Poster #109

Characteristics of Patients Achieving Complete or Partial Response With Tazemetostat in Wild-Type Relapsed/Refractory Follicular Lymphoma

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Introduction

- The epigenetic modifier enhancer of zeste homolog 2 (EZH2) expressed within germinal centers is an important regulator of follicular lymphoma (FL) growth and survival[1-3]
- Tazemetostat is a selective, oral, small-molecule EZH2 inhibitor approved by the US Food and Drug Administration for treatment of adults with relapsed or refractory (R/R) FL[4]
  - In a clinical study, tazemetostat demonstrated heightened objective response rates (ORRs) in mutant (MT) *EZH2* cohorts but similar progression-free survival (PFS) rates in wild-type (WT) and MT *EZH2* cohorts with R/R FL[5]
- A pivotal phase 2 study identified ORRs of 35% (19/54) in the WT *EZH2* cohort and 69% (31/45) in the MT *EZH2* cohort; PFS was 11.1 months in the WT and 13.8 months in the MT *EZH2* cohorts
  - Some baseline disease characteristics, such as progression of disease within 24 months (POD24), were not well balanced between cohorts (59%, WT *EZH2* cohort; 42%, MT *EZH2* cohort)
- Disease that is refractory to prior therapy, POD24, and baseline bone marrow involvement are factors associated with poor survival,[6-8] and elevated lactase dehydrogenase (LDH) level is a known prognostic feature of histologic transformation in FL[9]
- Here, we present an exploratory analysis of the phase 2 study to assess whether age at enrollment or baseline disease characteristics correlate with response to tazemetostat in the WT *EZH2* FL cohort
  - We also analyzed the MT *EZH2* FL cohort for comparison

Methods

- Detailed methods of this open-label multicenter phase 2 study (NCT01897571) are described in Morschhauser et al.[5]
- Oral tazemetostat 800 mg twice daily was assessed in adults with FL after ≥2 prior lines of systemic therapy
- Baseline demographics and disease characteristics were summarized using descriptive statistics
- The Cochran-Mantel-Haenszel approach was used for the comparison of frequency data. The analysis of variance (ANOVA) model was used for continuous data analysis, including response, population (WT vs MT *EZH2*), and their interaction as the only independent variables

Results

Population

- Of 99 patients who enrolled:
  - 19 patients with WT *EZH2* achieved a response to tazemetostat (2 complete response [CR], 17 partial response [PR])
  - 31 patients with MT *EZH2* achieved a response to tazemetostat (6 CR, 25 PR)
- Patients received a median of 3 (WT cohort) or 2 (MT cohort) prior lines of therapy before study enrollment

High-Risk Baseline Disease Characteristics and Age

- In the overall population, the WT *EZH2* group had more patients with high-risk features, such as POD24 or refractoriness to rituximab-containing regimen, compared with the MT *EZH2* group (**Table 1**)
- Patients with refractoriness to last therapy made up 26.3% and 51.6% of the WT and MT *EZH2* responder groups, respectively, but the populations were small
- The difference between median age at diagnosis was 9.9 (62.5 vs 52.6) years (P=0.01) between the WT *EZH2* responder and nonresponder groups, and 4.1 (56.7 vs 60.8) years (P=0.207) between the MT *EZH2* responder and nonresponder groups

Table 1. High-Risk Baseline Disease Characteristics and Age

Parameter	With CR/PR (WT *EZH2*) (n=19)	W/O CR/PR (WT *EZH2*) (n=35)	All WT *EZH2* (n=54)	With CR/PR (MT *EZH2*) (n=31)	W/O CR/PR (MT *EZH2*) (n=14)	All MT *EZH2* (n=45)
POD24, n (%)[a]	8 (42.1)	24 (68.6)	32 (59.3)	12 (38.7)	7 (50.0)	19 (42.2)
Refractory to rituximab-containing regimen, n (%)[a]	10 (52.6)	22 (62.9)	32 (59.3)	13 (41.9)	9 (64.2)	22 (48.9)
Refractory to last therapy, n (%)	5 (26.3)	17 (48.6)	22 (40.7)	16 (51.6)	6 (42.9)	22 (48.9)
Double refractory, n (%)[a,b]	4 (21.1)	11 (31.4)	15 (27.8)	7 (22.6)	2 (14.3)	9 (20.0)
Prior HSCT	7 (36.8)	14 (40.0)	21 (38.9)	3 (9.7)	1 (7.1)	4 (8.9)
Age at diagnosis[c]						
Median age (range), years[d,e]	63.5 (46, 81)	52.0 (31, 73)	55.0 (31, 81)	57.5 (34, 77)	62.0 (40, 81)	59.5 (34, 81)

[a]Differences between MT/WT *EZH2* responders and MT/WT *EZH2* nonresponders, and between WT and MT *EZH2* cohorts controlled for responses (CR/PR), were not significant (P>0.05).
[b]Double refractory is refractory to rituximab-containing regimen and to an alkylating agent-containing regimen.
[c]Age at diagnosis = year at initial diagnosis – year of birth + 1; ages of 1 patient in the CR/PR WT *EZH2* group and of 1 patient in the CR/PR MT *EZH2* group are missing.
[d]P=0.582 for the comparison between the WT and MT *EZH2* cohorts controlled for responses (CR/PR).
[e]P=0.001 for the comparison between the MT/WT *EZH2* responders and MT/WT *EZH2* nonresponders.
CR, complete response; HSCT, hematopoietic stem cell transplant; MT, mutant; POD24, progression of disease within 24 months; PR, partial response; W/O, without; WT, wild-type.

Histology

- There was no significant difference between the baseline histology profiles of responder and nonresponder patients in either the WT or MT *EZH2* groups, or in the general study population (**Table 2**)

Table 2. Histology Profile of Responders

Parameter	With CR/PR (WT *EZH2*) (n=19)	W/O CR/PR (WT *EZH2*) (n=35)	All WT *EZH2* (n=54)	With CR/PR (MT *EZH2*) (n=31)	W/O CR/PR (MT *EZH2*) (n=14)	All MT *EZH2* (n=45)
FL histology, n (%)[a]						
Grade 1	3 (15.8)	8 (22.9)	11 (20.4)	8 (25.8)	2 (14.3)	10 (22.2)
Grade 2	8 (42.1)	15 (42.9)	23 (42.6)	11 (35.5)	8 (57.1)	19 (42.2)
Grade 3A	1 (5.3)	6 (17.1)	7 (13.0)	7 (22.6)	4 (28.6)	11 (24.4)
Grade 3B	1 (5.3)	2 (5.7)	3 (5.6)	3 (9.7)	0	3 (6.7)
Transformed FL	1 (5.3)	2 (5.7)	3 (5.6)	0	0	0
Missing/unknown	6 (31.6)	4 (11.4)	10 (18.5)	2 (6.5)	0	2 (4.4)

[a]P=0.358 for the comparison between the WT and MT *EZH2* cohorts, controlled for responses (CR/PR).
CR, complete response; FL, follicular lymphoma; MT, mutant; PR, partial response; W/O, without; WT, wild-type.

Prognostic Factors

- 47.4% of patients in the WT *EZH2* responder group had high LDH levels compared with 46.7% of patients in the MT *EZH2* responder group. There was no significant difference in LDH profiles between the WT and MT *EZH2* patient groups (**Table 3**)
- The number of patients with bone marrow involvement was consistent between the WT and MT *EZH2* responders and nonresponders. However, a substantial number of missing bone marrow samples rendered the data inconclusive (**Table 3**)

Table 3. Prognostic Factors of Responders

Parameter	With CR/PR (WT *EZH2*) (n=19)	W/O CR/PR (WT *EZH2*) (n=35)	All WT *EZH2* (n=54)	With CR/PR (MT *EZH2*) (n=31)	W/O CR/PR (MT *EZH2*) (n=14)	All MT *EZH2* (n=45)
LDH category, n (%)						
High[a,b]	9 (47.4)	18 (51.4)	27 (50)	14 (46.7)	6 (42.9)	20 (45.5)
Normal[a,b]	10 (52.6)	17 (48.6)	27 (50)	16 (53.3)[c]	8 (57.1)	24 (54.5)
Bone marrow involvement,[d] n (%)						
Yes[e]	2 (10.5)	10 (28.6)	12 (22.2)	6 (19.4)	3 (21.4)	9 (20.0)
No[e]	15 (78.9)	16 (45.7)	31 (57.4)	21 (67.7)	8 (57.1)	29 (64.4)
Missing[f]	2 (10.5)	9 (25.7)	11 (20.4)	4 (12.9)	3 (21.4)	7 (15.6)

[a]P=0.841 for the comparison of LDH profiles between WT and MT cohort.
[b]P=0.778 for the comparison of LDH profiles between WT responders and nonresponders; P=0.815 for the comparison between MT responders and nonresponders.
[c]One subject had missing LDH level at baseline.
[d]Yes indicates that assessment of bone marrow at screening was abnormal.
[e]P=0.902 for the comparison of bone marrow involvement between the WT and MT cohorts.
[f]Missing includes assessment not done.
CR, complete response; LDH, lactate dehydrogenase; MT, mutant; PR, partial response; W/O, without; WT, wild-type.

Conclusions

- Characteristics of responders in the WT *EZH2* R/R FL cohort were reflective of the general study population, with a broad distribution of disease severity at baseline
- Responders with WT *EZH2* included patients with high-risk features, such as POD24, refractoriness to rituximab-based regimens, or double refractory disease
- Response to tazemetostat in patients with WT *EZH2* R/R FL appears to be independent of baseline clinical factors; however, small numbers preclude a definitive assessment. Additional correlative molecular analyses are in progress
- Other factors, such as epigenetic or genetic features, may be predictive factors and warrant testing

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