A Matching-Adjusted Indirect Comparison of Single-Arm Trials in Patients With Relapsed/Refractory Follicular Lymphoma Who Received at Least 2 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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Background

- Tazemetostat, a first-in-class, oral enhancer of zeste homolog 2 inhibitor, was recently approved in patients with relapsed/refractory (R/R) follicular lymphoma (FL) who previously received ≥2 prior systemic therapies[1]
- Phosphoinositide 3-kinase (PI3K) inhibitors idelalisib, duvelisib, and copanlisib are indicated for treatment of R/R FL in the third-line or later (≥3L) setting,[2-4] and the PI3K/casein kinase 1 inhibitor umbralisib is indicated in the fourth-line or later (≥4L) setting[5]
- Tazemetostat, idelalisib, duvelisib, copanlisib, and umbralisib were all approved based on single-arm studies[6-13]; therefore, an indirect treatment comparison (ITC) using a matching-adjusted indirect comparison (MAIC) is the appropriate approach to provide a comparison of these treatments

Objective

- To conduct an MAIC of tazemetostat with idelalisib, duvelisib, copanlisib, and umbralisib for treatment of R/R FL in the ≥3L setting and to provide a comparison of safety and efficacy outcomes

Methods

- A systematic literature review identified clinical trial publications for treatment of R/R FL in the ≥3L setting
- MAIC methodology was selected for the ITC because all comparator trials were single arm, and individual patient data were available for the tazemetostat E7438-G000-101 trial (N=99)
- Four pairwise MAIC analyses were conducted by weighting data from individual patients treated with tazemetostat to baseline characteristics reported from each comparator trial
  - Baseline characteristics and outcomes data of the patient subpopulation with FL were available for matching idelalisib (n=72)
  - Only full-trial mixed non-Hodgkin lymphoma (NHL) populations were reported for duvelisib (n=129 [FL, 64%]), copanlisib (n=142 [FL, 73%]) and umbralisib (n=208 [FL, 56%])
- Matched characteristics were age, Eastern Cooperative Oncology Group performance status, disease stage, histology (tumor grade, transformed FL), number of prior lines of treatment, prior stem cell therapy, refractory status (to last therapy), and progression of disease ≤2 years
  - Characteristics were selected based on clinical opinion and evaluation of prognostic or effect-modifying factors
  - Minor differences were observed between comparators in baseline data availability
- Safety outcomes
  - Any grade ≥3 treatment-emergent adverse event (TEAE) or treatment-emergent serious adverse event (TESAE)
  - TEAEs leading to dose reduction, drug discontinuation, or interruption
  - Individual grade ≥3 TEAEs (eg, anemia, diarrhea, neutropenia, or pneumonia)
- Efficacy outcome
  - Objective response rate

Results

- **Table 1** compares key details in the designs of each study and the eligibility criteria across the ITC trials

Table 1. Comparison of Key Study Design Details and Eligibility Criteria Across ITC Trials

	Tazemetostat E7438-G000-101[6,7]	Idelalisib DELTA[8,9]	Duvelisib DYNAMO[10]	Copanlisib CHRONOS-1 part B[11,12]	Umbralisib UNITY-NHL[13]
Trial design	Phase 2, open label, single arm, 2 cohorts	Phase 2, open label, single arm, 2 stages	Phase 2, open label, single arm	Phase 2, open label, single arm, 2 parts	Phase 2b, open-label, multicohort study
Population	N=99 (All FL)	N=125 (FL: n=72; SLL: n=28; MZL: n=15; LPL ± WM: n=10)	N=129 (FL: n=83; SLL: n=28; MSL: n=18)	N=142 (FL: n=104; MSL: n=23; SLL: n=8; WM/LPL: n=6; DLBCL: n=1)	N=208 (FL: n=117; MZL: n=69; SLL: n=22)
Select inclusion criteria	**Histology** Histologically confirmed FL (all grades) with R/R disease, *or* Histologically confirmed R/R DLBCL (including primary mediastinal BCL) **Prior therapy** ≥2 standard prior systematic treatment regimens in which ≥1 anti-CD20–based regimen used	**Histology** Histologically confirmed B-cell indolent NHL with histologic subtype limited to FL grades 1–3a, SLL, and LPL ± associated WM; and MZL (splenic, nodal, or extranodal) **Prior therapy** Prior treatment with ≥2 prior chemotherapy- or immunotherapy-based regimens for indolent NHL Prior treatment with rituximab and alkylating agent for indolent NHL Lymphoma R/R (± chemotherapy) and/or to alkylating agent	**Histology** Histologically confirmed FL, SLL, or MZL (splenic, nodal, and extranodal) **Prior therapy** Disease refractory to rituximab and chemotherapy/ radioimmunotherapy ≥1 prior chemotherapy regimen (± rituximab) must have contained alkylating agent/purine analog	**Histology** Histologically confirmed indolent BCL, including FL grades 1–3a, MZL, SLL, and WM/LPL **Prior therapy** Previously received rituximab and alkylating agent/regimen	**Histology** Histologically confirmed B-cell NHL, with histologic subtype limited to FL grades 1–3a, SLL, and MZL (splenic, nodal, or extranodal) **Prior therapy** For FL cohorts, ≥2 prior lines of systemic therapy and prior treatment with anti-CD20 monoclonal antibody and alkylating agent For MZL cohorts, ≥1 prior line of therapy where ≥1 CD20-directed regimen used
Select exclusion criteria	**Grade 3b tumor** Not excluded **Transformed NHL/FL** Not excluded **Prior allogeneic SCT** Not excluded	**Grade 3b tumor** Excluded **Transformed indolent NHL/FL** Evidence of histologic transformation **Prior allogeneic SCT** Excluded	**Grade 3b tumor** Excluded **Transformed NHL/FL** Clinical evidence of transformation to an aggressive lymphoma subtype **Prior allogeneic SCT** Excluded	**Grade 3b tumor** Excluded **Prior allogeneic SCT** Excluded	**Grade 3b tumor** Excluded **Prior allogeneic SCT** Excluded

BCL, B-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; ITC, indirect treatment comparison; LPL, lymphoplasmacytic lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; SCT, stem cell transplantation; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Safety

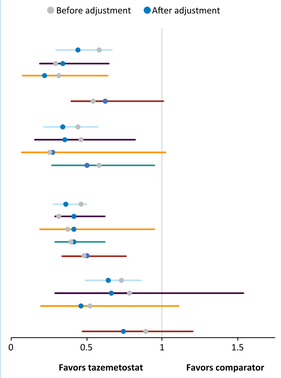
- Rates of grade ≥3 TEAEs of tazemetostat were compared with those reported with idelalisib, duvelisib, copanlisib, and umbralisib (**Table 2**)
- **Figure 1** details the relative risk of tazemetostat compared with the relative risk of idelalisib, duvelisib, copanlisib, and umbralisib

Table 2. Matching-Adjusted Indirect Comparison: Grade ≥3 TEAE Incidence in Tazemetostat vs Comparators

	DELTA		DYNAMO		CHRONOS-1 part B		UNITY-NHL	
Grade ≥3 TEAE, % (95% CI)	**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)	19 (10–29)	0 (0)	15 (9–21)	0 (0)	8 (4-13)	0 (0)	10 (6–14)
Dyspnea	5 (2–9)	4 (0–9)	—	—	—	—	—	—
Fatigue	—	—	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)	13 (5–20)	0 (0)	5 (2–9)	1 (0–2)	1 (0–2)	1 (0–3)	7 (3–10)
Increased AST	0 (0)	10 (3–17)	0 (0)	3 (0–6)	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)	11 (4–18)	0 (0)	5 (2–9)	0 (0)	11 (6–16)	—	—
Rash	—	—	0 (0)	5 (1–8)	0 (0)	1 (0–2)	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 transaminase; CI, confidence interval; TEAE, treatment-emergent adverse event.

Figure 1. Matching-Adjusted Indirect Comparison: Relative Risk of Tazemetostat vs Comparators



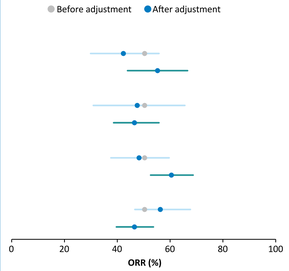
Outcome	Relative risk (95% CI)	*P* value	Effective sample size
Tazemetostat vs idelalisib			
Any grade ≥3 TEAE	0.45 (0.30–0.67)	<0.001	35.8
TEAEs that led to dose reduction	0.35 (0.19–0.65)	<0.001	
TEAEs that led to discontinuation	0.23 (0.08–0.64)	<0.01	
TEAEs that led to interruption	NR	NR	
Any TESAE	0.63 (0.40–1.01)	0.06	
Tazemetostat vs duvelisib			
Any grade ≥3 TEAE	0.35 (0.22–0.57)	<0.001	24.1
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	
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	65.7
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	
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	59.3
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	
TEAEs that led to interruption	NR	NR	
Any TESAE	0.75 (0.47–1.20)	0.24	

CI, confidence interval; NR, not reported; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Efficacy

- Key efficacy outcomes observed with tazemetostat vs idelalisib, duvelisib, copanlisib, and umbralisib are shown in **Figure 2**

Figure 2. Summary of Matching Adjusted Key Efficacy Outcomes



Treatment group	ORR (95% CI), %	*P* value	Effective sample size
Tazemetostat vs idelalisib			
Tazemetostat combined	43 (30–56)	0.16	35.8
Idelalisib	56 (44–67)		
Tazemetostat vs duvelisib			
Tazemetostat combined	48 (31–66)	0.91	24.1
Duvelisib	47 (39–56)		
Tazemetostat vs copanlisib			
Tazemetostat combined	49 (38–60)	0.11	65.7
Copanlisib	61 (53–69)		
Tazemetostat vs umbralisib			
Tazemetostat combined	57 (47–68)	0.10	59.3
Umbralisib	47 (40–54)		

CI, confidence interval; ORR, objective response rate.

Limitations

- As with any MAIC, unmeasured covariates that are potential effect modifiers cannot be adjusted
  - Individual patient data were unavailable for comparator PI3Ks
- As with any indirect treatment comparison, limitations exist to the interpretability of comparisons
- The study was not able to adjust for the effect modifier of *EZH2* mutation status due to lack of available data for comparators
  - The proportion of patients with mutation status in the tazemetostat trial (45%) was higher than typically seen in the real world
  - For 2 comparator trials, the populations included a minority of other NHL subtypes because FL-specific data were not reported
  - These points may have affected efficacy but are not expected to affect safety outcomes
  - Safety outcomes were assumed to have been primarily driven by the study drug and no major differences were observed in safety prognosis, based on different histologies or on *EZH2* status in the trial
- Comparator trials excluded patients with grade 3b tumors or transformed NHL because they were expected to have a worse prognosis
  - 9 patients from the tazemetostat trial with these characteristics were not included

Conclusions

- After adjusting for baseline population differences, results from this ITC suggest that tazemetostat is associated with lower relative risk for safety outcomes vs idelalisib, duvelisib, copanlisib, or umbralisib while achieving similar efficacy outcomes

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