relapsed and refractory follicular lymphoma is a heterogenous disease and may have an indolent course - Early relapse from first treatment, refractory disease and transformed lymphoma are associated with a poor prognosis - Approximately 20% of patients with follicular lymphoma have tumors that have a gain of function mutation of EZH2 which is associated with an increased sensitivity to EZH2 inhibition as a therapeutic modality	Relapsed and refractory follicular Lymphoma is a serious and life-threatening disease
Current Treatment Options	- Treatment options for relapsed and refractory FL include chemotherapy, immunochemotherapy, and anti-CD20 monoclonal antibodies. - Numerous patients with relapsed or refractory FL cannot tolerate intensive chemotherapy due to age or comorbidities. - Approved chemoimmunotherapy and immunotherapy combinations have response rates of 55%-80% in the 2nd line setting and beyond, including 57%-79% in the 3rd and 4th line setting, which includes patients with rituximab refractory disease.	New treatments are needed for patients with relapsed or refractory FL, including chemotherapy-free treatments. Treatment options should be considered in the context of prior therapies and patient comorbidities

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	• Tazemetostat was administered orally twice daily • Study E7438-G000-101 was a single-arm, phase 1/2 trial that included 99 patients with FL with FL who had received at least two prior therapies across two cohorts, determined by EZH2 mutation status. • ORR per IRC was 69% (95% CI: 53%, 82%) with a median duration of response of 10.9 months in a cohort of 42 patients who had tumors that contained an EZH2 mutation that was detected by the cobas[®] assay. • ORR by IRC was 34% (22%, 48%) with a median duration of response of 13 months in a cohort of 53 patients where an EZH2 mutation was not detected (EZH2 wild-type).	Based on ORR with durability in a single-arm trial, tazemetostat has clinically meaningful activity in patients with relapsed or refractory FL whose tumors are positive for an EZH2 mutation who have received at least 2 prior systemic therapies and patients with relapsed or refractory FL who have no satisfactory alternative treatment options.
<u>Risk and Risk Management</u>	• Of 99 patients with follicular lymphoma treated with tazemetostat 800 mg twice daily: ○ No patient had a fatal adverse reaction. ○ 30% experienced a serious reaction and 39% experienced a grade 3 or 4 toxicity, there was no specific safety issue that predominated ○ 9% discontinued tazemetostat due to an adverse reaction. ○ The most common adverse reactions (≥20% of patients) were fatigue, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and cytopenias • Two patients with follicular lymphoma developed a second primary malignancy (AML and MDS)	• The safety profile of tazemetostat is acceptable in the intended patient population • Second Primary Malignancies are a serious adverse reaction associated with tazemetostat require further evaluation which will be included as a postmarketing requirement.

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable [e.g., Section 6.1 Study endpoints]
☐	Clinical outcome assessment (COA) data, such as	
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	

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☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☒	Patient experience data was not submitted as part of this application.	

X

Cross Discipline Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Follicular Lymphoma is the second most common subtype of non-Hodgkin's lymphoma (NHL), with an estimated 13,960 new cases diagnosed in 2016 in the United States. The median age of diagnosis is 63 years old with approximately 15% of patients 75 years old or older at diagnosis (Teras et al. 2016. SEER-21 (2013-2017 database). The Incidence is highest among whites (80%) and lowest among blacks (4%) (Luminari, 2012; Nabhan, 2014). Patients with FL typically present with waxing and waning asymptomatic peripheral adenopathy. Bone marrow involvement occurs in 50% to 70% of patients (Freedman 2015; Luminari et al. 2012). FL is characterized by an indolent clinical course, with a 10 year survival in the post rituximab era of 64-92%, depending on age, but the majority of patients have advanced stage disease at diagnosis (Freedman, 2018). The follicular lymphoma prognostic index (FLIPI) and tumor grade have prognostic implications for newly diagnosed patients. The FLIPI-1 criteria are displayed below (Folal-Celigny, 2004, NCCN guidelines 2020):

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Age $\geq 60y$
 Ann Arbor Stage III-IV
 Hemoglobin Level $< 12g/dL$
 Serum LDH level $> ULN$
 Number of nodal sites ≥ 4

Patients with intermediate risk (2 risk factors) or high risk (3 or more risk factors) have a 2-year PFS of 70% and 42% respectively. (Freedman, 2018)

First line therapy generally consists of anti-CD-20 based therapy either as monotherapy or in combination with chemotherapy although due to the variability of presentation and patient factors, initial treatment can range from observation to stem cell transplant. Criteria for treatment include symptomatic nodal disease, organ involvement leading to functional impairment, and cytopenias. Responses rates to initial therapy are high, but response is followed by frequent relapses and shorter durations of response to subsequent treatments (Rivas-Delgado, 2017). A subset of patients (approximately 20%) have a more aggressive course. Patients with refractory or relapsed FL within 2 years of first-line therapy have a 5-year overall survival of 50% (range 40% to 59%) (Byrtek 2013, Casulo 2015). Suboptimal response to chemoimmunotherapy as well as transformation to aggressive B-cell lymphoma is also associated with a worse prognosis. There is a 2-3% risk each year of histologic transformation to aggressive B-cell lymphoma, which is associated with rapidly enlarging adenopathy, organomegaly, cytopenias, and elevated LDH.

Virtually all patients with FL eventually relapse after initial therapy. Patients with relapsed disease suffer from complications related to adenopathy, organ involvement and cytopenias, as well as from toxicity from prior chemotherapy. There are a number of options for patients with relapsed disease and treatment decisions take into consideration, comorbidities, symptomatic disease, as well as prior therapy. Treatment can consist of re-treatment with prior anti-CD20 monoclonal antibodies, chemoimmunotherapy combinations, radioimmunotherapy, and HSCT (Freeman 2018, NCCN Guidelines 2020)

Evolving knowledge in pathogenesis of follicular lymphoma has resulted in greater understanding of the heterogeneity of the disease. Follicular Lymphoma arises from malignant germinal center B-cells. A number of

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genetic abnormalities are associated with follicular lymphoma to include the translocation t(14; 18) as well as mutations in genes with epigenetic functions (Morin, 2011). The role that genetic abnormalities play in the prognosis and treatment of follicular lymphoma is an area on ongoing research (Pastore, 2015). Enhancer of zeste homolog 2 (EZH2) is a component of the polycomb repressive complex 2 and is overexpressed in many cancers and plays an important role in lymphoid cell development and function (Su, 2002, Margueron, 2011). In normal hematopoiesis, EZH2, by playing a role in mono, di and trimethylation of histone 3 at lysine 27 (H3k27), promotes B cell proliferation and egress from the germinal center. Trimethylation of histone H3 on lysine 27 (H3K27me3) is a repressive posttranslational modification. Repression of this gene silencing mechanism mediated by EZH2 results in B cell proliferation. In follicular lymphomas, EZH2 can be altered through somatic mutations resulting in gain of function and hypermethylation of H3k27. (McCabe, 2012). Approximately 25% of follicular lymphomas have been reported to have a mutation involving EZH2 resulting in a gain of function. The most common mutations of EZH2 reported in patients with follicular lymphoma are at Y646, A682, and A692. (Bodor, 2013). These mutations results in a gain of function via hypermethylation of EZH2 which subsequently results in down-regulation of repression which can result in lymphoid proliferation (Yap, 2011). Targeting and inhibiting EZH2 has been reported to result in decreased cell growth. In addition to single nucleotide variant (SNV) mutations, approximately 25% of patients with follicular lymphoma have been reported to have copy number gain (CNG) of EZH2 (Huet, 2017). The clinical significance of CNG and its role in response or lack of response to EZH2 inhibition remains unclear.

2.2. Analysis of Current Treatment Options

Treatment for patients with advanced stage FL ranges from observation to hematopoietic stem cell transplantation (HSCT). Patients with asymptomatic, advanced stage FL do not require immediate treatment and can be observed. Patients with symptomatic nodal disease, extranodal disease, B symptoms, cytopenias, and end organ dysfunction require treatment. The GELF criteria (listed below) are a commonly accepted set of clinical symptoms that warrant treatment.

The Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria are a set of clinical and laboratory criteria considered to determine if treatment is warranted (Brice, 1997, Solal-Celigny, 1998). GELF criteria include:

- Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm

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- Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes $< 1.0 \times 10^9/L$ and/or platelets $< 100 \times 10^9/L$)
- Leukemia ($> 5.0 \times 10^9/L$ malignant cells)

First-line therapy typically consists of rituximab monotherapy or combination chemotherapy plus rituximab (Martinelli et al. 2010;). Treatment of patients with refractory or relapsed FL can consist of rituximab monotherapy, combination chemotherapy plus anti-CD20 therapy, radioimmunotherapy, and HSCT (Matasar, 2019, Freedman 2018). Follicular lymphoma largely remains incurable and new therapies and approaches are still needed.

The choice of treatment for patients with relapsed and refractory is highly dependent on the patient and disease characteristics and depends on prior therapies and the duration and quality of initial response. There is no standard accepted therapy for patients who have received at least two prior therapies although several regimens have either regular or accelerated approval as detailed in the table below.

There are currently five agents with regular FDA approval and three agents with accelerated approval for the treatment of patients with relapsed or refractory FL or other low-grade non-Hodgkin lymphomas (NHLs). There are several agents with regular approval or that are considered accepted therapy for patients with relapsed refractory follicular lymphoma in the third line and greater setting. The three agents under accelerated approval for patients with at least two prior therapies include idelalisib, the first-in-class PI3K inhibitor, and copanlisib and duvelisib, next-in-class PI3K inhibitors. Agents with accelerated approval are not considered to be available therapy because clinical benefit is yet to be confirmed. The indications relevant to this FL application are listed in the table below.

Table 1: FDA-Approved Drugs for Patients with Relapsed and Refractory FL and Indolent Forms of NHL

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Agent	Year of Initial Approval	Type of Approval	Excerpted Relevant Indication(s)	Efficacy Data Supporting Approval
Rituximab	1997	Regular	Single Agent: - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent. Combination: - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy. - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with (cyclophosphamide, doxorubicin, vincristine, and prednisone) (CHOP) or other anthracycline-based chemotherapy regimens.	ORR 36% - 57%
⁹⁰ Y-ibritumomab tiuxetan	2002	Regular	Treatment of patients with relapsed or refractory, low-grade or follicular B-cell NHL, and previously untreated follicular NHL who achieve partial or complete response to first-line chemotherapy	ORR 74%
Bendamustine	2008	Regular	Indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen	ORR 74% CR 13%

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Agent	Year of Initial Approval	Type of Approval	Excerpted Relevant Indication(s)	Efficacy Data Supporting Approval
				ORR 75% on control arm of GADOLIN study
Obinutuzumab	2013	Regular	In combination with bendamustine followed by obinutuzumab monotherapy, for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen	ORR 78% CR 16% GADOLIN study
Idelalisib	2014	Accelerated Approval	Treatment of patients with relapsed follicular B-cell NHL in patients who have received at least two prior systemic therapies	ORR 54% CR 8%
Copanlisib	2017	Accelerated Approval	Treatment of adult patients with relapsed FL who have received at least two prior systemic therapies	ORR 59% CR 14%
Rituximab and hyaluronidase	2017	Regular	Treatment of adult patients with FL: • Relapsed or refractory FL as a single agent • Previously untreated FL in combination with chemotherapy and as single-agent maintenance therapy • Nonprogressing FL as a single-agent after first-line CVP chemotherapy	ORR 84% (previously untreated FL in combination with chemotherapy)
Duvelisib	2018	Accelerated Approval	Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies.	ORR 42% CR 1%

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Agent	Year of Initial Approval	Type of Approval	Excerpted Relevant Indication(s)	Efficacy Data Supporting Approval
Lenalidomide plus Rituximab (R ²)	2019	Regular	Previously treated follicular lymphoma (FL), in combination with a rituximab product	AUGMENT PFS benefit HR XX compared to rituximab plus Placebo ORR 80% Rituximab + Lenalidomide ORR 55% rituximab + placebo MAGNIFY ORR 59% CR 15%

Abbreviations: CR, complete response; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate

Source: FDA table, created from review of drug labeling

There are a number of chemotherapy agents or combinations (including some that are not FDA approved) that are used in the relapsed and refractory setting and are included in current guidelines.

Table 2: Agents and Combination Regimens Commonly Used for Patients with Relapsed and Refractory Follicular Lymphoma

Drug or Regimen
Bendamustine ± rituximab
Bendamustine + obinutuzumab
Chlorambucil ± rituximab

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Drug or Regimen
Cyclophosphamide ± rituximab
Lenalidomide
Obinutuzumab
Obinutuzumab or Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP or G-CHOP)
Rituximab or obinutuzumab + cyclophosphamide + vincristine + prednisone (CVP)

Source NCCN Guidelines B-Cell Lymphomas v1.2020

Radiation therapy, radioimmunotherapy, HSCT, CAR-T cell therapies and observation are other considerations.

In summary, overall response rates to available therapies, including those under accelerated approval, in patients with previously treated follicular lymphoma range from 36% to 80%. A summary and comparison with a description of the study populations of FDA approved therapies for relapsed and refractory follicular lymphoma are displayed in Table 3 and Table 4 below.

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Table 3: Summary of Efficacy from Trials Supporting FDA Approved Therapies for Relapsed or Refractory Follicular Lymphoma (Regular Approval)

Therapy Number of Patients	Monotherapy				Combination therapy		
	Rituximab N = 147 Control arm AUGMENT	Rituximab N = 296	Obinutuzumab N = 40	Bendamustine N = 166 (control arm GADOLIN)	Bendamustine + Obinutuzumab (GADOLIN) N = 155	Lenalidomide + Rituximab	
						MAGNIFY N = 177	AUGMENT N = 147
Population	1 prior	R/R low grade NHL or FL (3 studies)	R/R NHL	≥ 1 prior Rituximab refractory	≥ 1 prior Rituximab refractory	1 prior	1 prior
ORR 95% CI	55% (47,64)	36*-57% * retreatment	55% (32, 76)	75% (67, 81)	78% (72,84)	59% (51, 66)	80% (72,86)
CR	20%	6-14%	23%	19%	16%	15% CRu 20%	35%
Median DOR	15 mo (11, 25)	6.9-15 mo	Not reported	11.6 mo	NR	NE 80% ≥ 12 mo	36 mo (25, NE)

Source: USPIs for Rituximab, Obinutuzumab, Lenalidomide

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Table 4: Summary of Efficacy from Trials Supporting FDA Approved Therapies for Relapsed and Refractory Follicular Lymphoma (Accelerated Approval)

	Copanlisib N = 104	Duvelisib N = 83	Idelalisib N = 72
Population	2 prior therapies	1 prior therapy Rituximab refractory Excluded 3b and patients with prior transplant	2 prior therapies Refractory to rituximab and an alkylating agent
Prior Tx Median Range	3 (2,8)	3 (1,10)	4 (2, 12)
Rituximab Refractory	57%	100%	100%
ORR 95% CI	59% (49, 68)	42% (31, 54)	54% (42,66)
CR	14%	1%	8%
Median DOR	12.2 (0+, 23)	NE 17% ≥ 12 mo	NE (0,+ 14.8+)

Source: USPI for Copanlisib, Duvelisib, and Idelalisib

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To further evaluate the data for available therapies in patients with relapsed or refractory follicular lymphoma, the FDA performed a subanalysis evaluating the response rate in patients with at least 2 or 3 prior therapies and is summarized in the table below.

Table 5: FDA Subanalysis of Efficacy from Trials Supporting FDA Approved Therapies for Relapsed or Refractory Follicular Lymphoma After at Least 2 or 3 Prior Therapies (Regular Approval)

Trial	MAGNIFY Rituximab + Lenalidomide		AUGMENT Rituximab + Lenalidomide		GADOLIN Bendamustine + Obinutuzumab (BO) vs. Bendamustine (B)	
	N = 115	N = 74	N = 67	N = 44	N = 79 BO N = 94 B	N = 30 BO N = 36 B
Prior therapies	≥2	≥ 3	≥2	≥ 3	≥2	≥ 3
Median Prior Tx Range	3 (2,10)	4 (3,10)	3 (2,12)	3 (3,12)	2 (2,10)	3 (3,10)
Rituximab Refractory	47%	45%	0	0	100%	
ORR 95% CI	57% (48, 66)	59% (47, 70)	81% (69, 89)	80% (64, 90)	BO: 75% (63, 84) B: 79% (69, 86)	BO: 70% (50, 85) B: 75% (57, 87)

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Trial	MAGNIFY Rituximab + Lenalidomide		AUGMENT Rituximab + Lenalidomide		GADOLIN Bendamustine + Obinutuzumab (BO) vs. Bendamustine (B)	
	N = 115	N = 74	N = 67	N = 44	N = 79 BO N = 94 B	N = 30 BO N = 36 B
CR	13%	11%	34%	32%	BO: 20% B: 20%	BO: 27% B: 19%
DOR Median (Range)	5.1 (2.3, 8.5)	NR (8.8, *)	NR (19.6, -)	NR (19.3, -)	BO: NR (19.5, -) B: 13 (8.9, 16.8)	BO: 26.4 (20.4, -) B: 13.2 (7, -)
Abbreviations: CR, complete response; DOR; duration of response; NR, not reached; ORR, overall response rate						

Source: FDA analysis from efficacy datasets

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Tazemetostat received accelerated approved (NDA 211723) on January 23, 2020 for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection. Tazemetostat is not marketed in any other country.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 6: Summary of Regulatory Activity Tazemetostat in Lymphoma

Date /Sponsor	Event Summary
17 November 2014	Pre-IND meeting to reach agreement on the acceptability of the current E7438 nonclinical and clinical data to support the initiation of clinical studies in patients with tumors characterized by INI1 deficiency (including a pediatric study), as well as a phase 2 study in B-cell NHL
23 December 2015	IND 124025 was activated and opened in the United States.
23 October 2015	Type B, PIND meeting to reach agreement on the acceptability of data to support initiation of a clinical study for the treatment of patients with DLBCL or FL who have failed at least two prior therapies
13 January 2017	Type C meeting, written response providing advice regarding the acceptability of allowing the inclusion of US patients with FL in the ongoing arm of E7438-F000-101 regarding a registration study in indolent NHL and use of symptom-related endpoint.
01 March 2017	Fast track designation was granted for the treatment of patients with relapsed and refractory follicular lymphoma. Development program includes additional PK and DDI studies, NCI Molecular Analysis for Therapeutic Choice (MATCH), continued evaluation of expansion

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Date /Sponsor	Event Summary
	cohorts in phase 1/2 study, and a potential randomized study in combination with chemotherapy or chemoimmunotherapy backbone
06 September 2017	Orphan drug designation granted for treatment of patients with follicular lymphoma.
21 November 2017	WRO meeting to gain Agency's agreement on the proposed data collection and reporting plan to investigate therapeutic outcome of FL patients with or without EZH2-activating mutations in order to place into context the observed tazemetostat Phase 2 response data in FL patients with tumors containing EZH2-activating mutations.
20 April 2018	IND 124025 was placed on Partial Clinical Hold – after report of T-LBL in 9-year-old receiving tazemetostat on study EZH102
19 September 2018	Partial Clinical Hold removed for IND 124025 after Sponsor's response was reviewed and considered acceptable.
3 January 2019	Type B, EOP2 Pre-NDA meeting to discuss proposed registrational strategy to an accelerated approval submission for the treatment of patients with R/R FL and to discuss the proposed confirmatory trial. Division advised that companion diagnostic for EZH2 mutation status may be warranted and recommendation communication with CDRH. Agency advised further exploration to the impact of EZH2 copy number gain (CNG) on efficacy in the wild-type FL population. The Agency recommended that there be at least 12 months of follow up for all responders.
23 May 2019	NDA 211723 for the treatment of patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for (b) (4) was submitted to the FDA
25 July 2019	CDRH pre submission teleconference to seek advice from the Agency on the proposed strategy to interrogate the role of EZH2 CNG in the FL EZH2 WT patient population and whether those changes correlate with response to tazemetostat.

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Date /Sponsor	Event Summary
31 July 2019	Type B EOP2: Discuss and gain agreement with the Agency on the overall design of the proposed phase 3 study, EZH-302.
18 October 2019	RMS pre-submission meeting feedback on the clinical validation study and to propose the following dates for a teleconference meeting to discuss the content of this pre-submission.
16 September 2019	Type C meeting: WRO to gain agreement on statistical design for proposed phase 3 confirmatory study
28 October 2019	Type B, Pre-NDA meeting advising on the submission of a single-arm trial, the safety analysis, and additional technical aspects of the NDA submission. Agreement on planned PMA submission timeline.
18 December 2019	NDA submission complete
23 January 2020	NDA 211723 for the treatment of adult and pediatric patients 16 years and older with metastatic or locally advanced epithelioid sarcoma who are not eligible for complete resection (accelerated approval).
31 January 2020	Applicant Orientation Meeting at White Oak
5 May 2020	TCON with the Sponsor to discuss plan to limit indication to patient with EZH2 mutations as detected by cobas® assay
27 May 2020	Sponsor TCON to present to Agency rationale for request for approval for both WT and EZH2 mutated population.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical site inspections were requested for one U.S. and one foreign site. The Office of Scientific Investigations conducted inspections at one U.S. site, site #8006 and the Applicant. The inspection of the foreign site did not occur due to restrictions with the COVID-19 pandemic.

The inspection of site #8006, Dr. Tycel Phillips, Ann Arbor Michigan, which enrolled 4 patients, included review of source documents for study eligibility, informed consent, Institutional Review Board (IRB) review/approval, monitoring, test article accountability, concomitant medication, delegation of authority, primary efficacy endpoint, and adverse event/serious adverse event reporting. In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

The Applicant, Epizyme, Inc. was also inspected. The inspection included review of organizational charts, vendor oversight, transfer of obligations, investigator agreements, financial disclosures, monitoring plans, monitoring reports, monitor qualifications, safety reports, adverse events, protocol deviations, and standard operating procedures. Monitoring Reports principally for Site 1003 (Franck Morschhauser, M.D.), Site 1004 (Gilles Salles, M.D.) and Site 2003 (Aristeidis Chaidos, M.D.) were selected and reviewed. No underreporting of significant adverse events to the Agency was noted. A Form FDA 483 was not issued at the end of the study inspection. In general, the Applicant appeared to be in compliance with Good Clinical Practice. Clinical trial oversight and monitoring by the Applicant appeared to be adequate.

The COVID-19 global pandemic limited the ability to conduct on-site Good Clinical Practice (GCP) inspections. Following discussions between OSI and DHM2, the need to conduct inspection of Dr. Franck Morschhauser in

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Nord, France was revisited, and it was determined that assessment of this application could proceed without this inspection. Accordingly, this inspection was cancelled.

4.2. Product Quality

There is no new product quality information included in this supplemental NDA. All manufacturing and labeling sites are adequate and there are no pending issues from product quality for this application.

4.3. Clinical Microbiology

There are no issues from a microbiology standpoint. The drug product is a solid oral dosage form

(b) (4)

(b) (4)

4.4. Devices and Companion Diagnostic Issues

The Applicant proposed a broad indication for patients with relapsed or refractory follicular lymphoma who have received at least 2 prior therapies regardless of EZH2 mutation status. In study E7438-G000-101, the presence or absence of EZH2 mutations (EZH2 MT) was determined by local laboratory testing and subsequently evaluated centrally with the cobas® assay from formalin fixed paraffin embedded tumor tissue. Study participants whose tumor possessed a mutation of EZH2 as determined by the cobas® assay were enrolled in cohort 4 and those that did not possess a mutation were enrolled in cohort 5, considered wild-type follicular lymphoma. The cobas® assay is a real-time allelic specific polymerase chain reaction (PCR) that detects single nucleotide variant (SNV) mutations within codon 646 (Y646F, Y646N, Y646X (H,S,C)), 682 (A682G), and 692 (A692V). These mutations occur within the catalytic domain of the EZH2 protein resulting in high levels of methylation of Histone 3 on lysine 27. The Applicant proposed

(b) (4)

(b) (4)

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(b) (4)

The applicant submitted PMA 200014 for the Roche Molecular Systems, Inc cobas® EZH2 Mutation Test. Per CDRH, the data in the PMA application supports the reasonable assurance of safety and effectiveness of cobas® EZH2 Mutation Test when used in accordance with the indications for use. The results of the Method Comparison (Accuracy) Study support the intended use of the cobas EZH2 Test for diagnostic purposes as an aid in the clinical management of patients with FL eligible for treatment with tazemetostat.

Indication For Use:

The cobas® EZH2 Mutation Test is a real-time allele-specific PCR test for qualitative detection of single nucleotide mutations for Y646N, Y646F or Y646X (Y646H, Y646S, or Y646C), A682G, and A692V of the EZH2 gene in DNA extracted from formalin fixed paraffin embedded (FFPE) human follicular lymphoma tumor tissue specimens. The cobas® EZH2 Mutation Test is intended for the identification of follicular lymphoma patients with an EZH2 mutation for treatment with TAZVERIK™ tazemetostat, an EZH2 inhibitor.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Pharmacology/Toxicology data supporting the approval and labeling of tazemetostat has been reviewed under NDA 211723. The Tazverik (tazemetostat) prescribing information (label) contains the relevant nonclinical data needed for prescribing. For the current NDA, pharmacology information related to the proposed indication of relapsed/refractory follicular lymphoma has been reviewed.

Follicular lymphoma (FL) is presented as a germinal centre B-cell lymphoma. Germinal centres (GCs) are transient structures that form within peripheral lymphoid organs in response to T-cell-dependent antigen. Within GCs, B cells expressing high-affinity

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antibodies develop and differentiate into antibody-secreting plasma cells and memory B cells that mediate and sustain protection against invading pathogens¹. Enhancer of zeste homolog 2 (EZH2) is highly expressed in GC B cells². EZH2 is the catalytic subunit of the histone methyltransferase (HMT) complex (also known as polycomb repressive complex 2; PRC2) with the following 4 proteins constituting the core: EZH2, EED (embryonic ectoderm development), SUZ12 (suppressor of zeste 12) and RBAP48 (retinoblastoma-binding protein p48)³. The proposed function of PRC2 is to catalyze the methylation of lysine 27 of histone H3 (H3K27). Trimethylated H3K27 (H3K27me3)⁴ is associated with the repression of genes important for differentiation. One of the critical roles of EZH2 is to repress gene expression programs that would otherwise limit their proliferation and promote exit from the germinal center, such as differentiation genes, cell cycle regulators, and apoptotic machinery². Once B cells receive signals to exit the germinal center, the repressive effect of EZH2 is released, allowing its target genes to be re-expressed and terminal differentiation to proceed. Thus, EZH2 is required for the formation of GCs and immunoglobulin affinity maturation; this function is dependent on its histone methyltransferase activity.

The pathobiology of GC B-cell lymphomas is complex and combines broad somatic changes at the level of both the genome and the epigenome. Epigenetic modification includes highly recurrent mutations in chromatin-modifying genes, affecting histone methyltransferases, histone acetyltransferases or histone linker proteins, with several epigenetic modifiers including EZH2, lysine (K)-specific methyltransferase 2D (KMT2D), CREB binding protein (CREBBP), and E1A binding protein p300 (EP300 or histone acetyltransferase p300). Epigenetic modification is also accompanied with alterations of

¹ DeSilva and Klein, Nature Reviews Immunology 13: 137-148, 2015.

² Beguelin et al., Cancer Cell 23: 677-692, 2013.

³ Copeland, Clin Cancer Res, 19(23): 6344-6350, 2013.

⁴ Kuzmichev et al., Genes Dev. 16(22): 2893-2905, 2002.

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a number of key cellular pathways including BCL6, mTOR, TNFRSF14, and JAK-STAT¹. EZH2 regulates histone function via trimethylation of H3K27, and plays a pivotal role in the epigenetically regulated tumorigenesis pathway of GC B cells. EZH2 mutations occur frequently. Heterozygous activating mutations at the EZH2 enzymatic domain lead to aberrant accumulation of H3K27me3⁵ and sustained repression of differentiation and cell cycle regulatory genes, as well as genes involved in immune recognition⁶. Consequently, impairment of the ability of GC B cells to properly respond to GC exit signals from the immune system drive aberrantly persistent proliferation and the accumulation of malignant GC B-cells². Research data indicate that the accumulated malignant GC B cells naturally retain their EZH2 dependency. Overexpressed or mutated EZH2 is thus implicated in the oncogenesis of GC B-cell lymphomas, including FL and GCB-type diffused large B-cell lymphoma (DLBCL).

Human EZH2 may contain several gain of function (GOF) mutations in the catalytic domain. The mutants lead to aberrant repression of target genes and the induction of stem cell like programs and oncogenic transformation. Epigenomic and transcriptional profiling in mouse models and human patients indicate that in the presence of mutant-type (MT) EZH2, genes that are usually induced upon germinal center exit become functionally irreversibly silenced, likely due to spreading of the H3K27me3 at these loci. Nevertheless, EZH2 inhibition in both MT and wild-type (WT) backgrounds is proposed to lead to increased B-cell maturation and a greater dependence on B-cell activation signaling.

Although both wild type (WT) and mutant (MT) EZH2 are inhibited by EZH2 inhibitors, lymphoma cells with EZH2 mutations manifest a shorter time to maximal growth suppression as compared to WT cells in the laboratory setting. Data obtained from the xenograft murine models also indicated that the tumor growth inhibition (TGI) values were higher in mutant

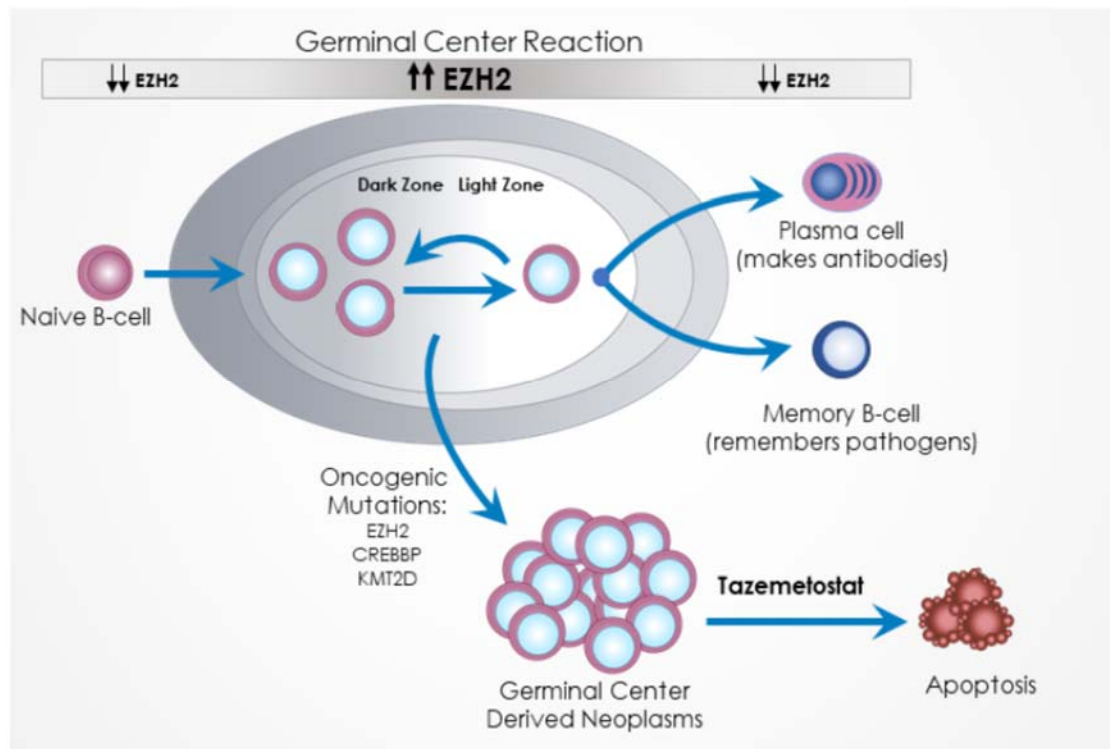
⁵ Yap et al., Blood 117(8): 2451-2459, 2011.

⁶ Ennishi et al., Cancer Discov, 9(4): 546-563, 2019.

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xenografted mice (such as the KARPAS-422 line) treated with tazemetostat than the TGI obtained in WT xenografted mice (such as Toledo).

Figure 1: Germinal Center B-Cell Lymphomas: EZH2 WT and MT Follicular Lymphoma



EZH2 = enhancer of zeste homolog 2; EZH2 MT = enhancer of zeste homolog 2 mutant; EZH2 WT = enhancer of zeste homolog 2 wild-type .

(Figure from the Applicant, Pharmacology Written Summary, Figure 1)

Tazemetostat (EPZ-6438) is an orally bioavailable, *S*-adenosylmethionine-competitive inhibitor of EZH2. The mechanism of action of tazemetostat, i.e., inhibition of H3K27 methylation, has

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been demonstrated in the in vitro and in vivo studies. Based on the review of NDA 211723, in non-cellular biochemical assays, tazemetostat inhibited the activity of wild type human EZH2 with an IC_{50} of 11 nM, which is approximately 17 times lower than the predicted free maximum concentration (C_{max}) of 188 nM tazemetostat in patients treated at the twice daily (BID) oral dose of 800 mg. Tazemetostat inhibited EZH1 with an IC_{50} value of 392 nM, approximately 36 times higher than the IC_{50} for the inhibition of EZH2. Tazemetostat showed concentration-dependent inhibition of H3K27 trimethylation in a panel of human lymphoma cancer cell lines bearing wild type EZH2 or EZH2 mutants (Y641F, Y641N, A677G), with IC_{50} values ranging from 2 to 260 nM.

The pharmacokinetic and pharmacodynamic properties of tazemetostat were determined in mice carrying various human lymphoma xenografts bearing EZH2 mutants (such as KARPAS-422 and WSU-DLCL2). Exposure, target inhibition (H3K27me3 levels) and antitumor activity were determined at several doses following various dosing schedules of tazemetostat alone or in combination with chemotherapy agents (such as cyclophosphamide or CHOP). Orally administered tazemetostat was generally tolerated with durable tumor regression/growth stasis. Dose-dependent tumor growth inhibition (TGI) was observed starting at 4 to 7 days of dosing. Additionally, the combination of tazemetostat with the standard of care regimen cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) resulted in increased TGI in comparison to either regimen/agent alone in EZH2 MT models. Intracellular H3K27 methylation in tumor cells was inhibited concentration-dependently, corresponding with the antitumor activity against xenografts of EZH2 mutant DLBCL. In non-xenograft models, the endogenous H3K27me3 levels were also reduced in peripheral blood mononuclear cells (PBMCs) and tissues (bone marrow, spleen and skin) of rats and monkeys administered tazemetostat. The inhibition was dose-dependent and the bone marrow was the most sensitive tissue.

The pharmacological assessment of metabolites EPZ-034163 (M1), EPZ-6931 (M3) and EPZ-6930 (M5) of tazemetostat were reviewed in NDA 211723. The IC_{50} values of the inhibition of EZH2 or H3K27me3 by the metabolites were in the micromolar (μ M) range, and were much greater than the nanomolar (nM) value by tazemetostat. There were no remarkable off-target

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activities of tazemetostat and no remarkably adverse effects of tazemetostat on vital organ functions.

In the mechanism of action section of the labeling (12. 1) for the current NDA, sentences have been added to mention the activity of tazemetostat in the suppression of proliferation of B-cell lymphoma cell lines in vitro and the antitumor activity in mouse xenograft models of B-cell lymphoma, and that the activity was greater for the cell lines and models with EZH2 mutations. This information supports the mechanism of tazemetostat in the treatment of patients with FL. Other pharmacology-toxicology related sections are remained unchanged.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant cross-references NDA 211723 for the nonclinical data (pharmacology-toxicology and CMC) of tazemetostat to support the current NDA for the indication of relapsed/refractory (R/R) follicular lymphoma (FL).

5.3. Pharmacology

Primary pharmacology

As most of the pharmacology-toxicology data that supported the approval of tazemetostat for the indication of patients (≥ 16 years) with metastatic or locally advanced epithelioid sarcoma (NDA 211723) are cross referenced, only primary pharmacology data to support the proposed indication of relapsed or refractory follicular lymphoma are reviewed in the current NDA submission.

According to the Applicant, nonclinical follicular lymphoma (FL) models are not amenable for use in in vitro or in vivo studies⁷. The xenografts employed in the pharmacology studies are

⁷ Pound and Gordon, Blood, 89(3): 919-928, 1997.

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mostly from human DLBCL cell lines. Such approaches exploit the close resemblance between DLBCL and FL because both are germinal center derived B-cell lymphomas, and EZH2 plays a role in the survival and potentially tumorigenesis of both lymphomas. In FL and DLBCL, EZH2 activating mutations are frequently observed.

In vitro studies

The characterization of tazemetostat in the inhibition of EZH2 activity was reviewed in NDA 211732. The assessment was performed in a panel of wild type EZH1 and EZH2 enzymes, or EZH2 enzymes bearing gain-of-function mutations in the catalytic domain (Y641F, Y641N, Y641S, Y641H, Y641C, A677G, and A687V), and additional histone methyl transferase enzymes (HMTs). The results indicated that tazemetostat was able to inhibit both wild type and mutated human EZH2. The table below contains the in vitro studies reviewed in NDA 211723 and cross-referenced for the current submission.

In vivo studies

Suppression of tumor growth and H3K27 methylation in xenograft murine models

The pharmacokinetic and pharmacodynamic properties of tazemetostat (EPZ-6438) were determined in mice carrying various human lymphoma xenografts bearing EZH2 mutants. Exposure, target inhibition (H3K27me3 levels) and antitumor activity were determined at several doses following various dosing schedules of EPZ-6438 alone or in combination with chemotherapy agents (such as cyclophosphamide or CHOP). Studies conducted in models of KARPAS-422 and WSU-DLCL2 cells (bearing EZH2 Y641N and Y641F mutants, respectively) are reviewed.

KARPAS-422 model

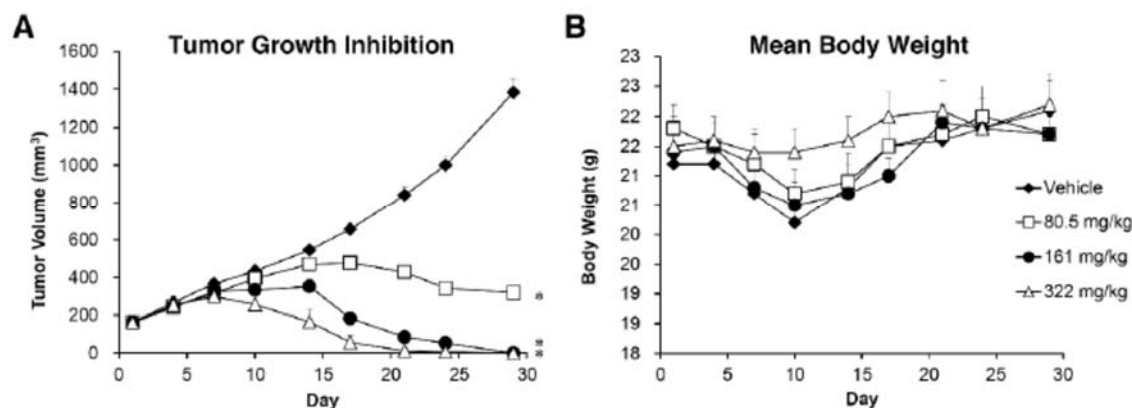
- o Study title: Effects of E7438 on Human Diffuse Large B Cell lymphoma KARPAS-422 xenograft in mice (Study #M11024, Eisai Research Report #W-20120482)
- o Study title: Inhibitory Effects of E7438 against Histone H3 Lysine 27 Trimethylation in Human Diffuse Large B Cell Lymphoma KARPAS-422 Xenograft in Mice (Eisai Research Report #W-20120483)

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The effects of oral tazemetostat against H3K27me3 levels were evaluated in mice inoculated with human diffuse large B cell lymphoma (DLBCL) KARPAS-422 cells bearing a Y641 EZH2 mutation. Female CAnN.Cg-Foxn1nu/CrlCrlj mice (n=9/group) with KARPAS-422 tumors were administered vehicle or tazemetostat at oral doses (80.5, 161, 322 or 644 mg/kg) once daily on Day 1 and Day 29 and twice daily from Day 2 to Day 28. Tumor volumes and body weights were measured twice a week.

Mortality occurred in mice treated with 644 mg/kg (deaths in 2/9 mice); tazemetostat was tolerated at ≤ 322 mg/kg, where no mortality or significant body weight changes were observed. Tazemetostat demonstrated significant dose-dependent antitumor effects against KARPAS-422 xenografts on Day 29. Tumor growth inhibition (TGI) was observed at 80.5 mg/kg and tumor regressions occurred at 161 and 322 mg/kg toward the end of the study (Day 29).

Figure 2: Antitumor Effects of Tazemetostat in KARPAS-422 Xenograft Model



(Figure from the Applicant)

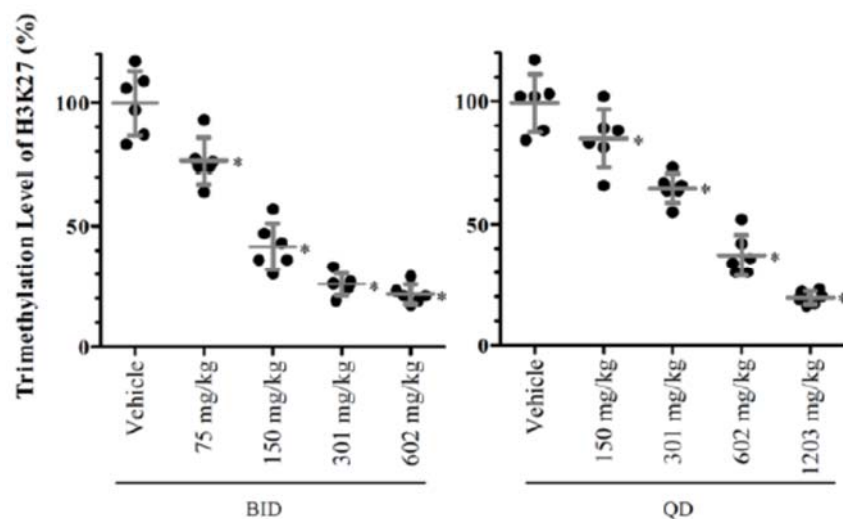
In a separate study employing the KARPAS-422 murine model (Study #W-20120483), the in vivo inhibitory effect of tazemetostat against H3K27me3 levels was evaluated. Mice (n = 6 per group) were orally administered vehicle or tazemetostat (75, 150, 301, or 602 mg/kg twice daily

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or 150, 301, 602, or 1203 mg/kg once daily) for 7 days. Tumors were collected 3 hours after the last dose administered, and H3K27me3 levels were quantified in extracted histones by ELISA.

Tazemetostat induced significant and dose-dependent decreases of H3K27me3 levels in tumors. Twice daily (BID) oral treatment exerted a greater H3K27me3 suppression effect than once daily (QD) treatment.

Figure 3: Reduction in H3K27me3 in Tazemetostat-Treated KARPAS-422 Mice



(Figure from the Applicant)

WSU-DLCL2 model

Study title: In vivo target inhibition by EPZ-6438 in WSU-DLCL2 xenograft tumor bearing mice (Study #E7438-PD001)

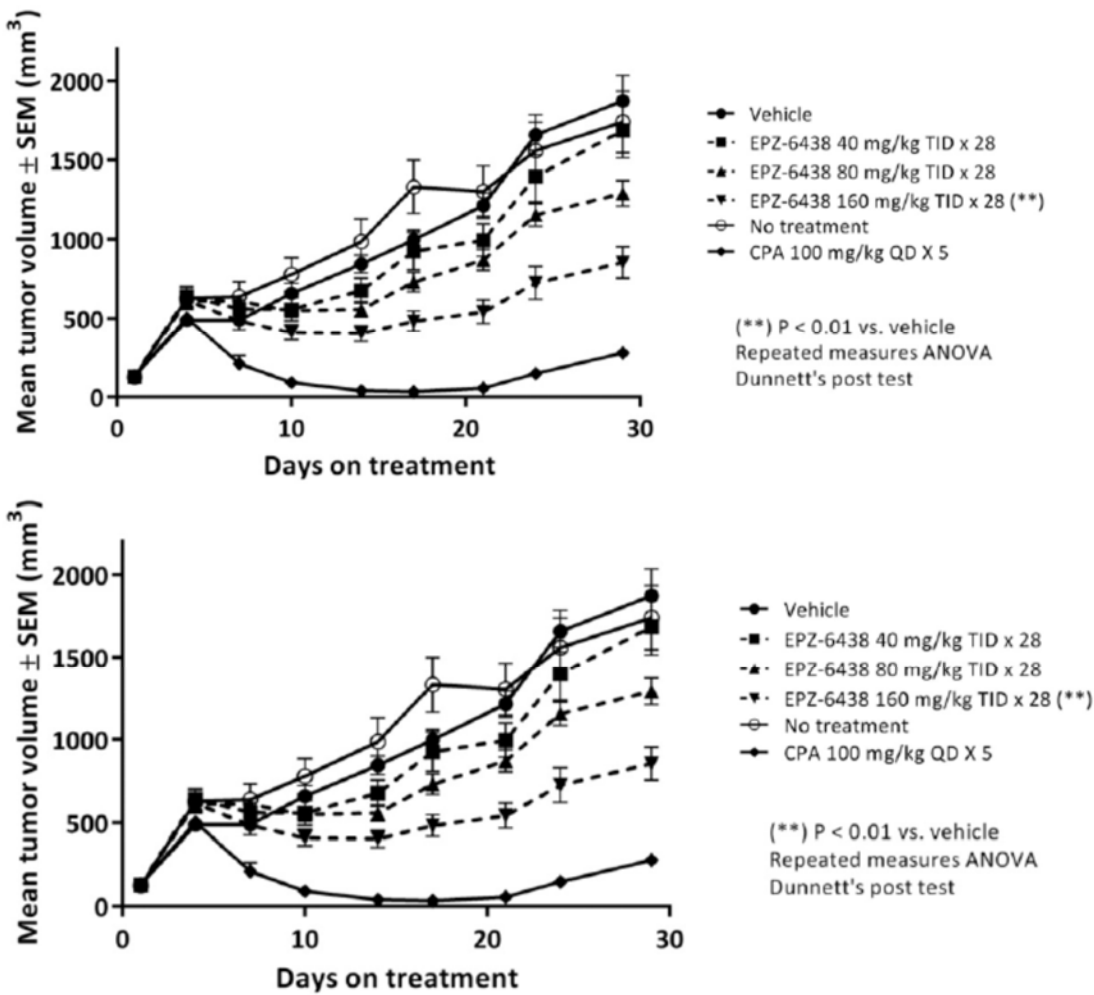
WSU-DLCL2 (DLBCL EZH2 mutant) xenograft tumors were planted in female SCID mice via SC inoculation. The tumor bearing SCID mice (n = 12 per group) were treated for 28 days with increasing doses of tazemetostat (40, 80, or 160 mg/kg; orally 3 times daily [TID]) or vehicle

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control. Two additional groups of mice (n = 6/group) received either no treatment or cyclophosphamide alone (100 mg/kg; intraperitoneal once daily [QD] × 5). Tumor volumes were measured every 3 or 4 days (twice a week) , and measurement of tazemetostat levels in the plasma and tumor homogenates was conducted by LC-MS/MS. Analysis of H3K27 methylation in histones isolated from the tumors was evaluated by ELISA using an anti-H3K27me3 or anti-total H3 antibody. Analysis of H3K27 methylation in fixed skin specimens was evaluated by IHC using an anti-H3K27me3 antibody. In addition, histones from tumors isolated from mice treated with either vehicle or 160 mg/kg TID for 7 days were included in ELISA assays to compare target inhibition on Days 7 and 28.

- All treatments were well tolerated in each group. Tazemetostat treatment induced a dose-dependent reduction in tumor size, with tumor growth inhibition (TGI) of 58% and 73% at the highest dose on Days 1 and 7, respectively. The tumor suppression corresponded with dose-dependent increases in plasma concentration of tazemetostat. The mean plasma exposure was above the lowest cytotoxic concentration level (1652 ng/mL).
- Corresponding with anti-tumor activity, tazemetostat treatment for 28 days resulted in statistically significant lower H3K27me3 levels than treatment for 7 days. Prolonged treatment with tazemetostat increased target inhibition in WSU-DLCL2 tumors. There was no change for H3K27 methylation in skin with 160 mg/kg TID for 7 days.
- High-dose cyclophosphamide treatment resulted in rapid tumor regressions at the beginning of the study but regrowth began by Day 28.

Figure 4: Tazemetostat Suppressed Tumor Growth and H3K27me3 Levels (WSU-DLCL2 Model)



(Figure from the Applicant)

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In a separate experiment, oral doses of tazemetostat were administered QD, BID or TID for 28 days, and the anti-tumor effect was compared. In addition, TGI with these tazemetostat dosing schedules was compared with the CHOP chemotherapy regimen used for non-Hodgkin's lymphoma (NHL), as well as combination therapy with tazemetostat and CHOP. A control group of tumor-bearing mice remained untreated. See the dose scheme in the table below.

Table 7: The Dose Scheme of Tazemetostat and CHOP Combination Treatment (WSU-DLCL2)

Group	Number of Animals	Treatment	Dose (mg/kg), Active Compound	Dose (mg/kg), With Salt Weight	Route	Schedule
1	12	Vehicle	-	-	po	BID × 28
2	12	Tazemetostat	134	160	po	TID × 28
3	12	Tazemetostat	201	239	po	BID × 28
4	12	Tazemetostat	268	319	po	BID × 28
5	12	Tazemetostat	536	638	po	QD × 28
6	12	Tazemetostat/CHOP*	201/*	239/*	po/*	BID × 28/*
7	12	CHOP*	*	*	*	*
8	8	No treatment	-	-	-	-

*CHOP = Cyclophosphamide, doxorubicin, vincristine, prednisone. Cyclophosphamide: administered once on Days 1 and 22 at 30 mg/kg intraperitoneal; doxorubicin: administered once on Days 1 and 22 at 2.475 mg/kg intravenously; vincristine: administered once on Days 1 and 22 at 0.375 mg/kg intravenously; prednisone: administered on Days 1 through 5 and 22 through 26 at 0.15 mg/kg once daily × 5 orally.

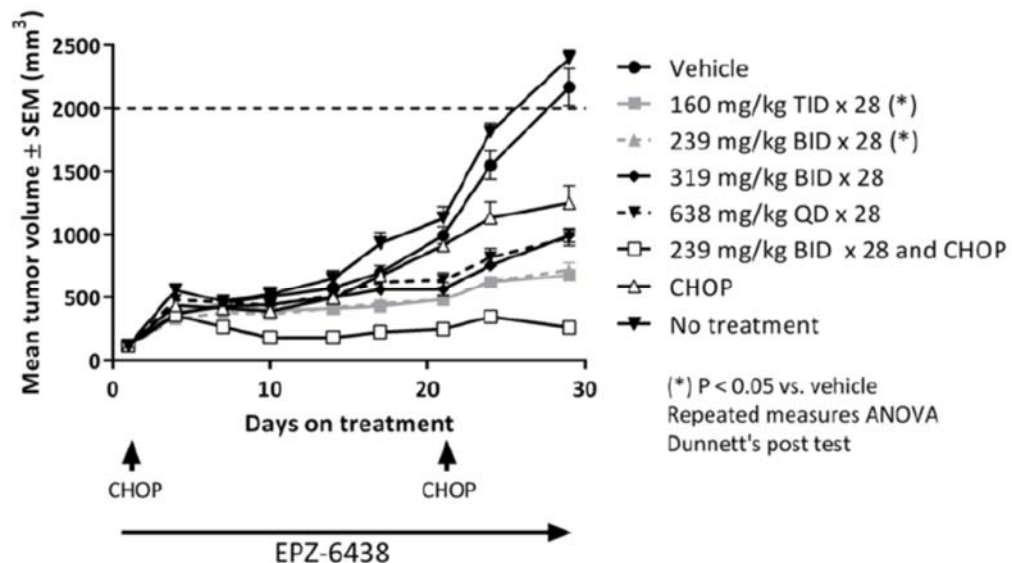
Anti-tumor effects

All single treatments were tolerated. At all tazemetostat doses and treatment schedules, terminal tumor sizes were significantly smaller than for the vehicle-treated group. At all dose levels and schedules with tazemetostat alone, the TGI values were better than CHOP chemotherapy alone. The combination therapy of tazemetostat (239 mg/kg BID) and CHOP

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induced an antitumor response with better TGI than either single agent alone (93% versus 45% and 71%).

Figure 5: Tumor Suppression of Tazemetostat Alone or in Combination with CHOP



Dashed horizontal line: WSU LCC with PPB considered = lowest cytotoxic concentration for WSU-DLCL2 lymphoma cells in vitro for tazemetostat with mouse plasma protein binding considered.

(Figure from the Applicant)

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Table 8: Tumor Growth Inhibition in WSU-DLCL2 Xenograft Model Treated with Tazemetostat and/or CHOP

Treatment	TGI from Day 1*	TGI from Day 7*
EPZ6438 160 mg/kg TID × 28	73	86
Tazemetostat 239 mg/kg BID × 28	71	80
Tazemetostat 319 mg/kg BID × 28	57	67
Tazemetostat 638 mg/kg QD × 28	58	70
Tazemetostat 239 mg/kg BID × 28 and CHOP	93	100
CHOP	45	51

* TGI was calculated considering the change in tumor volume over time.

(Table from Applicant)

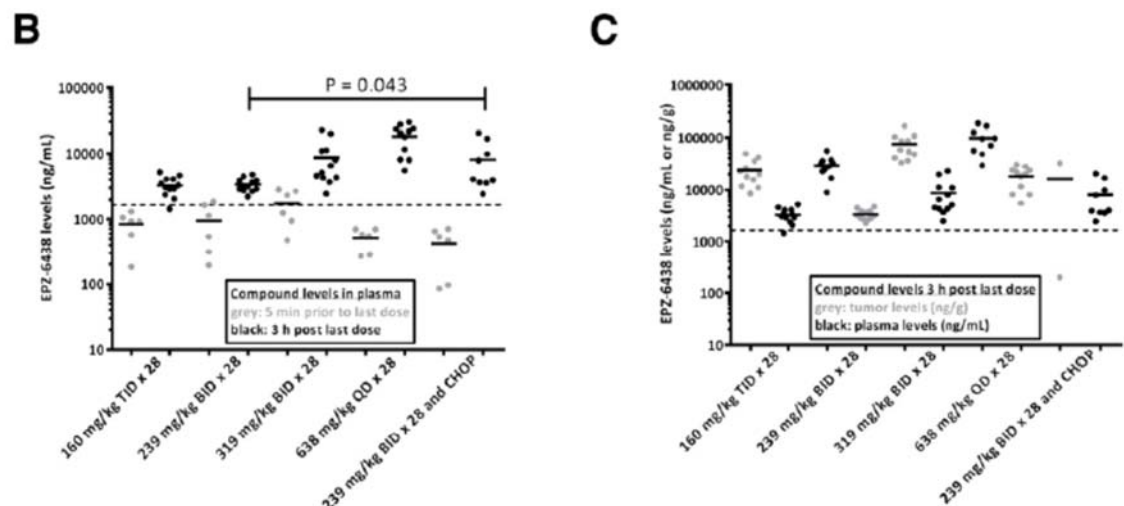
Corresponding exposures to tazemetostat: PK-PD analysis

On Day 28, plasma samples were collected 5 minutes before and 3 hours after the last dose. Tumors were collected 3 hours after the last dose, and tazemetostat levels were measured in tumor homogenates using LC-MS/MS.

- At both plasma time points, tazemetostat levels were similar between the 160 mg/kg TID and 239 mg/kg BID groups, while a dose-dependent increase was observed between 319 mg/kg BID and 239 mg/kg BID. The 638 mg/kg QD group showed the lowest trough levels but the highest levels at 3 hours after the last dose for all single agent groups (Panel B, figure below).
- Mean tazemetostat levels were slightly reduced in the presence of CHOP compared to single agent but slightly elevated at 3 hours after the last dose (Panel B, figure below).
- Tazemetostat levels in tumors at time points with sufficient tissue remaining after treatment for analysis were higher than those in plasma, suggesting accumulation in tumor tissue with prolonged treatment (Panel C, figure below).

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Figure 6: PK-PD analysis of Tazemetostat (WSU-DLCL2)



Dashed horizontal line: WSU LCC with PPB considered.

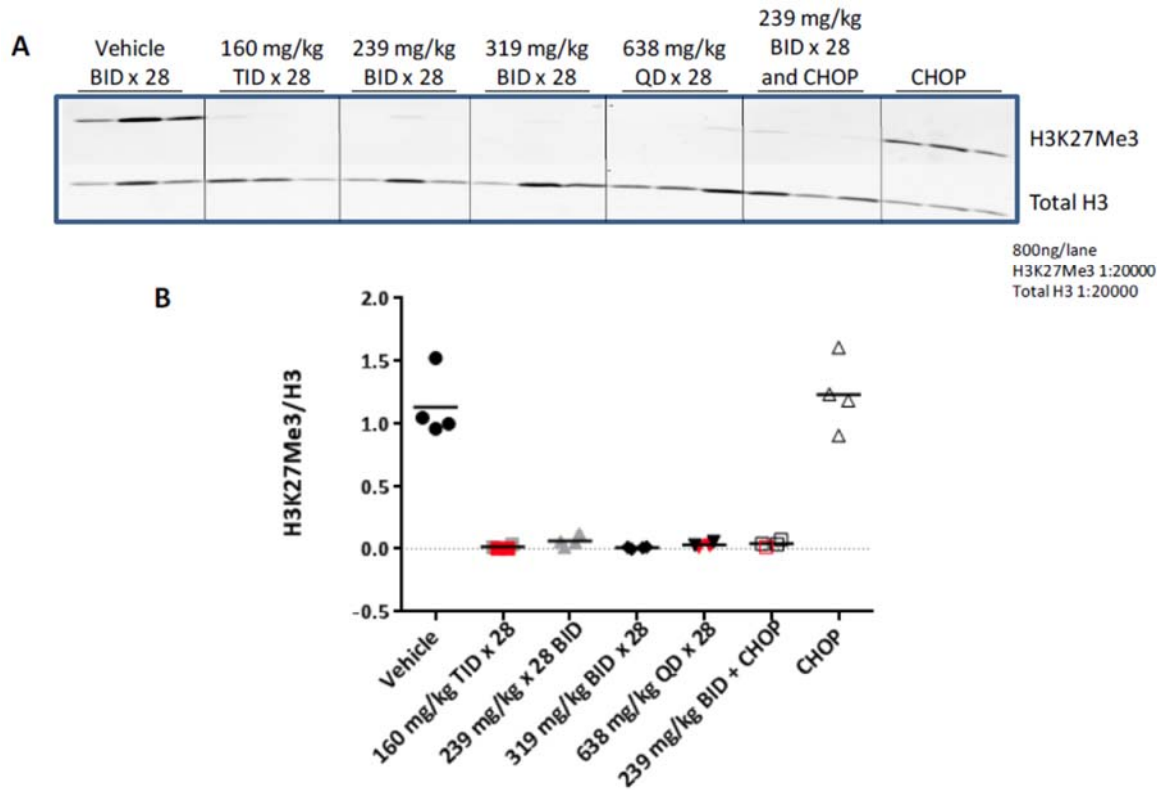
Tumor homogenates were generated and subjected to LC-MS/MS analysis, and EPZ-6438 tumor levels (grey dots) were compared with plasma levels (black dots). A slight increase in EPZ-6438 compound levels was detected in the presence of CHOP compared to single agent. Dots represent values of the individual animals; horizontal lines represent group mean values.

(Figure from the Applicant)

Suppression of H3K27me3 levels

Histones were isolated from frozen tumor tissue for western blot and ELISA analyses using H3K27me3 and H3-specific antibodies. The western blot and ELISA results both demonstrated maximal target inhibition that was comparable at all dosing schedules for tazemetostat as a single agent and in combination with CHOP. No change in H3K27 trimethylation was observed in tumors from mice treated with CHOP alone.

Figure 7: Suppression of H3K27me3 Levels in Tumors by Tazemetostat



Tumors were collected and flash frozen. Histones were extracted and subjected to either western blot (3 mice, panel A) or ELISA analyses (4 mice, panel B) with antibodies specific to the trimethylated form of histone H3 lysine 27 (H3K27me3) or all forms of histone H3 (total H3). Ratios of trimethylated H3K27 to total H3 were calculated and plotted under B, and horizontal lines represent group mean values. Histone concentrations for ELISA: H3 plate, 0.25 ng/ μ L and H3K27me3 plate, 0.5 ng/ μ L. Antibody dilutions for ELISA: H3K27me3 1:1000 and anti-Rb-IgG-HRP 1:2000; total H3 1:10000 and anti-Rb-IgG-HRP 1:6000. Red symbols are data points below the lower limit of quantification.

(Figure from the Applicant)

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The suppression of H3K27me3 by Tazemetostat in normal tissues from rats and monkeys

In repeat-dose toxicology studies in rats and monkeys, the effect of tazemetostat on the suppression of H3K27me3 levels in PBMCs, spleen, bone marrow and skin were evaluated in samples obtained after treatment of tazemetostat for 7 to 28 days (Studies E7468-PD004 and E7468-PD005). Samples showed a dose-dependent down regulation of trimethylation of H3K27 in bone marrow, peripheral blood mononuclear cells (PBMCs), spleen, and skin with the highest degree of inhibition occurring in the bone marrow. The data were reviewed in NDA 211723.

Secondary pharmacology and safety pharmacology

There are no secondary or safety pharmacology studies submitted to the current NDA.

5.4. ADME/PK

The nonclinical pharmacokinetics and ADME properties were evaluated in rats and monkeys. The toxicokinetics of tazemetostat and the major metabolite of tazemetostat, EPZ-6930, were assessed in rats and monkeys, as well as in rabbits in the embryofetal development studies. These studies were reviewed in NDA 211723.

5.5. Toxicology

There are no toxicology studies submitted to the current NDA. Toxicology assessments of tazemetostat, including general toxicology, genetic toxicology, reproductive and developmental toxicology and juvenile toxicity in rats were reviewed in NDA 211723 for the treatment of patients with advanced epithelioid sarcoma.

One of the key toxicities observed in the toxicology studies was lymphoblastic lymphoma. In the 13-week rat study, lymphoblastic lymphoma originating from the thymus occurred in 40% of the females (8/20 rats, with 5 deaths) and 15% of the males (3/20 rats, with one death) treated at 300 mg/kg/day. Notably, the lymphoma incidence was not dose-dependent; lymphoma was found in one surviving male (1/20, 5%) at 600 mg/day. Systemic exposures (AUC levels) at 300

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mg/kg/day were approximately 14-24 fold higher than the human AUC at the 800 mg BID dose. While no lymphoblastic lymphomas were found in the 13-week monkey study, hypertrophy or hyperplasia were observed in multiple organs at ≥ 300 mg/kg/day (approximately equal to the human AUC at the 800 mg BID dose) including the liver and bile duct, mesenteric lymph node, and stomach.

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Primary Reviewer

Shwu-Luan Lee, PhD

X

Team Leader (Acting)

Brenda Gehrke, PhD

6 Clinical Pharmacology

6.1. Executive Summary

The Clinical Pharmacology Section of the NDA is supported by PK characterization, population PK (PopPK) analysis and exposure-response (E-R) analyses. The key review question focuses on the appropriateness of the proposed dosing regimen.

The Office of Clinical Pharmacology has reviewed the information contained in NDA 213400. This NDA is approvable from a clinical pharmacology perspective. The review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Evidence of effectiveness	The primary evidence of effectiveness was from Trial E7438-G000-101 Phase 2 Portion Cohorts 4 and 5. The ORR (95% CI) was 69% (53%, 82%) in patients with mutated EZH2 R/R FL and 34% (22%, 48%) in patients with wild-type EZH2 R/R FL treated with tazemetostat 800 mg BID.
General Dosing instructions	The recommended dosage of TAZVERIK is 800 mg orally twice daily with or without food until disease progression or unacceptable toxicity. Do not take an additional dose if a dose is missed or vomiting occurs after TAZVERIK, but continue with the next scheduled dose.
Dosing in patient subgroups (intrinsic and extrinsic factors)	There is no additional data to support therapeutic individualization in patients with R/R FL. Dose adjustment in specific populations with R/R FL should follow the current recommendations in the labeling approved under NDA 211723.
Labeling	No clinical pharmacology related revision was made in the labeling.

There is no additional Post-Marketing Requirement (PMR) or Post-Marketing Commitment (PMC) from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Tazemetostat is an inhibitor of the methyltransferase, EZH2, and some EZH2 gain-of-function mutations including Y646X and A687V. EZH2 is highly expressed in germinal center B-cells from which the majority of B-cell lymphomas arise, and are essential for germinal center formation.

Inhibition of wild-type and mutant EZH2 with tazemetostat reduces the growth and survival of FL tumors.

The systemic exposure of tazemetostat is approximately dose proportional over the dose range of 200 to 1600 mg BID. Following tazemetostat 800 mg orally BID, steady-state was reached by Day 15. The mean (%CV) C_{max} was 829 (56%) ng/mL and the AUC_{0-12h} was 3340 (49%) ng·h/mL at steady-state. Tazemetostat exhibited time-dependent PK with clearance increasing over time, which is likely due to auto-induction of CYP3A. The mean accumulation ratio was 0.58. There was no clinically meaningful difference in PK parameters in patients with R/R FL and patients with metastatic or locally advanced epithelioid sarcoma.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is 800 mg orally BID with or without food. Do not take an additional dose if a dose is missed or vomiting occurs after TAZVERIK, but continue with the next scheduled dose.

Therapeutic Individualization

There is no additional data in the current submission to support therapeutic individualization in patients with R/R FL. Dose adjustment in specific populations with R/R FL should follow the current recommendations in the labeling approved under NDA 211723.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Tazemetostat is a selective inhibitor of enhancer of zeste homologue 2 (EZH2). EZH2 catalyzes mono-, di-, and tri-methylation of lysine 27 of histone H3 (H3K27) which represses certain tumor suppressors.
Active Moieties	Tazemetostat is the pharmacological active moiety. The most abundant metabolite (M5, EPZ-6930) exhibits low potency (IC_{50} : ~1.23 μ M) and is unlikely to contribute to the pharmacological activity in humans.
QT Prolongation	Tazemetostat and its most abundant metabolite EPZ-6930 did not cause large mean increase (i.e. >20 ms) on the QTc interval at the

	800 mg BID dose. The largest mean increase (upper bound of 90% CI) in QTc was 6.1 ms (8.5 ms) at the 800 mg BID and 9.3 ms (12.5 ms) at the 1600 mg BID dose.
General Information	
Bioanalysis	Tazemetostat (plasma and urine) and its metabolites (EPZ-6930, EPZ006931 and EPZ034163 in plasma) were quantified using validated LC/MS/MS methods. Refer to the multidisciplinary review (Reference ID: 4550626) Section 19.4.2 for NDA 211723 for detailed information.
Drug exposure after first dose	Following the first oral dose of 800 mg, the geometric mean (CV%) C_{max} and AUC_{0-12h} were 1460 (38.7%) ng/mL and 5750 (50.4%) ng·h/mL, respectively.
Drug total exposure at steady state following the therapeutic dosing regimen	Following the oral dose of 800 mg BID, the geometric mean (CV%) steady-state C_{max} and AUC_{0-12h} were 829 (56.3%) ng/mL and 3340 (49.3%) ng·h/mL, respectively.
Minimal effective dose or exposure	Tazemetostat demonstrated dose/exposure-dependent inhibition of H3K27me3 in skin (biomarker for target inhibition). The estimated steady-state AUC_{0-12h} achieving 50% of the inhibition was 734 ng·h/mL.
Maximal tolerated dose or exposure	MTD was not reached over the evaluated dose range of 100 to 1600 mg BID in Trial E7438-G000-101 phase 1 portion. There was one DLT case (grade 4 thrombocytopenia) at 1600 mg BID.
Dose Proportionality	Tazemetostat steady-state exposure (AUC_{0-12h} and C_{max}) increased approximately dose-proportionally with oral doses from 200 to 1600 mg BID.
Accumulation	The accumulation ratio was 0.58 for AUC_{0-12h} and 0.57 for C_{max} , which is probably due to the short elimination half-life and auto-induction of CYP3A.
Variability	Inter-subject variability (CV%) at steady-state was 56% for C_{max} and 42% for AUC_{0-12h} after repeat dosing of tazemetostat 800 mg BID in Trial E7438-G000-101.
Absorption	

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Oral Bioavailability	The estimated median [min, max] bioavailability was 34.0% [20.2%, 49.8%].
Oral T_{max}	The median T _{max} ranged from 1.1 to 2.2 hours following administration of a single oral dose of 800 mg tazemetostat.
Food effect	The GMR [95% CI] of C _{max} and AUC _{last} after a single oral dose of 200 mg tazemetostat under high-fat meal fed vs. fasted condition were 0.76 [0.46 - 1.25] and 0.82 [0.56 - 1.21], respectively.
Effect of Gastric acid reducing agents	The GMR [95% CI] of C _{max} and AUC _{last} after 800 mg BID tazemetostat with vs. without coadministration of proton-pump inhibitor omeprazole (20 mg QD) were 1.25 [0.76 - 2.03] and 1.26 [0.87 - 1.82], respectively.
Substrate transporter systems [in vitro]	Tazemetostat is a substrate of P-gp. Tazemetostat is not a substrate for BCRP, or renal transporters OCT2, OAT3 and MATE1 or hepatic transporters OATP1B1 and OATP1B3.
Distribution	
Volume of Distribution	The geometric mean (CV%) of apparent volume of distribution at steady-state (V _{ss} /F) was 1230 (45.8%) L
Plasma Protein Binding	In vitro, tazemetostat is 87.7 to 91.1% bound to human plasma proteins over the concentration range of 1 to 30 μM.
Blood to Plasma Ratio	The mean blood-to-plasma ratio is 0.71 for tazemetostat over 50 to 5000 ng/mL.
Elimination	
Clearance	Tazemetostat shows time-dependent PK. The apparent CL/F was 126 L/h after first dose and 274 L/h at steady state.
Mean terminal elimination half-life	The mean (CV%) terminal t _{1/2} was estimated to be 3.1 hours (13.9%).
Metabolism	
Primary metabolic pathway(s)	Tazemetostat is metabolized primarily by CYP3A4 in vitro to form the inactive major metabolites M5 (EPZ-6930, product of N-demethylation) and M3 (EPZ006931), which undergo sequential metabolism to form M1 (EPZ034163), and M5 also undergoes CYP3A4 mediated metabolism in vitro.

Inhibitor/Inducer	<u>Clinical DDIs</u> <i>Effect of CYP3A inhibitor on tazemetostat</i> Coadministration of fluconazole (a moderate CYP3A inhibitor) with tazemetostat 400 mg BID increased tazemetostat steady-state C_{max} by 2.3-fold and AUC_{last} by 3.1-fold. <i>Effect of tazemetostat on CYP3A substrate</i> Coadministration of tazemetostat 800 mg BID with oral midazolam (a sensitive CYP3A substrate) decreased midazolam C_{max} by 21% and AUC_{last} by 40%. <i>Effect of tazemetostat on CYP2C8 and 2C19 substrates</i> Coadministration of tazemetostat 800 mg BID with an oral cocktail of repaglinide (a sensitive CYP2C8 substrate) and omeprazole (a sensitive CYP2C19 substrate) increased repaglinide C_{max} by 51% and AUC_{last} by 80%; and decreased omeprazole C_{max} by 18% and AUC_{last} by 20%. <u>In vitro DDIs</u> Tazemetostat is an inhibitor of CYP2C8 (IC_{50}: 1.27 μM), 2C9 (IC_{50}: 15 μM), 2C19 (IC_{50}: 6.65 μM), CYP3A4 (IC_{50}: 3.06 μM) and CYP2D6 (IC_{50}: 9.16 μM). The IC_{50} value were >20 μM for CYP1A2 and CYP2B6. Tazemetostat is a time-dependent inhibitor of CYP3A, but not for CYP2C8, CYP2C9, CYP2C19, and CYP2D6. The major tazemetostat metabolites (EPZ-6930, EPZ006931 and EPZ034163) do not inhibit CYP enzymes at clinically relevant concentrations ($IC_{50} \geq 45.9 \mu$M). Tazemetostat is an inducer of CYP3A. It also exhibits potential to induce CYP1A2, CYP2B6, CYP2C8 and CYP2C9 and 2C19 in vitro; however, the effects are expected to be weak at the clinically relevant concentrations. Tazemetostat and EPZ-6930 are inhibitors of MATE1 with IC_{50} of 2.65 μM and 4.79 μM, respectively, and MATE2-K with IC_{50} of 1.89 μM and 12.1 μM, respectively. The IC_{50} values of tazemetostat and its major metabolites are $\geq 10 \mu$M for P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, and BSEP.
Excretion	

Primary excretion pathways (% dose)	After a single oral dose of 800 mg [^{14}C]-tazemetostat, 94% of the total radioactivity was recovered over 12 days, with a mean 79% excreted in feces and 15% in the urine.
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6.3.2. Clinical Pharmacology Questions

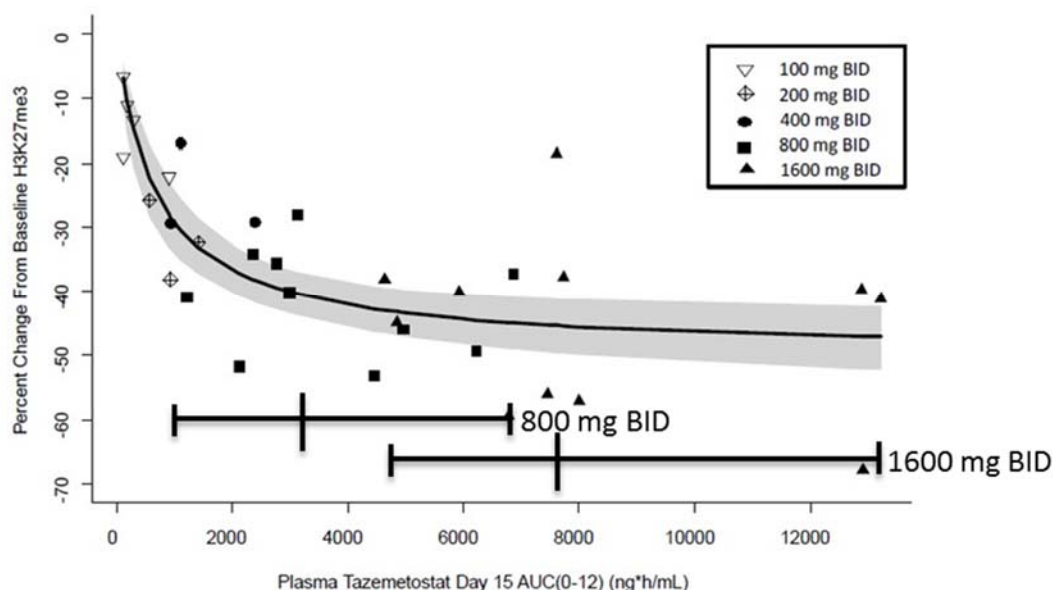
For brevity, only questions related to the current submission are addressed below. For additional information, please refer to the multi-disciplinary review for the original NDA 211723 submission (DARRTS ID: 4550626).

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of 800 mg BID for tazemetostat in patients with R/R FL is supported by a generally favorable benefit/risk profile demonstrated in Trial E7438-G000-101.

The proposed dosing regimen of 800 mg BID was selected based on the totality of PD, preliminary efficacy and safety data obtained from patients with advanced solid tumors or B-cell lymphomas in Trial E7438-G000-101 phase 1 portion. Tazemetostat demonstrated an exposure-dependent inhibition of trimethylated lysine 27 of histone (H3K27me3) in skin, a biomarker for target (EZH2) engagement, from 100 to 1600 mg BID (Figure 8). The inhibition of H3K27me3 appeared to reach the plateau over the exposure range at 800 to 1600 mg BID.

Figure 8: Fit of an Inhibitory Emax Model to the Percentage Change from Baseline in H3K27me3 Versus AUC0-12 in the Stratum Spinosum Layer (Trial E7438-G000-101 Phase 1 Portion)

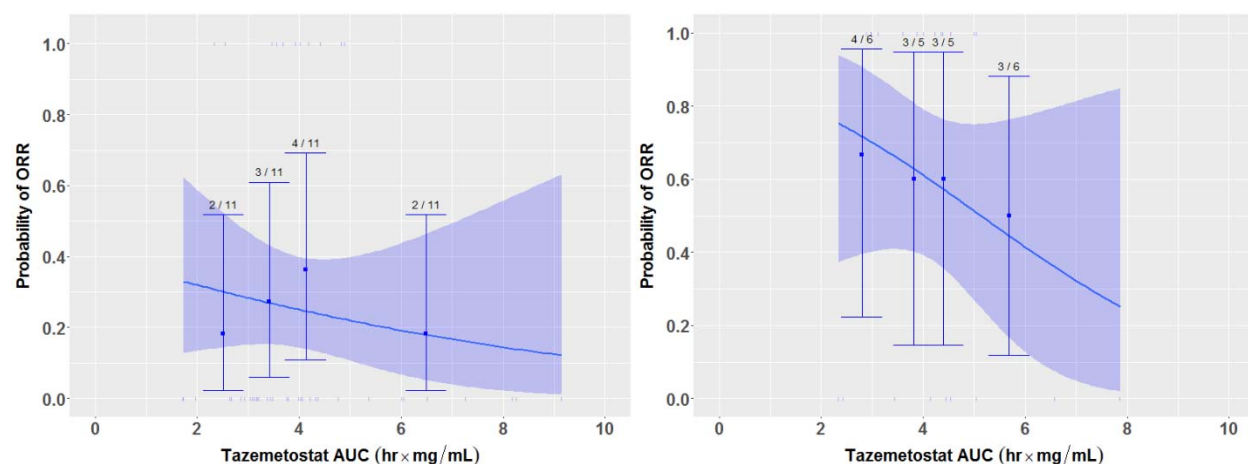


Source: Summary of Clinical Pharmacology Studies, Figure 45.

In Trial E7438-G000-101 phase 1 portion, the preliminary efficacy results showed that 2 of the 43 (5%) patients achieved an objective response, including one CR at tazemetostat 800 mg BID and one PR at 1600 mg BID. Maximum tolerated dose (MTD) was not reached within the dose range of 100 mg to 1600 mg BID. However, the 800 mg BID dosing regimen showed less treatment-related TEAE of any grade (81% vs. 92%), and less TEAE leading to dose interruption of any grade (11% vs. 25%) compared to the 1600 mg BID dosing regimen. In addition, one patient experienced a DLT (Grade 4 thrombocytopenia) at 1600 mg BID. Overall, 800 mg BID dosing regimen exhibited a similar PD effect with a more favorable safety profile than the 1600 mg BID dosing regimen.

In the Phase 2 portion of Trial E7438-G000-101, only 800 mg BID was evaluated for patients with mutant EZH2 R/R FL in Cohort 4 and for patients with wild-type EZH2 R/R FL in Cohort 5. The reviewer's independent analyses confirmed the Applicant's analysis. The FDA analysis showed a generally flat exposure-response (E-R) relationship for ORR in patients with R/R FL regardless of EZH2 genotype (Figure 9). However, caution should be taken when interpreting this relationship due to the small sample size (59 patients with wild-type EZH2 and 22 patients with mutant EZH2) in the E-R dataset and the limited range of exposure with one dose level. In addition, the E-R relationships for ORR may also be confounded by the potential imbalanced patient characteristics and disease status at baseline.

Figure 9: Reviewer's Exposure-Response Analyses for ORR in Patients with Wild-type EZH2 (Left) and Mutant EZH2 (Right) Relapsed or Refractory Follicular Lymphoma

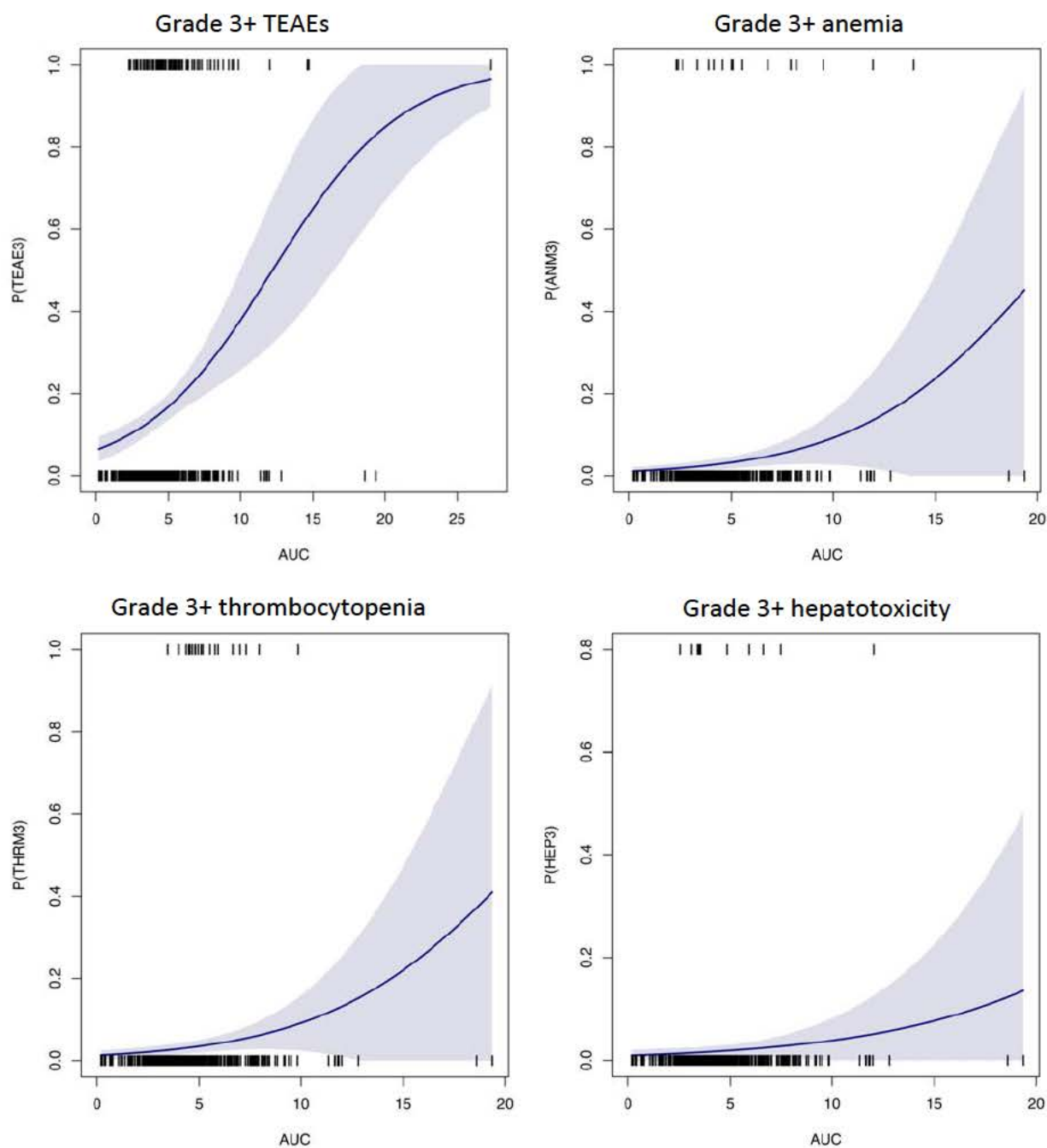


Source: Reviewer's analysis.

The Applicant's E-R analyses for safety using pooled data at 100 - 1600 mg BID from Trials E7438-G000-101, EZH-105 and EZH-202 showed positive E-R relationships for Grade 3+ TEAEs, Grade 3+ anemia, Grade 3+ thrombocytopenia and Grade 3+ hepatotoxicity (Figure 10), but no apparent E-R relationship for Grade 4+ neutropenia. These findings are consistent with the Reviewer's independent analyses. But overall the safety profile of tazemetostat in Trial E7438-G000-101 phase 2 portion mutant and wild-type EZH2 cohorts demonstrated generally acceptable tolerability in patients with R/R FL at the proposed dosing regimen of 800 mg BID. Dose reduction, dose interruption and treatment discontinuation due to any TEAEs were reported in 9.1%, 28.3

and 8.1% of all patients with R/R FL, respectively. Dose modifications due to TEAEs were reported with similar incidence in the mutant and wild-type EZH2 cohorts.

Figure 10: Applicant's Exposure-Response Analyses for Safety in Patients with Relapsed or Refractory Follicular Lymphoma at Tazemetostat 100 – 1600 mg BID



Source: EZH-P103 Exposure-Response Analysis of Tazemetostat, Figures 28, 31, 34, and 37.

In summary, the proposed dosing regimen of 800 mg BID is supported by the overall favorable benefit/risk profile for the general patient population with R/R FL.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No additional data is provided in the current submission to support therapeutic individualization in patients with R/R FL. Dose adjustment in specific populations with R/R FL should follow the current recommendations in the labeling approved under NDA 211723.

EZH2 Mutation status and response

Patients with relapsed or refractory (R/R) follicular lymphoma (FL) were enrolled in two single-arm cohorts (Cohorts 4 and 5) in Study E7438-G000-101 based on EZH2 mutation status. EZH2 status was assessed centrally in formalin-fixed, paraffin-embedded tumor samples using the cobas® EZH2 Mutation Test, which was designed to detect the following EZH2 mutations within the catalytic SET domain: Y646F, Y646N, Y646X (where X=S, H, or C), A682G, and A692V. Patients with EZH2 mutant (MT) R/R FL were enrolled in Cohort 4 (N=45) and patients with EZH2 R/R FL wild-type (i.e., absence of detection of the above-specified mutations by the cobas test) were enrolled in Cohort 5 (N=54). Of these, 42 patients with EZH2 mutant and 53 patients with EZH2 wild-type comprised the efficacy population (N=95). The IRC-determined objective response rate (ORR) of Cohort 4 was 69% with a median duration of response of 10.9 months vs. an ORR of 34% in Cohort 5 with a median duration of response of 13.0 months. For detailed efficacy results in these cohorts refer to Section 8.

Table 9 summarizes the number of patients and best overall responses in Cohort 4 subgroups defined by identified EZH2 mutation(s)(N=45). Most patients in Cohort 4 (89%) had a mutation at Y646, including 2 patients with co-occurring EZH2 mutations. Responses (CR or PR) were observed in patients with mutations affecting codon Y646 and in patients with A682G. Only one patient with mutation at A692V was enrolled and the patient had a best response of SD. Overall, clinical data support targeted activity of tazemetostat in patients with Y646 and A682G mutations as determined by the cobas test. Although no clinical data are available for activity of tazemetostat in tumors with the A692V mutation, this mutation resides in the same domain of the protein as Y646 and A682G and is supported by nonclinical evidence. Consistent with the FDA Guidance: Developing Targeted Therapies in Low-Frequency Molecular Subsets of Disease, the absence of a rare subset from the clinical study may be acceptable if there is evidence supporting that the molecular grouping defined by the inclusion criteria will respond similarly. Therefore, based on current evidence, inclusion of A692V in the test and thus the population covered by the indication is acceptable.

Table 9: Distribution of EZH2 Mutations and IRC-determined Best Overall Response in Cohort 4 (EZH2 MT) Patients of Study E7438-G000-101 (N=45)[&]

EZH2 Mutation(s)*	Number of patients N (%)	Best Overall Response N (%)			
		CR	PR	SD	PD
Y646X (X = S, H, or C)	15 (33)	4 (27)	7 (47)	3 (20)	1 (7)
Y646F	12 (27)	1 (8)	5 (42)	6 (50)	0
Y646N	11 (24)	0	10 (91)	1 (9)	0
A682G	4 (9)	1 (25)	2 (50)	1 (25)	0
A692V	1 (2)	0	0	1	0
Y646X/A682G	1 (2)	0	1	0	0
Y646F/Y646N	1 (2)	0	0	1	0

Source: Reviewer exploratory analysis.

*As determined by central testing using the Cobas EZH2 Mutation Test. [&]Three patients (Y646X/CR, Y646N/PR and Y646F/SD) were not included in the efficacy population; for additional details refer to Section 8. IRC=Independent Review Committee, CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, Best Overall Response (CR/PR confirmed). EZH2 reference sequence: NP_004447.2 (histone-lysine N-methyltransferase EZH2 isoform a).

X

Primary Reviewers

Liang Li, Ph.D.

Sarah Dorff, Ph.D.

X

Team Leaders

Ruby Leong, Pharm.D.

Lian Ma, Ph.D.

Rosane Charlab Orbach, Ph.D.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant Submitted data from 7 clinical studies of tazemetostat monotherapy or in combination with other agents and one retrospective natural history study evaluating the impact of EZH2 mutation status on response to standard of care. Of the 7 clinical studies, one study E7438-G000-101 was included to support safety and efficacy in patients with follicular lymphoma. Study E7438-G000-101 included 6 dose expansion cohorts in patients with B-cell malignancies which contributed to the safety pool. The 2 cohorts of patients with follicular lymphoma, (cohorts 4 and 5) were the primary efficacy and safety population. Cohort 4 included patients whose tumors was determined to have a mutation of EZH2 as detected by the cobas® PCR assay. Cohort 5 included patients with follicular lymphoma whose tumor did not have a mutation of EZH2 based on the cobas® assay. Four additional studies detailed in Table 10 in patients with solid tumors were considered in the overall safety assessment.

Table 10: Table of Clinical Trials Relevant to this NDA

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
E7438-G000-101 NCT01897571	Multicenter, Open-Label Phase 1 Food Effect and DDI cohort	Dose Escalation: Tazemetostat 100-1600mg PO twice daily	MTD PK parameters	Phase 1 = 38 Phase 2 = 333	Solid Tumors Non-Hodgkin Lymphoma	39 sites 9 Countries Australia, Canada, Germany, France, Great Britain, Italy, Poland, Ukraine, United States

NDA/BLA Multi-disciplinary Review and Evaluation 213400
Tazverik (tazemetostat)

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
E7438-G000-101 NCT01897571 Dose Expansion Cohorts 4 and 5	Multicenter, Open-Label	Dose Expansion: Tazemetostat 800 mg orally twice daily	Overall Response Rate per IRC (Cheson 2007) Duration of Response	Follicular Lymphoma = 99 Cohort 4 EZH2 MT = 45 Cohort 5 EZH2 WT = 54 Diffuse Large B Cell Lymphoma = 234	Patients with Follicular Lymphoma who have received at least two prior therapies DLBCL who have received at least 2 lines of prior therapy	28 sites 8 Countries Australia, Canada, France, Great Britain, Italy, Poland, Ukraine, United States
EZH-107	Multicenter, retrospective non- interventional analysis of clinical outcome and molecular data Retrospective	NA A variety of chemoimmunotherapy combinations that were administered as part of standard of care	Overall Response Rate	908	Patients treated at Academic Centers with Clinical Outcome and EZH2 mutation status available	4 Centers 4 Countries
Abbreviations: DDI: drug-drug interaction; EZH2 MT: EZH2 mutated per the cobas assay; EZH2 WT: EZH2 wild-type, i.e. patients whose tumors did not have an EZH2 mutation per the cobas® assay						

Table 11: Additional Studies Contributing to Overall Safety Assessment

NDA/BLA Multi-disciplinary Review and Evaluation 213400
Tazverik (tazemetostat)

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	No. of patients	Study Population	No. of Centers and Countries
EZH 102	Phase I	Starting dose of 240mg/m ² - 1200mg/m ² twice daily	MTD RP2D	46 dose escalation 44 dose expansion	Pediatric patients with R/R atypical teratoid rhabdoid (ATRT) tumors, non- ATRT, INI1-negative tumors, and synovial cell sarcoma with SS18- SSx rearrangement	23 Sites 9 Countries Australia, Canada Denmark France, Germany, Italy, Netherlands United States, United Kingdom Phase II
EZH 202	Phase II	800 mg PO BID	ORR	397	Adults INI1-negative Tumor or Synovial Sarcoma	32 sites 9 Countries France, United Kingdom, Germany, Australia, Taiwan, Italy, Canada, Belgium, United States
EZH-203	Phase II	800 mg PO BID	Primary: Disease Control Rate Secondary: AEs ORR PFS OS Efficacy Disease Control Rate	74	Adults, Mesothelioma	16 sites 3 Countries France United Kingdom United States

NDA/BLA Multi-disciplinary Review and Evaluation 213400
Tazverik (tazemetostat)

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	No. of patients	Study Population	No. of Centers and Countries
EZH-501 (Ongoing)	Extension (rollover) Study	Tazemetostat 800 mg PO BID	Primary: AEs Secondary: OS	41 out of a planned 300	Patients who had demonstrated clinical benefit from treatment with tazemetostat and were currently receiving tazemetostat on an Epizyme sponsored clinical trial or any other clinical trial being conducted with tazemetostat.	18 Sites 5 Countries France Poland United Kingdom United States Australia
Abbreviations: AE: adverse event; BID: twice daily; MTD: maximum tolerated dose; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RP2D: recommended phase 2 dose						

7.2. Review Strategy

The key materials used for the review of safety and efficacy included:

- NDA datasets, clinical study reports, case report forms and responses to the review teams information requests
- Relevant published literature
- Relevant information in the public domain

The FDA efficacy review was based on data from E7438-G000-101 (Phase 2), relevant published literature, and relevant information in the public domain. The review of safety was primarily based on data from 99 patients with follicular lymphoma on study E7438-G000-101 in phase 2 cohorts 4 and 5. Safety data from an additional 234 patients with DLBCL in cohorts 2, 3 and 6 of study E7438-G000-101 contributed to the B-cell malignancy safety pool. A 120-day safety update which included an additional 3 patients with FL contributed to the safety review. In addition, Summary safety data from other studies evaluating tazemetostat in adult and pediatric patients in solid tumors was considered.

The phase 2 part of study E7438-G000-101 was used for the primary analysis of efficacy. The phase 2 part of the study included 6 cohorts of patients with relapsed or refractory (R/R) follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL) who had received at least 2 prior therapies. Patients with both enhancer of zeste homolog 2 (EZH2) mutation positive (MT) and those without an identified mutation (wild type (WT)) disease were enrolled. Patients with R/R DLBCL were enrolled in Cohorts 1 to 3 based on GCB subtype and EZH2 mutation status. Patients with EZH2 MT R/R FL were enrolled in Cohort 4 and patients with EZH2 WT R/R FL were enrolled in Cohort 5. Cohort 6, which was designed to evaluate tazemetostat in combination with prednisolone, enrolled patients with DLBCL with EZH2 WT disease regardless of GCB subtype.

The focus of this efficacy review is on the evaluation of tazemetostat monotherapy in patients with R/R FL enrolled in Cohort 4 and 5. Efficacy results are based on data entered into the study database through (b) (6) for patients with FL enrolled as of (b) (6).

Items reviewed included the primary datasets submitted by applicant, Clinical Study Report of Study E7438-G000-101 (Phase 2), review of FDA databases regarding the regulatory history for the tazemetostat IND/NDA.

Summaries of the data and statistical analyses by the reviewer were performed using JMP 12.0, SAS Version 9.4 (both SAS Institute, Inc., Cary, NC) and Excel 2010 (Microsoft, Redmond, WA). For additional statistical methodologies, see Section 8.1.1.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.2. Study E7438-G000-101 – 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

Clinical Trials.gov identifier: NCT01897571

First patient enrolled: (b) (6)

Study Status: Ongoing

Clinical cut-off dates for this submission:

(b) (6) (Safety and enrollment)
(b) (6) (Efficacy)
(b) (6) (120-day safety update)

Trial Design

Study E7438 was an open-label, single-arm, multicenter, study of tazemetostat in patients with advanced tumors or with B cell lymphomas. The phase 1 portion of the study consisted of a dose escalation portion in patients with advanced or metastatic solid tumors or B cell lymphomas with a goal to establish the MTD and/or RP2D. The phase 2 portion of the study evaluated single-agent tazemetostat in 5 cohorts of patients with relapsed or refractory B-cell lymphomas. Cohorts 4 and 5 enrolled patients with relapsed and refractory follicular lymphoma and support this application. Cohort 4 included patients with EZH2 mutated disease and cohort 5 included patients without EZH2 mutations, considered by the Applicant as wild-type (WT). Patients were enrolled onto either cohort 4 (EZH2 mutation positive) or Cohort 5 (EZH2 mutation negative) based on local EZH2 mutation assessment which was verified centrally from paraffin embedded tumor tissue using the cobas® PCR assay, which detects mutations of Y646X [S,H,C], Y646F, Y646N, A682G and A692V.

The original study design planned enrollment of up to 30 patients in each of Cohorts 1 to 5 in a 2-stage design. The initial assessment of efficacy was conducted within each cohort when 10 patients had been enrolled (stage 1) and reached at least Week 24 of treatment or terminated prior to that time. For each DLBCL cohort, if zero responders (with CR or PR) out of the initial 10 patients was observed, further enrollment in the cohort was terminated for futility. For each FL cohort, if ≤1 responder (CR or PR) out of the initial 10 patients was observed, further enrollment in the cohort was terminated for futility. To avoid disruptions in the study, enrollment and treatment of patients was not halted in order to conduct the futility analysis.

Subsequent to the futility analysis on stage 1 in the DLBCL cohorts, the IDMC at their meeting on (b) (6) supported a study design change to a modified 2-stage Green-Dahlberg design for each cohort. This was implemented with Amendment 9 to the protocol. For the purpose of calculating an expanded cohort size using the Green-Dahlberg method, the stage 1 futility sample size was set to the original protocol design of 10 patients per cohort (for Cohorts 1-5) 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). As noted, the IDMC reported that futility was surpassed and the cohorts were expanded for stage 2 for each of the DLBCL cohorts in (b) (6) (b) (6) for the FL EZH2 MT cohort on (b) (6) and for the FL EZH2 WT cohort on (b) (6). Stage 2 was designed to enroll an additional 50 patients in each of the DLBCL cohorts (1 to 3) and an additional 35 patients in each of the FL cohorts (4 and 5). The stage 2 rejection criteria were 14 responders of the total of 60 patients with DLBCL and 13 responders for the total of 45 patients with FL separately for the MT and WT cohorts.

Reviewer's Comments:

The phase 2 part of this study was designed in 2 stages, with futility hurdles based on protocol-specified efficacy criteria included at the end of each stage to determine if the cohorts should be expanded to allow enrollment of additional patients. The futility boundaries were surpassed for stage 1 for all cohorts and the cohorts were expanded.

Primary Objective for the FL cohorts:

The primary objective of the phase 2 portion of the study for patients with follicular lymphoma is to determine the ORR (complete response + partial response [CR + PR]) of tazemetostat in patients with EZH2 mutation positive (MT) or those without an identified EZH2 mutations (wild-type, WT) with histologically confirmed DLBCL or FL with relapsed or refractory disease.

Secondary Objectives for the FL cohorts:

- To assess the effect of tazemetostat monotherapy on duration of response (DOR)
- To assess the safety and tolerability of tazemetostat monotherapy
- To assess the PK profile of tazemetostat monotherapy

Exploratory Objectives:

- To explore the effect of tazemetostat monotherapy on overall survival
- To explore the PK and PD relationship of tazemetostat
- To investigate biomarkers and their correlation with biologic activity for tazemetostat
- To explore the effects of tazemetostat on H3K27 methylation, target gene expression, and phenotypic markers
- To explore the role of DNS sequence variability on absorption, metabolism

Study Population – Follicular Lymphoma (Key Eligibility Criteria)

- 18 years of age or greater, ECOG 0-2
- Histologically confirmed follicular lymphoma of all grades
- Relapsed/Refractory disease following at least 2 prior systemic treatments where at least one anti-CD20 therapy was used
- Sufficient archival tumor tissue that has been successfully tested for EZH2 mutation status
- Measurable disease as defined by international Working Group Non-Hodgkin's Lymphoma criteria (Cheson, 2007)
- Organ and Marrow function:
 - o Serum AST or ALT $\leq 3 \times$ upper limit of normal (ULN), $\leq 5 \times$ ULN if liver metastasis
 - o Total bilirubin $\leq 1.5 \times$ ULN
 - o Creatinine clearance ≥ 40 mL/min
 - o Absolute Neutrophil Count (ANC) $\geq 0.75 \times 10^9$ /L
 - o Hemoglobin ≥ 9.0 g/dL with or without transfusion support
 - o Platelet count $\geq 75,000/\mu\text{L}$ without transfusion support within 7 days
- At least 21 days since cytotoxic chemotherapy
- At least 14 days since non-cytotoxic therapy (i.e., small molecule inhibitor)
- At least 28 days since monoclonal antibody therapy
- At least 14 days since local site radiation therapy, and 6 weeks from radioisotope therapy, at least 12 weeks from 50% pelvic or total body irradiation
- At least 60 days since autologous stem cell transplant, at least 90 days from allogeneic transplant
- Exclude patients with leptomeningeal or brain metastasis
- Exclude patients with a history of prior myeloid malignancy including myelodysplastic syndrome
- Exclude patients with a history of T-Cell lymphoblastic lymphoma (T-LBL) or T-Cell lymphoblastic leukemia (T-ALL)
- Exclude patients receiving medications that are known potent CYP3A4 inducers or inhibitors
- Exclude patients with active infection requiring systemic therapy
- Exclude patients with venous thrombosis or pulmonary embolism within the last 3 months before starting tazemetostat
- Exclude patients with history of New York Heart Association (NYHA) Class II or greater
- Exclude patients with myocardial infarction or stroke within 6 months of study drug
- Exclude patients with prolongation of corrected QT interval (QTcF) to > 480 msec

Treatment:

All patients received tazemetostat 800 mg orally twice daily, continuously in repeated 28-day cycles. Treatment continued until confirmed disease progression, unacceptable toxicity or withdrawal of consent. Patients who remained on treatment for 24 months or longer and who

were eligible were transferred to rollover study EZH-501.

Study Endpoints

Phase 1: Maximum Tolerated Dose and Recommended Phase 2 Dose

Phase 2: Primary Efficacy Endpoint: Overall Response Rate (ORR) per Cheson 2007 criteria (Cheson 2007)

Secondary Efficacy Endpoints: Duration of Response
Progression-free survival

Clinical and Laboratory Assessments:

Clinical exam, vital signs and laboratory (hematology and chemistry) assessments were obtained at screening, and at days 1 and 15 of cycles 1 through 3. Assessments were once per cycle after cycle 3 in laboratory assessments were not required on and clinical follow up could be by phone on day 15.

Response Assessments: Radiologic tumor assessments were obtained (IWG-NHL [Cheson, 2007]) every 8 weeks during Cycles 2-6, and every 12 weeks starting at Cycle 7 and beyond. Tumor assessments were assessed by CT or MRI of the chest, abdomen, pelvis and other areas of known and suspected disease. FDG-PET was performed at screening and at the first assessment demonstrating PR or CR. Bone marrow biopsies were performed at screening, at first sign of CR and if clinically indicated.

Reviewer comment: The clinical and laboratory assessments were acceptable to adequately assess the safety of tazemetostat. The types and intervals of response assessment were acceptable for the primary endpoint of ORR.

Sample Size Calculation

The original study design planned enrollment of up to 30 patients in each monotherapy Cohort for Phase 2. The initial assessment of efficacy was to be conducted within each cohort when 10 patients had been enrolled (stage 1). For each DLBCL cohort, if zero responders (with CR or PR) out of the initial 10 patients 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 patients. For each FL cohort, if 1 or zero responders (CR or PR) out of the initial 10 patients 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 patients. 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 patients with DLBCL (GCB or non-GCB, EZH2 wild-type) were 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 patients 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 the table below.

Table 12: 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

Data Source: Applicant's SAP Table 2

Reviewer's Comment

Based on agreement with the Agency, the efficacy analyses included in this CSR were provided for patients with R/R FL enrolled in Cohort 4 and 5 prior to the data cutoff of (b) (6). At that time, enrollment in the EZH2 WT Cohort 5 was closed with 54 patients treated, 45 patients with EZH2 MT FL had been treated in Cohort 4. Data for 3 patients with EZH2 MT FL enrolled after the (b) (6) cutoff and will be provided in the final CSR once all cohorts are closed and all patients are off treatment.

Statistical Analysis Plan

Analysis Population

Efficacy endpoints were evaluated in the intent-to-treat (ITT) population which included all patients with R/R FL who received at least 1 dose of tazemetostat.

Safety population includes all patients in the ITT population set who had at least 1 post-dose safety observation recorded. The safety population was used for all safety analyses.

Efficacy Analysis

The primary analysis of the primary and secondary efficacy endpoints was performed using IRC response assessments. The investigator response assessment was analyzed as supportive evidence.

The primary efficacy endpoint is ORR, defined as the percentage of patients with a response of CR or PR. Patients with a best overall response (BOR) of stable disease (SD) or progressive disease (PD), or with non-evaluable, unknown, or missing response, were included as non-responders. ORR was presented with corresponding 2-sided Clopper-Pearson exact 95% CIs for each FL cohort and overall.

The following secondary efficacy endpoints were assessed for patients with R/R FL:

- Duration of response was defined as the time (in months) from the date of the initial response (CR or PR, whichever was first) until the date of first documented disease progression or death due to any cause. Patients who were alive and progression free at the time of the analysis were censored at the last date where the subject was known to be in response. DOR was analyzed using Kaplan-Meier methods, including median, first and third quartiles, and associated 2-sided 95% CIs. Kaplan-Meier estimates of DOR and the percent of patients in response at 6, 12, and 18 months, along with the associated 2-sided 95% CIs, are presented.
- Progression-free survival was defined as the time (in months) from the date of first dose of tazemetostat until the earliest date of disease progression or death from any cause. PFS was summarized using Kaplan-Meier methods; Kaplan-Meier estimates of PFS at 6, 12, 18 and 24 months, along with the associated 2-sided 95% CIs, are presented. Patients that did not die or progress on study were censored at the last adequate assessment.

Concordance of the IRC and Investigator assessments for BOR, ORR and disease control rate (DCR) are summarized.

Overall survival (OS) is an exploratory efficacy endpoint and was defined as the time (in months) from the date of first dose of tazemetostat until the date of death from any cause and was summarized in the same manner as PFS.

Reviewer's Comment:

Based on the protocol and SAP, there was no planned statistical hypotheses testing for comparison between cohorts.

Results from time-to-event analysis in single arm study is difficult to interpret, since single arm trials do not adequately characterize the time-to-event endpoints.

Protocol Amendments

Study E7438-G000-101 was amended 11 times. Amendments 1-6 were implemented prior to phase 2 enrollment. Amendments 7-11 occurred after phase 2 enrollment was initiated. A summary of major amendments 7-11 impacting the follicular lymphoma population is included in the table below. Patients with follicular lymphoma were permitted to be enrolled on the study in the U.S. per amendment 10. Prior to amendment 10, enrollment in the U.S. was restricted to DLBCL patients only due to second malignancy safety concern in patients with follicular lymphoma.

Original protocol: 1 November 2012

Table 13: Summary of Protocol Amendments Relevant to the Phase II study population

Amendment Number	Date	Amendment
7	11 February 2013	Included recommended phase 2 dose 800 mg PO BID - Added Secondary Objective of DOR, defined as the time from the first date of response (CR or PR, whichever is first), to recurrence, objectively documented disease progression or death - Added overall survival as an exploratory endpoint - Modified inclusion criteria to require at least 2 prior standard treatment regimens to include at least 1 anti-CD20 based regimen as well as an alkylating agent and have no curative option with other available therapies OR have a contra-indication to their use - Clarified that patients with prior stem cell transplant could be included - Added a requirement that an EZH2 mutation is required per central laboratory testing using the cobas® EZH2 mutation test, which is a real time allelic specific PCR test to detect mutations within codon Y646, A682, and A692 in formalin fixed paraffin-embedded tumor specimens Provided sample size rationale based on sample size of 30, if ORR is assumed as 40%, a sample size of 30

Amendment Number	Date	Amendment
		will provide a 95% Clopper Pearson exact CI of 22.7% to 59.4%. Safety: - Clarified that patients with a DVT who are receiving anticoagulation therapy with low molecular weight heparin could be included - Added AEs of special interest to include lymphoblastic lymphoma/T-ALL and events related to abnormal bone formation - Clarified that for patients who discontinue study therapy for reasons other than disease progression, tumor assessments will be performed every 8 weeks from the last tumor assessment until disease progression is documented or another anti-cancer therapy is initiated
8	15 September 2015	Revised inclusion criteria - Permitted patients with a history of hepatitis B who are surface antigen negative and/or have undetectable HCV RNA - Clarified that hematologic criteria must be met without growth factor support for at least 14 days and for at least 7 days since the last platelet transfusion - Clarified time required from last anticancer therapy - Clarified that all grades of FL were eligible - Permitted one of the prior therapies to be radiation if given for treatment - Excluded patients with venous thrombosis or pulmonary embolism within 3 months before starting therapy Specified that patients who remain on therapy for greater than 18 months and are eligible to continue receiving tazemetostat will transfer to a rollover study for monitoring and continued treatment Included PK and PD data from phase 1, food effect and DDI study

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Tazverik (tazemetostat)

Amendment Number	Date	Amendment
		- Added hematologic criteria prior to continuing therapy after cycle 1 - Clarified that tumor assessment would be per Cheson 2007 criteria and reviewed by and independent review committee - Specified that a PET scan would be performed on patient with NHL and a bone marrow biopsy would be performed on all subjects with follicular lymphoma at screening - Specified that tumor assessment would occur every 12 weeks
9	15 April 2016	- Clarified that does escalation at food effect study were closed - Removed requirement to measure respiratory rate and removed MUGA and echocardiogram requirement - Increased cohort size for both follicular lymphoma cohorts to 45 subjects each as recommended by the Data Monitoring Committee based on a study design change to a modified 2-stage Green-Dahlberg design - Decreased ANC criteria for continuing treatment beyond cycle 2 from $1.0 \times 10^9/\text{L}$ to $\geq 0.75 \times 10^9/\text{L}$ - Prohibited potent CYP3A4 inhibitors and inducers within 14 days prior to the first dose of tazemetostat
10	21 November 2016	- Added additional DLBCL cohort evaluating tazemetostat in combination with prednisolone - Allowed to treatment to continue upon disease progression if subjects do not have signs and symptoms that indicate unequivocal PD, have no decline in ECOG performance status, and have absent tumor growth and critical sites

Amendment Number	Date	Amendment
		- Removal of US specific requirement to only enroll DLBCL - Removal of histologically transformed FL from the inclusion criteria
11	24 September 2018	This amendment was submitted as a part of a response to partial clinical hold due to the report of a second malignancy (T-LBL) reported in a child in study EZH-202. The amendment included: - Information regarding the adverse events of special interest (T-LBL/T-ALL and MDS and risk mitigation and monitoring steps - Dose modification recommendations to discontinue tazemetostat for any cases of T-LBL, T-ALL or any suspected MDS - New exclusion criteria of cytopenias, prior myeloid malignancies or MDS, T-LBL, or T-ALL - Optional chest ultrasound every 8 weeks to monitor for early signs of LBL - Requirement for review of peripheral smear and performance of bone marrow aspirate and biopsy for any patients who have abnormal morphology on peripheral smear - Inclusion of tazemetostat safety committee that will review all adverse event of special interest cases - Revised the inclusion criteria to clarify that patients with histologically confirmed follicular lymphoma should have at least 2 standard lines of systemic therapy prior to study enrollment and that radiotherapy alone is not considered a separate systemic therapy - Clarification that bone marrow biopsies should be performed at the first notation of complete response

Study Results – Follicular Lymphoma Population

Compliance with Good Clinical Practices

The study was conducted under a U.S. Investigational New Drug application, in accordance with International Council for Harmonization (ICH) guidelines for Good Clinical Practice (GCP), and consistent with the Code of Federal Regulations (CFR), Title 21. The study protocols and informed consent documents were reviewed by a local Institutional Review Board/Independent Ethics Committee as required by regulations prior to implementation at practicing institutions.

Financial Disclosure

The Applicant submitted financial disclosure information from 495 investigators from the E7438-G000-101 study indicating that one of the investigators had disclosable financial interests or arrangements. For details, refer to the Clinical Investigator Financial Disclosure Review Template in Section 19.2

Data Quality and Integrity

The Contract Research Organizations (CROs), (b) (4) monitored this study following transfer from the previously contracted CRO (Biotrial monitored the Phase 1 part) to study conclusion. An initiation visit occurred at each site before patients were enrolled. (For US Oncology sites, this was completed through their training database once an eligible patient was identified; training was not on-site from an (b) (4) monitor.) During the site initiation visit, the protocol, eCRFs, procedures for obtaining informed consent, record keeping, reporting of all safety measurements, including AEs/SAEs, and investigator obligations and responsibilities were reviewed with the investigator and site research staff. Monitoring visits also included inspection of facilities, study drug storage area, and other study documentation. The investigator maintained a list of sub-investigators and other appropriately trained and qualified persons to whom he/she delegated significant study-related duties.

Reviewer's Comments

The Applicant implemented and maintained quality assurance and quality control systems with written standard operating procedures to ensure that trials were conducted and data were generated, documented, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirement(s).

No issues were identified with the data quality or integrity from the pivotal study which could affect the efficacy results. The submitted datasets are generally consistent, and variables are clearly labeled and/or explained.

Upon further clarification from the applicants per FDA's information requests (IRs), the reviewers were able to:

- ***Reproduce the applicant's analysis and analysis results for the primary and secondary efficacy endpoints***
- ***Conduct FDA's sensitivity analyses for the primary efficacy endpoint and subgroup analysis for the primary and secondary efficacy endpoints.***

Patient Disposition

A total of 99 patients with histologically confirmed R/R FL were enrolled in the phase 2 part of this study as of the data cutoff including 45 in the MT cohort and 54 in the WT cohort. All patients were treated with tazemetostat 800 mg twice daily.

As of the current data cutoff date, 13 (29%) of the 45 patients with FL in the MT cohort remained on treatment, while all of the 54 patients in the WT cohort discontinued the study drug. Among the patients that discontinued the study drug, 3 patients (7%) of the 45 in the MT cohort and 8 patients (15%) of the 54 in the WT cohort had gone on to continued treatment with tazemetostat in the rollover study EZH-501.

The primary reason for discontinuation of tazemetostat was disease progression, reported in 23 (51%) of 45 patients in the MT cohort, and 39 (72%) of 54 patients in the WT cohort, respectively. Discontinuation of treatment due to TEAEs was reported in 7% and 9% of patients in the MT and WT cohort, respectively.

As of the data cutoff, 34 (76%) of the 45 patients in the MT cohort and 19 (35%) of the 54 patients in the WT cohort were alive and remained in follow-up, including patients who remained on treatment. Overall, 29 patients with FL had died, the percent of patients who had died was 18% in the MT cohort and 39% in the WT cohort.

Table 14: Patient Disposition (ITT Population)

Disposition Status	FL MT (N=45) n (%)	FL WT (N=54) n (%)	R/R DLBCL (N=234), n (%)
Treated with tazemetostat	45 (100)	54 (100)	234 (100)
Discontinued study drug	32 (71.1)	54 (100)	232 (99.1)
Adverse event	3 (6.7)	5 (9.3)	20 (8.5)
Disease progression	23 (51.1)	34 (63.0)	154 (65.8)
Unconfirmed progression	0	5 (9.3)	38 (16.2)
Patient choice	2 (4.4)	1 (1.9)	6 (2.6)
Enrolled in rollover study	3 (6.7)	8 (14.8)	8 (3.4)
Withdrawal of consent	0	1 (1.9)	1 (1.0)
Other	1 (2.2)	0	5 (2.1)
Status at last contact, n (%)			
Alive and continuing follow-up	34 (75.6)	19 (35.2)	39 (16.7)
Dead	8 (17.8)	21 (38.9)	176 (75.2)
Lost to follow-up	0	1 (1.9)	5 (2.1)
Withdrawal of consent	0	3 (5.6)	3 (1.3)
Enrolled in rollover study	3 (6.7)	8 (14.8)	8 (3.4)

Disposition Status	FL MT (N=45) n (%)	FL WT (N=54) n (%)	R/R DLBCL (N=234), n (%)
Unknown status	0	2 (3.7)	3 (1.3)

Data Source: Reviewer's Analysis

Reviewer's Comments:

FDA's analysis results of patient disposition are consistent with those from the applicant.

Protocol Violations/Deviations

Three patients had major protocol deviations reported, all were patients with DLBCL (all were related to lack of measurable disease per radiographic scans as required by the study entrance criteria). As the focus of efficacy results for this interim CSR is on patients with R/R FL, these deviations have no impact on the analyses.

Two patients in the EZH2 mutated population had protocol violations related to prior therapies. These are considered major protocol violations as these patients had only one prior systemic therapy regimen which violated the protocol inclusion criteria of two prior systemic therapies.

Subject (b) (6) was a 65-year-old female who only received one prior line of therapy, R-CHOP. The Applicant has considered this as a minor protocol violation with no explanation. Root cause is listed as unknown.

Subject (b) (6) was a 53-year-old enrolled in the EZH2 mutation positive cohort. The patient received prior bendamustine and rituximab as a single regimen prior to enrollment in the study. No prior radiation therapy was administered. The Applicant listed this as a minor protocol violation with the reason listed as the study team determined that maintenance rituximab was considered a second therapy.

Reviewer comment:

The two protocol violations as listed above are problematic as these patients were both responders and do not reflect the indicated population as defined by the eligibility criteria following amendment 11 (the most up to date protocol version), which is the treatment of patients with follicular lymphoma who have received two prior systemic therapies. Removing these patients from the efficacy analysis does not significantly impact the ORR, 95% CI or the median DOR. These two patients should be excluded from the MT population efficacy analysis and efficacy results included in the USPI.

The remainder of protocol violations were due to missed assessments or missed doses. No other protocol violations were identified that would be expected to alter interpretation of the study results.

Table of Demographic Characteristics

Among the 99 patients with FL included in the ITT population for analysis of efficacy results, median age was 62 years in the MT cohort (range: 38 to 80 years) and 60.5 years in the WT cohort (range: 36 to 87 years). Males comprised 42% of patients with FL in the MT cohort and 63% in the WT cohort. Most patients had ECOG performance status of 0 or 1. White comprised 69% and 28% of the patients in the MT and WT cohort respectively.

Table 15: Demographic Characteristics of the Primary Efficacy Population

Demographic Characteristic	FL MT (N=45)	FL WT (N=54)	R/R DLBCL (N=234)
Age (years)			
Mean (SD)	61.8 (9.02)	61.1 (11.38)	63.9 (13.63)
Median	62.0	60.5	68.0
Min, Max	38, 80	36, 87	21, 87
Age Group (years)			
≥65	20 (44.4)	22 (40.7)	140 (59.8)
<65	25 (55.6)	32 (59.3)	94 (40.2)
Sex, n(%)			
Male	19 (42.2)	34 (63.0)	130 (55.6)
Female	26 (57.8)	20 (37.0)	104 (44.4)
Race, n (%)			
White	31 (68.9)	15 (27.8)	99 (42.3)
Asian	0	1 (1.9)	4 (1.7)
Black or African American	0	0	1 (0.4)
Other/Unknown	14 (31.1)	38 (70.4)	130 (55.6)
Ethnicity, n (%)			
Hispanic or Latino	0	3 (5.6)	4 (1.7)
Not Hispanic or Latino	36 (80.0)	26 (48.1)	165 (70.5)
Other/Unknown	9 (20.0)	25 (46.3)	65 (27.8)
Region			
Europe	29 (64.4)	47 (87.0)	194 (82.9)
North America	12 (26.7)	2 (3.7)	30 (12.8)
Rest of World	4 (8.9)	5 (9.3)	10 (4.3)
ECOG Performance Status, n(%)			
0	21 (46.7)	26 (48.1)	93 (39.7)
1	24 (53.5)	23 (42.6)	112 (47.7)
2	0	4 (7.4)	30 (9.0)
3	0	0	2 (0.6)
Missing	0	1 (1.9)	2 (0.6)

Data Source: Reviewer's Analysis

Reviewer's Comments:

There were only 12 patients in the MT cohort from North America, and none of patients in the

WT cohort from the U.S. There is a concern as to whether the efficacy results are generalizable to a representative US patient population. This will be addressed as part of post marketing requirements which will require study of a diverse population representative of the U.S. population in the confirmatory studies.

FDA's analysis results of demographic characteristics are consistent with those from the applicant.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 16 below shows a summary of baseline disease characteristics in the ITT population. About 78% of patients with FL had Stage III or IV disease at diagnosis in each of the MT and WT cohort. Myelosuppression (grade ≥ 1 cytopenias) was reported at baseline in 51% and 63% of FL patients in the MT and WT cohort respectively. Notably, 42% and 59% of FL patients in each of the MT and WT cohort had early progression following front-line therapy (POD24), a known poor prognostic factor.

Table 16: Baseline Disease Characteristics (ITT Population)

Disease Characteristic	FL MT (N=45)	FL WT (N=54)	R/R DLBCL (N=234)
Stage at Diagnosis, n (%)			
I	2 (4.4)	3 (5.6)	15 (6.4)
II	5 (11.1)	6 (11.1)	24 (10.3)
III	10 (22.2)	9 (16.7)	49 (20.9)
IV	25 (55.6)	33 (61.1)	122 (52.1)
Unknown	2 (4.4)	1 (1.9)	17 (7.3)
Missing	1 (2.2)	2 (3.7)	7 (3.0)
Myelosuppression at Baseline	23 (51.1)	34 (63.0)	182 (77.8)
POD24	19 (42.2)	32 (59.3)	NE
Met GELF Criteria	31 (68.9)	40 (74.1)	195 (83.3)
Presence of Target Lesions, IRC, n (%)			
Lymph nodes	42 (93.3)	45 (83.3)	NA
Non-lymph nodes	4 (8.9)	7 (13.0)	NA
SPD of All Target Lesions, IRC (mm ²), n	44	48	NA
Mean (SD)	2861 (3279.5)	3125 (2660.3)	NA
Median	2041	2471	NA
Min, Max	110, 20940	127, 11682	NA

Data Source: Reviewer's Analysis

Table below shows a summary of prior cancer-related therapies. The median number of lines of prior systemic therapy among FL patients was 2.0 with a range from 1 to 11 in the MT cohort and 3.0 with a range from 1 to 8 in the WT cohort. In the MT and WT cohort, 16% and 30% of

patients had received 5 or more prior treatment lines, respectively. About 49% of the MT patients and 59% of the WT patients were refractory to a rituximab-containing regimen, and 49% of MT and 41% of the WT patients were refractory to their last regimen before enrolling into the study; 20% of the MT and 28% of the WT patients were double refractory to rituximab and an alkylating agent.

Table 17: Prior Cancer-Related Therapies (ITT Population)

Prior Cancer-Related Therapies	FL MT (N=45)	FL WT (N=54)
Any prior radiotherapy, n (%)	13 (28.9)	12 (22.2)
Prior stem cell transplant, n (%)	4 (8.9)	21 (38.9)
Prior lines of systemic anticancer therapy, n		
Median	2.0	3.0
Min, Max	1, 11	1, 8
Prior lines of systemic anticancer therapy, n (%)		
1	2 (4.4)	1 (1.9)
2	22 (48.9)	16 (29.6)
3	10 (22.2)	11 (20.4)
4	4 (8.9)	10 (18.5)
≥5	7 (15.6)	16 (29.6)
Refractory to rituximab	22 (48.9)	32 (59.3)
Refractory to last therapy	22 (48.9)	22 (40.7)
Double refractory	9 (20.0)	15 (27.8)

Source: Reviewer's Analysis

Reviewer's Comments:

Overall, 69% and 74% of FL patients in each of MT and WT cohort met Group d-Etude des Lymphomas Follicular (GELF) criteria, respectively. A total of 22.2% of patients in the MT and 20.4% of patients in WT cohort had received 3 prior treatment lines, respectively.

FDA's analysis results of baseline characteristics are consistent with those from the applicant.

Additional Clinical Analysis of Trial Population

An additional analysis was performed by the clinical review team of the types of prior therapies to determine if prior treatment regimens were consistent with what would be considered standard accepted therapy for patients with R/R follicular lymphoma at the present time with a focus on the recently approved regimens of rituximab + lenalidomide and bendamustine plus obinutuzumab. The table below summarizes the number of patients who had received currently accepted approved therapies.

Table 18: Percentage of Patients Receiving Current Approved therapies for R/R Follicular Lymphoma

Prior Therapy	EZH2 WT N = 54	EZH2 MT N = 45	TOTAL FL N = 99
Prior anti-CD20	54 (100%)	45 (100%)	99 (100%)
Prior Bendamustine	25 (46%)	25 (55%)	50 (50%)
Prior Obinutuzumab	5 (9%)	4 (9%)	9 (9%)
Prior Lenalidomide	9 (17%)	6 (13%)	15 (15%)
Prior Lenalidomide + Rituximab	6 (11%)	4 (9%)	10 (10%)
Prior Transplant	21 (39%)	4 (9%)	25 (25%)

Reviewer Comment:

A review of the types of prior therapies received in the overall and individual MT and WT cohorts revealed that an overall low (9-17%) number of patients had received obinutuzumab or lenalidomide containing regimens. This is likely, in part, due to the timing of the study which enrolled patients in the primary efficacy population from (b) (6) through (b) (6) of (b) (6). The lenalidomide and rituximab (R²) regimen was approved in 2019 and bendamustine + obinutuzumab was approved in 2016. Therefore, the clinical trial population may not reflect a population who had failed all currently available therapies.

During the review of prior therapies, 4 patients were identified who had not received at least two prior systemic therapies. One patient was in the WT cohort and the other three were in the MT cohort. Three of the 4 patients were responders. These patients are summarized in the table below:

Table 19: Summary of Patients Who Received Less than 2 Prior Systemic Therapies

USUBJID	Best Overall Response	MT / WT	Reason for only 1 prior therapy
(b) (6)	PR	WT	Prior radiation considered prior therapy prior to amendment 11
(b) (6)	SD	MT	Prior radiation considered prior therapy prior to amendment 11
(b) (6)	PR	MT	Protocol Violation
(b) (6)	CR	MT	Protocol Violation

The patient in the wild-type cohort, Subject (b) (6) was reported to only have received one prior therapy. Since this was discrepant from the most recent protocol inclusion criteria, an information request was sent to the Applicant to clarify.

The Applicant clarified that subject (b) (6) was enrolled onto the study prior to protocol amendment 11 which stipulated that patients must have received at least 2 prior systemic therapies. This patient had received local radiation therapy plus one course of R-CHOP plus rituximab maintenance and was enrolled on the trial at time when radiation therapy could be considered a prior therapy. Since this patient does not reflect the indicated population or *the eligibility criteria following amendment 11*, an analysis was performed of ORR and DOR that excludes this patient.

Reviewer Comment:

Excluding this patient from the WT population decreases the ORR to 34% (95% CI 22, 48%) and does not significant impact approval decisions.

A second patient in the MT cohort, subject (b) (6) also received local radiation therapy only plus one additional systemic therapy.

Reviewer comment:

This patient's best response was SD and therefore does not significantly change the assessment of the primary endpoint ORR.

Two additional patients (both MT), and both responders (one CR and PR) were enrolled with only one prior therapy which was considered a protocol violation.

Subject (b) (6) in the EZH2 mutation cohort received one prior therapy (R-CHOP) and was enrolled on the study only having one prior therapy. This was considered a protocol violation. No further information was provided regarding this protocol violation. This patient had a best

overall response of partial response.

Subject (b) (6) in the EZH2 mutation positive cohort received one prior therapy regimen (BR) and was enrolled on the study due to the study team considering rituximab maintenance therapy as a second line of therapy. This was considered a protocol violation.

Clinical Reviewer comment: The enrollment of four patients with only one prior systemic therapy is problematic as this does not reflect the indicated population or the eligibility criteria following amendment 11 and these patients, having less prior therapy may have a higher response rate than those with 2 prior therapies. Inclusion of these patients in the in the ORR may inflate the response rates of the true third line and greater population. For this reason additional analysis were performed, excluding these patients from the analysis which did not significantly change the ORR, 95% CI or DOR for the indicated population, however, only the patients who received protocol defined two prior systemic therapies should be included in label.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The median average dose of tazemetostat for patients with FL was 800 mg, mean 764 mg and range (379, 805) suggesting adequate compliance. There were no identified issues related to compliance.

Of concomitant medications taken by $\geq 20\%$ of patients with FL, the most common were proton pump inhibitors (38%), antipyretics (32%), penicillin (30%), antivirals (valaciclovir and acyclovir) (27%), HMG COA reductase inhibitors (25%), glucocorticoids (22%), benzodiazepines (20%)

The most common reason for glucocorticoid administration was and adverse event or pre-existing condition. The median duration of exposure was 3 days with 75% of patients receiving less than 7 days. Due to protocol specified requirements for PJP prophylaxis and antivirals, 92% of patients received these medications.

Reviewer comment:

A review of the concomitant medication use does not demonstrate any significant AE signal. Of the common concomitant medications administered, glucocorticoids are the only class that could potentially impact efficacy by an anti-tumor effect. A review of the duration of treatment (less than 7 days for most patients) and the reasons for administration make any contribution to efficacy unlikely.

Efficacy Results – Primary Endpoint-ORR

Among the 45 patients in the MT cohort, the ORR based on IRC assessment was 69% (95% CI: 53.4, 81.8), including 6 patients achieving CR and 25 achieving PR as of the data cutoff. Among the 54 patients in the WT cohort, the ORR based on IRC assessment was 35% (95% CI: 22.7,

49.4), including 2 patients achieving CR and 17 achieving PR as of the data cutoff.

Table 20: Summary of Objective Response Rates (ORR) by Cohort (ITT Population)

Endpoint	FL MT (N=45)		FL WT (N=54)	
	IRC	Investigator	IRC	Investigator
Objective Response Rate				
n (%)	31 (68.9)	35 (77.8)	19 (35.2)	18 (33.3)
[95% CI]	[53.4, 81.8]	[62.9, 88.8]	[22.7, 49.4]	[21.1, 47.5]
BOR, n (%)				
Complete response	6 (13.3)	4 (8.9)	2 (3.7)	3 (5.6)
Partial response	25 (55.6)	31 (68.9)	17 (31.5)	15 (27.8)
Stable disease	13 (28.9)	10 (22.2)	18 (33.3)	16 (29.6)
Progressive disease	1 (2.2)	0	12 (22.2)	16 (29.6)
NE/Unknown	0	0	5 (9.3)	4 (7.4)
Abbreviations: BOR, best overall response; CI, confidence interval; FL, follicular lymphoma; IRC, independent review committee, MT, EZH2 mutated; NE, not evaluable; WT, EZH2 wild-type				

Source: Reviewer's Analysis

Reviewer's Comments:

FDA's analysis results of primary efficacy endpoint are consistent with those from the applicant.

The reviewer's descriptive analyses result also showed that there were slight numerical differences for the analysis results of ORR and CR/PR between IRC assessment and Investigator assessment for both MT cohort and WT cohort (Table 20). The observed ORR in the MT group was 68.9% (95% CI: 53.4, 81.8) using IRC assessment and 77.8% (95% CI: 62.9, 88.8) using investigator assessment. The observed ORR in the WT group was 35.2% (95% CI: 22.7, 49.4) using IRC assessment and 33.3% (95% CI: 21.1, 47.5) using investigator's assessment.

The approval was based upon the efficacy in 95 patients (42 EZH2 MT cohort, 53 EZH2 wild type) who had received at least 2 prior systemic therapies and is presented in the table below.

Table 21: Summary of Efficacy Results (FDA's Efficacy Population)

Endpoint	FL MT (N=42)		FL WT (N=53)	
	IRC	Investigator	IRC	Investigator
Objective Response Rate				
n (%)	29 (69.1)	33 (78.6)	18 (34.0)	18 (34.0)
[95% CI]	[52.9, 82.4]	[63.2, 89.7]	[21.5, 48.3]	[21.5, 48.3]
BOR, n (%)				
Complete response	5 (11.9)	3 (7.1)	2 (3.8)	3 (5.7)
Partial response	24 (57.1)	30 (71.4)	16 (30.2)	15 (28.3)
Stable disease	12 (28.6)	9 (21.4)	18 (34.0)	15 (28.3)
Progressive disease	1 (2.4)	0	12 (22.6)	16 (30.2)
NE/Unknown	0	0	5 (9.4)	4 (7.6)
Abbreviations: BOR, best overall response; CI, confidence interval; FL, follicular lymphoma; IRC, independent review committee, MT, EZH2 mutated; NE, not evaluable; WT, EZH2 wild-type				

Subgroup Analysis

Table 22 provides a summary of ORR per IRC-assessment across subgroups for patients in both MT and WT cohorts. As shown, all 95% CIs around the point estimates for each subgroup overlapped; further, 95% CIs for each subgroup included the point estimate for the overall population.

Table 22: Summary of ORR per IRC by Subgroups (ITT Population)

Subgroup	FL MT (N=45)	FL WT (N=54)
Age Group (years)		
<65 ORR (95% CI)	18/25 72.0 (50.6, 87.9)	9/32 28.1 (13.7, 46.7)
≥65 ORR (95% CI)	13/20 65.0 (40.8, 84.6)	10/22 45.5 (24.4, 67.8)
Sex, n(%)		
Male ORR (95% CI)	13/19 68.4 (43.4, 87.4)	9/34 26.5 (12.9, 44.4)
Female ORR (95% CI)	18/26 69.2 (48.2, 85.7)	10/20 50.0 (27.2, 72.8)
Race, n (%)		
White ORR (95% CI)	21/31 67.7 (48.6, 83.3)	5/15 33.3 (11.8, 61.6)
Asian ORR (95% CI)	0	1/1 100.0 (25.0, 100)
Black or African American ORR (95% CI)	0	0

Subgroup	FL MT (N=45)	FL WT (N=54)
Other/Unknown ORR (95% CI)	10/14 71.4 (41.9, 91.6)	13/38 34.2 (19.6, 51.4)
Region		
Europe ORR (95% CI)	20/29 69.0 (49.2, 84.7)	18/47 38.3 (24.5, 53.6)
North America ORR (95% CI)	7/12 58.3 (27.7, 84.8)	0/2 0.0 (0.0, 84.2)
Rest of World ORR (95% CI)	4/4 100 (39.8, 100)	1/5 20.0 (0.5, 71.6)
Abbreviations: CI, confidence interval; FL, follicular lymphoma; IRC, independent review committee, MT, EZH2 mutated; ORR, overall response rate; WT, EZH2 wild-type		

Data Source: Reviewer's Analysis

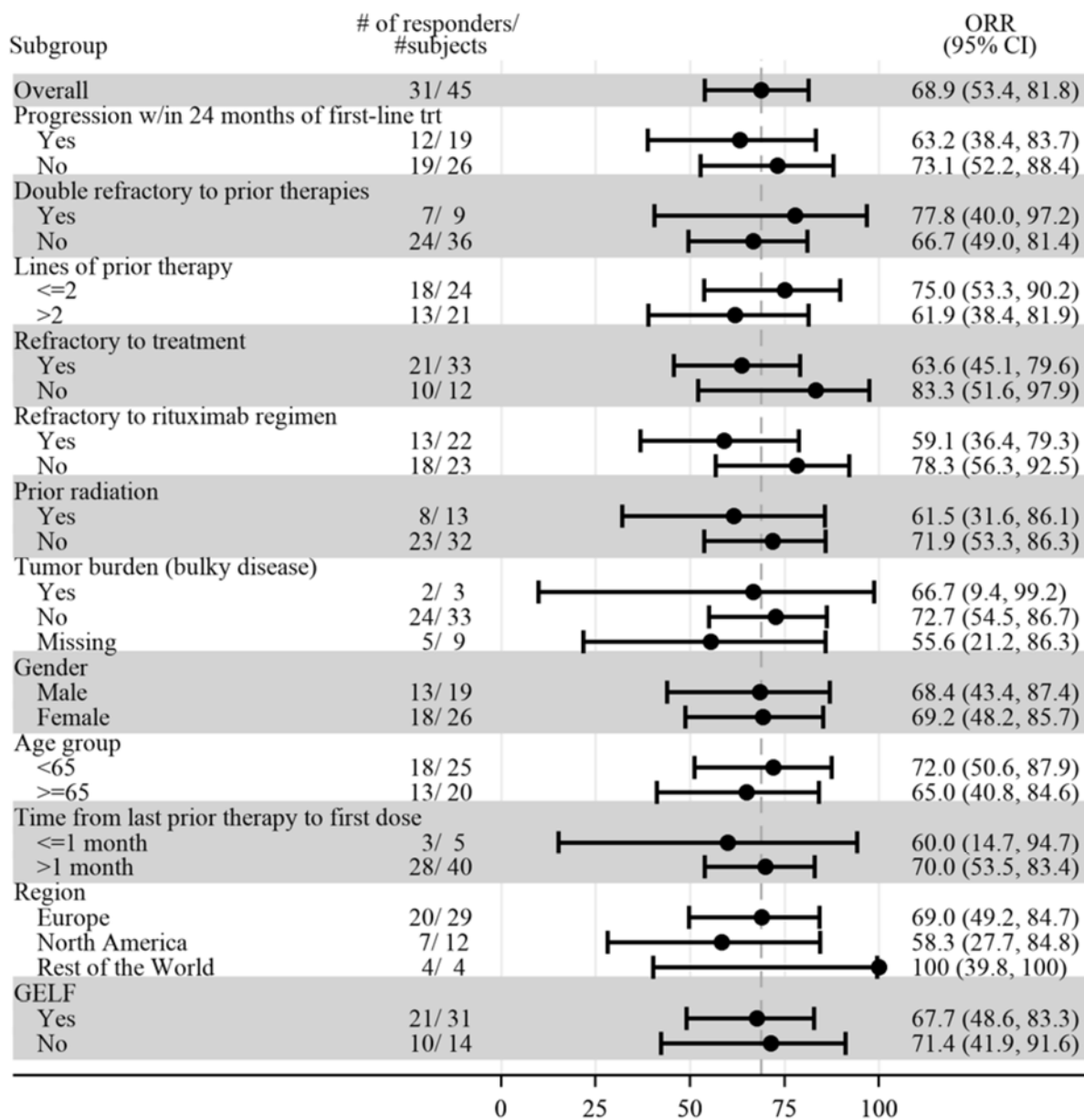
Reviewer's Comment:

FDA's analysis results subgroup analyses are consistent with those from the applicant.

Subgroup analysis was not inconsistent with homogeneous treatment effect across subgroups. For MT cohort, the observed ORR by IRC assessment was 58.3% (95% CI: 27.7, 84.8) from North America. Given the small sample size in the subgroups, caution should be taken in the interpretation of the subgroup analysis results.

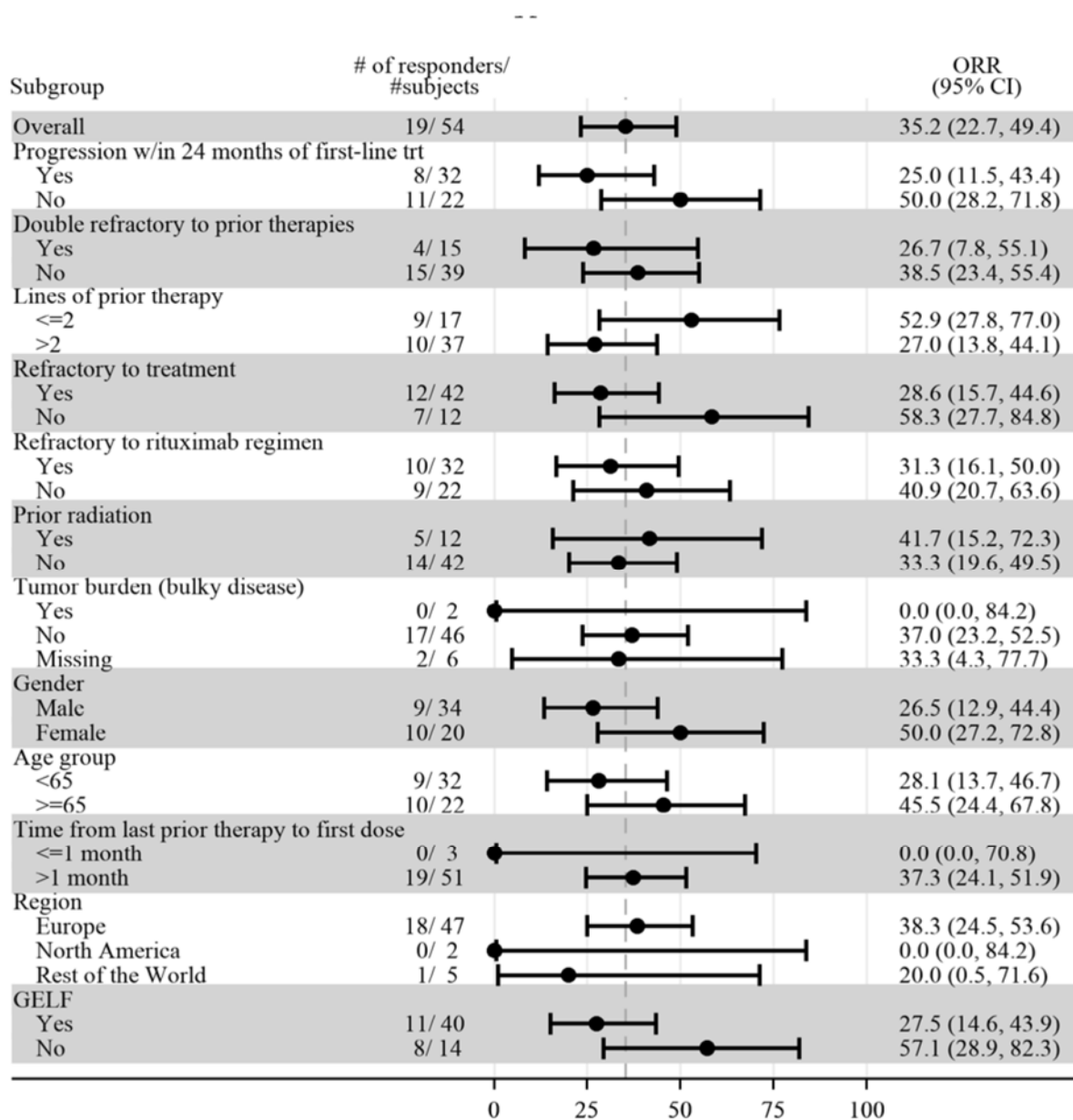
The forest plot below shows overall response rate by subgroup per IRC assessment using ITT population in EZH2 mutant cohort.

Figure 11: ORR by Subgroup per IRC for MT Cohort (ITT)



The forest plot below shows overall response rate by subgroup per IRC assessment using ITT population for EZH2 wild-type cohort.

Figure 12: ORR by Subgroup per IRC for WT Cohort (ITT)



Reviewer's Comment:

FDA's analysis results of subgroup analyses are consistent with those from the applicant.

For subgroup analysis in the WT cohort, the ORR for the patients received >2 lines of prior therapy at baseline appears to be worse than that in the overall population. The observed ORR by IRC assessment with >2 lines of prior therapy at baseline was 27% (95% CI: 13.8, 44.1).

There is no response in the 2 patients from North America. Given the small sample size in the subgroups, caution should be taken in the interpretation of the subgroup analysis results.

Dose/Dose Response

See Clinical Pharmacology Section. One dose level 800 mg twice daily was explored.

Efficacy Results – Secondary endpoints

Duration of Response

The following table shows the summary of objective duration of response (DOR) by cohort per IRC assessment. The median duration of response for patients with EZH2 MT and WT FL is 10.9 and 13.0 months, respectively.

Table 23: Summary of Objective Duration of Response (DOR) by Cohort per IRC (ITT Population)

Endpoint	FL MT (N=45)	FL WT (N=54)
DOR (months), n	31	19
Median [95%]	10.9 [7.2, NE]	13.0 [5.6, NE]
Range	(0.0, 22.1)	(0.5, 22.5)
Median time to first response (months), n	31	19
Median (range)	3.7 [1.6, 10.9]	3.7 [1.6, 16.3]
Median follow-up time (months)		
Median (range)	22.0 (2.8, 43.5)	35.9 (0.3, 48.8)
Abbreviations: DOR, duration of response; FL, follicular lymphoma; IRC, independent review committee, MT, EZH2 mutated; NE, not estimable; WT, EZH2 wild-type		

The following table shows the summary of objective duration of response (DOR) by cohort per investigator assessment. The median duration of response for patients for EZH2 MT Cohort and WT Cohort is 8.3 months and 14.7 months, respectively.

Table 24: Summary of Objective Duration of Response (DOR) by Cohort per Investigator Assessment (ITT Population)

Endpoint	FL MT (N=45)	FL WT (N=54)
DOR (months), n	35	18
Median [95%]	8.3 [5.5, NE]	14.7 [7.6, NE]
Range	(0.0, 22.1)	(1.7, 22.5)
Median time to first response (months), n	35	18
Median (range)	3.8 [1.6, 11.0]	3.5 [1.6, 16.3]
Abbreviations: DOR, duration of response; FL, follicular lymphoma; MT, EZH2 mutated; NE, not estimable; WT, EZH2 wild-type		

Reviewer Comments

In the MT cohort, the median time to first response was 3.7 months based on IRC assessment and ranged from 1.6 to 10.9 months; the median DOR was 10.9 months with a maximum duration of 22.1 months as of the data cutoff.

In the WT cohort, the median time to first response was 3.7 months based on IRC assessment and ranged from 1.6 to 16.3 months; the median DOR was 13.0 months with a maximum duration of 22.5 months as of the data cutoff.

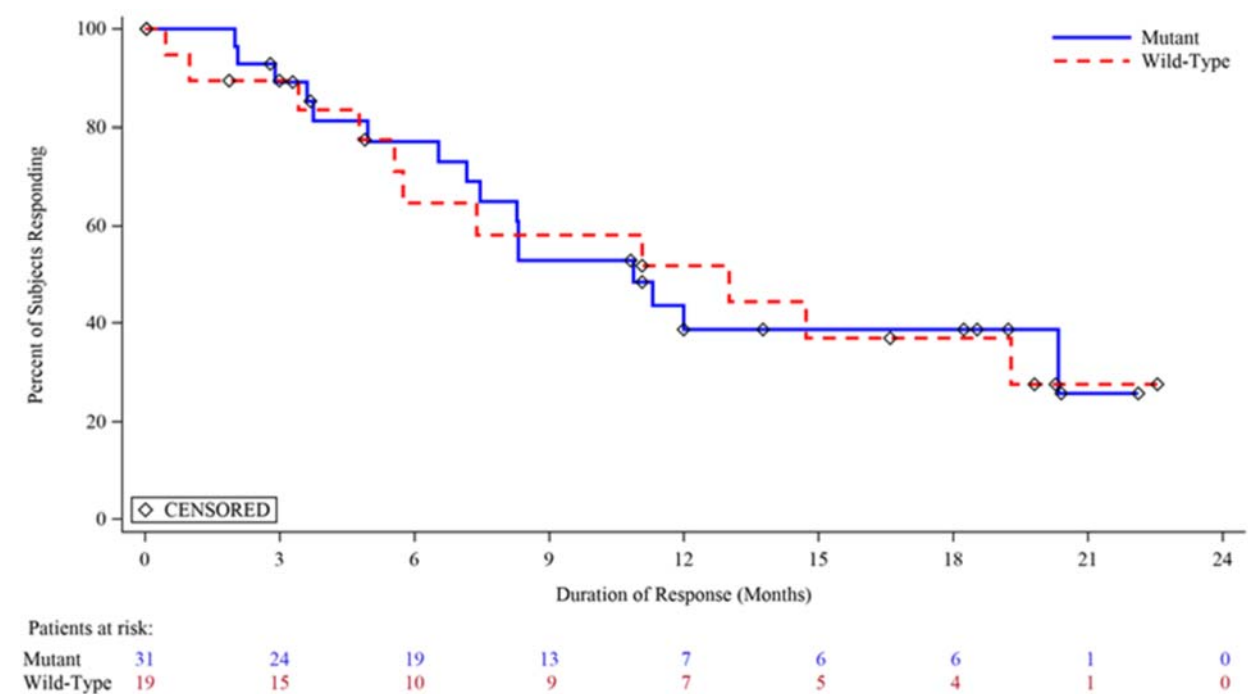
The following table shows the summary of objective duration of response (DOR) by cohort using the adjusted efficacy population including patients that had received at least 2 prior systemic therapies. The median duration of response for patients for EZH2 MT Cohort and WT Cohort is 10.9 months and 13.0 months, respectively.

Table 25: Summary of Objective Duration of Response (DOR) by Cohort -FDA's Population

Endpoint	FL MT (N=42)	FL WT (N=53)
DOR (months), n	29	18
Median [95%]	10.9 [7.2, NE]	13.0 [5.6, NE]
Range	(0.0*, 22.1*)	(0.99, 22.5*)
Abbreviations: DOR, duration of response; FL, follicular lymphoma; MT, EZH2 mutated; NE, not estimable; WT, EZH2 wild-type		

The figure below shows the Kaplan-Meier curve of duration of response per IRC assessment using ITT population.

Figure 13: Kaplan-Meier Plot of DOR per IRC Assessment (ITT)



Reviewer's Comment:

Based on the protocol and SAP, there was no planned statistical hypotheses testing for comparison between cohorts. Therefore, this KM plot is for illustration only.

Progression-Free Survival

Table below shows summary of progression-free survival by cohort using ITT population. The median PFS based on IRC assessment was 13.8 months in the MT cohort. Results were consistent among patients in the WT cohort with median PFS based on IRC assessment of 11.1 months.

Table 26: Summary of Progression-Free Survival (PFS) by Cohort (ITT Population)

Endpoint	FL MT (N=45)		FL WT (N=54)	
	IRC	Investigator	IRC	Investigator
Events, n (%)	25 (55.6)	26 (57.8)	32 (59.3)	40 (74.1)
PFS (months)				
Median [95%]	13.8 [10.7, 22.0]	13.8 [8.4, 16.4]	11.1 [3.7, 14.6]	5.6 [3.3, 11.1]
Min, Max	1.3, 24.7*	1.5*, 24.7*	0.0*, 27.6	0.0*, 30.4*

* = censored observation

Data Source: Reviewer's Analysis

Reviewer's Comments:

FDA's analysis results of PFS endpoint are consistent with those from the applicant.

There are 56% of patients in the MT cohort and 59% of patients in the WT cohort had PFS events per the IRC assessment. A higher proportion of patients were reported to have PFS events in the WT cohort per Investigator assessment (74%). In both analyses, the primary reasons for censoring were related to patients who were alive and progression-free or patients who had received new anticancer therapy without documented progression (64% of the patients censored for both the IRC and Investigator-based analyses)

Figure below shows Kaplan-Meier plot of progression-free survival per IRC assessment using ITT population.

Figure 14: KM Plot of PFS per IRC Assessment (ITT)

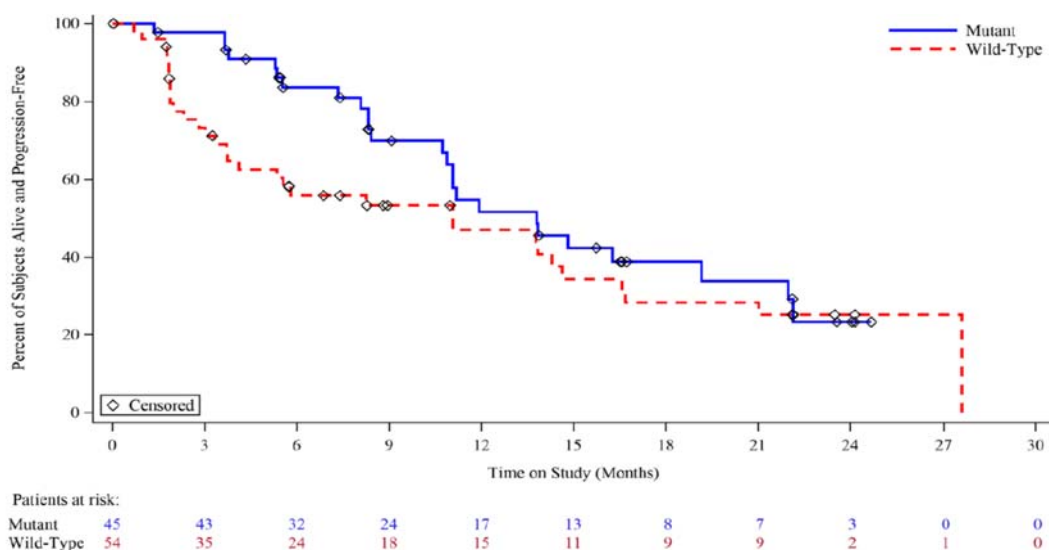
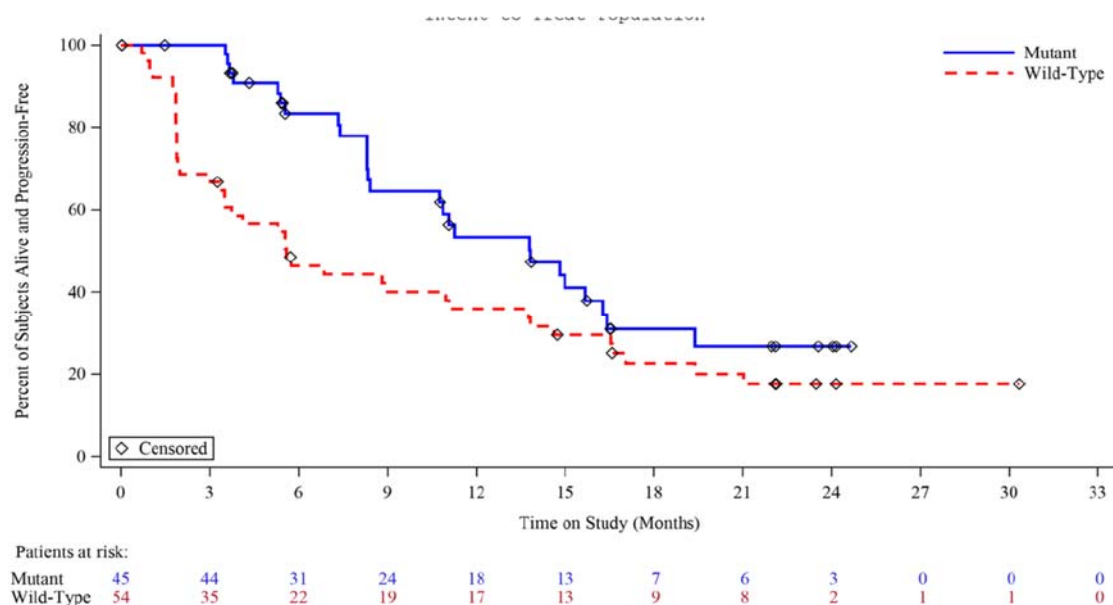


Figure below shows Kaplan-Meier plot of progression free survival per investigator assessment using ITT population

Figure 15: KM Plot of PFS per Investigator Assessment (ITT)



Reviewer's Comment

PFS K-M curves for the 2 cohorts per IRC assessment shows an early separation, but similar results after 12 months, while PFS K-M curves for the 2 cohorts per investigator assessment shows separation results after 16 months.

The reviewer's descriptive analyses result also showed that there were numerical differences for the analysis results of median PFS between IRC assessment and Investigator assessment for WT cohort (Table 26). The observed median PFS in the WT cohort was 11.1 months (95% CI: 3.7, 14.6) using IRC assessment and 5.6 months (95% CI: 3.3, 11.1) using investigator assessment.

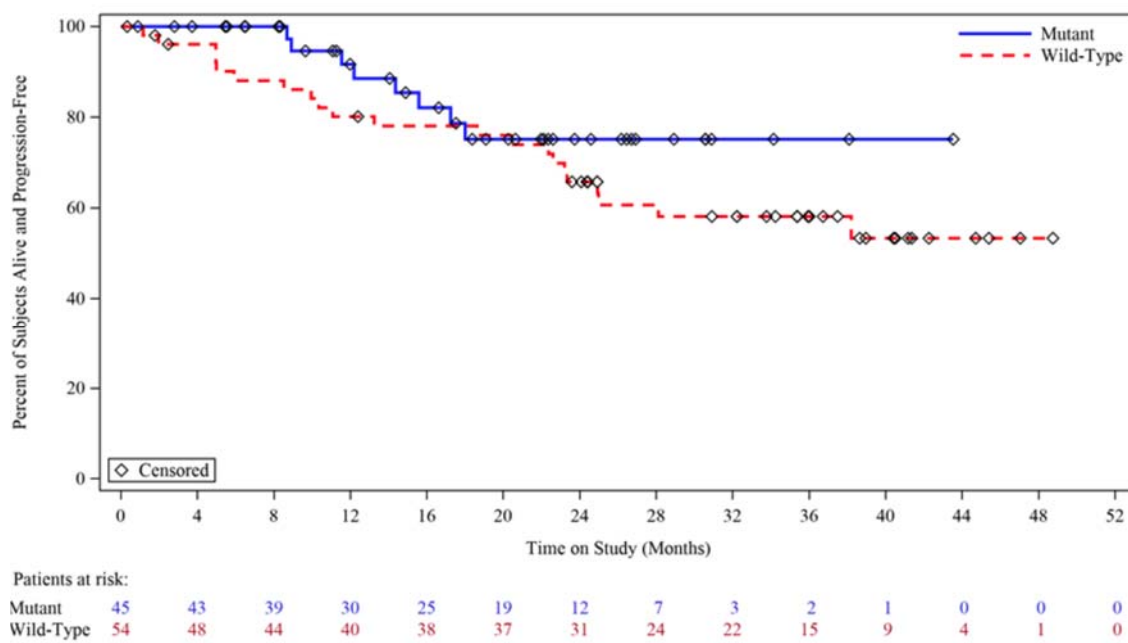
Based on the protocol and SAP, there was no planned statistical hypotheses testing for comparison between cohorts. Therefore, this KM plot is for illustration only. The patient samples being compared are not a randomized and any observed difference could be from several confounding factors other than biomarker.

Overall Survival

As of the data cutoff, 37 (82%) of the 45 patients in the MT cohort and 33 (61%) of the 54 patients in the WT cohort were alive. Median OS was not reached in either cohort.

Figure below shows Kaplan-Meier plot of overall survival using ITT population

Figure 16: KM Plot of OS (ITT)



Reviewer's Comment:

The data for analysis of OS are immature. Median OS was not reached in either cohort as of the data cutoff.

Based on the protocol and SAP, there was no planned statistical hypotheses testing for comparison between cohorts. Therefore, this KM plot is for illustration only.

PRO Endpoint

There is no patient-reported outcome data submitted in this submission.

Additional Efficacy Considerations

In addition to the subgroup analysis performed by the Applicant in patients with early progression (POD24) and included above, additional analysis were performed to evaluate response in high risk populations, such as patients with early relapse (POD24), rituximab refractory, and more than three prior therapies. The results of these analysis are included in the subgroup analysis displayed below:

Table 27: Exploratory Analysis of ORR and DOR in Patients who have received 3 or more prior Therapies

	FL MT N = 21	FL WT N = 37	Total N = 58
ORR	13 (62%) (38, 82)	10 (27%) (14, 44)	23 (40%) (27, 53)
CR	3 (14%) (3, 36)	2 (5%) (1%, 18%)	5 (9%) (3, 20)
PR	10 (48%) (26, 70)	8 (22%) (10, 38)	18 (31%) (20, 45)
Median DOR (95% CI)	8.3 (2.1, 11.3)	19.2 (3.4, NE)	11.1 (7.4, 19.2)
Abbreviations: CR, complete response; FL, follicular lymphoma; MT, EZH2 mutated; ORR, overall response rate; PR, partial response; WT, EZH2 wild-type			

Source: Clinical Reviewer generated table from ADSL, ADEFF, ADTTE datasets

Reviewer comment: *Although these analyses are limited by small numbers and the exploratory nature, these analysis in patients with 3 or more prior therapies in addition to the subgroup analysis provided by the Applicant and confirmed by the Agency in patients with POD24, and rituximab refractory status, suggests that tazemetostat has activity in some high-risk patients. This was considered in the overall assessment of efficacy and the indication to include wild type patients who have no other satisfactory alternative therapies.*

8.3. Integrated Assessment of Effectiveness

The efficacy of tazemetostat for the treatment of patients with R/R follicular lymphoma whose tumors are positive for an EZH2 mutation or without an identified EZH2 mutation (wild-type) as detected by an FDA approved test was based on a single-arm trial, E7438-G000-101. Data included results from 99 patients with relapsed or refractory follicular lymphoma, 45 with EZH2 mutations detected in tumors and 54 without EZH2 mutations detected. The major issue impacting the review decision is the difference in overall response rate (69% vs 34%) between the EZH2 mutated and the EZH2 wild-type and a consideration of whether the lower 34% overall response rate with a lower bound of the confidence interval at 22% in the WT population constitutes a demonstration of a meaningful therapeutic advantage when considering available therapies. EZH2 mutations identified in this study are gain of function mutations and therefore there is scientific rationale that patients with EZH2 mutations may be more susceptible to EZH2 inhibition.

Patients with R/R follicular lymphoma whose tumors are positive for an EZH2 Mutation as detected by an FDA approved test:

A total of 45 patients were included in the overall assessment of efficacy for the EZH2 mutated patients. The efficacy of tazemetostat was demonstrated by a high overall response rate (69%) per IRC. Duration of response was also demonstrated with a median DOR of 10.9 months with 77% of patients maintaining response at 6 months and 39% maintaining response at 12 months.

The use of overall response rate in follicular lymphoma is considered an intermediate endpoint and is clinically meaningful with supporting evidence from duration of response. Overall response rate with verified durable response as an endpoint has been the basis for accelerated approval in past reviews. Approvals based on demonstration of an improvement on ORR for follicular lymphoma and other non-Hodgkin lymphomas have required confirmation of benefit based on an accepted clinically meaningful endpoint such as PFS or OS in a randomized trial to support regular approval.

Patients with R/R follicular lymphoma whose tumors are negative for an EZH2 Mutation as detected by an FDA approved test:

A total of 54 patients were included in the overall assessment of efficacy for the EZH2 wild-type patients. EZH2 wild-type is defined as patients whose tumors do not have a mutation of EZH2 as detected by an FDA approved test. The efficacy of tazemetostat was lower for this population with an ORR of 34% with a lower bound of the confidence interval of 22%, providing evidence of uncertainty and is not considered sufficient to support an indication for patients with relapsed and refractory follicular lymphoma who have received at least two prior therapies. However, an ORR of 34% and the associated confidence interval, along with durability, is considered meaningful for a heavily pretreated population with limited available treatment options. In the WT population for study E7438-G000-101, durable responses were observed in heavily pretreated patients including patients who were rituximab refractory (ORR 31%), had received 3 prior therapies (ORR 27%), and had early disease progression (ORR 29%), supporting activity in this disease setting (Figure 12, Table 27).

The indication statement for WT patients should stipulate that these patients should have no available therapies as the overall response rate of 34% with a lower bound of the confidence interval of 22% provides evidence of uncertainty for demonstrating a meaningful therapeutic advantage for patients who are candidates for current approved therapies. Available therapy includes anti-CD20 therapy (i.e., rituximab and obinutuzumab) as a single agent and in combination, bendamustine monotherapy and in combination, and immunotherapy combinations such as rituximab plus lenalidomide. In the 2nd line setting and beyond, the ORRs for these therapies, including single-agent and combinations, range from 36% (rituximab re-treatment) to 80% with rituximab and lenalidomide (Table 3). Although these approved therapies were evaluated and approved for patients with at least one prior therapy, an analysis of patients receiving these therapies with 2 or more prior therapies demonstrated response rates of 57% to 80% (Table 5). Furthermore, additional efficacy considerations include the limited sample size of 53 patients, the prior therapies received in the WT cohort were not consistent with the therapies administered in a representative U.S population, and no U.S. patients were enrolled in this cohort. Therefore, for patients with relapsed or refractory FL who are not eligible or have failed available therapies and have no satisfactory alternative acceptable treatment options, tazemetostat may provide clinical benefit.

Additional data is needed in the WT population to support a broader third line and greater indication for tazemetostat in patients who do not have EZH2 mutations as detected by an FDA approved test. This will be addressed with post marketing requirements.

8.4. Review of Safety

8.4.1. Safety Review Approach

The primary safety review is based on data from trial E7438-G000-101 with a cutoff date of 24 May 2020. The safety population is defined as all patients in the phase 2 portion of the study who received the recommended phase 2 dose of tazemetostat (800 mg twice daily).

The clinical review of safety for this NDA is based on all-causality treatment-emergent adverse events (TEAEs) in recipients of study drug on study E7438-G000-101. TEAEs were defined as adverse events that are new or worsened from baseline grade or are unknown to have worsened from baseline. TEAEs were reported from the start of study drug to 30 days following the last dose of study drug.

Safety data from 6 studies was included in this submission (refer to section 7.1 for details) and considered in the overall safety analysis. The safety review was focused on the patients with B - cell lymphoma in the phase 2 portion of the trial (N = 333) with a particular focus on the follicular lymphoma population which consisted of 99 patients. Safety results from both the broad B-cell population and the follicular lymphoma population are presented in this review. There were no identified clinically meaningful difference in the safety profile of tazemetostat between the two populations and therefore the remainder of the safety review will focus on the follicular lymphoma population.

Particular attention was given the adverse event of second primary malignancy, a known and reported AE reported in pre-clinical studies and in observed in one pediatric patient receiving tazemetostat. The primary study supporting safety and efficacy E7438-G000-101 was placed on clinical hold from 20 April 2018 to 19 September 2018 due to the AE of a second primary malignancy, T-cell Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma reported in a pediatric patient in study EZH-102. The clinical hold was removed after the Applicant submitted a plan for increased monitoring, revised inclusion and exclusion criteria, mitigation strategies and a revised consent, informing of the risk of second malignancies.

8.5. Review of the Safety Database

Overall Exposure

In the broad safety pool, 333 patients were exposed to at least one dose of tazemetostat 800 mg BID. The median duration of treatment was 14.4 weeks. The relatively short duration of

exposure in the overall population was driven by a median duration of exposure in the DLBCL population. In the follicular lymphoma population, 99 patients were exposed to at least one dose of tazemetostat 800 mg BID. Median duration of exposure was 49.9 weeks for the follicular lymphoma population. In the follicular lymphoma population, exposure was slightly longer in the EZH2 mutated population compared to the WT population.

Table 28: Exposure of Efficacy and Safety Populations

	Follicular Lymphoma			B cell malignancies B Cell Lymphoma N = 333
	EZH2 MT N = 54	EZH2 WT N = 45	Total FL N = 99	
Exposure time (weeks)				
Median	49.9	31.9	40.2	14.4
Range	12, 112	1.2, 108	(1.2, 112)	(0.1,126)
Duration of Exposure (months)				
≥ 3 months	100%	69%	83%	54%
≥ 6 months	87%	59%	72%	37%
≥ 9 months	67%	46%	56%	25%
≥ 12 months	44%	35%	39%	18%
≥ 18 months	28%	29%	28%	14%
Average Daily Dosing (mg/day)				
Median	800	800	800	800
Range	(636, 805)	(378, 801)	(378, 805)	(296, 964)

Reviewer comment:

Within the FL population a median duration of exposure of approximately 50 weeks provides adequate exposure for a reasonable safety analysis. An analysis of the reason for the significantly longer exposure in the FL population compared to the DLBCL population demonstrated that discontinuations in the DLBCL population occurred primary due to progressive disease and were not driven by AEs as demonstrated in the table below.

Table 29: Reasons for Discontinuation by Subgroups

Reason Discontinued	FL N = 17	DLBCL N = 137	Total N = 154
Adverse Event	0	15/11%	15/10%

Disease Progression	16/94%	111/81%	135/88%
Physician Decision	0	3/2%	3/1.5%
Withdrew Consent	1/6%	2/1.5%	3/1.5%

Demographics and Baseline Characteristics of the Follicular Lymphoma Population

The patient characteristics of the patients with follicular lymphoma is shown in the table below. In the patients with follicular lymphoma, the median age was 62 years, 53% were male, 46% were white, and all had an ECOG score ≤ 2 . The median number of prior therapies was 3 with a range from 1 to 11.

Table 30: Demographics and Baseline Characteristics in Patients with Follicular Lymphoma

Characteristic	EZH2 MT N = 45 n (%)	EZH2 WT N = 54 n (%)	Follicular Lymphoma N = 99 n (%)	B-Cell Malignancies N = 333 n (%)
Age (years)				
<65	25 (56)	32 (59)	57 (58)	151 (45)
≥ 65	20 (44)	22 (41)	42 (42)	182 (55)
Median (Range)	62 (38–80)	60.5 (36–87)	62 (36, 87)	66 (21–87)
Sex (SEX)				
F	26 (58)	20 (37)	46 (46)	150 (45)
M	19 (42)	34 (63)	53 (53)	183 (55)
Race				
White	31 (69)	15 (28)	46 (46)	145 (44)
Other	7 (16)	15 (28)	22 (22)	68 (20)
Unknown	7 (16)	23 (43)	30 (30)	114 (34)
Asian	0	1 (1.9)	1 (1)	5 (1.5)
Black or African American	0	0	0	1 (0.3)
ECOG Status (ECOG)				
1	24 (53)	23 (43)	47 (47)	159 (48)
0	21 (47)	26 (48)	47 (47)	141 (42)

Characteristic	EZH2 MT N = 45 n (%)	EZH2 WT N = 54 n (%)	Follicular Lymphoma N = 99 n (%)	B-Cell Malignancies N = 333 n (%)
missing	0	1 (1.9)	1 (1)	1 (0.3)
2	0	4 (7)	4 (4)	30 (9)
Hepatic Impairment Status				
Normal	38 (84)	48 (89)	86 (86)	281 (84)
Grade 1	7 (16)	5 (9)	12 (12)	46 (14)
Grade 2	0	1 (1.9)	1 (1)	5 (1.5)
Renal Impairment Status				
Normal	24 (53)	27 (50)		143 (43)
Grade 1	18 (40)	16 (30)		123 (37)
Grade 2	3 (7)	11 (20)		65 (20)
Number of Systemic Anticancer Therapy				
Median	2	3	3	3
Min, Max	1,11	1,8	1,11	1,11

Adequacy of the safety database:

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions that may be observed with tazemetostat and the duration of tazemetostat exposure is adequate to allow assessment of adverse reactions over time. Blacks and Hispanics are underrepresented in the safety pool compared to the overall follicular lymphoma patient population in the United States. There is a relatively high percentage (30%) of patients with unknown race due to country specific reporting regulations. Overall, a reasonable assessment of safety can be made from the database.

8.5.1. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data submitted to this NDA was of adequate quality to perform the safety review. Overall, there were no concerns regarding the integrity of the NDA submission.

Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1 and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. TEAEs were defined as any event that started or worsened in severity on or after the day of the first dose of tazemetostat through 30 days after the last dose of tazemetostat.

The Applicant reported adverse events using single MedDRA preferred terms, whereas the FDA used a combination of ungrouped and custom grouped PTs, as defined in Appendix 19.6.

Routine Clinical Tests

Study participants underwent clinical examination, vital signs, hematologic and chemistry laboratory assessments at screening, days 1 and 15 of cycle 1 and 2 and then once per cycle for subsequent cycles plus at the time of treatment discontinuation. On day 15 of cycles 3 and beyond follow up was via phone follow up and laboratory assessments were not performed unless clinically indicated.

Reviewer comment: *The schedule of routine tests was adequate for safety evaluation.*

8.5.2. Safety Results

Deaths

Deaths were assessed during treatment and up to 30 days following treatment discontinuation. Narratives were submitted for all deaths. In the follicular lymphoma population, 4 (4%) of the patients died within 30 days of tazemetostat therapy. One death was not related to progressive disease and was due to worsening of chronic kidney disease. Two additional deaths in the DLBCL population occurred within 30 days of study treatment and were not due to progressive disease. After review of the narratives, the conclusion of this reviewer is consistent with the Applicant. There were no deaths occurring within 30 days of tazemetostat that were considered treatment-related. A summary of deaths is provided in the table below.

Table 31: Summary of Deaths in Recipients of Tazemetostat

	FL MT N = 45 n (%)	FL WT N = 54 n (%)	FL N = 99 n (%)	Safety Pool N = 333 n (%)
<u>All Deaths</u>	8 (18%)	21 (39%)	29 (29%)	204 (61%)
Progressive Disease	6 (13%)	16 (30%)	22 (22%)	188 (56%)
Non-PD	2 (4%)	5 (9%)	7 (7%)	16 (5%)

Deaths < 30 days from last dose of tazemetostat				
Total	2 (4%)	2 (4%)	4 (4%)	56 (17%)
AE	1 (2%)	0	1 (1%)	3 (1%)
PD	1 (2%)	2 (4%)	3 (3%)	52 (16%)
Unknown	0	0	0	1 (0.3)
Abbreviations: AE, adverse event; FL, follicular lymphoma; MT, EZH2 mutated; PD, progressive disease; WT, EZH2 wild-type				

A summary of TE deaths that did not occur in the presence of progressive disease is below.

Follicular Lymphoma

Subject (b) (6) was a 71-year-old female with follicular lymphoma who had received 4 prior treatment regimens. Prior therapies included cyclophosphamide and vincristine, prednisone and rituximab, cyclophosphamide, doxorubicin and vincristine, and bendamustine. Significant medical history was hypertension, obesity, acute coronary syndrome, type 2 diabetes mellitus, lymphedema, and chronic renal failure diagnosed in (b) (6). The patient began therapy in (b) (6) of (b) (6). On study day 217, creatinine was noted to be 1.8, creatinine clearance 40mL/min. Baseline creatinine was 0.8 and baseline creatinine clearance was 66mL/min. Creatinine ranged between 1.1-1.3 and creatinine clearance was between 50-71ml/min during study therapy. On study day 243 the patient was hospitalized for weakness and diagnosed with chronic kidney disease (grade 4) and study drug was discontinued. The patient's chronic kidney disease worsened, and she was reported to have died from chronic kidney disease with a urinary tract infection and sepsis. The investigator and Applicant considered this death to be due to worsening of chronic kidney disease. The study narrative notes that the worsening of chronic renal failure was due to urinary tract infection and sepsis, however there is no AE recorded for the event of urinary tract infection or sepsis. On review of the patient's laboratory evaluations, there was no noted neutropenia preceding the event of worsening chronic renal failure in the setting of a urinary tract infection and sepsis.

Reviewer comment: This reviewer does not agree that this event was not related to study therapy. The events of urinary tract infection and sepsis should be considered as TEAEs and may have contributed to the patients worsening kidney disease and death, although the onset of the urinary tract infection 21 days after stopping study therapy makes this less likely and does support the Applicant conclusion that the event was not related to study therapy. There was no additional data available regarding this event. This death should be considered possibly related to study therapy.

Diffuse Large B-Cell lymphoma:

Subject (b) (6) was a 73-year-old male with DLBCL who had previously received gemcitabine/oxaliplatin/rituximab, and R-CHOP therapy. The patient began tazemetostat in (b) (6) of (b) (6). The patient was diagnosed with disease progression on study day 112 and

discontinued therapy. On study day 125, 13 days after discontinuation of tazemetostat, the patient was diagnosed with bronchopneumonia. White blood cell count was $17.8 \times 10^9/L$. The patient's condition deteriorated, and he died of bronchopneumonia on study day 127.

Reviewer comment: The investigator and Applicant assessed the AE of bronchopneumonia as not related to study therapy. The assessment of the AE resulting in this patient's death is confounded by the recent diagnosis of progressive disease. Since bronchopneumonia occurred shortly after discontinuing tazemetostat, study therapy may have contributed to this AE.

Subject (b) (6) was a 68-year-old male with DLBCL who died 12 days after the last dose of study treatment after discontinuing tazemetostat on study day 30 due to intestinal obstruction. The etiology of intestinal obstruction was unclear, imaging showed enlarged retroperitoneal adenopathy to include enlargement of the index lesion. The patient's intestinal obstruction worsened on study day 39 and he died on study day 40. The investigator considered the event possibly related to study treatment.

Reviewer comment: This reviewer agrees that the AE of intestinal obstruction resulting in death was possibly related to study treatment.

Subject (b) (6) was a 67-year-old female with DLBCL who began study therapy in (b) (6) of (b) (6). On study day 18, the patient died at home. The cause of death was unknown. No autopsy was performed. Death was considered possibly related to tazemetostat.

Reviewer comment: This reviewer agrees that death was possibly related to tazemetostat.

Overall, deaths not due to progressive disease were rare in both the follicular lymphoma (1%) and large B-cell lymphoma population 1.3%. Two of the deaths were not considered related to study therapy by the Applicant. While both deaths were confounded by comorbidities, this reviewer does not agree that the two AEs resulting in death were not at least partially related to tazemetostat as infections were contributing factors in both cases and may be related to study therapy.

There was one additional death within 30 days of receiving tazemetostat reported in a patient with follicular lymphoma as part of the 120-day safety update.

Subject (b) (6) was a 61-year-old male with follicular lymphoma previously treated with cyclophosphamide, vincristine, and doxorubicin, prednisolone plus rituximab, and most recently prior to tazemetostat, pizantone. The patient initiated tazemetostat on (b) (6). On (b) (6) a PET scan revealed a hypermetabolic mesenteric lymph node. The study drug was continued but interrupted in (b) (6) for abdominal pain. Biopsies performed in (b) (6) and (b) (6) revealed pancreatic adenocarcinoma. The patient received brachytherapy for pancreatic adenocarcinoma. On (b) (6) the patient died of pancreatic adenocarcinoma. Autopsy revealed vascular stomach invasion and massive bleeding as the cause of sudden death.

Serious Adverse Events

Treatment Emergent Serious Adverse Events (SAEs) occurred in 27% in the follicular lymphoma population. The incidence of SAEs was 24% in the EZH2 MT and 30% in the EZH2 WT population. The most frequently occurring serious adverse events in the FL population were sepsis, pneumonia, general health deterioration, and cytopenias.

Table 32: Treatment Emergent Serious Adverse Events Occurring in > 1 Patient

Adverse Event	FL N = 99 n (%)	Safety Pool N = 333 n (%)
Any	27 (27)	159 (48)
<u>Infections and Infestations</u>	5 (5)	33 (10)
Sepsis	2 (2)	5 (2)
Pneumonia ^a	2 (2)	8 (2)
<u>Blood and Lymphatic System</u>	3 (3)	40 (12)
Anemia ^b	2 (2)	8 (2)
Neutropenia ^c	2 (2)	19 (6)
Thrombocytopenia ^c	2 (2)	16 (5)
<u>General disorders and administration site</u>	4 (4)	37 (11)
General Health Deterioration	2 (2)	20 (6)

Source: Reviewer generated table from ADSL and ADAE datasets

^aIncludes grouped terms with PTs pneumonia and lung infection

^b includes grouped terms with PT anemia

^c includes pancytopenia

Dropouts and/or Discontinuations Due to Adverse Effects

In general, in the follicular lymphoma population, there were few study drug discontinuation and modifications. A total of 9% of patients with follicular lymphoma discontinued study treatment due to an AE. Two patients discontinued study therapy due to either AML or MDS (one each). There were no other AEs resulting in study drug discontinuation that occurred in more than one patient. A summary of AEs leading to drug discontinuation and reduction in patients with follicular lymphoma are listed in the table below.

Table 33: AEs Resulting in Dose Discontinuation, Reduction or Interruption in Patients with Follicular Lymphoma N = 99

Type of Dose Modification	
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TEAE leading to discontinuation (one patient each) - Acute myeloid leukemia - Myelodysplastic syndrome - Worsening of chronic kidney disease - Thrombocytopenia - Dysaesthesia and dysgeusia (same patient) - Herpes labialis, weight loss, tongue mycosis (same patient) - QTc prolongation - Pneumonia	8 (8%)
TEAE leading to dose interruption Events occurring in more than one patient Thrombocytopenia Fatigue* Diarrhea Herpes Zoster Dizziness	27 (27%) 7 (7%) 5 (5%) 2 (2%) 2 (2%) 2 (2%)
TEAE leading to dose reduction Events occurring in more than one patient Alopecia Anemia	9 (6%) 3 (3%) 2 (2%)

*grouped term, includes asthenia

Reviewer comment: *There was no clear pattern for AEs resulting in discontinuation of tazemetostat and overall, the discontinuation rate was low. It is notable that two patients discontinued study therapy due to the AE of a second primary malignancy. This AE is included in the Warnings and Precautions section of the proposed USPI as well as recommendations to monitor patients for this AE.*

Significant Adverse Events

In study G7438-G000-101, two (0.6%) of the 333 patients, both with FL, including 1 in each of the FL cohorts, experienced AESIs: MDS in a 61-year-old male with WT disease after 465 days on tazemetostat and AML in a 66-year-old male with MT disease after 786 days on treatment. Both patients were withdrawn from the study. A brief description of the events is summarized below:

Subject (b) (6) was a 61-year-old male treated in the UK who was diagnosed with FL in (b) (6). He was enrolled on study E7438-G000-101 in (b) (6) in the EZH2 WT cohort. In addition to radiation, prior therapy for follicular lymphoma included:

- chlorambucil/prednisone/vincristine (1)
- chlorambucil/prednisone/vincristine (2)
- etoposide/bleomycin/cyclophosphamide/doxorubicin/methotrexate/vincristine
- lomustine/cytarabine (3)

- bleomycin/cyclophosphamide/doxorubicin/etoposide/chlorambucil/prednisone/vincristine (4)
- rituximab/carmustine/hydrocortisone/melphalan (5) -
dexamethasone/gemcitabine/vinorelbine (6)
- rituximab (7)
- bendamustine/idelalisib/rituximab (8)

At screening, the patient was reported to have a normal white blood cell and platelet count. Baseline bone marrow showed mild megakaryocytic dysplastic changes, there were no cytogenetic abnormalities reported from the bone marrow biopsy. On study day 295, a CBC revealed a WBC of $23 \times 10^9/L$, ANC $1.6 \times 10^9/L$ and platelet count of $1045 \times 10^9/L$. Tazemetostat had been interrupted on study day 281 due to grade 1 arrhythmia which was resumed on Study day 297. No changes in study drug administration were made due to the abnormal CBC. The patient was hospitalized on study day 449 due to a grade 3 CVA. At that time, CBC was significant for a WBC of $21.5 \times 10^9/L$ and platelets of $1158 \times 10^9/L$. Study drug had been interrupted due to CVA and was reinitiated on study day 456.

On study day 465 he was diagnosed with grade 3 myelodysplastic syndrome (MDS). Bone marrow biopsy showed histological features of MDS. Cytogenetic testing of the bone marrow revealed two mutations in the EZH2 gene at exon 18 and one in the ASXL1 gene at exon 9.

Tazemetostat was discontinued due to the event of MDS. The patient died on study 567 due to an infection, 63 days after discontinuing tazemetostat.

Reviewer comment: The patient's extensive prior therapy to include treatment with alkylating agents, in addition to baseline bone marrow demonstrating megaloblastic changes confounds assessment of the causality of MDS due to tazemetostat. The development of CBC changes while on therapy as well as an identification of a mutation in EZH2 raises the possibility of a contribution of tazemetostat to the development of MDS.

Subject 3003-2003 was a 66-year-old male treated in Australia who was enrolled on study E7438-G000-101 in August of 2016 in the EZH2 MT cohort. Prior therapy for follicular lymphoma included:

- chlorambucil (1)
- rituximab /cyclophosphamide/doxorubicin/vincristine (2)

At screening, the patient was reported to have a normal white blood cell and platelet count. Baseline bone marrow was reported to be normal. On study day 588, tazemetostat was interrupted due to grade 3 thrombocytopenia (platelet count $42 \times 10^9/L$). Tazemetostat was resumed at a reduced dose on 600mg BID on study day 623 after recovery to grade 1 thrombocytopenia. Tazemetostat was interrupted again on study day 763 due to grade 3 thrombocytopenia (platelet count $47 \times 10^9/L$). On study day 786, he was diagnosed with grade

4 AML. Bone marrow revealed 53% myeloblasts and tazemetostat was discontinued. The patient-initiated therapy on clinical trial for AML.

Reviewer comment: The prior therapy to include treatment with alkylating agents, confounds assessment of the causality of MDS due to tazemetostat. The contribution of tazemetostat to the patient's development of AML cannot be excluded.

Significant Adverse Events from other studies

On (b) (6), an event of T-lymphoblastic lymphoma (T-LBL) was observed in a pediatric patient on study EZH-102. Study E7338-G000-101 was placed on partial clinical hold. The Applicant performed a comprehensive analysis of other events of second malignancies in the development program and identified a case of secondary myelodysplastic syndrome (MDS). As a response to partial clinical hold, the Applicant submitted protocol amendment dated (b) (6) which added a description of the events as well as risk mitigation and monitoring required to minimize the risk of occurrence of these events in patients taking tazemetostat. Patients with prior history of T-LBL/T-ALL; thrombocytopenia, neutropenia, or anemia of Grade ≥ 3 (per CTCAE 4.03 criteria) or any prior history of myeloid malignancies, or had an abnormality known to be associated with MDS (e.g. del 5q, chr 7 abn) and myeloproliferative neoplasm (MPN) (e.g. JAK2 V617F) observed in cytogenetic testing and DNA sequencing were excluded from enrolling.

Because of the sentinel event, the Applicant identified secondary malignancies as an AESI. The AESIs were defined as MDS, MPN, acute myeloid leukemia (AML), and T-LBL/T-ALL. In the data reviewed as part of this application, at the adult target dose of 800 mg BID, there were 5 (0.7%) of 729 patients who experienced six cases of secondary malignancies. Three patients were reported to have AML, including one patient who had transformation from MDS. MDS was reported in 2 patients. Across the development program for tazemetostat, 6 (0.7%) of 857 adult and pediatric patients and 4 (1.1%) of the 358 adult patients with NHL developed a secondary malignancy. Overall, the time from initiation of tazemetostat to the secondary malignancy diagnosis ranged from 14 months to more than 4 years. All but one patient who developed a secondary malignancy had received prior chemotherapy. The table below summarizes the cases of secondary malignancies across the tazemetostat development program.

Table 34: Secondary Malignancies Across the Tazemetostat Development Program

Patient Age (years)/Sex	Initial Diagnosis	Prior Radiation	Prior Systemic Therapy	Prior SCT	Secondary malignancy	Dose of Tazemetostat	Duration of Treatment Prior to Secondary Malignancy
61, male	Follicular lymphoma	Yes	6 chemotherapy regimens including doxorubicin, cyclophosphamide, and etoposide	Yes	MDS*	800 mg BID	15 months (Day 465)
69, male	DLBCL	No	2 chemotherapy regimens including doxorubicin and	No	MDS	800 mg BID	27 months (Day 843)
9, female	Chordoma	Yes	Doxorubicin, ifosfamide, pazopanib	No	T-LBL	900 mg/m ²	14 months
57, male	Rhabdoid sarcoma	Yes	No	No	AML	800 mg BID	Over 4 years (Day 1591)

Source: Reviewer Generated Table from Safety Narratives and data included in the response to clinical hold

Reviewer Comment: *The two cases of either MDS or AML in patients with follicular lymphoma plus the additional AEs of second hematologic malignancy in a pediatric patient and an adult with DLCL highlight the potential risk of secondary hematologic malignancies with tazemetostat therapy. As described in Section 5.5 of this review, second primary malignancies have also been identified in pre-clinical studies evaluating tazemetostat, supporting a causative role of tazemetostat and second primary malignancies. It is unclear at this time, the true risk of second malignancies as these cases are confounded by prior therapy and the pediatric case may be related to higher tazemetostat exposure or an increased risk in the pediatric population due to differences in lymphoid development. This is a particularly important consideration in patients with follicular lymphoma who may have an indolent*

course and other therapy options. Both of these patients achieved a PR with tazemetostat and had a significant exposure (71 weeks and 108 weeks) prior to discontinuing tazemetostat due to AML or MDS. These AEs highlight the need to include the development of second malignancies in the Warnings and Precautions section of the USPI as well as the additional data needed regarding this AE, which is the goal of a PMR to be included in with this approval.

Treatment Emergent Adverse Events and Adverse Reactions

Table 35: Summary of Treatment Emergent Events

Greater than Grade 3 TEAEs Reported in ≥ 1 patient	
SOC Preferred Term	FL N = 99 n(%)
Patients with any Grade ≥3 TEAE	39 (39)
Infections and Infestations	4 (4)
Sepsis	2 (2)
Pneumonia/Lung Infection*	2 (2)
General Disorders and Administration Site Conditions	6 (6)
Fatigue/Asthenia*	5 (5)
General Physical Health Deterioration	2(2)
Respiratory, thoracic and mediastinal disorders	5 (5)
Dyspnea	3 (3)
Gastrointestinal Disorders	6 (6)
Abdominal Pain*	2 (2)
Blood and Lymphatic System	9 (9)
Anemia	5 (5)
Neutropenia	4 (4)
Thrombocytopenia	5 (5)

Table 36: TEAE occurring in > 5% of patients with follicular lymphoma

TEAE BODY System Preferred Term*	Follicular Lymphoma N = 99	
	All grades n (%)	≥ Grade 3 n (%)
Any TEAE	97 (97)	39 (39)
Gastrointestinal Disorders	62 (62)	6 (6)
Nausea	23 (23)	0
Diarrhea	18 (18)	0
Abdominal Pain*	20 (20)	2 (2)
Gastroesophageal reflux disease	6 (6)	0
Constipation	7 (7)	0
Infections and infestations	57 (57)	4 (4)
Respiratory Infection (broad)	53 (53)	1 (1)
Upper respiratory tract infection*	30 (30)	0
Lower respiratory Tract infection*	16 (16)	0
Urinary Tract Infection*	10 (10)	1 (1)
Pneumonia*	7 (7)	1 (1)
Herpes Virus Infection*	7 (7)	1 (1)
Skin and subcutaneous tissue disorders	40 (40)	0
Alopecia	17 (17)	0
Rash*	14 (14)	0
Xerosis*	5 (5)	0
General disorders and administration site conditions	47 (47)	6 (6)
Fatigue*	36 (36)	5 (5)
Edema	6 (6)	0
Pyrexia	10 (10)	0
Mucositis*	7 (7)	0
Nervous system disorders	38 (38)	5 (5)
Headache	12 (12)	0
Peripheral Neuropathy	6 (6)	0
Dysguesia	8 (8)	0
Dizziness	7 (7)	1
Musculoskeletal and connective tissue disorders	33 (33)	0
Musculoskeletal Pain*	24 (24)	0
Muscle spasms	9 (9)	0
Arthralgia	7 (7)	0
Metabolism and nutrition disorders	24 (24)	8 (8)
Decreased appetite	8 (8)	0

TEAE BODY System Preferred Term*	Follicular Lymphoma N = 99	
	All grades n (%)	≥ Grade 3 n (%)
Respiratory, thoracic and mediastinal disorders	26 (26)	5 (5)
Cough*	17 (17)	0
Dyspnea	8 (8)	3 (3)
Vascular disorders	14 (14)	2 (2)
Hypertension	5 (5)	2 (2)
Psychiatric disorders	15 (15)	0
Insomnia	7 (7)	0
Blood and lymphatic system disorders**	95 (95)	9 (9)
Anemia**	15 (15)	5 (5)
Thrombocytopenia**	10 (10)	5 (5)
Neutropenia**	7 (7)	5 (5)

Source: Reviewer generated table from ADAE data set

* includes grouped terms per appendix 19.6

** includes AEs under Blood and lymphatic system disorders and investigations

Laboratory Findings

The table below summarizes the common (>10%) treatment emergent hematologic laboratory abnormalities in patients with follicular lymphoma and in the B cell safety pool treated with tazemetostat.

Table 37: Hematologic Laboratory Abnormalities occurring in >10% of patients

Hematologic Laboratory Abnormality	FL (N = 99)		Safety Pool (N = 333)	
	All grades	≥ Grade 3	All grades	≥ Grade 3
Lymphocytes Decreased	57%	18%	55%	25%
Platelets Decreased	50%	7%	52%	13%
Hgb Decreased	50%	9%	53%	8%
Leukocytes Decreased	41%	9%	46%	15%
Neutrophils Decreased	19%	6%	46%	15%

Source: FDA analysis OF ADLB dataset

^a Represents new or worsening abnormalities, or worsening with baseline unknown

Cytopenias of all grades were common, although cytopenias ≥ grade 3 anemia, thrombocytopenia, and neutropenia were all less than 10% in the follicular lymphoma

population. Greater than grade 3 cytopenias were noted more commonly in the large safety pool driven by cytopenias occurring in the DLBCL population.

Reviewer comment: Greater than grade 3 cytopenias occurred in less than 10% of the follicular lymphoma population with the exception of lymphocytosis, in which greater than grade 3 lymphopenia occurred in 18% of patients. Patients with hematologic malignancies routinely are monitored for cytopenias and providers are experienced at evaluating and managing cytopenias. The USPI conveys the need to monitor for secondary malignancies to include hematologic malignancies.

The table below summarizes the common (>10%) treatment emergent hematologic laboratory abnormalities in patients with follicular lymphoma and in the B cell safety pool treated with tazemetostat.

Table 38: Chemistry laboratory abnormalities occurring in ≥ 10% of patients receiving tazemetostat

	FL (N = 99)		Safety Pool (N = 333)	
	All grades	≥ Grade 3	All grades	≥ Grade 3
Chemistry value				
Glucose increased	53%	10%	47%	6%
Albumin decreased	31%	2%	10%	0
AST increased	24%	0	23%	0.3%
ALT increased	21%	2%	15%	1%
Creatinine Increased	17%	0	22%	0.3%
Alkaline Phosphatase increased	18%	1%	16%	1%
Glucose Decreased	13%	0	10%	0
Bilirubin Increased	7%	2%	8%	3%

Reviewer comment: Laboratory chemistry abnormalities were generally low grade and occurred commonly. Although there was no laboratory chemistry pattern indicative of a specific toxicity based on the data included, routine laboratory monitoring that would occur in patients with hematologic malignancies as part of standard of care is adequate.

Vital Signs

Vital sign assessment was performed at baseline, every two weeks for two cycles and then once per cycle until treatment discontinuation. Measurements included blood pressure heart rate,

temperature and respiratory rate. A review of weight, heart rate, blood pressure, and temperature did not reveal any identified safety signals.

Electrocardiograms (ECGs)

ECGs were performed at baseline, on day 1 of subsequent cycles, at the end of therapy and otherwise as clinically indicated. There was one ECG abnormality, grade 3 QT prolonged, reported as a TEAE in a follicular lymphoma patient. This event resulted in treatment discontinuation but was not considered treatment related per investigator. A narrative provided for the event indicated that the patient had QTc prolongation at screening and at subsequent visits on study days 1 and 5. On study day 86, the event of prolonged QT was reported as a non-serious event. Study drug was discontinued.

Reviewer comment: The were rare ECG abnormalities noted in the FL population and no indication of a cardiac conduction safety signal.

QT

Heart rate corrected QT interval as based on Frederica's equation. Across all assessments 22% of patients had at least 1 QTcF that was grade 1 prolongation. Four patients in the FL population had grade 2 prolongation and 1 patient had grade 3 prolongation with resulting in discontinuation of tazemetostat. Prolongation of QT was reported in one patient with a history of prolonged QT at screening.

The effect of tazemetostat on the QTc interval was also evaluated in a cardiac safety from patients in the phase 1 study of E7438-G000-101 to include a concentration QTc modeling report. This report was reviewed by the interdisciplinary review team for QT studies during the review of NDA 211723. No large QTc prolongation effect was observed in that study. The review noted that a small QTc prolongation effect could not be ruled out.

Reviewer comment: The cardiac safety study as well as the AEs reported in the FL population do not indicate that there is a large QTc prolongation effect from tazemetostat.

8.5.3. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There were no additional COA data included in the application.

8.5.4. Safety Analyses by Demographic Subgroups

In general, in the FL population, the number of patients was too small to draw conclusions regarding safety in specific subgroups. There were no noted major differences in safety in patients 65 years or older compared younger than 65 or for males compared to females. A

brief summary of safety by subgroup is displayed in the table below.

Table 39: Summary of AEs by Age and Gender

	Any TEAE n(%)	≥ Grade 3 n(%)	SAE n(%)
Age < 65 y N = 57	56 (98%)	23 (40%)	15 (26%)
Age ≥ 65y N = 42	42 (100%)	16 (38%)	12 (29%)
Male N = 53	52 (98%)	22 (42%)	16 (30%)
Female N = 46	46 (100)	17 (37%)	11 (24%)

8.5.5. Specific Safety Studies/Clinical Trials

There were no special safety studies or clinical trials in this application

8.5.6. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Second Primary malignancies (SPM) have been reported in patients receiving tazemetostat. One case of T-Lymphoblastic Lymphoma (T-LBL) occurred in a pediatric patient receiving tazemetostat for chordoma. Cases of AML and MDS have been reported in adult patients receiving tazemetostat for NHL although determining causality is confounded by the patients underlying malignancy and previous chemotherapy. Second primary malignancies are the subject of a PMR for NDA 211723. An additional PMR to specifically address the risk of second malignancies in patients with lymphoma will be included in this approval. See section 13 for additional details.

Human Reproduction and Pregnancy

There were no pregnancies documented during this trial.

Pediatrics and Assessment of Effects on Growth

There were no pediatric patients enrolled on the study supporting the follicular lymphoma indication. In other studies evaluating tazemetostat in pediatrics, no adverse drug reaction regarding growth have been identified. Nonclinical toxicology studies revealed skeletal

abnormalities in fetuses of pregnant rats and increased trabecular bone in juvenile animals exposed to tazemetostat.

In the clinical trial population, one 9-year-old pediatric patient developed T-cell lymphoblastic lymphoma while receiving tazemetostat for chordoma. T-cell ALL and lymphoblastic lymphoma is an AR that has been identified in preclinical studies and in other same-in-class agents. The development of T-cell Lymphoblastic Lymphoma and/or ALL may be an AR limited to the pediatric age group although additional data is needed to further evaluate.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The applicant did not provide any reported cases of overdose of tazemetostat. No data were available on the potential for abuse or dependence. A formal study has not been conducted by the applicant to investigate withdrawal and/or rebound.

8.5.7. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Tazemetostat was approved for epithelioid sarcoma January 23, 2020 under NDA 211723. There have been no new safety findings identified in the post marketing setting to date.

Expectations on Safety in the Postmarket Setting

Safety in the post market setting is expected to be similar to that observed in the clinical trial reviewed in this application.

8.6. Integrated Assessment of Safety

Overall tazemetostat appears to be relatively well tolerated in the follicular lymphoma population.

The safety evaluation was based primarily on a safety analysis of AEs occurring in the FL population (N = 99) with considerations of AEs occurring in a broader B-Cell malignancy pool (N = 333) and in the solid tumor population. Patients received tazemetostat 800 mg PO twice daily until unacceptable toxicity or progressive disease. The median exposure duration for patients with follicular lymphoma was 49.9 weeks (range 1.2, 112 weeks) with 39% of patients having at least 12 months of exposure. The population of patients with follicular lymphoma for the study supporting approval was representative of the expected demographic population for follicular lymphoma with a median of 2 prior therapies to include 58 % of patients with greater than 3 prior lines of systemic therapy with a variety of prior chemotherapy and immunotherapies. Safety data from an additional 234 patients with diffuse large B cell lymphoma who received tazemetostat 800 mg BID supported the safety conclusions from the primary safety population.

The most common (>20%) adverse events (AEs) experienced by patients with FL of any grade were upper respiratory infection (30%), musculoskeletal pain (24%), nausea (23%), and abdominal pain (20%). The most common hematological adverse events (hematologic TEAEs and laboratory abnormalities) were anemia (15%), thrombocytopenia (10%), and neutropenia (7%).

Treatment discontinuation occurred due to any adverse reaction was reported in 9% of patients with follicular lymphoma, highlighting the tolerability in this lymphoma population. No one adverse reaction was predominant in leading to treatment discontinuation.

Serious adverse events were reported in 27% of patients. SAEs occurring in more than one patient with follicular lymphoma were sepsis (2%), anemia (2%), and general physical health deterioration (2%).

The following adverse events of special interest were also evaluated:

Second Malignant Neoplasm: Patients with prior treatment for lymphoma have an increased risk for second malignancies. Tazemetostat therapy has been associated with the development of secondary malignancies, particularly T cell lymphoblastic lymphoma and T cell ALL in the preclinical setting and observed clinically in one pediatric patient. Therapy with tazemetostat may also be associated with other hematologic malignancies and pre-malignant conditions such as AML and MDS, which were observed in this study in one patient each. This potentially serious AE associated with tazemetostat may also be associated with duration of therapy, a particularly important issue when considering patients with follicular lymphoma who may have indolent disease and may receive extended therapy. The risk of second malignancies from this small study with relatively short follow up requires additional evaluation to fully understand the rates, types, and risk factors for second malignancies with tazemetostat. This will be included as a PMR. Since early detection of some forms of SPMs may benefit patients, it is appropriate to include this in warnings and precautions.

Reviewer comment: A comprehensive review of the safety data demonstrates that tazemetostat demonstrated a favorable safety profile and was well tolerated in patients with follicular lymphoma. Additional follow up is needed for the important safety issue of second primary malignancies.

8.7. Statistical Issues

There are no major statistical issues identified from this submission. The following caveats may need to be taken into account in the final decision:

- According to the clinical study report, race was not reported due to local privacy in 55% of all patients.
- The reviewer's descriptive analyses results showed that there were slightly numerical differences for the analysis results of ORR and CR and PR between IRC assessment and Investigator assessment for both MT cohort and WT cohort (Table 20). The observed ORR in the MT group was 68.9% (95% CI: 53.4, 81.8) using IRC assessment and 77.8% (95% CI: 62.9, 88.8) using investigator assessment. The observed ORR in the WT group was 35.2% (95% CI: 22.7, 49.4) using IRC assessment and 33.3% (95% CI: 21.1, 47.5) using investigator's assessment.
- The reviewer's descriptive analyses result also showed that there were numerical differences for the analysis results of median PFS between IRC assessment and Investigator assessment for WT cohort. The observed median PFS in the WT cohort was 11.1 months (95% CI: 3.7, 14.6) using IRC assessment and 5.6 months (95% CI: 3.3, 11.1) using investigator assessment.
- For subgroup analysis in MT cohort, the ORR for the patients from North America appears to be worse than that in the overall population. The observed ORR by IRC assessment was 58.3% (95% CI: 27.7, 84.8). Given the small sample size in the subgroups, caution should be taken in the interpretation of the subgroup analysis results.
- For subgroup analysis in the WT cohort, the ORR for the patients received >2 lines of prior therapy at baseline appears to be worse than that in the overall population. The observed ORR by IRC assessment with >2 lines of prior therapy at baseline was 27% (95% CI: 13.8, 44.1). There is no response in the 2 patients from North America. Given the small sample size in the subgroups, caution should be taken in the interpretation of the subgroup analysis results.
- There were only 12 patients in the MT cohort from North America, and none of patients in the WT cohort from US due to partial clinical hold. We are concerned if the efficacy results are representative of the US patient population.

8.8. Conclusions and Recommendations

Patients with R/R follicular lymphoma whose tumors are positive for an EZH2 Mutation as detected by an FDA approved test:

The benefit-risk assessment supports accelerated approval of tazemetostat for the treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least two prior therapies. A companion diagnostic for the identification of EZH2 mutations in tumor tissue is required to ensure safe use of tazemetostat for this intended patient population.

Efficacy in the EZH2 mutated population: Efficacy in patients with relapsed or refractory follicular lymphoma who have received least two prior systemic therapies and whose tumors are positive for an EZH2 mutation is based on the results of a single, multicenter, open-label, single-arm phase 2 trial of tazemetostat monotherapy 45 adult patients with follicular lymphoma who had received at least two prior systemic therapies and whose tumors had an EZH2 mutation as detected by the cobas® assay. In the analysis of the primary endpoint, ORR per IRC, patients who received tazemetostat had an ORR of 69% (95% CI 53.4, 81.8) with a median duration of response of 10.9 (95% CI 7.2, NE). Tazemetostat was administered as monotherapy, and therefore therapeutic effect can be attributed to tazemetostat. Relapsed and refractory lymphoma is considered incurable and efficacy was demonstrated in a heavily pretreated population with a median number of prior therapies of 2 (range 1,11).

According to FDA's Guidance for Industry: Expedited programs for serious conditions – Drugs and Biologics (2014), accelerated approval may be considered for a drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on an intermediate clinical endpoint. When considering the totality of the data, the rationale for the recommendation of accelerated approval for tazemetostat is founded upon the following considerations:

- Uncertainty as to the relationship of ORR and DOR to ultimately supporting confirmation of clinical benefit, through an endpoint such as overall survival. Although the ORR was 69% in patients with EZH2 mutations per independent review committee, 56% of patients experienced progressive disease and 18% of patients died at the time of the data cut-off.
- The most optimal use of tazemetostat for the treatment of follicular lymphoma is not known. The Applicant's ongoing randomized controlled trial of tazemetostat plus rituximab and lenalidomide versus rituximab and lenalidomide in patients with follicular lymphoma who have received at least one prior therapy (Subpart H postmarketing requirement) would allow for adequate evaluation of time-to-event endpoints and the role of tazemetostat in a combination regimen.

Overall, tazemetostat was well tolerated with the most frequently reported greater than grade 3 AEs occurring in > 2 patients of anemia (5%), thrombocytopenia (5%), fatigue, neutropenia (4%), Fatigue (5%), and dyspnea (3%). The overall incidence of SAEs was 27% in patients with

relapsed and refractory follicular lymphoma who had received at least two prior therapies. There was one fatal AE from worsening of chronic kidney disease. Few patients discontinued study drug due to adverse events (8%).

Considering the totality of the efficacy and safety data, this reviewer recommends accelerated approval for patients with follicular lymphoma whose tumors have an EZH2 mutation, as durable ORR in this population is reasonable likely to predict clinical benefit and an ORR of 69% with monotherapy provides evidence of a meaningful therapeutic advantage in the context of available therapies.

Patients with R/R follicular lymphoma whose tumors are negative for an EZH2 Mutation as detected by an FDA approved test:

The benefit-risk assessment supports accelerated approval of tazemetostat for the treatment of adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

Efficacy in the EZH2 wild-type population: Efficacy in patients with relapsed or refractory follicular lymphoma who have received least two prior systemic therapies and whose tumors did not have an identified EZH2 mutation is based on the results of a single, multicenter, open-label, single-arm phase 2 trial of tazemetostat monotherapy 54 adult patients with follicular lymphoma who had received at least two prior systemic therapies and whose tumors did not have an identified EZH2 mutation as detected by the cobas® assay. In the analysis of the primary endpoint, ORR per IRC, patients who received tazemetostat had an ORR of 34% (95% CI 21.5, 48.3) with a median duration of response of 13.3 months. Tazemetostat was administered as monotherapy, and therefore therapeutic effect can be attributed to tazemetostat.

Overall, tazemetostat was well tolerated with the most frequently reported greater than grade 3 AEs occurring in > 2 patients of anemia (5%), thrombocytopenia (5%), fatigue, neutropenia (4%), Fatigue (5%), and dyspnea (3%). The overall incidence of SAEs was 27% in patients with relapsed and refractory follicular lymphoma who had received at least two prior therapies. There was one fatal AE from worsening of chronic kidney disease. Few patients discontinued study drug due to adverse events (8%).

For patients with relapsed or refractory FL with EZH2 wild-type who have received at least 2 prior therapies, the recommended indication is restricted to patients with no satisfactory alternative treatment options. The ORR of 34% with a lower bound of the confidence interval of 22% provides evidence of uncertainty regarding the clinical benefit of tazemetostat in these patients. Additional considerations include the limited sample size of 53 patients, the prior therapies received were not consistent with the therapies administered in a representative U.S population, and no U.S. patients were enrolled in this cohort. Further, the efficacy data is evaluated in the context of available therapy in the 2nd line setting and beyond (Table 3).

Available therapy includes anti-CD20 therapy (i.e., rituximab and obinutuzumab) as a single agent and in combination, bendamustine monotherapy and in combination, and immunotherapy combinations such as rituximab plus lenalidomide. In the 3rd line setting and beyond, which is comparable to the EZH2 wild-type population enrolled, the ORRs for these therapies, including single-agent and combinations, range from 57% to 80% with associated durability (Table 5). Therefore, there is residual uncertainty regarding the benefit of tazemetostat in patients with EZH2 wild-type FL who have received at least 2 prior systemic therapy, which warrants restriction of the indication to a patient population with no satisfactory alternative treatment options where there benefit-risk balance is favorable and the data provides evidence of a meaningful therapeutic advantage in the context of available therapies.

According to FDA's Guidance for Industry: Expedited programs for serious conditions – Drugs and Biologics (2014), accelerated approval may be considered for a drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on an intermediate clinical endpoint. When considering the totality of the data, the rationale for the recommendation of accelerated approval for tazemetostat is founded upon the following considerations:

- Uncertainty as to the relationship of ORR and DOR to ultimately supporting confirmation of clinical benefit, through an endpoint such as overall survival. Although the ORR was 34% in patients without an identified EZH2 mutation per independent review committee, 59% of patients experiences progressive disease and 39% of patients died as of the data cut-off
- The most optimal use of tazemetostat for the treatment of follicular lymphoma is not known. The Applicant's ongoing randomized controlled trial of tazemetostat plus rituximab and lenalidomide versus rituximab and lenalidomide in patients with follicular lymphoma who have received at least one prior therapy (Subpart H postmarketing requirement) would allow for adequate evaluation of time-to-event endpoints and the role of tazemetostat in a combination regimen.

X

Primary Statistical Reviewer

X

Statistical Team Leader

X

Primary Clinical Reviewer

X

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

This application was not presented to the Oncologic Drug Advisory Committee or other external consultants because tazemetostat is not first-in-class, and the application did not raise new efficacy or safety issues for the recommended indications.

10 Pediatrics

Patients less than 18 years of age were excluded from Applicant-sponsored clinical studies of tazemetostat in B-cell malignancies. Tazemetostat was granted orphan designation in November 2017 and therefore Pediatric Research and Equity Act mandated studies are not required.

The safety and effectiveness of tazemetostat in pediatric patients has not been established.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

The following are recommendations for the tazemetostat prescribing information based on this review. Refer to the PI for the final language.

Table 40: Summary of Recommended Labeling Changes

Section	Proposed Labeling	Approved Labeling
Highlights, Adverse Reactions	--	Revised most common adverse reactions to separately list the adverse reactions of follicular lymphoma and sarcoma.
Indication	Stated tazemetostat is indicated for patients with relapsed and refractory follicular lymphoma who have received at least 2 prior therapies.	Tazemetostat is indicated for the treatment of adult patients with relapsed and refractory follicular lymphoma (1) whose tumors are positive for an EZH2 mutation as detected by and FDA-approved test and (2) have received at least 2 prior therapies and who have no satisfactory alternative treatment options.
Dosage and Administration	--	Added instructions to select patients based on presence of EZH2 mutation.
Warnings and Precautions, Secondary Malignancies	--	Included instructions to monitor patients long-term for the development of secondary malignancies.
Adverse Reactions, Clinical Trials Experience	(b) (4)	• Revised description of the safety population. • Included listed adverse reactions leading to permanent discontinuation, and omitted most frequent adverse reaction leading to dose reduction. • Revised adverse reaction table to include FDA analysis of rates of adverse reactions based on

		grouping and moved lab-based adverse reactions to the lab table. Added clinically relevant less common adverse reactions.
Geriatric Use	Stated that no significant differences in efficacy and safety were noted between younger and geriatric patients with follicular lymphoma.	Revised statement to say that the small number of patients did not allow for conclusions to be drawn about the geriatric subpopulation.
Clinical Pharmacology, Mechanism of Action	(b) (4)	
Clinical Studies, Relapsed or Refractory Follicular Lymphoma		

11.2 Patient Labeling

The Medication Guide was revised to include the indications for follicular lymphomas.

12 Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team and Division of Risk Management (DRISK) agree that a REMS is not necessary for the safe use of tazemetostat. There are no additional risk management strategies needed beyond recommended labeling.

13 Postmarketing Requirements and Commitment

The clinical team recommends three PMRs and two PMCs. The goal of the post marketing requirements are to confirm clinical benefit in patients with follicular lymphoma from a population of patients reflective of the U.S. population with and without EZH2 mutations based on the randomized trial with based on progression free survival as a primary endpoint and to further evaluate the risk of second malignancies in patients receiving tazemetostat.

Post Marketing Requirements:

1. Submit the final report and datasets from a randomized, Phase 3 clinical trial that verifies and describes the clinical benefit of tazemetostat in patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test. The trial should include sufficient numbers of racial and ethnic minority patients to better reflect the U.S. patient population and allow for the interpretation of the results in these patient populations. Patients should be randomized to receive immunotherapy with or without tazemetostat. The primary endpoint should be progression-free survival, with secondary endpoints that include overall survival and objective response rate.

Milestone dates:

Final Protocol Submission	02/2020
Study Completion	12/2024
Final Report Submitted	07/2025

2. Submit the final report and datasets from a randomized, phase 3 clinical trial that verifies and describes the clinical benefit of tazemetostat in patients with relapsed or refractory follicular lymphoma whose tumors do not have an EZH2 mutation as detected by an FDA-approved test. The trial should include sufficient numbers of racial and ethnic minority patients to better reflect the U.S. patient population and allow for the interpretation of the results in these patient populations. Patients should be randomized to receive immunotherapy with or without tazemetostat. The primary endpoint should be progression-free survival, with secondary endpoints that include overall survival and objective response rate.

Protocol Submission	02/2020
Study Completion	12/2024
Final Report Submitted	07/2025

3. Submit annual safety updates for 10 years from a cumulative, integrated safety analyses of patients with lymphoid malignancies enrolled in clinical trials and from post-marketing reports to characterize the risk of acute myeloid leukemia, myelodysplastic syndrome, T-lymphoblastic lymphoma, and other secondary malignancies in patients receiving TAZVERIK. Include

incidence rates, time to onset, predisposing factors, and outcomes in the interim and final reports. These safety evaluations may inform labeling of patient populations at highest risk and to provide evidence-based monitoring recommendations.

Protocol Submission	09/2019 (completed)
Study Completion	03/2029
Interim Report Submission	04/2022
Interim Report Submission	04/2023
Interim Report Submission	04/2024
Interim Report Submission	04/2025
Interim Report Submission	04/2026
Interim Report Submission	04/2027
Interim Report Submission	04/2028
Interim Report Submission	04/2029
Interim Report Submission	04/2030
Final Report Submitted	04/2030

Post Marketing Commitments:

The goals of the post marketing commitments are to obtain additional information on ORR and durability in patients who received tazemetostat on study E7438-G00-101 with longer follow up and to obtain additional information on efficacy in patients without EZH2 mutations.

1. Submit the final results and datasets for overall response rate and duration of response from clinical trial E7438-G000-101 in patients with relapsed or refractory follicular lymphoma to further characterize the clinical benefit of tazemetostat.

PMC Schedule Milestones

Final Protocol Submission:	09/2018 (completed)
Trial Completion:	12/2020
Final Report Submission:	06/2021

2. Submit the final results and datasets for overall response rate and duration of response from a clinical trial in patients with relapsed or refractory follicular lymphoma whose tumors do not have an EZH2 mutation and have received prior therapies including bendamustine, obinutuzumab, rituximab plus lenalidomide, and other therapies consistent with those used in a U.S. population to further characterize the clinical benefit of tazemetostat monotherapy that may inform product labeling.

PMC Schedule Milestones

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Final Protocol Submission: 08/2020
Trial Completion: 08/2023
Final Report Submission: 12/2023

3. Submit a final report containing data from clinical trials, post-marketing reports, compassionate use/expanded access program, real-world evidence, and other sources to further characterize the safety and efficacy of tazemetostat monotherapy and tazemetostat in combination with other immunotherapy among U.S. racial and ethnic minority patients with follicular lymphoma.

PMC Schedule Milestones

Final Report Submission: 03/2026

14 Division Director (DHOT)

X

15 Division Director (OCP)

X

16 Division Director (OB) Comments

X

17 Division Director (Clinical) Comments

X

18 Office Director (or designated signatory authority) Comments

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1 References

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19.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): E7438-G000-101

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>495</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3 Additional Clinical Outcome Assessment Analyses

No additional COA Analysis were included in the submission

19.6 FDA Grouped Terms

Table 41: FDA Grouped Preferred Terms

FDA Grouped PT	Included in Grouping	Not Included
Abdominal pain	All PTs containing "abdominal pain", Abdominal discomfort, Abdominal tenderness	Abdominal distension
Anemia	All PTs containing "anemia"; RBC count decreased; Hematocrit decreased	
Bacterial Infection	Bacterial Infection, any specific bacterial infection i.e. "staphylococcal infection", Erysipelas	
Blood Bilirubin Increased	Bilirubin conjugated increased, blood bilirubin increased	
Bruising	All PTs containing "bruise," "contusion," or "ecchymosis"	Petechiae, Purpura
Cardiac arrhythmias	Ventricular extrasystoles, arrhythmia, Bradycardia	
Cardiac failure	All PTs containing "cardiac failure", Left ventricular failure, Cor pulmonale, Cardiopulmonary failure, Cardiogenic shock, Ischemic cardiomyopathy	
Cataract	All PTs containing "cataract"	
Chest Pain	PTs chest pain, angina pectoris	
Cough	All PTs containing "cough"	
Depression	All PTs containing "depression", Depressed mood	
Dyspnea	All PTs containing "dyspnea"	Orthopnea
Edema	All PTs containing "edema" with exception of localized sites	Localized sites of edema
Fatigue	Asthenia, Fatigue,	General physical health deterioration, Malaise, lethargy
Febrile neutropenia	Febrile neutropenia, Febrile bone marrow aplasia, Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs.	
Fungal Infection	Fungal infection, fungal oesophagitis, fungal skin infection	
Gastrointestinal hemorrhage	All PT with "gastrointestinal hemorrhage", lower gastrointestinal hemorrhage, upper gastrointestinal hemorrhage, melaena	
Headache	All PTs containing "headache"; migraine	
Hemorrhage	All PTs containing "hemorrhage", Hemoptysis, Hematuria, Epistaxis,	Petechiae, Purpura, FDA's grouping for "Bruising"
Hematoma	Haematoma, intra-abdominal haematoma	
Hepatitis	All PTs containing "hepatitis", Hepatocellular injury,	FDA's "Transaminase elevation" grouping, Hepatitis PTs indicating infection

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FDA Grouped PT	Included in Grouping	Not Included
Herpesvirus infection	All PTs containing "herpes," "zoster," or "varicella"	
Hypotension	All PTs involving "hypotension" or "blood pressure decrease"	
Hypercalcemia	Hypercalcaemia, hypercalcaemia of malignancy	
Hyperglycemia	Hyperglycemia, Glucose tolerance impaired	
Hypertension	Hypertension, blood pressure increased	
Hypotension	Hypotension, orthostatic hypotension	
Intestinal Obstruction	Intestinal obstruction Distal intestinal obstruction syndrome, duodenal obstruction, Large intestinal obstruction, small intestinal obstruction	
Influenza or influenza like illness	Influenza, influenza like illness	
Jaundice	Jaundice, jaundice cholestatic	
Leukopenia	Leukopenia, White blood cell count reduced	
Lower respiratory tract infection	Lower respiratory tract infection, any PT with lower respiratory tract infection, bronchitis, tracheobronchitis	
Mood Disorder	Mood altered, mood swings	
Musculoskeletal pain	Back pain, Limb discomfort, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity, Pain in jaw, Spinal pain	Arthralgia, Musculoskeletal stiffness, osteoarthritis, axillary pain, groin pain
Myocardial infarction or ischemia	Myocardial infarction, myocardial ischemia	
Nausea	All terms containing "nausea"; Retching	
Neuropathy peripheral	Neuropathy peripheral, peripheral sensory neuropathy, paraesthesia, neuralgia, peripheral motor neuropathy, hypoaesthesia	
Oral fungal infection	Oesophageal candidiasis, oral candidiasis, oral fungal infection	
Neutropenia	Neutropenia, Neutrophil count decreased, Granulocytopenia, Agranulocytosis	
Pancreatitis	Pancreatitis, pancreatitis acute	
Pneumonia	All PTs containing "pneumonia", All PTs containing lung infection	Respiratory tract infection, Lower respiratory tract infection
pruritis	Pruritis, pruritis generalized	
Rash	All PTs containing "rash, Skin erythema, excoriation, skin hyperpigmentation	Urticaria, Drug hypersensitivity, Herpes dermatitis,
Renal insufficiency	Acute kidney injury, renal failure, renal failure acute, renal failure chronic, renal impairment, creatinine renal clearance abnormal	
Respiratory Tract Infection	PTs with "Respiratory tract infection" or respiratory tract infection with specification "parainfluenzae virus infection", respiratory syncytial virus infection, respiratory tract infection viral	
Sepsis	All PTs containing "Bacteremia" or "Sepsis", including within another word (e.g. urosepsis); Septic shock	

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FDA Grouped PT	Included in Grouping	Not Included
Stomatitis	Stomatitis, aphthous stomatitis, cheilitis, Glossitis, lip disorder, mouth ulceration. Odynophagia, oral discomfort, oropharyngeal pain, pharyngeal erythema,	
Thrombosis or thromboembolism	Deep vein thrombosis, Pulmonary embolism, thrombosis, sites of thrombosis (e.g., jugular vein, pelvic, subclavian) , Embolism venous, venous occlusion	Air embolism, Embolism, Septic embolism, Thrombophlebitis superficial
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	PTs with "thrombocytopenic purpura"
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, Alanine aminotransferase, Aspartate aminotransferase, Transaminase increased, Hypertransaminasemia, Hepatic enzyme increased	PTs under FDA's "Hepatitis" grouping, PTs containing "hepatic failure", Hepatic function abnormal
Upper respiratory tract infection	all PTs containing "upper respiratory tract infection," "upper respiratory infection", "sinusitis," "rhinovirus", "rhinitis", "laryngitis," "tonsillitis," or "pharyngitis," including within another word (e.g. nasopharyngitis); upper respiratory tract inflammation, upper respiratory tract congestion	PTs containing the descriptor "allergic" (e.g. rhinitis allergic, allergic sinusitis); Rhinorrhea; Reflux laryngitis, Epiglottitis
Xerosis	Dry skin, Dry eye, Dry mouth, Xerosis, mucosal dryness, Xerophthalmia	

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