Kinetics of Response to Tazemetostat in Patients With Relapsed or Refractory Follicular Lymphoma

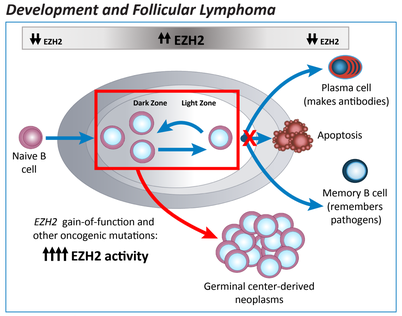
Phillip Campbell, MB, ChB[1]; Hervé Tilly, MD[2]; Aristeidis Chaidos, MD, PhD[3]; Pamela McKay, MD[4], Tycel Phillips, MD[5]; Sarit Assouline, MD[6]; Connie Lee Batlevi, MD, PhD[7]; Vincent Ribrag, MD[8]; Gandhi Laurent Damaj, MD, PhD[9]; Michael Dickinson, DMed Sci[10]; Wojciech Jurczak, MD, PhD[11]; Maciej Kaźmierczak, MD, PhD[12]; Stephen Opat, MBBS[13]; John Radford, MD[14]; Anna Schmitt, PhD[15]; Jennifer Whalen, DHS[16]; Anand Rajarethinam, MD[16]; Beth Kamp, PharmD[16]; Deyaa Adib, MD[16]; Gilles Salles, MD[17]; Franck Morschhauser, MD[18]

[1]Barwon Health–University Hospital Geelong, Geelong, VIC, Australia; [2]Centre Henri Becquerel, Rouen University, Rouen, France; [3]Centre for Haematology, Imperial College London, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK; [4]Beatson West of Scotland Cancer Centre, Glasgow, Scotland, UK; [5]Division of Hematology and Oncology, University of Michigan, Ann Arbor, MI, USA; [6]Division of Hematology, Sir Mortimer B. Davis-Jewish General Hospital, Department of Oncology, McGill University, Montreal, Quebec, Canada; [7]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [8]Gustave Roussy, Villejuif, France; [9]Hematology Institute University Hospital School of Medicine, Caen, France; [10]Clinical Haematology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [11]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [12]Examen sp. z o.o, Poznan, Poland; [13]School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [14]NIHR Manchester Clinical Research Facility, University of Manchester and the Christie NHS Foundation Trust, Manchester, UK; [15]Institut Bergonie, Bordeaux, France; [16]Epizyme, Inc., Cambridge, MA, USA; [17]Lyon-Sud Hospital Center, Pierre-Bénite, France; [18]Centre Hospitalier Universitaire, Lille, France

Background

- Follicular lymphoma (FL) is an incurable malignancy arising from germinal center (GC) B cells[1,2]
- Patients progressing early after frontline therapy have a poor prognosis, with an undefined optimal therapeutic strategy
- Enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase that is essential for GC formation during B-cell development[4,5]
- EZH2 has a role in governing B-cell proliferation and can contribute to the growth and survival of FL tumors, regardless of the oncogenic drivers (**Figure 1**)

Figure 1. Function of EZH2 in Germinal Center B-Cell Development and Follicular Lymphoma



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

- Tazemetostat, a first-in-class, oral, selective methyltransferase inhibitor of EZH2 activity, is approved by the US Food and Drug Administration for treatment of relapsed or refractory (R/R) FL[6]
- A phase 2 study (NCT01897571) of tazemetostat demonstrated objective response rates (ORRs) of 35% and 69% in patients with wild-type (WT) and mutant (MT) *EZH2* R/R FL, respectively[7,8]
  - Median time to first response (range) by independent radiology committee (IRC) was 3.7 (1.6–16.3) months and 3.7 (1.6–10.9) months, in the WT and MT *EZH2* cohorts, respectively
- In this study, time to first response was assessed using the Cheson criteria (**Table 1**), requiring a complete or partial response (≥50% decrease in sum of product of diameters of target lesions) to be recorded
- While useful for the rigors of clinical trials, results for time to response reported using these criteria may not adequately describe the activity of a drug on tumor shrinkage
- Similarly, despite being censored for disease progression for efficacy analyses, some patients were kept on therapy by the investigator
- To address this, we conducted a post hoc analysis to assess the time to 25% reduction in tumor size (TT25%) in patients who achieved a partial or complete response, and to assess the characteristics of patients who remained on therapy after disease progression

Table 1. IWG-NHL 2007 Response Definitions for Clinical Trials[9]

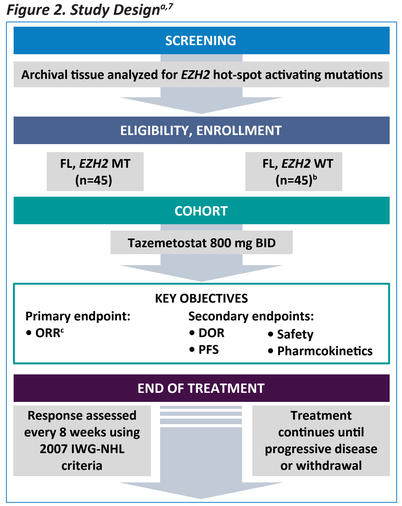
Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	• (A) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative • (B) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	• ≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes • (A) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site • (B) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR, or PD	• (A) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET • (B) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	• Appearance of new lesion(s) 1.5 cm in any axis, ≥50% increase in SPD of >1 node, or ≥50% increase in longest diameter of a previously identified node ≥1 cm in short axis • Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	≥50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

CR, complete remission; CT, computed tomography; FDG, [18F]fluorodeoxyglucose; IWG-NHL, International Working Group for non-Hodgkin lymphoma; PD, progressive disease; PET, positron emission tomography; PR, partial remission; SD, stable disease; SPD, sum of the product of the diameters.

Methods

- This open-label phase 2, multicenter study evaluated tazemetostat 800 mg orally twice daily in patients with WT or MT *EZH2* R/R FL (**Figure 2**)[7]

Figure 2. Study Design[a,7]



[a]Ongoing study, preliminary data as of August 9, 2019. [b]Actual enrollment, N=54. [c]ORR defined as the number of patients with a best objective response of complete or partial response.
BID, twice daily; DOR, duration of response; EZH2, enhancer of zeste homolog 2; FL, follicular lymphoma; IWG-NHL, International Working Group for non-Hodgkin lymphoma; MT, mutant; ORR, objective response rate; PFS, progression-free survival; WT, wild-type.

- Imaging was performed before administration of the first tazemetostat dose, every 8 weeks up to month 6, then every 12 weeks thereafter
- Time to first response was an exploratory endpoint
- Data from patients who achieved PR/CR per Cheson criteria were analyzed to characterize TT25% in target lesions as an indication of antitumor activity prior to PR/CR
- TT25% was based on determinations by the IRC and investigator assessment

Key Eligibility Criteria[7,8]

- Aged ≥18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of 0–2
- Life expectancy ≥3 months
- Histologically confirmed FL, all grades. Patients may have R/R disease following ≥2 standard prior systemic treatment regimens where ≥1 anti-CD20–based regimen was used
- Measurable disease based on International Working Group criteria for non-Hodgkin lymphoma[9]
- For a full list of study eligibility criteria, see www.clinicaltrials.gov/NCT01897571

Results

Demographics

- Patient demographics and baseline characteristics for the intent-to-treat population are shown in **Table 2**

Table 2. Demographics and Baseline Characteristics, Intent-to-Treat Population[7,8]

Characteristic	WT *EZH2* n=54	MT *EZH2* n=45
Median age (range), years	61 (36–87)	62 (38–80)
Male, n (%)	34 (63)	19 (42)
Female, n (%)	20 (37)	26 (58)
ECOG PS, n (%)		
0	26 (48)	21 (47)
1	23 (43)	24 (53)
2	4 (7)	0
Missing	1 (2)	0
Prior lines of systemic anticancer therapy,[a] n (%)		
1[b]	1 (2)	2 (4)
2	16 (30)	22 (49)
3	11 (20)	10 (22)
4	10 (19)	4 (9)
≥5	16 (30)	7 (16)
Median (range)	3 (1–8)	2 (1–11)
Refractory to last regimen,[c] n (%)	22 (41)	22 (49)
Refractory to rituximab-containing regimen,[d] n (%)	32 (59)	22 (49)
Double refractory,[e] n (%)	15 (28)	9 (20)
Prior HSCT, n (%)	21 (39)	4 (9)
POD24	32 (59)	19 (42)
GELF criteria satisfied	40 (74)	31 (69)

[a]Excludes maintenance, consolidation, adjuvant and neoadjuvant therapies when counted as their own line. [b]Radiotherapy qualified as prior therapy at study initiation; subsequent protocol amendments required 2 prior systemic therapies. The intent-to-treat population (N=99) was used for the primary analysis (includes the 4 patients with <2 prior lines of systemic therapy). [c]Patients with stable disease or progressive disease to the most recent previous anticancer therapy. [d]Refractory to either rituximab monotherapy or rituximab-containing therapy or progressive disease within 6 months of completion of rituximab-containing therapy. [e]Refractory to rituximab (as a monotherapy or as part of a combination therapy) and a chemotherapy induction regimen containing one or more alkylating agent or purine nucleoside antagonist and have relapsed within 6 months.
ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; HSCT, hematopoietic stem cell transplant; MT, mutant; POD24, progression of disease within 24 months of prior therapy; WT, wild-type.

Efficacy

Time to 25% Reduction in Tumor Size in the Intent-to-Treat Population

- Protocol-defined median time to first response (PR/CR) per IRC was 3.7 months in both the WT *EZH2* and MT *EZH2* cohorts
- Median TT25% per IRC was shorter than the protocol-defined time to first response (PR/CR): 2.0 months (range, 1.6–13.6; n=50 responders) (**Table 3**)
- Median TT25% per IRC and investigator assessments were similar
  - Median TT25% was longer in the WT *EZH2* cohort than in the MT *EZH2* cohort by IRC assessment but similar per investigator assessment

Table 3. Median Time to 25% Reduction in Tumor Size in Patients With R/R FL per IRC and Investigator Assessments in the Responder Population[a]

Population	Median TT25%	
	IRC Assessment Months (Range)	Investigator Assessment Months (Range)
All patients	2.0 (1.6–13.6) n=50	1.9 (0.7–13.6) n=53
EZH2 WT	3.6 (1.7–13.6) n=19	1.9 (1.6–13.6) n=18
EZH2 MT	1.8 (1.6–5.5) n=31	1.8 (0.7–5.5) n=35

[a]Patients achieving best response of partial or complete response during study.
EZH2, enhancer of zeste homolog 2; IRC, independent radiology committee; MT, mutant; TT25%, time to 25% reduction in tumor size; WT, wild type.

- 17 of 99 patients (17.2%) continued to receive tazemetostat, despite a censoring outcome of disease progression
  - 9 patients with WT *EZH2* FL received therapy past progression for a median (range) of 5.6 (2.8–23.5) months
  - 8 patients with MT *EZH2* FL received therapy past progression for a median (range) of 4.1 (2.6–9.6) months

Safety

- Treatment with tazemetostat was generally well tolerated
  - 8% of patients discontinued treatment due to treatment-emergent adverse events (TEAEs)
  - 9% of patients had a dose reduction due to TEAEs
  - 27% of patients had a dose interruption due to TEAEs
  - Low rate of grade ≥3 treatment-related TEAEs
- Most common TEAEs are shown in **Table 4**
- There were no treatment-related deaths

Table 4. Treatment-Emergent and Treatment-Related Adverse Events Occurring in ≥10% of Patients in the Phase 2 Study Safety Population[a,7]

Category, n (%)	TEAEs (n=99)		Treatment-Related AEs (n=99)	
	Grade 1–2[a]	Grade 3–4[b]	Grade 1–2[a]	Grade 3–4[b]
Nausea	23 (23)	0 (0)	19 (19)	0 (0)
Diarrhea	18 (18)	0 (0)	12 (12)	0 (0)
Alopecia	17 (17)	0 (0)	14 (14)	0 (0)
Cough	16 (16)	0 (0)	2 (2)	0 (0)
Asthenia	15 (15)	3 (3)	13 (13)	1 (1)
Fatigue	15 (15)	2 (2)	11 (11)	1 (1)
Upper respiratory tract infection	15 (15)	0 (0)	1 (1)	0 (0)
Bronchitis	15 (15)	0 (0)	3 (3)	0 (0)
Abdominal pain	12 (12)	1 (1)	2 (2)	0 (0)
Headache	12 (12)	0 (0)	5 (5)	0 (0)
Vomiting	11 (11)	1 (1)	6 (6)	0 (0)
Back pain	11 (11)	0 (0)	0 (0)	0 (0)
Pyrexia	10 (10)	0 (0)	2 (2)	0 (0)
Anemia	9 (9)	5 (5)	7 (7)	2 (2)
Thrombocytopenia	5 (5)	5 (5)	5 (5)	3 (3)

[a]Grade 1–2 TEAEs reported as occurring in ≥10% of patients. [b]Grade ≥3 TEAEs reported in ≥5% patients.
AE, adverse event; TEAE, treatment-emergent adverse event.

Conclusions

- Tazemetostat demonstrated single-agent antitumor activity and clinically meaningful responses in patients with R/R FL
- This post hoc analysis of patients with R/R FL treated with tazemetostat in a phase 2 study revealed clinically meaningful reductions in tumor burden—25% reduction in tumor size—in ≈2 months in patients with WT or MT *EZH2* R/R FL
- Treatment was well tolerated, which enabled investigators to keep patients on study drug for roughly 4 months beyond disease progression
- The kinetics of observed responses suggest that strict, objective criteria used in clinical trials may not adequately convey drug activity

References

1. Küppers R, Stevenson FK. *Blood*. 2018;131:2297-306.
2. Lymphoma - Non-Hodgkin: Subtypes. 2019. Available at: https://www.cancer.net/cancer-types/lymphoma-non-hodgkin/subtypes.
3. NCCN Clinical Practice Guidelines in Oncology. B-Cell Lymphomas v1.2021. 2021. Available at: https://www.nccn.org/professionals/physician_gls/default_nojava.aspx.
4. Gan L, et al. *Biomark Res*. 2018;6:10.
5. Béguelin W, et al. *Cancer Cell*. 2013;23:677-92.
6. Tazverik [package insert]. Cambridge, MA: Epizyme, Inc.; 2020.
7. Morschhauser F, et al. *Lancet Oncol*. 2020;21:1433-42.
8. Morschhauser F, et al. [oral presentation]. Presented at the 61st Annual Meeting of the American Society of Hematology, December 7–10, 2019, Orlando, FL, USA.
9. Cheson BD, et al. *J Clin Oncol*. 2007;25:579-86.

Acknowledgments

Epizyme thanks all study sites, study coordinators, and, most of all, the patients, caregivers, and families who have contributed to this study. Medical writing and editorial support for this poster were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Epizyme, Inc. This study was sponsored by Epizyme, Inc.