Preliminary evidence of a molecular predictor of tazemetostat response, beyond EZH2 mutation, in NHL patients via characterization of archive tumor and circulating tumor DNA

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*EZH2* gene is frequently altered in hematologic malignancies, and EZH2-containing complexes play a key role in transcriptional repression. EZH2 mutations are Oncogenic drivers in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), and tazemetostat (TAZ), a BET bromodomain inhibitor, has shown clinical activity in EZH2-mutant NHL. EZH2 mutant DNA can be detected in plasma and tumor samples. The aim of this study was to identify EZH2 mutant DNA in archived tumor samples and to determine if EZH2 mutations were associated with nonresponse to tazemetostat.

Two phase 2 studies (NCT02594160 and NCT02594161) were conducted to examine the role of EZH2 activating mutations in response to tazemetostat in DLBCL. Patients with EZH2 mutations had a significantly improved response rate (RR) compared to patients with wild-type EZH2 (28% vs 11%). A phase 1 study (NCT01897571) examined tazemetostat in patients with diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and in patients with hematologic malignancies. In this study, EZH2 mutant DNA was detected in 13% of DLBCL and 2% of FL patients. The median overall response rate (ORR) in the EZH2 mutant cohort was 38% versus 16% in the EZH2 wild-type cohort. In a subsequent study (NCT03277577) examining tazemetostat in patients with relapsed/refractory NHL, EZH2 mutant DNA was detected in 13% of patients, and the median ORR in the EZH2 mutant cohort was 33% versus 10% in the EZH2 wild-type cohort.

To further explore the role of EZH2 mutations in NHL outcomes, we performed retrospective analysis of archived tumor DNA and plasma-based ctDNA from 100 NHL patients. EZH2 wild-type DNA was detected in 11% of patients, and EZH2 mutant DNA was detected in 26% of patients. The median ORR in the EZH2 wild-type cohort was 17% versus 36% in the EZH2 mutant cohort. These studies suggest that EZH2 mutation status may be a predictive biomarker for tazemetostat response in DLBCL and FL patients.