A Matching-Adjusted Indirect Comparison of Single-Arm Trials in Patients with Relapsed or Refractory Follicular Lymphoma Who Received at Least Two Prior Systemic Treatments: Tazemetostat was Associated with a Lower Risk for Safety Outcomes Versus the PI3-Kinase Inhibitors Idelalisib, Duvelisib, Copanlisib, and Umbralisib

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ABSTRACT

Introduction: Tazemetostat is an enhancer of zeste homolog 2 (EZH2) inhibitor recommended for patients with relapsed/refractory (R/R) follicular lymphoma (FL) after demonstrating single-agent, antitumor activity in patients with wild-type or mutant *EZH2*. The phosphoinositide 3-kinase (PI3K) inhibitors idelalisib, copanlisib, umbralisib and (formerly) duvelisib are indicated for third-line, fourth-line, and later (3L/4L+) treatment of R/R FL. The objective of this analysis was to provide an indirect treatment comparison of tazemetostat with each PI3K inhibitor for 3L/4L+ R/R FL treatment.

Methods: A systematic literature review was conducted to identify trials for idelalisib (DELTA), duvelisib (DYNAMO), copanlisib (CHRONOS-1 Part B), and umbralisib (UNITY-NHL) in 3L+ R/R FL. Matching-adjusted indirect comparisons were conducted by weighting tazemetostat individual patient data with

available baseline characteristics from each comparator trial: age, Eastern Cooperative Oncology Group performance status, disease stage, histology, prior treatment lines, prior stem cell therapy, progression within 24 months, and refractory status to last therapy. Only the tazemetostat trial included patients with grade 3b or transformed FL, or recorded *EZH2* mutation status. Primary safety outcomes included risk of grade ≥ 3 treatment-emergent adverse events (TEAEs); primary efficacy outcomes included objective response rate (ORR).

Results: Matched patients treated with tazemetostat had lower relative risk (RR) for all grouped safety outcomes, including any grade ≥ 3 TEAEs, compared with idelalisib (RR = 0.45), duvelisib (RR = 0.35), copanlisib (RR = 0.37), and umbralisib (RR = 0.65; all, $p < 0.01$), any serious TEAE, and any TEAE leading to dose reduction, drug discontinuation, or interruption. The ORR was not significantly different for tazemetostat versus other treatments (idelalisib 43% vs 56%, $p = 0.16$; duvelisib 48% vs 47%, $p = 0.91$; copanlisib 49% vs 61%, $p = 0.11$; and umbralisib 57% vs 47%, $p = 0.10$).

Conclusions: In this statistically adjusted comparison, tazemetostat was associated with lower RR for safety outcomes versus idelalisib, duvelisib, copanlisib, and umbralisib, while achieving similar efficacy outcomes.

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Key Summary Points

Tazemetostat, a first-in-class, oral enhancer of zeste homolog 2 (EZH2) inhibitor, was recently approved by the US Food and Drug Administration in patients with relapsed/refractory (R/R) follicular lymphoma (FL) after demonstrating single-agent, antitumor activity in patients with wild-type (WT) or mutant (MT) *EZH2*.

The objective of this analysis was to provide a matching-adjusted indirect treatment comparison of tazemetostat against the phosphoinositide 3-kinase (PI3K) inhibitors idelalisib, duvelisib, copanlisib, and umbralisib for the third-line, fourth-line, and later treatment of R/R FL.

Primary safety outcomes included risk of grade ≥ 3 treatment-emergent adverse events (TEAEs), while primary efficacy outcomes included objective response rate (ORR).

Matched patients treated with tazemetostat had lower relative risk (RR) for all grouped safety outcomes, including any grade ≥ 3 TEAEs, any serious TEAE, and any TEAE leading to dose reduction, drug discontinuation, or interruption. The ORR was not significantly different for tazemetostat versus other treatments.

INTRODUCTION

Follicular lymphoma (FL) is a common indolent lymphoma that accounts for approximately 20% of non-Hodgkin lymphoma (NHL) and up to 70% of indolent NHL cases [1]. The Surveillance, Epidemiology, and End Results (SEER) program registry estimates that the incidence of FL in the USA from 2013 to 2017 was 2.7 per 100,000, and the reported incidence has risen since 1975, with an increase of 1.7 incident cases per 100,000 [1].

Current treatments in FL (e.g., anti-CD20-based chemoimmunotherapy regimens with rituximab) may induce durable remissions and/or slow disease progression, but treatment is not expected to be curative [1]. Thus, patients with FL eventually require retreatment following relapse, and/or they become refractory to anti-CD20 therapy. However, response rates associated with anti-CD20-based therapy retreatment become lower with each successive attempt [2]. Another treatment class, phosphoinositide 3-kinase (PI3K) inhibitors, is indicated for patients with relapsed/refractory (R/R) FL who have received at least two prior systemic therapies, However, the use of these therapies has been associated with adverse reactions and serious toxicities, including hepatotoxicity, infections, severe diarrhea, colitis, pneumonitis, and intestinal perforation [3–5]. The PI3K/casein kinase 1 (CK1) inhibitor umbralisib, which is indicated for treatment of patients with relapsed or refractory (R/R) FL who have received at least three prior systemic therapies, appeared to show lower rates of adverse events in clinical trial, albeit with some of the same toxicity issues observed [6].

Approximately 17–29% of patients with FL are reported to have gain-of-function mutations in the *EZH2* gene, an oncogenic driver of FL [7–11]. Enhancer of zeste homolog 2 (EZH2) signaling has been shown to sustain or promote tumor cell growth in FL and other forms of cancer [12]. In FL specifically, inhibition of EZH2 has been associated with the downregulation of oncogenic polycomb repressive complex 2 signaling activity and promotion of differentiation and apoptosis, even among patients whose tumors are not positive for gain-of-function mutations in *EZH2* [9, 13, 14].

Tazemetostat (Tazverik; Epizyme, Inc.) was approved for the treatment of adult patients with R/R FL whose tumors are positive for an *EZH2* mutation, as detected by a US Food and Drug Administration (FDA)-approved test, and who have received at least two prior systemic

therapies; and for the treatment of adult patients with R/R FL who have no satisfactory alternative treatment options regardless of *EZH2* status [15]. Tazemetostat is also listed in the National Comprehensive Cancer Network (NCCN) Guidelines for B-cell Lymphomas as a category 2A recommended treatment for patients with FL in this indication [16].

Data on the efficacy of tazemetostat compared with other treatments are needed to inform treatment decision-making by patients and health care providers. Given the absence of head-to-head trials among approved treatments in R/R FL, an indirect treatment comparison (ITC) was conducted to compare the safety and efficacy profile of tazemetostat versus agents approved for the treatment of R/R FL in the third or fourth line or later (3L/4L+), adjusting for potential differences in baseline characteristics. On the basis of the most recent NCCN guidelines, treatments specifically FDA approved for R/R FL in 3L are idelalisib and copanlisib, while duvelisib was formerly approved (all 3 are PI3K inhibitors), and umbralisib is approved in 4L; therefore, these four treatments were considered most relevant for indirect comparison with tazemetostat.

METHODS

Evidence Base

A systematic literature review was conducted to identify published clinical trials to support the ITC. Overall, 514 publications were identified and screened on the basis of their titles and abstracts; of these, 20 full-text articles were reviewed, and six were selected for data extraction and inclusion in this analysis. On the basis of the literature review, four comparator clinical trials were identified for the ITC: DELTA (idelalisib) [17], DYNAMO (duvelisib) [18], CHRONOS-1 Part B (copanlisib) [19, 20], and UNITY-NHL (umbralisib) [6]. The E7438-G000-101 trial clinical study report (data on file; Epizyme, Inc.) and two published articles were reviewed for tazemetostat [21, 22]. In all of the evaluated trials, patients with R/R FL represented a subset of the enrolled NHL trial population. Where trial publication data for the R/R FL subpopulation were unavailable, supplemental targeted searches were conducted to fill in evidence gaps. For the DELTA trial, the National Institute for Health and Care Excellence (NICE) submission for idelalisib as a treatment for FL refractory to two treatments (TA604) was identified as the primary source for efficacy and safety data in place of the trial publication, as FL-specific data were available [23]. For the DYNAMO trial, the FDA submission for duvelisib was used to supplement baseline information not reported in the trial publication; however, separate FL population data were not found [24]. Follicular lymphoma-specific population baseline data were also not found for CHRONOS-1 Part B. Additional targeted searches were conducted to identify prognostic factors otherwise not available in the full trial publications, including progression of disease within 24 months of first treatment (POD24) [25]. POD24 data for idelalisib were obtained from an idelalisib-only study, where the patient population was comparable to the study population from the DELTA trial.

The identified trials were subsequently assessed for comparability in terms of study design and trial eligibility criteria. Trial designs were found to be sufficiently comparable, as detailed in Table 1. Each of the studies included in this analysis was conducted in accordance with the ethical standards of the local institutional review boards for each study site and with the Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants before study participation.

Notable differences in trial design included the following:

- The E7438-G000-101 trial (tazemetostat) was the only evaluated trial that identified patients' *EZH2* mutation status and reported results by mutant or wild-type *EZH2* mutation status. Although *EZH2* mutation was not found to be a treatment effect modifier in patients with R/R FL prior to the approval of tazemetostat (data on file; Epizyme, Inc.) [26], tazemetostat acts on EZH2 and does

Table 1 Study design and eligibility criteria across trials [6, 15, 17–20, 23]

	Tazemetostat E7438-G000-101	Idelalisib DELTA	Duvelisib DYNAMO	Copanlisib CHRONOS-1 Part B[a]	Umbralisib UNITY-NHL
Trial design	Phase 2, open-label	Phase 2, open-label, single-arm, 2-stage	Phase 2, open-label, single-arm	Phase 2, open-label, single-arm, 2-part	Phase 2b, open-label, multicohort study
Population	$N = 333$	$N = 125$	$N = 129$	$N = 142$	$N = 208$ (117 with FL, 69 with MZL, 22 with SLL)
	(234 with DLBCL, 45 with mutant EZH2 FL, 54 with wild-type EZH2 FL)	(72 with FL, 28 with SLL, 15 with MZL, 10 with LPL with or without WM)	(83 with FL, 28 with SLL, 18 with MZL)	(104 with FL, 23 with MZL, 8 with SLL, 6 with WM/LPL, 1 with DLBCL)	
Select inclusion criteria	Histology	Histology	Histology	Histology	Histology
	Histologically confirmed FL (all grades) with R/R disease or	Histologically confirmed B cell indolent NHL, with histological subtype limited to FL of grade 1, 2, or 3a; SLL; LPL, with or without associated WM; and MZL (splenic, nodal, or extranodal)	Histologically confirmed FL, SLL, or MZL (splenic, nodal, and extranodal)	Histologically confirmed indolent B cell lymphoma, including FL grades 1 to 3a, MZL, SLL, and WM/LPL	Histologically confirmed B cell NHL, with histological subtype limited to FL of grade 1, 2, or 3a; SLL; and MZL (splenic, nodal, or extranodal)
	Histologically confirmed R/R DLBCL (including primary mediastinal B cell lymphoma), with R/R disease	Prior standard therapy	Prior standard therapy	Prior standard therapy	Prior standard therapy
	Prior standard therapy	Prior treatment with ≥ 2 prior chemotherapy- or immunotherapy-based regimens for indolent NHL	Disease refractory to both rituximab and to either chemotherapy or radioimmunotherapy	Previously received rituximab and an alkylating agent or regimen	For FL cohorts, ≥ 2 prior lines of systemic therapy and prior treatment with an anti-CD20 monoclonal antibody and an alkylating agent
	For FL cohorts, ≥ 2 standard prior systemic treatment regimens where ≥ 1 anti-CD20-based regimen was used	Prior treatment with rituximab and with an alkylating agent for indolent NHL	At least 1 prior chemotherapy regimen (with or without rituximab) containing an alkylating agent or a purine analogue		For MZL cohorts, ≥ 1 prior line of therapy where ≥ 1 CD20-directed regimen was used
		Lymphoma refractory to rituximab (with or without chemotherapy) and/or to an alkylating agent			
Select exclusion criteria (i.e., grade 3b tumors, transformed NHL/FL, prior PI3K inhibitor use)	–	Grade 3b tumors, transformed indolent NHL/FL	Grade 3b tumors, transformed NHL/FL, prior PI3K inhibitor use	Grade 3b tumors, prior PI3K inhibitor use	Grade 3b tumor Excluded Prior PI3K inhibitor use Excluded

CD cluster of differentiation, DLBCL diffuse large B cell lymphoma, EZH2 enhancer of zeste 2 polycomb repressive complex 2 subunit, FL follicular lymphoma, LPL lymphoplasmacytic lymphoma, MZL marginal zone lymphoma, NHL non-Hodgkin lymphoma, PI3K phosphatidylinositol 3-kinase, R/R relapsed/refractory, SLL small lymphocytic lymphoma, WM Waldenström macroglobulinemia

[a]Although not explicitly excluded on the basis of clinicaltrials.gov, Dreyling [19] reported results only based on patients with grade 1–3a tumors

Table 2 Baseline population characteristics for tazemetostat versus idelalisib comparison [15, 17, 23]

Parameter	Before matching			After matching		
	E7438-G000-101, n (%) [A]	DELTA, n (%) [B]	p value [A] vs [B]	E7438-G000-101, % [A]	DELTA, % [B]	p value [A] vs [B]
Treatment	800 mg tazemetostat BID	150 mg idelalisib BID	–	800 mg tazemetostat BID	150 mg idelalisib BID	–
Cohort	FL	FL		FL	FL	
Population	$n = 99$	$n = 72$		ESS = 36	$n = 72$	
Age $\leq$ 62 years	55 (56)	36 (50)	0.5730	50	50	–
ECOG PS						
0	47 (48)	31 (43)	0.6764	43	43	–
> 0	51 (52)	41 (57)	0.5839	57	57	0.9999
1	47 (48)	35 (49)	1.0000	49	49	–
2	4 (4)	6 (8)	0.3249	8	8	–
Missing	1 (1)	0	1.0000	0	0	0.3264
Ann Arbor stage						
III or IV	77 (78)	60 (83)	0.4810	83	83	–
Unknown/missing	6 (6)	0	< 0.05	0	0	–
Tumor histology						
Grade 3b tumor	6 (6)	0	< 0.05	0	0	–
Transformed FL	3 (3)	0	0.2644	0	0	–
Prior autologous stem cell transplant[a]	24 (24)	12 (17)	0.3126	17	17	–
Treated with $\leq$ 4 lines of prior therapy[b]	76 (77)	36 (50)	< 0.001	50	50	–
Refractory to rituximab	54 (55)	72 (100)	< 0.001	70	100	< 0.001
Refractory to last therapy	44 (44)	62 (86)	< 0.001	86	86	–
Double refractory	24 (24)	57 (79)	< 0.001	39	79	< 0.001
POD24 occurrence	51 (52)	37 (51)	1.0000	51	51	–

BID twice daily, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ESS* effective sample size, *FL* follicular lymphoma, *POD24* progression of disease within 2 years

[a]Hematopoietic stem cell transplant was treated as the same as autologous stem cell transplant

[b]Treatment regimens were assumed to be the same as systemic anticancer therapies

Table 3 Baseline population characteristics for tazemetostat versus duvelisib comparison [15, 18]

	Before matching			After matching		
	E7438-G000-101, n (%) [A]	DYNAMO, n (%) [B]	p value [A] vs [B]	E7438-G000-101, n (%) [A]	DYNAMO, n (%) [B]	p value [A] vs [B]
Treatment	800 mg tazemetostat BID	25 mg duvelisib BID	–	800 mg tazemetostat BID	25 mg duvelisib BID	–
Cohort	FL	Indolent NHL		FL	Indolent NHL	
Population	n = 99	N = 129 (83 with FL, 28 with SLL, 18 with MZL)		ESS = 24	N = 129 (83 with FL, 28 with SLL, 18 with MZL)	
Age ≤ 65 years	63 (64)	65 (50)	0.0547	50	50	–
ECOG PS						
2	4 (4)	7 (5)	0.7603	5	5	–
< 2 (0 or 1)	94 (95)	122 (95)	1.0000	95	95	–
Missing	1 (1)	0	0.4342	0	0	0.3296
Ann Arbor stage						
I or II	16 (16)	19 (15)	0.9304	15	15	0.9999
III or IV	77 (78)	109 (85)	0.2080	85	85	–
Unknown/missing	6 (6)	1 (1)	< 0.01	0	0	–
Tumor histology						
Grade 3b tumor	6 (6)	0	< 0.01	0	0	–
Transformed FL	3 (3)	0	0.0805	0	0	–
Prior autologous stem cell transplant[a]	24 (24)	6 (5)	< 0.001	5	5	–
Treated with ≤ 3 lines of prior therapy[b]	61 (62)	65 (50)	0.1067	50	50	–
Refractory to rituximab	54 (55)	127 (98)	< 0.001	71	98	< 0.001
Refractory to last therapy	44 (44)	124 (96)	< 0.001	96	96	–
Double refractory	24 (24)	99 (77)	< 0.001	47	77	< 0.001

BID twice daily, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ESS* effective sample size, *FL* follicular lymphoma, *MZL* marginal zone lymphoma, *NHL* non-Hodgkin lymphoma, *SLL* small lymphocytic lymphoma

[a]Hematopoietic stem cell transplant was treated as the same as autologous stem cell transplant

[b]Treatment regimens were assumed to be the same as systemic anticancer therapies

demonstrate differential results, depending on *EZH2* status [22].

- All trials except for the tazemetostat trial excluded grade 3b tumors. DELTA (idelalisib) and DYNAMO (duvelisib) also excluded transformed FL.

Baseline variables in the FL-specific population were available for the DELTA (idelalisib) comparison. For DYNAMO (duvelisib) and CHRONOS-1 Part B (copanlisib) baseline data were available only for the full-trial population (mixed histology) (64% and 73% of patients with FL, respectively). For UNITY-NHL

(umbralisib), baseline data were available for the FL-specific population; however, safety outcomes were only reported for the full-trial population. Therefore, the full-trial population was used for the matching analysis (56% of patients with FL). Safety and efficacy outcomes evaluated corresponded to the populations with the matched baseline data.

Efficacy and Safety Parameters

The primary safety outcomes assessed in the ITC were the incidence of any grade ≥ 3 treatment-emergent adverse event (TEAE; grouped and individual); incidence of any adverse event of special interest (AESI); incidence of any treatment-emergent serious adverse event (TESAE); incidence of any TEAE leading to study drug interruption; incidence of any TEAE leading to dose reduction; and incidence of any TEAE leading to study drug discontinuation.

The primary efficacy outcome assessed was objective response rate (ORR; FL population for DELTA, and mixed histology population in line with baseline variables for DYNAMO, CHRONOS-1 Part B, and UNITY-NHL). The median duration of response (DOR) was also assessed.

A feasibility assessment for the analysis was conducted to determine if the studies were sufficiently comparable. Definitions of key safety and efficacy outcomes were found to be comparable. Among safety outcomes, all trials except DELTA explicitly specified that TEAEs were evaluated; adverse events (AEs) reported in DELTA were assumed to be equivalent to TEAEs. With respect to efficacy outcomes, response definitions were based on the 2007 International Working Group criteria for non-Hodgkin lymphoma (IWG-NHL) by Cheson et al. and were assessed by central radiographic review or an independent review committee in all trials except for UNITY-NHL, in which response definitions were assessed on the basis of the 2014 Lugano classification by Cheson et al., which was deemed comparable [27, 28]. The ORR was the primary endpoint in all trials. The median DOR was reported for the FL subgroup in the DELTA, DYNAMO, and UNITY-NHL trials only.

Follow-up duration differed across trials. Patients enrolled in the DELTA trial had a minimum follow-up time of 20 months (FL subpopulation); those who enrolled in the DYNAMO trial had a median follow-up time of 32.1 months, and patients enrolled in the CHRONOS-1 Part B trial had a median follow-up time of 6.7–31.5 months (follow-up differed by type of data: safety, 6.7 months; DOR, 16.1 months); and patients in UNITY-NHL had a median follow-up time of 21.4 months for safety outcomes, and 27.7 months for efficacy outcomes. In comparison, the median (interquartile range) follow-up time for the tazemetostat E7438-G000-101 trial was 22.2 months (12.0–26.7) and 35.9 months (32.2–39.0) for the mutant $EZH2$ and wild-type $EZH2$ cohorts, respectively [22].

The duration of exposure was roughly similar for all four comparator trials (DELTA 6.5 months [only patients with FL], DYNAMO 6.7 months, CHRONOS-1 Part B 26 weeks, UNITY-NHL 8.4 months), while the duration of exposure for the E7438-G000-101 trial was numerically higher (9.3 months).

Statistical Methods for Matching-Adjusted Indirect Comparison

Given that all comparator trials were single-arm, and individual patient data (IPD) were available for the tazemetostat E7438-G000-101 trial [22], the matching-adjusted indirect comparison (MAIC) methodology was chosen for the ITC, as described by Signorovitch et al. [29]. The MAIC approach adjusts for baseline differences in potential effect modifiers between trials by reweighting the available IPD to match the average baseline characteristics reported in any trial with aggregate data. Outcomes for each treatment are then compared between balanced trial populations. In this analysis, the MAIC approach was used to reweight IPD from the tazemetostat E7438-G000-101 trial for each of the four pairwise comparisons, so that the reweighted tazemetostat E7438-G000-101 trial population was matched to the average baseline characteristics reported for each comparator trial in turn.

Table 4 Baseline population characteristics for tazemetostat versus copanlisib comparison [15, 19, 20]

	Before matching			After matching		
	E7438-G000-101, n (%) [A]	CHRONOS-1 Part B, n (%) [B]	p value [A] vs [B]	E7438-G000-101, n (%) [A]	CHRONOS-1 Part B, n (%) [B]	p value [A] vs [B]
Treatment	800 mg tazemetostat BID	60 mg copanlisib on days 1, 8, and 15 of a 28-day cycle	–	800 mg tazemetostat BID	60 mg copanlisib on days 1, 8, and 15 of a 28-day cycle	–
Cohort	FL	Indolent B cell lymphoma		FL	Indolent B cell lymphoma	
Population	n = 99	N = 142 (104 with FL, 23 with MZL, 8 with SLL, 6 with WM/LPL, 1 with DLBCL)		ESS = 66	N = 142 (104 with FL, 23 with MZL, 8 with SLL, 6 with WM/LPL, 1 with DLBCL)	
Age ≤ 63 years	56 (57)	71 (50)	0.3825	50	50	–
ECOG PS						
0	47 (48)	80 (56)	0.2207	56	56	–
> 0	51 (52)	62 (44)	0.2843	44	44	1.0000
1	47 (48)	57 (40)	0.3179	40	40	–
2	4 (4)	5 (4)	1.0000	4	4	–
Missing	1 (1)	0	0.4108	0	0	0.3234
Ann Arbor stage						
I	5 (5)	3 (2)	0.2787	2	2	–
II	11 (11)	25 (18)	0.2271	18	18	–
III	19 (19)	32 (23)	0.6420	23	23	–
IV	58 (59)	82 (58)	1.0000	58	58	–
I or II	16 (16)	28 (20)	0.5935	20	20	1.0000
III or IV	77 (78)	114 (80)	0.7564	80	80	1.0000
Unknown/missing	6 (6)	0	< 0.01	0	0	< 0.05
Tumor histology						
Grade 3b tumor	6 (6)	0	< 0.01	0	0	–
Treated with ≤ 3 lines of prior therapy[a]	62 (63)	71 (50)	0.0707	50	50	–
Refractory to rituximab	54 (55)	100 (70)	< 0.05	61	70	0.1810
Refractory to last therapy	44 (44)	86 (61)	< 0.05	61	61	–
POD24 occurrence	51 (52)	68 (48)	0.6721	48	48	–

BID twice daily, *ECOG PS* Eastern Cooperative Oncology Group performance status, *DLBCL* diffuse large B cell lymphoma, *ESS* effective sample size, *FL* follicular lymphoma, *LPL* lymphoplasmacytic lymphoma, *MZL* marginal zone lymphoma, *SLL* small lymphocytic lymphoma, *WM* Waldenström macroglobulinemia

[a]Treatment regimens were assumed to be the same as systemic anticancer therapies

Table 5 Baseline population characteristics for tazemetostat versus umbralisib comparison [6, 15]

	Before matching			After matching		
	E7438-G000-101, *n* (%) [A]	UNITY-NHL *n* (%) [B]	*p* value [A] vs [B]	E7438-G000-101, *n* (%) [A]	UNITY-NHL, *n* (%) [B]	*p* value [A] vs [B]
Treatment	800 mg tazemetostat BID	800 mg umbralisib QD	–	800 mg tazemetostat BID	800 mg umbralisib QD	–
Cohort	FL	NHL		FL	NHL	
Population	*n* = 99	*N* = 208 (117 with FL, 69 with MZL, 22 with SLL)		ESS = 60	*N* = 208 (117 with FL, 69 with MZL, 22 with SLL)	
Age ≤ 66 years	56 (57)	104 (50)	< 0.01	50	50	–
ECOG PS						
0	47 (48)	117 (56)	0.1874	56	56	–
> 0	51 (52)	91 (44)	0.2489	44	44	0.9999
1	47 (48)	85 (41)	0.3320	41	41	–
2	4 (4)	6 (3)	0.7322	3	3	–
Missing	1 (1)	0	0.3225	0	0	0.3238
Ann Arbor stage						
I	5 (5)	19 (9)	0.3084	9	9	–
II	11 (11)	25 (12)	0.9670	12	12	–
III	19 (19)	54 (26)	0.2465	26	26	–
IV	58 (59)	106 (51)	0.2587	51	51	–
I or II	16 (16)	44 (21)	0.3804	21	21	0.9997
III or IV	77 (78)	160 (77)	0.9830	77	77	0.9996
Unknown/missing	6 (6)	4 (2)	0.0818	0	0	0.9998
Tumor histology						
Grade 3b tumor	6 (6)	0	< 0.01	0	0	–
Prior autologous stem cell transplant[a]	24 (24)	12 (6)	< 0.001	6	6	–
Treated with ≤ 3 lines of prior therapy[a]	41 (41.4)	104 (50)	0.1984	50	50	–
Refractory to last therapy	44 (44)	71 (34)	0.1056	34	34	–

BID twice daily, *ECOG PS* Eastern Cooperative Oncology Group performance status, *DLBCL* diffuse large B cell lymphoma, *ESS* effective sample size, *FL* follicular lymphoma, *LPL* lymphoplasmacytic lymphoma, *MZL* marginal zone lymphoma, *SLL* small lymphocytic lymphoma, *WM* Waldenström macroglobulinemia

[a]Treatment regimens were assumed to be the same as systemic anticancer therapies

Table 6 Unadjusted safety comparison of tazemetostat versus idelalisib, duvelisib, copanlisib and umbralisib

Comparator	Outcome	Incidence, % (95% CI)		RR (95% CI)	*p* value
		Tazemetostat	Comparator		
Idelalisib	Any grade ≥ 3 TEAE	39 (30, 49)	67 (56, 78)	0.59 (0.44, 0.79)	< 0.001
	Any TESAE	27 (18, 36)	50 (38, 62)	0.55 (0.37, 0.81)	< 0.01
	Any AESI	2 (0, 5)	–	–	–
	Any TEAE leading to study drug interruption	27 (18, 36)	–	–	–
	Any TEAE leading to dose reduction	9 (3, 15)	31 (20, 41)	0.30 (0.15, 0.61)	< 0.001
	Any TEAE leading to study drug discontinuation	8 (3, 13)	25 (15, 35)	0.32 (0.15, 0.70)	< 0.01
Duvelisib	Any grade ≥ 3 TEAE	39 (30, 49)	88 (83, 94)	0.45 (0.35, 0.57)	< 0.001
	Any TESAE	27 (18, 36)	–	–	–
	Any AESI	2 (0, 5)	–	–	–
	Any TEAE leading to study drug interruption	27 (18, 36)	47 (38, 55)	0.59 (0.40, 0.85)	< 0.01
	Any TEAE leading to dose reduction	9 (3, 15)	19 (13, 26)	0.47 (0.23, 0.96)	< 0.05
	Any TEAE leading to study drug discontinuation	8 (3, 13)	31 (23, 39)	0.26 (0.13, 0.53)	< 0.001
Copanlisib	Any grade ≥ 3 TEAE	39 (30, 49)	83 (77, 89)	0.47 (0.37, 0.61)	< 0.001
	Any TESAE	27 (18, 36)	56 (47, 64)	0.49 (0.34, 0.70)	< 0.001
	Any AESI	2 (0, 5)	7 (3, 11)	0.29 (0.06, 1.29)	0.103
	Any TEAE leading to study drug interruption	27 (18, 36)	68 (61, 76)	0.40 (0.28, 0.56)	< 0.001
	Any TEAE leading to dose reduction	9 (3, 15)	28 (21, 36)	0.32 (0.16, 0.64)	< 0.01
	Any TEAE leading to study drug discontinuation	8 (3, 13)	21 (14, 28)	0.38 (0.18, 0.80)	< 0.05
Umbralisib	Any grade ≥ 3 TEAE	39 (30, 49)	53 (47, 60)	0.74 (0.56, 0.97)	< 0.05
	Any TESAE	27 (18, 36)	30 (24, 37)	0.90 (0.61, 1.32)	0.592
	Any AESI	2 (0, 5)	–	–	–
	Any TEAE leading to study drug interruption	27 (18, 36)	–	–	–
	Any TEAE leading to dose reduction	9 (3, 15)	12 (7, 16)	0.79 (0.38, 1.64)	0.522
	Any TEAE leading to study drug discontinuation	8 (3, 13)	15 (10, 20)	0.53 (0.25, 1.10)	0.088

AESI adverse event of special interest, *CI* confidence interval, *RR* relative risk, *TEAE* treatment-emergent adverse event, *TESAE* treatment-emergent serious adverse event

Baseline characteristics were identified on the basis of availability of data, and prognostic factors associated with efficacy and safety were identified for matching and confirmed by clinical input. Within demographic factors, only age was selected as a matching variable for population adjustment (as data were available and age is expected to be prognostic). Sex was assumed not to be prognostic for the ORR in FL [30]. Geographic region was not included, as it is not typically independently associated with disease or patient characteristics, although prior treatment use may vary by region. Disease severity was measured through objective disease-related characteristics such as those described below. Race could not be included owing to a lack of data availability in the E7438-G000-101 tazemetostat trial.

The following disease characteristics were available and were selected for inclusion because they were expected to be prognostic and/or treatment effect modifiers (identified by expert clinical input): Eastern Cooperative Oncology Group performance status (ECOG
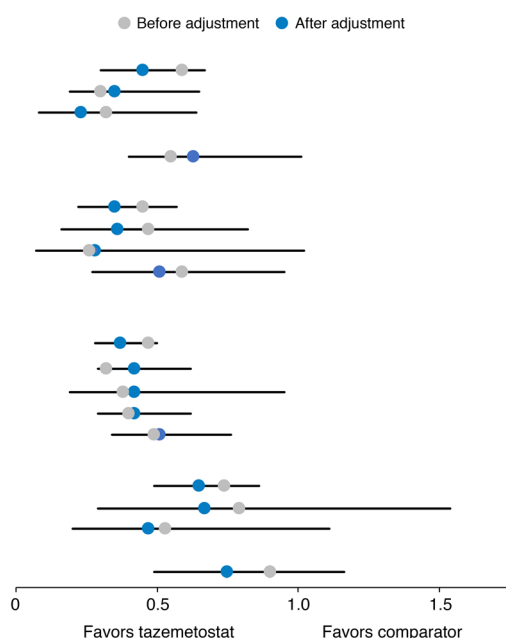
Outcome	Relative risk (95% CI)	P value	Effective sample size
Tazemetostat vs idelalisib			
Any grade ≥3 TEAE	0.45 (0.30–0.67)	<0.001	
TEAEs that led to dose reduction	0.35 (0.19–0.65)	<0.001	
TEAEs that led to discontinuation	0.23 (0.08–0.64)	<0.01	35.8
TEAEs that led to interruption	NR	NR	
Any TESAE	0.63 (0.40–1.01)	0.06	
Tazemetostat vs duvelisib			
Any grade ≥3 TEAE	0.35 (0.22–0.57)	<0.001	
TEAEs that led to dose reduction	0.36 (0.16–0.82)	<0.05	
TEAEs that led to discontinuation	0.28 (0.07–1.02)	0.05	24.1
TEAEs that led to interruption	0.51 (0.27–0.95)	<0.05	
Any TESAE	NR	NR	
Tazemetostat vs copanlisib			
Any grade ≥3 TEAE	0.37 (0.28–0.50)	<0.001	
TEAEs that led to dose reduction	0.45 (0.23–0.85)	<0.05	
TEAEs that led to discontinuation	0.42 (0.19–0.95)	<0.05	65.7
TEAEs that led to interruption	0.42 (0.29–0.62)	<0.001	
Any TESAE	0.51 (0.34–0.76)	<0.001	
Tazemetostat vs umbralisib			
Any grade ≥3 TEAE	0.65 (0.49–0.86)	<0.05	
TEAEs that led to dose reduction	0.67 (0.29–1.54)	0.34	
TEAEs that led to discontinuation	0.47 (0.20–1.11)	0.08	59.3
TEAEs that led to interruption	NR		
Any TESAE	0.75 (0.47–1.20)	0.24	

Fig. 1 Summary of matching-adjusted key safety outcomes. Gray dots denote RR before adjustment and blue dots denote RR after adjustment. The horizontal line represents the 95% CI for each adjusted outcome. *CI* confidence interval, *ESS* effective sample size, *TEAE* treatment-emergent adverse event, *TESAE* treatment-emergent serious adverse event, *RR* relative risk

PS), disease stage at diagnosis (Ann Arbor), histology (tumor grade), number of prior lines of treatment (median), prior stem cell transplantation, POD24 (previously shown to be linked to survival [31]), and previous response to treatment. The presence of myelosuppression, *EZH2* mutation status, Follicular Lymphoma International Prognostic Index (FLIPI) risk group, number of nodal sites, and presence of bulky disease were excluded because of a lack of published data in the comparators. For previous response to treatment, data were available on the number of patients who were double refractory as well as for patients who were refractory to the last line of therapy; however, as these are partially overlapping and, in order not to excessively reduce the sample size, only refractory status to last therapy was included in the analysis.

As *EZH2* status could not be included as a matching variable because of a lack of comparator data, but may be a treatment effect modifier, a scenario analysis was carried out with an *EZH2* weighting of 28.9% (using a published figure based on genetic sequencing of 159 patients recruited for the PRIMA clinical trial [9] of rituximab in previously untreated FL).

Comparison of Efficacy and Safety Outcomes Before and After Matching

For each head-to-head comparison, comparative analyses were conducted both before and after weighting. Before matching, binary outcomes, such as ORR, and safety outcomes were summarized in proportions and compared using the chi-square test. Risk differences comparing tazemetostat versus each of the comparator treatments were also reported. Using the weights generated in the MAIC, ORR and selected safety outcomes were compared between balanced trial populations. Risk differences comparing tazemetostat versus comparator treatments were reported for the ORR and selected safety outcomes. The standard error, 95% confidence interval, and *p* value for the

Table 7 Adjusted safety comparison of tazemetostat versus idelalisib, duvelisib, copanlisib, and umbralisib

Comparator	Outcome	Incidence, % (95% CI)		RR (95% CI)	p value
		Tazemetostat	Comparator		
Vs idelalisib	Any grade ≥ 3 TEAE	30 (19, 41)	67 (56, 78)	0.45 (0.30, 0.67)	< 0.001
	Any TESAE	32 (19, 45)	50 (38, 62)	0.63 (0.40, 1.01)	0.057
	Any AESI	–	–	–	–
	Any TEAE leading to study drug interruption	–	–	–	–
	Any TEAE leading to dose reduction	11 (5, 16)	31 (20, 41)	0.35 (0.19, 0.65)	< 0.001
	Any TEAE leading to study drug discontinuation	6 (0, 11)	25 (15, 35)	0.23 (0.08, 0.64)	< 0.01
Vs duvelisib	Any grade ≥ 3 TEAE	31 (16, 46)	88 (83, 94)	0.35 (0.22, 0.57)	< 0.001
	Any TESAE	–	–	–	–
	Any AESI	–	–	–	–
	Any TEAE leading to study drug interruption	24 (9, 38)	47 (38, 55)	0.51 (0.27, 0.95)	< 0.05
	Any TEAE leading to dose reduction	7 (2, 12)	19 (13, 26)	0.36 (0.16, 0.82)	< 0.05
	Any TEAE leading to study drug discontinuation	9 (0, 20)	31 (23, 39)	0.28 (0.07, 1.02)	0.054
Vs copanlisib	Any grade ≥ 3 TEAE	31 (22, 40)	83 (77, 89)	0.37 (0.28, 0.50)	< 0.001
	Any TESAE	28 (18, 39)	56 (47, 64)	0.51 (0.34, 0.76)	< 0.001
	Any AESI	1 (0, 2)	7 (3, 11)	0.09 (0.01, 0.68)	< 0.05
	Any TEAE leading to study drug interruption	29 (18, 40)	68 (61, 76)	0.42 (0.29, 0.62)	< 0.001
	Any TEAE leading to dose reduction	13 (5, 20)	28 (21, 36)	0.45 (0.23, 0.85)	< 0.05
	Any TEAE leading to study drug discontinuation	9 (2, 16)	21 (14, 28)	0.42 (0.19, 0.95)	< 0.05

Table 7 continued

Comparator	Outcome	Incidence, % (95% CI)		RR (95% CI)	*p* value
		Tazemetostat	**Comparator**		
Vs umbralisib	Any grade ≥ 3 TEAE	34 (26, 43)	53 (47, 60)	0.65 (0.49, 0.86)	< 0.01
	Any TESAE	23 (13, 32)	30 (24, 37)	0.75 (0.47, 1.20)	0.235
	Any AESI	–	–	–	–
	Any TEAE leading to study drug interruption	–	–	–	–
	Any TEAE leading to dose reduction	8 (2, 13)	12 (7, 16)	0.67 (0.29, 1.54)	0.344
	Any TEAE leading to study drug discontinuation	7 (1, 13)	15 (10, 20)	0.47 (0.20, 1.11)	0.083

AESI adverse event of special interest, *CI* confidence interval, *RR* relative risk, *TEAE* treatment-emergent adverse event, *TESAE* treatment-emergent serious adverse event

indirect comparison were based on a robust estimate of the variance using a sandwich estimator that accounts for the variability in the propensity score weights [29, 32].

RESULTS

Baseline Characteristics

Prior to matching, ECOG PS (0, > 0, and 1), tumor histology (grade 3b tumor and transformed FL), and refractory status to last therapy were the main characteristics that were significantly different when the E7438-G000-101 FL population was compared with that of each comparator arm.

After matching, all adjusted population baseline variables were successfully balanced between the reweighted tazemetostat data and the baseline population for each comparison trial. Baseline characteristics across trial populations, both before and after matching, are presented in Tables 2, 3, 4, and 5.

Safety Outcomes

Tazemetostat safety outcomes after population matching were compared with the outcomes from the idelalisib, duvelisib, copanlisib, and umbralisib trials, including any grade ≥ 3 TEAEs, any TESAEs, any AESIs, and any TEAE leading to dose reduction, drug discontinuation, or drug interruption. Unmatched safety comparisons are presented in Table 6.

Overall, tazemetostat showed a lower incidence and lower relative risk for all grouped safety outcomes when data were available (Fig. 1; Table 7). In particular, for any grade ≥ 3 TEAE, tazemetostat had a relative risk of 0.45 (95% CI 0.30, 0.67) versus idelalisib, 0.35 (95% CI 0.22, 0.57) versus duvelisib, 0.37 (95% CI 0.28, 0.50) versus copanlisib, and 0.65 (95% CI 0.49, 0.86) versus umbralisib. For TEAEs leading to dose reduction, tazemetostat had a relative risk of 0.35 (95% CI 0.19, 0.65) versus idelalisib, 0.36 (95% CI 0.16, 0.82) versus duvelisib, 0.45 (95% CI 0.23, 0.85) versus copanlisib, and 0.67 (95% CI 0.29, 1.54) versus umbralisib. For TEAEs leading to drug discontinuation, tazemetostat had a relative risk of 0.23 (95% CI 0.08, 0.64) versus idelalisib, 0.28

Table 8 Adjusted safety comparison of tazemetostat versus idelalisib, duvelisib, copanlisib and umbralisib by grade ≥ 3 TEAEs: incidence of individual TEAEs

Grade ≥ 3 TEAE, % (95% CI)	DELTA		DYNAMO		CHRONOS-1 Part B		UNITY-NHL	
	Tazemetostat	Idelalisib	Tazemetostat	Duvelisib	Tazemetostat	Copanlisib	Tazemetostat	Umbralisib
Anemia	9 (3, 15)	7 (1, 13)	6 (1, 12)	15 (9, 21)	4 (1, 7)	5 (1, 8)	3 (0, 7)	0 (0, 1)
Asthenia	5 (1, 8)	6 (0, 11)	3 (2, 4)	2 (0, 5)	–	–	–	–
Diarrhea	0 (0, 0)	19 (10, 29)	0 (0, 0)	15 (9, 21)	0 (0, 0)	8 (4, 13)	0 (0, 0)	10 (6, 14)
Dyspnea	5 (2, 9)	4 (0, 9)	–	–	–	–	–	–
Fatigue	–	–	0 (0, 0)	5 (1, 8)	2 (0, 5)	2 (0, 4)	2 (0, 6)	3 (1, 6)
Hyperglycemia	–	–	–	–	1 (0, 3)	40 (32, 48)	–	–
Hypertension	–	–	–	–	2 (0, 5)	24 (17, 31)	–	–
Hypokalemia	5 (1, 8)	7 (1, 13)	3 (2, 4)	3 (0, 6)	–	–	–	–
Increased ALT	0 (0, 0)	13 (5, 20)	0 (0, 0)	5 (2, 9)	1 (0, 2)	1 (0, 2)	1 (0, 3)	7 (3, 10)
Increased AST	0 (0, 0)	10 (3, 17)	0 (0, 0)	3 (0, 6)	0 (0, 0)	0 (0, 0)	0 (0, 0)	7 (4, 11)
Neutropenia	3 (0, 8)	22 (13, 32)	3 (0, 7)	25 (17, 32)	4 (0, 8)	24 (17, 31)	2 (0, 4)	12 (7, 16)
Pneumonia	0 (0, 0)	11 (4, 18)	0 (0, 0)	5 (2, 9)	0 (0, 0)	11 (6, 16)	–	–
Rash	–	–	0 (0, 0)	5 (1, 8)	0 (0, 0)	1 (0, 2)	0 (0, 0)	1 (0, 2)
Thrombocytopenia	3 (0, 8)	10 (3, 17)	3 (0, 7)	12 (6, 17)	4 (0, 8)	5 (1, 8)	2 (0, 5)	1 (0, 3)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CI* confidence interval, *TEAE* treatment-emergent adverse event
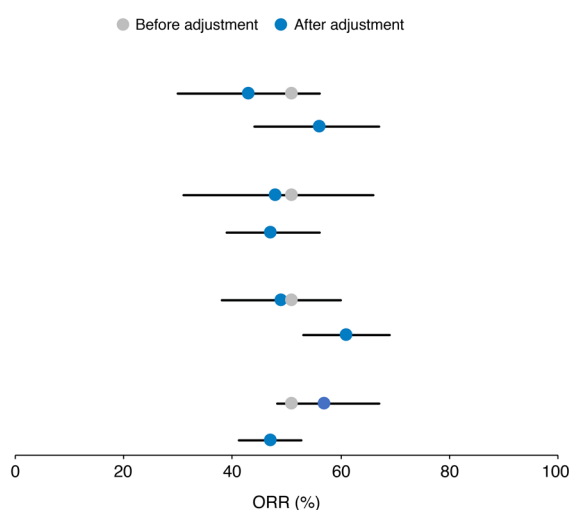
Treatment group	ORR (95% CI). %	P value	Effective sample size
Tazemetostat vs idelalisib			
Tazemetostat	43 (30-56)	0.16	35.8
Idelalisib	56 (44-67)		
Tazemetostat vs duvelisib			
Tazemetostat	48 (31-66)	0.91	24.1
Duvelisib	47 (39-56)		
Tazemetostat vs copanlisib			
Tazemetostat	49 (38-60)	0.11	65.7
Copanlisib	61 (53-69)		
Tazemetostat vs umbralisib			
Tazemetostat	57 (47-68)	0.10	59.3
Umbralisib	47 (40-54)		

Fig. 2 Summary of matching-adjusted key efficacy outcomes. Gray dots denote ORR before adjustment and blue dots denote ORR after adjustment. The horizontal line represents the 95% CI for each adjusted outcome. The ORR reported for duvelisib, copanlisib, and umbralisib reflect the full trial population, as per the availability of baseline variable data. FL-specific ORR is 42% for duvelisib, 59% for copanlisib, and 45% for umbralisib. *CI* confidence interval, *ESS* effective sample size, *FL* follicular lymphoma, *ORR* objective response rate

(95% CI 0.07, 1.02) versus duvelisib, 0.42 (95% CI 0.19, 0.95) versus copanlisib, and 0.47 (95% CI 0.20, 1.11) versus umbralisib.

Several individual grade $\geq$ 3 TEAEs occurred at a significantly lower incidence with tazemetostat compared with matched patients treated with idelalisib, duvelisib, copanlisib, or umbralisib (Table 8). For example, the incidence of neutropenia was lower for tazemetostat versus all comparators (idelalisib 3% vs 22%; duvelisib 3% vs 25%; copanlisib 4% vs 24%; and umbralisib 2% vs 12%; all $p < 0.05$). Other individual grade $\geq$ 3 TEAEs that had a significantly lower incidence included hyperglycemia and hypertension (only copanlisib). There were no individual AEs with significantly higher incidence for tazemetostat in any comparison.

Efficacy Outcomes

After matching and adjustment for baseline characteristics, ORR for tazemetostat compared to each of idelalisib, duvelisib, copanlisib, and umbralisib showed no statistically significant difference between therapies (Fig. 2).

After adjustment to match the aggregate baseline characteristics of the idelalisib and duvelisib trials, the median DOR for tazemetostat decreased compared with the pre-adjustment value. The median DOR for tazemetostat in the idelalisib, duvelisib, copanlisib, and umbralisib comparisons was 7.5 (95% CI 3.8, 19.3), 7.5 (95% CI 3.4, 19.3), 11.3 (95% CI 7.2, not reached), and 13.1 (95% CI 7.2, not reached) months, respectively. Statistical tests for the difference in median DOR against the four comparators were not conducted, given the low effective sample size (defined as the remaining sample size after matching adjustment) and the lack of individual patient data for comparators.

In the scenario analysis where tazemetostat data were adjusted to an *EZH2* mutation weight of 28.9% for all comparisons, ORR was slightly lower than in the base case. Results were as follows: tazemetostat versus idelalisib 37% (95% CI 24, 49) versus 56% (95% CI 44, 67), $p < 0.05$; tazemetostat versus duvelisib 39% (95% CI 20, 59) versus 47% (95% CI 39, 56), $p = 0.49$; tazemetostat versus copanlisib 44% (95% CI 33, 55) versus 61% (95% CI 53, 69), $p < 0.05$; and tazemetostat versus umbralisib

54% (95% CI 43, 64) versus 47% (95% CI 40, 54), $p = 0.29$. Safety outcomes were comparable to the base case analysis.

DISCUSSION

Results from the ITC indicate that, after adjustment for baseline population differences, tazemetostat has better overall safety and tolerability when comparing grade ≥ 3 TEAEs and TEAEs leading to dose reduction or drug discontinuation than idelalisib, duvelisib, copanlisib, and umbralisib, while achieving similar response rates and duration of response. In particular, tazemetostat showed significantly lower relative risk in 13 out of 17 grouped AE categories (e.g., AEs that led to discontinuation, interruption, or dose reduction, TESAEs, and AESIs), and there was no category where point estimates were higher for tazemetostat.

This ITC provides a comprehensive evaluation of cross-trial heterogeneity and addresses potential sources of bias. Late-line cancer treatments are often approved on single-arm trials, and populations may often need adjustment in order to give a more accurate comparison between treatments and to provide clinicians with a more robust basis to compare treatments. This paper provides an illustration of such an adjustment for population differences across a group of comparators. Prior to adjustment, the E7438-G000-101 trial patients had lower ECOG PS, a higher proportion of grade 3b tumors and transformed FL, and fewer patients with a history of refractory status to therapy. These differences in the baseline population make the head-to-head comparison challenging. Using E7438-G000-101 trial IPD to adjust for observed cross-trial differences in patient characteristics allowed for estimates of the indirect treatment effect of tazemetostat, with sources of bias addressed.

There were several limitations associated with the ITC analysis. As with all such analyses, differences in some trial characteristics, such as operational design (e.g., different routes of treatment administration), cannot be addressed analytically. Similarly, another limitation concerns the suitability of using an ITC analysis to compare safety data that may not typically be of a dichotomous nature, but with a gradation in severity. The E7438-G000-101 trial had a longer duration of exposure, which may have led to an overestimation of tazemetostat safety events relative to those of the PI3K inhibitors (including the PI3K/CK1 inhibitor umbralisib). Additionally, adjustment variables for matching are limited to those for which published summary statistics from the comparator trials are available; thus, differences in unmeasured or unadjusted factors are not addressed and remain a potential source of bias. The evidence presented should thus be interpreted with caution until evidence from a direct randomized head-to-head trial between tazemetostat and each of the comparators is available.

There is evidence that *EZH2* status is not prognostic for health outcomes in patients with FL treated beyond first line [7]; however, given the mechanism of action of tazemetostat and differential efficacy reported by *EZH2* status, *EZH2* status should be considered a potential effect modifier for treatment with tazemetostat. *EZH2* mutation status was identified as a treatment effect modifier for tazemetostat, but the *EZH2* mutation frequency for comparator trials was not available. The scenario analysis with a lower weighting of *EZH2* patients shows that this has an influence on ORR results. Nonetheless, this variable is not likely to have had a major influence on safety outcomes, particularly since AEs are typically defined as treatment emergent.

The DOR point estimates decreased in two of the comparisons; however, the median DOR appears to remain adequate, validating the meaningfulness of the ORR. Effective sample size was reduced further for the DOR analysis, as only responders were included, which resulted in confidence intervals with wide ranges; the DOR results should therefore be interpreted with caution. We also note that the DOR was based on follow-up times as of the cutoff in published data, and the absolute median DOR values are likely to rise with additional follow-up data due to censoring involved.

Three of the comparator trials were mixed histology populations, for which separate FL data on baseline characteristics and safety were

not published. An assumption can be made that comparator safety outcomes were driven primarily by study drug, and that there were no major differences in safety prognoses between different histologies included in the trial. This assumption regarding safety is reinforced first by the fact that most safety events were defined as treatment emergent across comparator trials, and second, because the three mixed histology trials still showed a clear majority of the population who had FL. Different histologies are more likely to have different prognoses for efficacy outcomes, suggesting that efficacy results for the comparisons should be interpreted with caution. Published ORR results in the FL-only population were slightly lower for duvelisib (FL only 42%, full-trial population 47%), copanlisib (FL only 59%, full-trial population 61%), and umbralisib (FL-only population 45%, full-trial FL/MZL/SLL population 47%). Although these differences are not large, and it remains possible that the patients with FL had baseline characteristics indicating a worse prognosis, the assumption that the full mixed histology results are comparable to tazemetostat's FL-only results appears reasonable and is more likely to reflect unfavorably on tazemetostat.

The tazemetostat trial was the only one without an exclusion criterion for prior allogeneic stem cell transplant, and this has not been adjusted for; the authors are not aware if this could have affected results in either direction. Separately, only the tazemetostat trial included patients with grade 3b or transformed NHL. Our methodology adjusts for this difference by excluding nine patients with these characteristics from the tazemetostat data. In light of this, the results should be taken as reflecting outcomes in FL without these types of patients. Although patients with these disease characteristics may be expected to have a poor prognosis, the tazemetostat individual patient data reveal that five out of nine of these patients showed a response on tazemetostat; therefore, not including these patients may result in potentially excluding positive outcomes for tazemetostat in patients with a worse prognosis.

CONCLUSIONS

More tolerable treatment options are needed for R/R FL because patients in this setting are often elderly and have exhausted multiple prior lines of treatment. Results from this ITC indicate that, after adjustment for baseline population differences, tazemetostat is associated with substantially lower relative risk for safety outcomes versus idelalisib, duvelisib, copanlisib, or umbralisib while achieving similar efficacy outcomes. This adjusted comparison, while an improvement over naive single-arm comparisons, is nonetheless based on statistical adjustment methods rather than direct evidence, and should ideally be confirmed by randomized controlled trials between tazemetostat and comparators in future.

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the work as a whole, and have given their approval for this version to be published

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Disclosures. David Proudman, Dave Nellesen, and Deepshekhar Gupta are employees of Analysis Group, Inc., which was retained for consulting services to conduct the study. Deyaa Adib, Jay Yang, and Khalid Mamlouk are current or former employees of Epizyme, Inc and own stock.

Compliance with Ethics Guidelines. The results presented in this manuscript are based on previously published studies. All procedures performed in those studies were in accordance with the ethical standards of the local institutional review boards for each site and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the E7438-G000-101 (ClinicalTrials.gov identifier NCT01897571), DELTA (ClinicalTrials.gov identifier NCT01282424), DYNAMO (ClinicalTrials.gov identifier NCT01882803), CHRONOS-1 (ClinicalTrials.gov identifier NCT01660451), and UNITY-NHL (ClinicalTrials.gov identifier NCT02793583) trials.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to the E7438-G000-101 trial IPD being commercial-in-confidence.

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