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***EZH2* Mutation Screening in Hungarian Follicular Lymphoma Patients: Paving the Way to Epigenetic Therapy**

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Introduction: Mutations emerging in different epigenetic regulators play a major role in the pathogenesis of follicular lymphoma. The *EZH2* histone methyltransferase harbouring gain-of-function mutations in 25% of the patients emerged as a promising therapeutic target in follicular lymphoma. The *EZH2* inhibitor tazemetostat proved to be effective in a phase II clinical trial for the treatment of follicular lymphoma, demonstrating increased efficacy in patients harbouring *EZH2* mutations. To identify the patients most likely benefiting from *EZH2* inhibitor therapy, we aimed to perform *EZH2* mutation analysis in a cohort of Hungarian follicular lymphoma patients.

Methods: We evaluated the *EZH2* mutation status of 321 patients with follicular lymphoma, by performing a digital droplet PCR (ddPCR) mutation analysis of the Y646, A682, and A692 hotspots in DNA samples from bone marrow or lymph node biopsy specimens. We also analyzed the association of *EZH2* mutation status and clinical data.

Results: Gain-of-function *EZH2* mutations were identified in 24.3% (78/321) of the patients. Three patients presented with more than one mutation. In most cases the mutation resulted in Y646N (35%, 28/81), Y646F (20%, 16/81), or Y646S (16%, 13/81) amino acid change. *EZH2* mutation status did not show significant association with survival data in our cohort.

Discussion: We performed *EZH2* mutation analysis of 321 Hungarian follicular lymphoma patients. The observed mutation frequencies are in line with previously published data. However, in contrast to previous studies suggesting a superior progression-free survival in *EZH2* mutant patients, we found no significant correlation between *EZH2* mutation status and survival data.

Conclusion: In this study, 24.3% of follicular lymphoma patients harboured *EZH2* mutations providing rationale for their recruitment into an *EZH2* inhibitor clinical trial in the future. We also optimized *EZH2* mutation testing using a highly sensitive ddPCR assay and included this test in the routine molecular diagnostic algorithm of follicular lymphoma.

Ethical Committee or Institutional Animal Care and Use Committee Approval: The study was approved by the Ethical Committee of the Hungarian Medical Research Council (ETT TUKEB) under the registration number: 14383-2/2017/EKU (2017-03-10).

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