Poster #IBCL-165

Tazemetostat in Relapsed/Refractory Follicular Lymphoma: Propensity Score–Matched Analysis of E7438-G000-101 Trial Outcomes

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Introduction

- Tazemetostat, a first-in-class, oral enhancer of zeste homolog 2 (EZH2) inhibitor, was approved by the US Food and Drug Administration for treatment of 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*[1]
- Patients of both *EZH2* genetic mutation types, MT and WT, were included in the phase 2 trial (E7438-G000-101). Patients with both MT and WT *EZH2* showed response in trials, with the objective response rate (ORR) in the MT population meaningfully higher than that in the WT group (NCT01897571)
- Notable differences were observed in baseline characteristics between the WT and MT *EZH2* cohorts, with the WT *EZH2* cohort enrolling more patients with features that suggest a worse prognosis (eg, mean of 3.7 prior lines of prior anticancer therapy in the WT cohort vs 3.0 in the MT cohort)

Objective

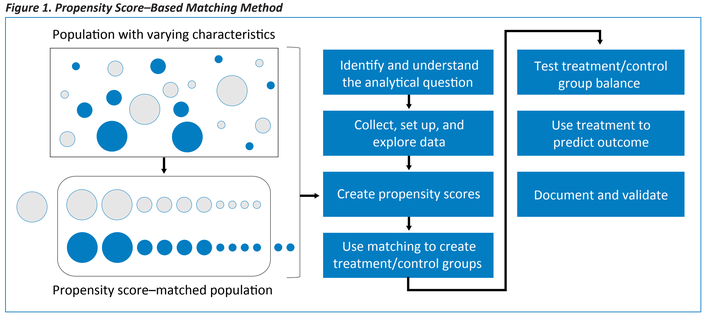
- To assess outcomes in the WT and MT *EZH2* cohort groups after minimizing differences in baseline characteristics by creating a matched sample of comparable WT and MT *EZH2* patients

Methods

Study Design

- Propensity scores for each WT (n=54) and MT (n=45) *EZH2* patient in the study were generated using a logistic regression model in which propensity score was defined as the conditional probability of having the *EZH2* mutation, given the set of observed covariates included in the model
- Baseline characteristics prognostic for clinical outcomes with appreciable differences between cohorts at baseline were selected for inclusion in the model: Eastern Cooperative Oncology Group (ECOG) performance status, number of prior lines of systemic anticancer therapy, progression of disease within 24 months (POD24), double refractory status, and prior history of hematopoietic stem cell transplant
- Patients were matched based on their propensity scores using a 1:1 nearest-neighbor approach within a 0.2-caliper threshold (**Figure 1**)
- ORR estimates were measured for the matched WT and MT *EZH2* groups, and progression-free survival (PFS) was described using Kaplan-Meier analyses

Figure 1. Propensity Score–Based Matching Method



Results

- The propensity score–based approach produced a matched sample of 28 MT *EZH2* and 28 WT *EZH2* patients
- The model estimated a Hosmer-Lemeshow goodness-of-fit test, with a P-value of 0.191, and displayed a good visual overlap in propensity score density (**Figure 2**). Baseline characteristics of MT and WT *EZH2* groups were more comparable after matching (**Table 1**)
- Prior to matching, ORR was 35% (95% confidence interval [CI]: 22–48) in the WT and 69% (95% CI: 55–83) in the MT *EZH2* groups; after matching, ORR was 50% (95% CI: 31–69) and 71% (95% CI: 54–88), respectively (**Table 2**)
- Median PFS was 11.1 months (95% CI: 5.4–16.7) in the WT and 13.8 months (95% CI: 11.1–22.1) in the MT *EZH2* groups prior to matching, and 14.3 months (95% CI: 11.1–inf]) and 14.8 (95% CI: 10.7–inf) months in the WT and MT matched groups, respectively (**Figure 3**)

Figure 2. Propensity Score Density Plots, Before and After Matching

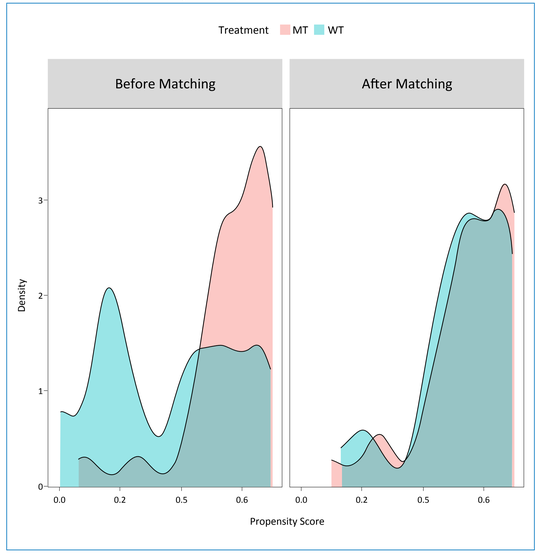
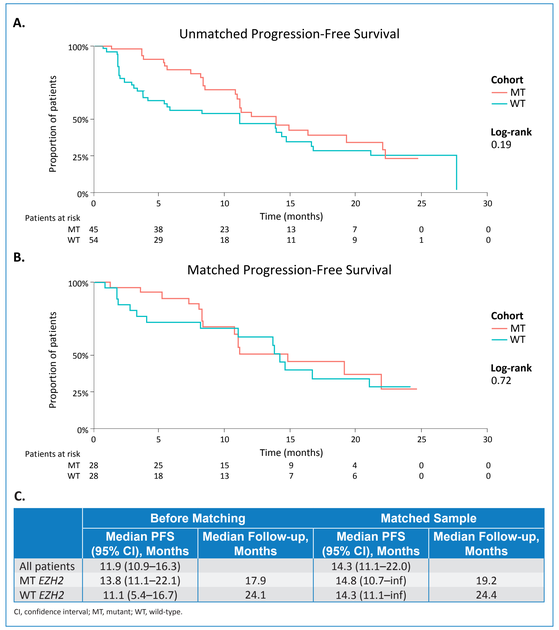


Table 1. Baseline Characteristics, Before and After Matching

Parameter	Before Matching					After Matching				
	Cohort Group					Cohort Group				
	WT N=54	MT N=45	Mean Difference [MT] - [WT]	Standardized Mean Difference	P	WT N=28	MT N=28	Mean Difference [MT] - [WT]	Standardized Mean Difference	P
ECOG PS, n (%)										
0	26 (48.2)	21 (46.7)	-1.5%			16 (57.1)	15 (53.6)	−3.6%		
1	23 (42.6)	24 (53.3)	10.7%	0.47	0.18	12 (42.9)	13 (46.4)	3.6%	0.07	1.00
2	4 (7.4)	0 (0.0)	−7.4%			0 (0.0)	0 (0.0)	0.0%		
Unknown	1 (1.9)	0 (0.0)	−1.9%			0 (0.0)	0 (0.0)	0.0%		
POD24, n (%)	32 (59.3)	19 (42.2)	−17.0%	0.35	0.14	14 (50.0)	12 (42.9)	−7.1%	0.14	0.79
Prior autologous stem cell transplant, n (%)	20 (37.0)	4 (8.9)	−28.2%	0.71	<0.01	3 (10.7)	3 (10.7)	0.0%	0.00	1.00
Number of lines of anticancer therapy	3.7 ± 1.7	3.0 ± 1.7	−0.7 ± 0.3	0.40	0.05	3.1 ± 1.2	2.8 ± 1.4	−0.3 ± 0.4	0.25	0.36
Double refractory, n (%)	15 (27.8)	9 (20.0)	−7.8%	0.18	0.51	6 (21.4)	8 (28.6)	7.1%	0.17	0.76

ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; MT, mutant; POD24, progression of disease within 24 months; SD, standard deviation; WT, wild-type.

Figure 3. Progression-Free Survival Before and After Matching



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	Before Matching		Matched Sample	
	Median PFS (95% CI), Months	Median Follow-up, Months	Median PFS (95% CI), Months	Median Follow-up, Months
All patients	11.9 (10.9–16.3)		14.3 (11.1–22.0)	
MT *EZH2*	13.8 (11.1–22.1)	17.9	14.8 (10.7–inf)	19.2
WT *EZH2*	11.1 (5.4–16.7)	24.1	14.3 (11.1–inf)	24.4

CI, confidence interval; MT, mutant; WT, wild-type.

Table 2. Objective Response Rate, Before and After Matching

	Before Matching ORR (95% CI)	After Matching ORR (95% CI)
WT *EZH2* group	35% (22–48) n=54	50% (31–69) n=28
MT *EZH2* group	69% (55–83) n=45	71% (54-88) n=28

CI, confidence interval; ORR, overall response rate; MT, mutant; WT, wild-type.

Limitations

- Small sample size for each genetic mutation group limits the performance of the matching algorithm and provides limited candidates for matching. Differences between groups in the matched sample cannot be eliminated entirely
- Baseline characteristics for matching were limited to those for which individual patient data were available; therefore, the model cannot account for other sources of variability that are unmeasured/unpublished

Conclusions

- This hypothesis-generating analysis suggests that efficacy outcomes in patients with WT *EZH2* R/R FL treated with tazemetostat may have been more similar to those in the MT *EZH2* group in phase 2 of the E7438-G000-101 trial if the baseline disease characteristics had been more equally matched. The indication that the difference in tazemetostat by *EZH2* mutation status may be smaller than suggested in the trial results should be further investigated through clinical trial, or analysis of real-world outcomes

Reference

1. Tazverik [package insert]. Cambridge, MA: Epizyme, Inc.; 2020.

Author Disclosures

D. Proudman, D. Gupta, D. Nellesen, and A. Wong are or were employees of Analysis Group, Inc., which was paid by Epizyme, Inc., for consulting during this study. J. Yang, B. Kamp, and K. Mamlouk are or were employees of Epizyme, Inc., and may own stock/options in the company. B. Cheson has received fees from Epizyme, Inc., for serving on advisory boards and as a speaker.

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