EZH2 Gain-of-Function Mutations Are Not Associated With More Favorable Prognosis in Relapsed/Refractory Follicular Lymphoma: A Preliminary Analysis on 908 Patients

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AUTHOR DISCLOSURES

Disclosures for Csaba Bödör to be added

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BACKGROUND

- Enhancer of zeste homolog 2 (EZH2) is an epigenetic regulator of gene expression and plays a critical role in multiple forms of cancer
  - Activating mutations of *EZH2* act as an oncogenic driver, especially in follicular lymphoma (FL), and are present in ≈20%–25% of patients[1,2]
- Small published studies suggest *EZH2* gain-of-function mutations may provide a prognostic benefit in the first-line setting (1L) in patients with FL treated with immunochemotherapy regimens[3,4]
- However, one study suggested that the impact of *EZH2* mutations over the long term were lost when overall survival (OS) was evaluated[2]
- Tazemetostat, a selective, oral inhibitor of the histone methyltransferase EZH2, has shown antitumor activity in patients with relapsed and/or refractory (R/R) FL treated with at least 2 prior lines of therapy. It is unknown whether *EZH2* mutations confer prognostic benefits in this setting
- This multicenter study is intended to evaluate the impact of *EZH2*-activating mutations on outcomes in patients with R/R FL from 5 academic sites. Results of an interim analysis of data from 4 (of 5) academic sites are presented

1L, first line; 2L, second line; EZH2, enhancer of zeste homolog 2; FL, follicular lymphoma; OS, overall survival; R/R, relapsed or refractory.

1. Morin RD, et al. *Nature Genetics*. 2010;42(2):181-5. **2.** Bödör C, et al. *Blood*. 2013;122(18):3165-8. **3.** Pastore A, et al. *Lancet Oncol*. 2015;16(9):1111-22. **4.** Huet S, et al. *Blood Cancer J*. 2017;7(4):e555.

METHODS

- Retrospective data on therapy types and clinical outcomes were collected from 4 academic sites
  - Barts Cancer Institute, London
  - Institut Gustave Roussy, Paris
  - Memorial Sloan Kettering Cancer Center, New York City
  - Semmelweis University, Budapest
- Tumor tissues collected at the time of diagnosis, in most cases, were analyzed for activating mutations of *EZH2* (Y646X, A682G, A692V) using the following approaches:
  - Next-generation sequencing, including use of targeted exome sequencing or a targeted gene panel, such as the MSK-IMPACT panel
  - Digital droplet polymerase chain reaction (PCR; BioRad)
- Data were analyzed to compare clinical outcome parameters between patients with R/R FL with MT *EZH2* and WT *EZH2*
  - Best ORR, based on each center's response criteria, was compared by *EZH2* status and stratified by line of therapy using the Cochran-Mantel-Haenszel chi-square test
  - Best responses were assessed by the treating physician at each site based on the site's criteria of clinical response (rather than by International Working Group criteria)
  - PFS and OS were calculated using the Kaplan-Meier method and compared by the log-rank test

EZH2, enhancer of zeste homolog 2; FL, follicular lymphoma; MT, mutant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory; WT, wild-type.

Baseline Demographics

Characteristic	Total Number of Patients (N=908)
Age, median (range), years	54 (21–90)
Males/females, n (%)	453 (50) / 455 (50)
Median follow-up from diagnosis to last follow-up or death, years	8.92 (range, 0.03-38.52)
ECOG performance status 0–1, n (%)	414 (46)
ECOG performance status ≥2, n (%)	43 (5)
ECOG performance status NA or missing, n (%)	451 (50)
Frequency of *EZH2*-activating mutations, %	21
Y646 (H, N, S, C, F)	81
A682G	11
A692V	8
Patients receiving each therapy type at any time, n (%)	
Systemic anticancer therapy	805 (89)
Stem cell transplantation	190 (21)
Radiotherapy	270 (30)

ECOG, Eastern Cooperative Oncology Group; EZH2, NA, not applicable.

Systemic Anticancer Therapy Types, by Line of Therapy

Line of Therapy	MT *EZH2* (n=193)[a]	WT *EZH2* (n=713)[a]
1L, n[b] (%)	n=178	n=625
Chemotherapy	69 (39)	228 (36)
Immunochemotherapy[c]	100 (56)	348 (56)
Targeted therapy	1 (<1)	3 (<1)
Anti-CD20 monotherapy	7 (4)	35 (6)
Other[d]	1 (<1)	11 (2)
2L, n[b] (%)	n=102	n=411
Chemotherapy	47 (46)	160 (39)
Immunochemotherapy[c]	37 (36)	167 (41)
Targeted therapy	0	7 (2)
Anti-CD20 monotherapy	6 (6)	24 (6)
Other[d]	12 (12)	53 (12)
3L, n[b] (%)	n=77	n=297
Chemotherapy	41 (53)	124 (42)
Immunochemotherapy[c]	17 (22)	91 (31)
Targeted therapy	2 (3)	20 (7)
Anti-CD20 monotherapy	6 (8)	22 (7)
Other[d]	11 (14)	40 (13)
4L, n[2] (%)	n=50	n=215
Chemotherapy	36 (72)	94 (44)
Immunochemotherapy[c]	5 (10)	52 (24)
Targeted therapy	2 (4)	14 (7)
Anti-CD20 monotherapy	1 (2)	19 (9)
Other[d]	6 (12)	36 (16)

[a]n=number of patients defined as either MT or WT *EZH2*, respectively, who received systemic anticancer therapy. [b]n=total number of patients defined as MT or WT *EZH2* who received the specified line of systemic anticancer therapy. [c]Anti-CD20 antibody + chemotherapy (eg, CHOP). [d]Other = all other types of systemic anticancer therapy that could not be defined as immunochemotherapy, chemotherapy, targeted agent, or anti-CD20 monotherapy (eg, radioimmunotherapy, immunomodulatory agent, antibody-drug conjugate, etc).
L, line; MT, mutant; WT, wild-type.

ORR for Patients With FL With MT and WT EZH2, Across Lines of Therapy

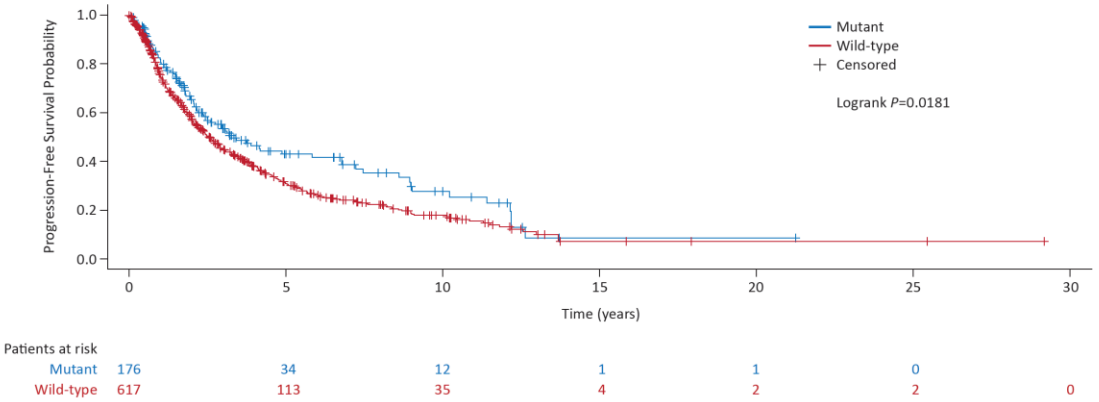
All Sites	MT *EZH2*, # Responders/ # Treated (%)	WT *EZH2*, # Responders/ # Treated (%)	All, # Responders/ # Treated (%)	*P*-value
1L	162/178 (91)	540/625 (86)	704/805 (87)	0.1019
2L	75/102 (74)	290/411 (71)	365/515 (71)	0.5539
3L+[a]	66/77 (86)	241/297 (81)	308/376 (82)	0.3521

- No significant differenced observed in ORR for MT and WT EZH2 across lines of therapy
- Differences in treatment regimens, methods of evaluating clinical response, regional patient populations, and era in which patients were treated make it challenging to evaluate ORR in these patients

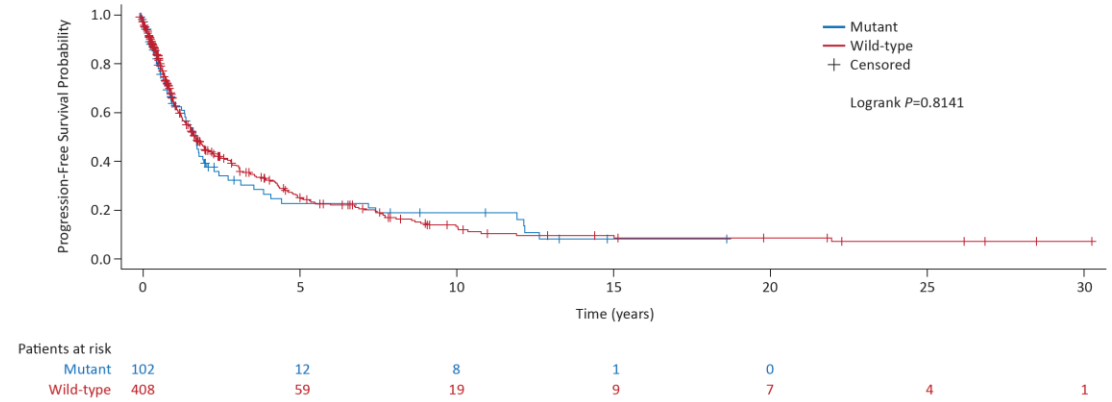
[a]The # responders is the sum of all patients who responded during any line of therapy, including 3L or any subsequent line of therapy.
L, line; MT, mutant; ORR, objective response rate; WT, wild-type.

PFS by Line of Therapy for Patients With FL With MT vs WT EZH2

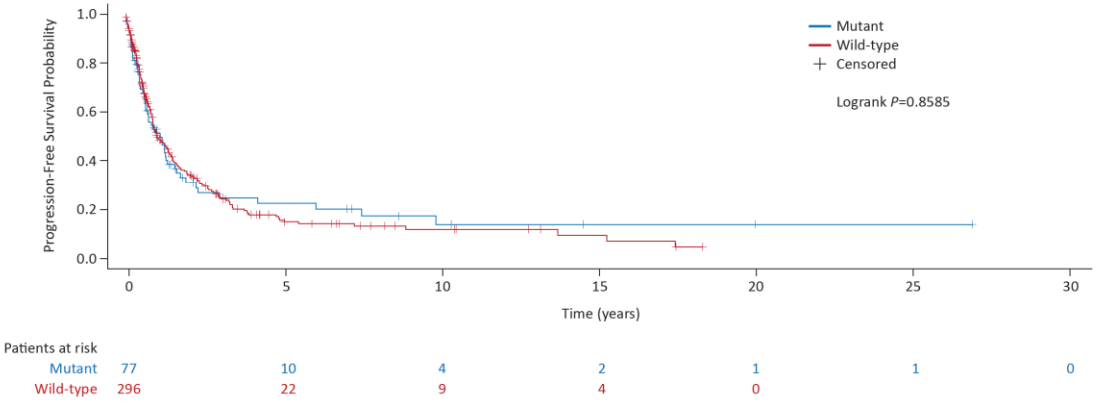
A. 1L PFS



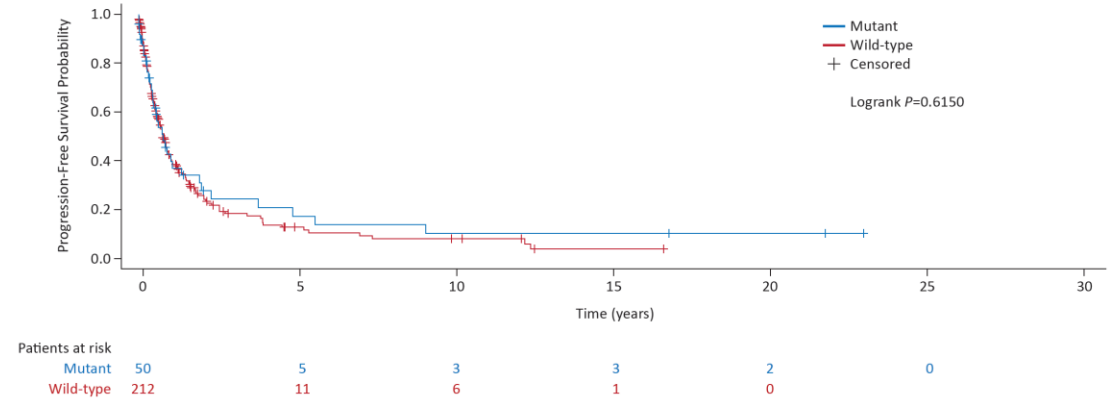
B. 2L PFS



C. 3L PFS



D. 4L PFS



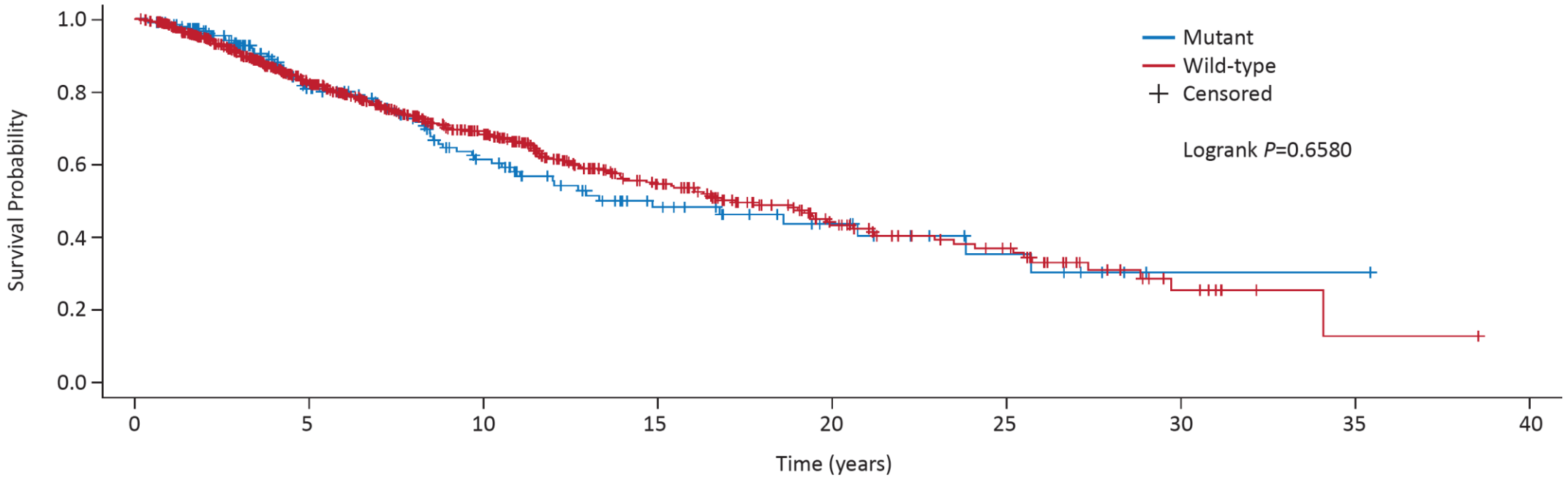
In each panel, the total number of MT and WT *EZH2* patients evaluable for PFS is shown at time=0 for that line of therapy.
L, line; MT, mutant; PFS, progression-free survival; WT, wild-type.

PFS for Patients With FL With MT and WT EZH2 Receiving Systemic Anticancer Treatment, by Line of Therapy

Line of Therapy	MT *EZH2*	WT *EZH2*	*P*-value
1L	n=178[a]	n=625[a]	
Median PFS, years	3.27	2.52	0.0181
95% CI, years	2.38, 6.77	2.18, 2.91	
2L	n=102[a]	n=411[a]	
Median PFS, years	1.77	1.73	0.8141
95% CI, years	1.32, 2.12	1.46, 2.08	
3L	n=77[a]	n=297[a]	
Median PFS, years	1.07	0.99	0.8585
95% CI, years	0.61, 1.53	0.84, 1.33	
4L	n=50[a]	n=215[a]	
Median PFS, years	0.77	0.76	0.6150
95% CI, years	0.44, 1.35	0.62, 0.95	

[a]n is defined as the total number of MT or WT *EZH2* patients who received that respective line of systemic anticancer therapy. In a small number of cases, it was not possible to calculate PFS, which is reflected in the smaller number of patients at time=0 for MT and/or WT *EZH2* for some lines of therapy in the first figure than depicted in the fourth table.
CI, confidence interval; L, line; PFS, progression-free survival; MT, mutant; WT, wild-type.

OS for Patients With FL With MT vs WT EZH2



Patients at risk									
Mutant	178	97	56	28	15	7	1	1	0
Wild-type	624	377	214	108	50	30	8	1	0

The number of MT and WT *EZH2* patients evaluable to determine OS from time of diagnosis to death or time of last follow-up is shown at time=0.
FL, follicular lymphoma; MT, mutant; OS, overall survival; WT, wild-type.

CONCLUSIONS

- ORR was similar between patients with MT *EZH2* compared with WT *EZH2* in all lines of therapy
- Analysis of OS indicates that there are no significant differences between MT and WT *EZH2* patients with R/R FL followed for more than 30 years
- Improved PFS was observed in the 1L setting in patients with MT *EZH2* compared with WT *EZH2*, similar to results reported by Pastore et al.[1] and Huet et al[2]
  - However, MT *EZH2* did not act as a positive prognostic factor in patients with R/R FL treated in 2L+
- Based on this large retrospective analysis, these data suggest that the clinical activity observed in patients with R/R FL with standard of care agents or tazemetostat is due to the drugs' mechanisms of action and not due to a prognostic effect of *EZH2* mutation

1. Pastore A, et al. *Lancet Oncol*. 2015;16(9):1111-22. **2.** Huet S, et al. *Blood Cancer J*. 2017;7(4):e555.