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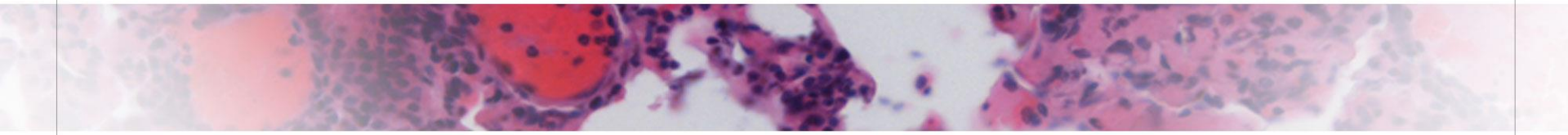

Tazemetostat Is Associated With Lower Risk for Safety Outcomes Versus the PI3-Kinases Idelalisib, Duvelisib and Copanlisib, in Patients With Relapsed/Refractory Follicular Lymphoma Who Have Received at Least 2 Prior Systemic Treatments: a Matching-Adjusted Indirect Comparison of Single-Arm Trials

David Proudman, MPH[1]; Dave Nellesen, PhD[1]; Deepshekhar Gupta, MS[1]; Deyaa Adib, MD[2]; Jay Yang, PhD[2]; Michael Keith, PhD, PharmD[2]; Khalid Mamlouk, PharmD, BCOP[2]

[1]Analysis Group, Inc., Menlo Park, CA; [2]Epizyme, Inc., Cambridge, MA

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Background

- Tazemetostat, a first-in-class, oral EZH2 inhibitor, was recently approved in patients with R/R FL who have received at least 2 prior systemic therapies
- The PI3K inhibitors idelalisib, duvelisib, and copanlisib are indicated for third-line or later (3L+) treatment of R/R FL
- Tazemetostat, idelalisib, duvelisib, and copanlisib were all approved based on single-arm studies; therefore, an ITC using an matching-adjusted indirect comparison (MAIC) is the appropriate approach to provide a comparison of these treatments

Objectives

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

EZH2, enhancer of zeste homolog 2; FL, follicular lymphoma; ITC, indirect treatment comparison; PI3K, phosphoinositide 3-kinase; R/R, relapsed or refractory.

Methods

- A systematic literature review identified clinical trial publications for treatment of patients with 3L+ R/R FL
- The MAIC methodology was selected for the ITC because all comparator trials were single arm, and IPD were available for the tazemetostat E7438-G000-101 trial (N=99)
- Three pairwise MAIC analyses were conducted by weighting individual patients treated with tazemetostat to baseline characteristics reported from each comparator trial
  - FL subpopulation baseline characteristics and outcomes data were available for matching idelalisib (n=72). Only full trial mixed-NHL populations were reported for duvelisib (n=129, 64% FL) and copanlisib (n=142, 73% FL)
- Matched characteristics were age, ECOG 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 POD24
  - Characteristics were selected based on clinical opinion and an evaluation of prognostic or effect modifying factors; there were minor differences between comparators in baseline data availability
- Safety outcomes:
  - Any grade ≥3 TEAE or TESAE
  - TEAEs leading to dose reduction, drug discontinuation, or interruption
  - Individual grade ≥3 TEAEs (eg, anemia, diarrhea, neutropenia, pneumonia)
- Efficacy outcome:
  - Objective response rate

ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; IPC, individual patient data; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; POD24, progression of disease within 2 years; R/R, relapsed or refractory; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Methods, cont'd

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

	Tazemetostat E7438-G000-101[1,2]	Idelalisib DELTA[3,4]	Duvelisib DYNAMO[5]	Copanlisib CHRONOS-1 Part B[6,7]
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
Population	N=99 (All FL)	N=125 (72 with FL, 28 with SLL, 15 with MZL, 10 with LPL with or without WM)	N=129 (83 with FL, 28 with SLL, 18 with MZL)	N=142 (104 with FL, 23 with MZL, 8 with SLL, 6 with WM/LPL, 1 with DLBCL)
Select inclusion criteria	Histology • Histologically confirmed FL (all grades) with R/R disease, or • Histologically confirmed R/R DLBCL (including primary mediastinal B-cell lymphoma), with R/R disease Prior standard therapy • For FL cohorts, ≥2 standard prior systematic treatment regimens, where ≥1 anti-CD20–based regimen was used	Histology • Histologically confirmed B-cell indolent NHL, with histologic subtype limited to FL of grade 1, 2, or 3a; SLL; LPL, with or without associated WM; and MZL (splenic, nodal, or extranodal) Prior standard therapy • Prior treatment with ≥2 prior chemotherapy- or immunotherapy-based regimens for indolent NHL • Prior treatment with rituximab and with an alkylating agent for indolent NHL • Lymphoma that is refractory to rituximab (with or without chemotherapy) and/or to an alkylating agent	Histology • Histologically confirmed FL, SLL, or MZL (splenic, nodal, and extranodal) Prior standard therapy • Disease refractory to both rituximab and to chemotherapy or radioimmunotherapy • At least 1 prior chemotherapy regimen (with or without rituximab) must have contained an alkylating agent or a purine analog	Histology • Histologically confirmed indolent B-cell lymphoma, including FL grades 1 to 3a, MZL, SLL, and WM/LPL Prior standard therapy • Previously received rituximab and an alkylating agent or regimen
Select exclusion criteria	Grade 3b tumor • Not excluded Transformed NHL/FL • Not excluded Prior PI3K inhibitor use/prior BTK inhibitor use • Not excluded	Grade 3b tumor • Excluded Transformed indolent NHL/FL • Evidence of histologic transformation was excluded	Grade 3b tumor • Excluded Transformed NHL/FL • Clinical evidence of transformation to an aggressive lymphoma subtype was excluded Prior PI3K inhibitor/BTK inhibitor use • Excluded	Grade 3b tumor • Excluded Prior PI3K inhibitor use • Excluded

BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; ITC, indirect treatment comparison; 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.

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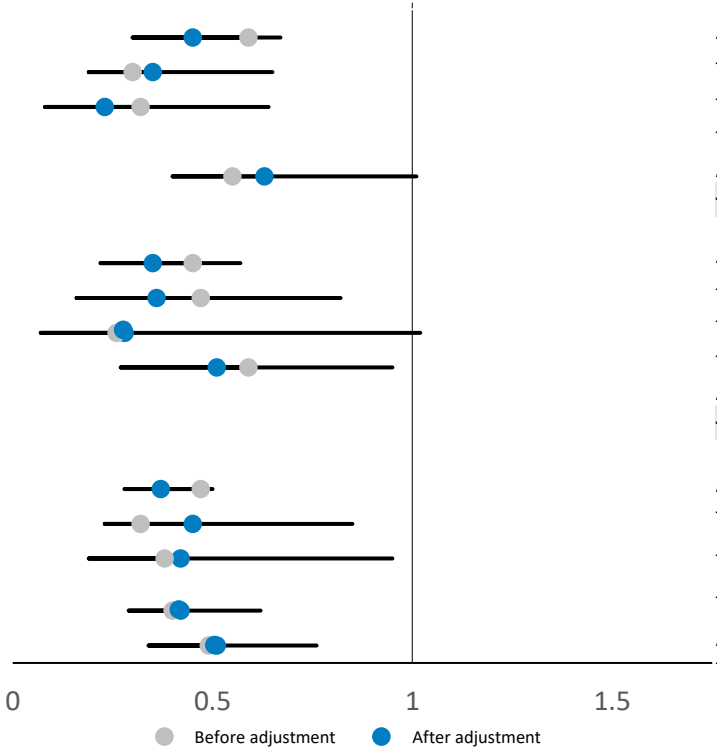
Safety Results



Matching-Adjusted Indirect Comparison, Safety Results: Relative Risk, 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	Not reported	Not reported	
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	Not reported	Not reported	
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	

CI, confidence interval; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

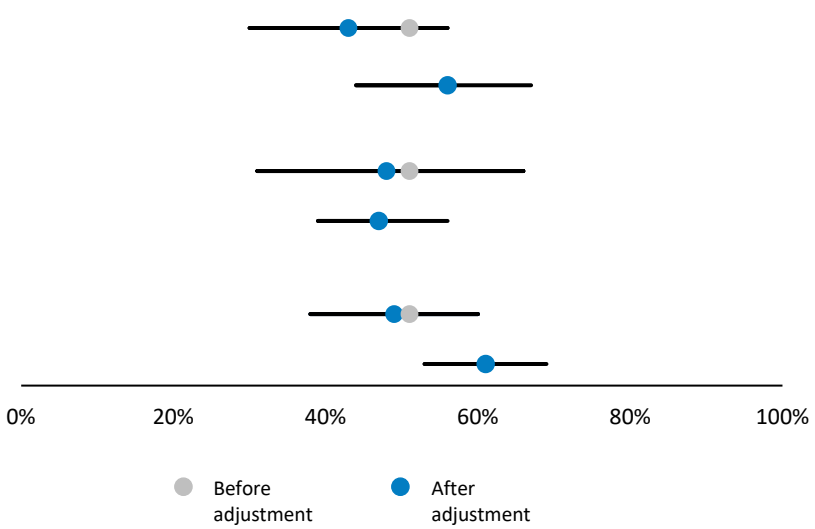
Safety Results, cont'd

Matching-Adjusted Indirect Comparison, Individual Safety Results: Incidence, Tazemetostat vs Comparators

Grade ≥3 TEAE, % (95% CI)	DELTA		DYNAMO		CHRONOS-1 Part B	
	Tazemetostat	Idelalisib	Tazemetostat	Duvelisib	Tazemetostat	Copanlisib
Anemia	**9** (3, 15)	**7** (1, 13)	**6** (1, 12)	**15** (9, 21)	**4** (1, 7)	**5** (1, 8)
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)
Dyspnea	**5** (2, 9)	**4** (0, 9)	—	—	—	—
Fatigue	—	—	**0** (0, 0)	**5** (1, 8)	**2** (0, 5)	**2** (0, 4)
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)
Increased AST	**0** (0, 0)	**10** (3, 17)	**0** (0, 0)	**3** (0, 6)	**0** (0, 0)	**0** (0, 0)
Neutropenia	**3** (0, 8)	**22** (13, 32)	**3** (0, 7)	**25** (17, 32)	**4** (0, 8)	**24** (17, 31)
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)
Thrombocytopenia	**3** (0, 8)	**10** (3, 17)	**3** (0, 7)	**12** (6, 17)	**4** (0, 8)	**5** (1, 8)

ALT, alanine aminotransferase ; AST, aspartate transaminase; CI, confidence interval; TEAE, treatment-emergent adverse event.

Efficacy Results



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]		

CI, confidence interval; ORR, objective response rate.

Limitations

- As with any MAIC, unmeasured covariates that are potential effect modifiers cannot be adjusted. IPD was not available for the comparator PI3Ks. In addition, as with any indirect treatment comparison, there are limitations to the interpretability of the comparisons
- The study was not able to adjust for the effect modifier of *EZH2* mutation status, due to lack of available data for comparators. Additionally, for two comparator trials, the populations included a minority of other NHL subtypes as FL-specific data were not reported. This may have affected efficacy but is not expected to affect safety outcomes
  - An assumption was made that safety outcomes were driven by primarily by study drug, and that there were no major differences 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, which are expected to have a worse prognosis. Nine patients from the tazemetostat trial with these characteristics were accordingly not included

Conclusions

- More tolerable treatment options are needed for 3L+ treatment of R/R FL, particularly as the disease occurs mainly in an elderly population
- Tazemetostat is associated with significantly lower relative risk for safety outcomes versus idelalisib, duvelisib, and copanlisib, while achieving similar efficacy outcomes

Disclosures

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  - David Proudman - *Analysis Group, Inc.*: consultancy.
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  - Deepshekhar Gupta - *Analysis Group, Inc.*: consultancy.
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  - Jay Yang – *Epizyme, Inc.*: employee.
  - Michael Keith – *Epizyme, Inc.:* employee, holds stock/options in the company.
  - Khalid Mamlouk – *Epizyme, Inc.*: employee, holds stock/options in the company.

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