The role of tazemetostat in relapsed/refractory follicular lymphoma

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Abstract: Large strides have been made in the treatment of follicular lymphoma (FL) over the last few years. Although the majority of patients respond to upfront therapy, many experience disease progression with a progressive shortening of subsequent treatment free intervals. New treatment options are therefore crucial for such patients. Tazemetostat is a first-in-class, selective, oral inhibitor of enhancer of zester homolog 2 (EZH2), a histone methyltransferase that is mutated in about a quarter of FL cases. Tazemetostat was recently approved for the treatment of patients with relapsed FL after 2 or more prior lines of therapy in the presence of an EZH2 mutation and for those without any other available therapeutic option, independently of EZH2 mutation status. In this review, we will summarize the background and key data that led to the development of tazemetostat, and, ultimately, to its approval for this indication.

Keywords clinical trial, Enhancer of zester homologue 2 (EZH2), epigenetic, follicular lymphoma, targeted therapy

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Follicular lymphoma

Follicular lymphoma (FL) is the most common indolent lymphoma and the second most common lymphoma overall, with about 16,000 new diagnoses per year in the United States.1 Over the past 3 decades, the overall survival of patients with FL has improved, from an average of 6 years to more than 20 years.2 This is mainly due to the introduction of the monoclonal anti-CD20 antibody rituximab, in addition to an improvement in diagnostic tools and supportive care. Long-term follow-up of three large prospective trials, SWOG-S0016, PRIMA and FOLL05, in patients with advanced-stage FL presenting with a high tumor-burden showed that standard immunochemotherapy can achieve a median progression free survival (PFS) close to 10 years.3–5 In addition, several new drugs have been approved for patients with FL in the past decade, including the new anti-CD20 antibody obinutuzumab, four phosphoinositide 3-kinase (PI3K) inhibitors (idelalisib, copanlisib, duvelisib, and umbralisib), and lenalidomide (in combination with rituximab). Most recently in the United States, the chimeric antigen receptor (CAR) T-cell therapy, axicabtagene ciloleucel, has also been approved.6–11 While a significant subset of patients achieve long-term remission after responding to upfront therapy, many patients will experience disease progression and require further treatment.12 A detailed understanding of the underlying pathobiology of the disease and a rational targeted drug development approach is crucial for ongoing progress in the management of patients with this disease.

The pathobiology of follicular lymphoma

FL is a mature B-cell neoplasm that arises from germinal center (GC) B-cells via a multistep process.12 The hallmark of FL is the acquisition of the t(14;18)(q32;q21) translocation, which is thought to be an early event and which is present in approximately 90% of patients.13 This usually places the B-cell lymphoma 2 (BCL2) gene under the transcriptional control of a immunoglobulin heavy chain (IGH) gene promoter. This results in the constitutive expression of the anti-apoptotic protein BCL-2.14,15 It has been found that this genetic alteration is not, however, sufficient for lymphomagenesis; it is also detectable in otherwise
healthy individuals.\textsuperscript{16} While the majority of said individuals will not develop FL, a small subset with a high frequency of the t(14;18)(q32;q21) translocation may be at increased risk.\textsuperscript{17}

Using next generation sequencing, it has been revealed that mutations in histone modifying genes are present in the vast majority of FL samples; further experimental work has demonstrated their crucial role in the pathogenesis of FL.\textsuperscript{18}

Morin and colleagues found mutations in the histone methyltransferase MLL2 [also known as histone-lysine N-methyltransferase 2D (KMT2D)], which play an important role in GC B-cell development, which is present in approximately 90% of patients with FL.\textsuperscript{19,20} Other, frequently mutated genes include the acetyltransferases CREB-binding protein (CREBBP) and histone acetyltransferase p300 (EP300). The methyltransferase enhancer of zester homologue 2 (EZH2) is also affected. All of these proteins are involved in catalyzing posttranslational modifications of histones.\textsuperscript{19,21} In general, many of these mutations lead to a more closed chromatin, with repression of transcription. This thereby favors the accumulation of aberrant B-cells in GCs.

The role of EZH2 in normal and malignant B-cells and their microenvironments

EZH2 was one of the first mutated histone modifier genes to be identified in in FL; it is present in up to 25% of cases.\textsuperscript{19} The EZH2 enzyme is the catalytic subunit of the chromatin remodeling Polycomb Repressive Complex 2 (PRC2); as a result, it contributes to the silencing of gene transcription by mono-, di- and tri-methylating histone H3 at the lysine 27 residue (H3K27me3).\textsuperscript{22} EZH2 is highly expressed in lymphoid progenitors and its knock-out results in profound defects in immunoglobulin heavy chain rearrangement and lymphopoiesis.\textsuperscript{23} EZH2 is expressed at a low level in non-stimulated B-cells; however, these levels are higher in GC B-cells.\textsuperscript{24} GC formation is partly accomplished by the EZH2-mediated silencing of cell-cycle checkpoint genes such as cyclin-dependent kinase inhibitor 1a (CDKN1A) and the repression of genes responsible for plasma cell differentiation, such as interferon regulatory factor 4 (IRF4) and PR domain zinc finger protein 1 (PRDM1).\textsuperscript{25} As a result, EZH2 expression and activity are tightly regulated during normal B-cell maturation in GCs.

The role of EZH2 in GC-derived B-cell malignancies has been revealed over the last decade. It was first demonstrated in experimental and animal models that overexpression of EZH2 results in GC hyperplasia and, in combination with BCL2 overexpression, can lead to lymphomagenesis.\textsuperscript{25,26} The most frequent EZH2 mutation (in ~25% of cases) in human lymphoma affects the tyrosine Y641 residue located within the catalytic SET domain of EZH2. It is an activating mutation, facilitating the conversion of mono-methylated to di- and tri-methylated H3K27.\textsuperscript{27,28} In addition, activating mutations involving EZH2 have been described. These include A687, A677, A682, and A692, with variant allele frequencies (VAF) ranging from 2% to 61%, with the Y641 mutation found in 25% of FL cases.\textsuperscript{29,30} Other genetic alterations leading to EZH2 hyperexpression have also been described.\textsuperscript{31}

Of note, Y641-mutated EZH2 alone is unable to monomethylate H3K27; it requires the heterozygous wild type allele to exert its pathogenic functions.\textsuperscript{27,28} Therefore, it is not surprising that malignant GC B-cells also require EZH2 wild-type function in order to maintain cell proliferation and survival.\textsuperscript{25,32,33}

Additional steps are required for the development of FL. The role of the tumor microenvironment is increasingly appreciated in lymphomagenesis. FL cells rely on the expression of surface immunoglobulins with a positive selection of motifs. This facilitates the addition of glycan into antigen-binding sites and the placement of mannoses to engage the microenvironment.\textsuperscript{34} T-follicular helper cells (TFHs) and follicular dendritic cells (FDCs) also play crucial roles; they facilitate interactions between surface receptors such as inducible costimulatory (ICOS) and ICOS ligand, the major histocompatibility complex (MHC), the T-cell receptor (TCR), B-cell-activating factor (BAFF), and the BAFF-receptor.

EZH2 was recently found to profoundly modulate the B-cell tumor microenvironment.\textsuperscript{35} Activating mutation of EZH2 leads to a decreased dependence on TFHs. It also results in the formation of an aberrant immunological niche which may constitute an early step in the development of FL.\textsuperscript{36} It should be noted that EZH2 is also expressed in T cells, playing an important role in
Clearly, EZH2 plays a crucial role in FL biology by blocking the exit of B cells from GCs and by remodeling their environment. Genetic alterations of its gene increase the EZH2-dependency of tumor cells.

The prognostic effect of EZH2 in FL
Given its important biological function in FL, EZH2 has also been investigated for its prognostic effect. EZH2 has been incorporated into the m7-FL international prognostic index (m7-FLIPI), which combines clinical parameters with biological information, that is, the mutational status of 7 genes [EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, and CARD11].

While the m7-FLIPI score still needs to be validated prospectively, mutations in the EZH2 gene appear to be associated with a favorable outcome in several studies.

The pre-clinical efficacy of tazemetostat
Given the extensive data demonstrating the importance of EZH2 in the development of FL, selective inhibitors have been an area of significant focus. A lead compound, EPZ-6438 (tazemetostat), selectively inhibits intracellular lysine 27 of histone H3 (H3K27) methylation in both EZH2 wild-type and mutant lymphoma cells. This leads to selective cell-killing, especially in cell lines bearing point mutations in the EZH2 catalytic domain. The treatment of EZH2-mutant non-Hodgkin’s lymphoma (NHL) xenograft mice with this compound caused tumor growth inhibition, including complete and sustained tumor regressions with a concordant decrease in H3K27me3 levels. While Beguelin and colleagues found that GC-derived DLBCLs are addicted to EZH2, independent of its mutational state, data by Knudson et al. suggests that EZH2 inhibition may only be cytotoxic in EZH2-mutated lymphoma cell lines and cytostatic in those that are EZH2 wild-type. These results may reflect differences in the experimental design, including the use of different EZH2-inhibitors with likely differential target effects.

The clinical efficacy of tazemetostat
The pre-clinical studies mentioned thus far laid the foundation for the first in-human, open-label, phase I study of tazemetostat in patients with relapsed or refractory B-cell NHL and advanced solid tumours (ClinicalTrials.gov identifier: NCT01897571). In this study, 64 patients (21 with B-cell NHL, and 43 with advanced solid tumors) underwent treatment with tazemetostat. The most common treatment-related adverse events (AEs) were asthenia (33%), anemia (14%), anorexia (6%), muscle spasms (14%), nausea (20%), and emesis (9%), which were mostly grade 1 or 2 in severity. A single dose-limiting toxicity of grade 4 thrombocytopenia was identified at the highest dose of 1600 mg twice daily, but no treatment-related deaths occurred. Grade 3 or worse treatment-related treatment-emergent AEs were uncommon and limited to thrombocytopenia and neutropenia in two patients, respectively, and hypertension and transaminase/bilirubin elevation in one patient each. The recommended phase II dose was determined to be 800 mg twice daily, based on the evaluation of AEs, pharmacokinetics, and clinical efficacy. Interestingly, the study showed a down-regulation of H3K27m3 in the skin biopsies of treated patients, supporting the on-target effect of the drug.

Durable objective responses, including complete responses, were observed in eight (38%) of 21 patients with B-cell NHL and two (5%) of 43 patients with solid tumors. The three patients with B-cell NHL who achieved a complete response had durable responses and continued on treatment for over 2 years.

This study formed the basis for the subsequent registrational multicenter, single-arm phase II trial in patients with relapsed/refractory FL (ClinicalTrials.gov identifier: NCT01897571). A total of 99 patients were enrolled in the study: 45 in the EZH2mut cohort and 54 in the EZH2WT cohort. The primary endpoint was objective response rate, as determined by the 2007 International Working Group criteria for NHL. Secondary endpoints were the duration of...
response and PFS, as well as safety and tolerability.

The median follow-up was 22 months [interquartile range (IQR) 12–27] for the $\text{EZH2}^{\text{mut}}$ cohort and 36 months (25–41) for the $\text{EZH2}^{\text{WT}}$ cohort. The objective response rate was 69% [95% confidence interval (CI) 53–82; 31 of 45 patients] in the $\text{EZH2}^{\text{mut}}$ cohort and 35% (23–49) in the $\text{EZH2}^{\text{WT}}$ cohort. This included complete responses in 13% (6) of patients in the $\text{EZH2}^{\text{mut}}$ cohort and 4% (2) of patients in the $\text{EZH2}^{\text{WT}}$ cohort. The median time to first response was 3.7 months in both the $\text{EZH2}^{\text{mut}}$ and the $\text{EZH2}^{\text{WT}}$ cohorts. The median duration of response was 11 months (95% CI 7–not estimable [NE]) in the $\text{EZH2}^{\text{mut}}$ cohort and 13 months (6–NE) in the $\text{EZH2}^{\text{WT}}$ cohort. The median PFS was respectively 14 months (11–22) and 11 months (4–15). Responses were observed across previously established adverse subgroups, including in patients with bulky disease, with refractory disease or early relapse. This suggests that this targeted therapy may partially overcome some of these risk factors.

It should be noted, that while both the overall and the complete response rates have been as expected markedly higher in the $\text{EZH2}^{\text{mut}}$ cohort compared with the $\text{EZH2}^{\text{WT}}$ cohort, the duration of response and the PFS were surprisingly similar. This suggests that tazemetostat activity on this epigenetic pathway may impair the FL cells survival, even in the absence of an $\text{EZH2}$ mutation and/or that other effects of this drug on the B-cell microenvironment might have clinical relevance.

Among all 99 patients, treatment-related grade 3 or worse AEs included thrombocytopenia and neutropenia in 3%, respectively, and anemia in 2%. Serious treatment-related AEs were reported in 4% of 99 patients and included neutropenia, pancytopenia, and transient global amnesia in one patient each, and arrhythmia and myelodysplastic syndrome in one patient. There were no treatment-related deaths. Dose reductions occurred in 9% of patients, while dose interruptions occurred in 27% of the patients. Eight (8%) patients discontinued tazemetostat because of a treatment-emergent AE, five (5%) of which were deemed to be treatment related. There were eight deaths in the $\text{EZH2}^{\text{mut}}$ cohort and 21 in the $\text{EZH2}^{\text{WT}}$ cohort; median overall survival was not reached in either cohort.

These results formed the basis for the accelerated approval by the United States Federal Drug Agency (FDA) in June 2020, for the use of tazemetostat in the treatment of adult patients with relapsed or refractory FL. These patients must have received a least two lines of prior therapy and have tumors that carry an $\text{EZH2}$ mutation (documented with an FDA-approved test). The treatment was also approved for those patients with relapsed or refractory FL who have no satisfactory alternative treatment options, independent of their $\text{EZH2}$ mutation status.

A variety of other EZH-2 inhibitors have been evaluated and are at various stages of early development in patients with lymphoma or solid tumors (see Table 1). Of these, the EZH1/2 dual inhibitor valemetostat appears to be the furthest along in its development; it has demonstrated activity on a broad range of lymphomas, including peripheral T-cell lymphomas. A phase I study of the intravenously administered, highly selective $\text{EZH2}$ inhibitor GSK2816126 was conducted with 41 patients with solid tumors or B-cell lymphomas. While the authors were able to establish a maximum tolerated dose, the relatively short half-life limited effective exposure, resulting in a very modest anticancer activity and early closure of the study.

Although most of the therapeutic approaches evolve around $\text{EZH2}$ enzymatic inhibition, recently, MS1943, an $\text{EZH2}$ degrader, has been identified with promising preclinical activity. Given the excellent tolerability of tazemetostat, combinatorial strategies are being pursued, both in newly-diagnosed and in relapsed FL and diffuse large B-cell lymphoma (DLBCL) (Table 2). The results of the dose escalation phase of the phase Ib tazemetostat plus rituximab, cyclophosphamide, doxorubicin, and vincristine (R-CHOP)
combination in patients 60–80 years of age with newly diagnosed DLBCL have been published and a recommended phase II dose of tazemetostat 800 mg twice daily has been established.\textsuperscript{49}

**Conclusion and future directions**
The approval of tazemetostat is a noteworthy example of ‘bench-to-bedside’ project built on the collaboration between academic centers.
around the world and a pharmaceutical company. While the results are remarkable, particularly in the double-refractory FL patients (defined as not responding or having relapsed after rituximab and alkylating agent containing therapy), no plateau is observed in the PFS curves. This underscores the fact that FL is characterized by a complex interplay composed of the tumor microenvironment as well as genetic and epigenetic heterogeneity.50

The observed tolerability of single-agent tazemetostat lends itself to combinatorial approaches with other immune-modulatory compounds. This is currently pursued in the double-blind, placebo-controlled phase III study of lenalidomide, rituximab plus or minus tazemetostat for patients with relapsed FL. Given its tolerability, other combinatorial approaches can be envisioned in lymphomas of GC origin, both in the relapsed and in the upfront setting. Because of its effect on the tumor microenvironment, combinatorial approaches with checkpoint inhibitors, bispecific T-cell engagers or even CAR T-cell therapy could be considered.

While chemo-immunotherapy remains the standard for patients with newly-diagnosed advanced-stage FL, newer approaches with distinct toxicity profiles offer promise and may ultimately replace current approaches. We envision that this will occur in a biomarker-driven fashion; likely composed of combinatorial strategies to accomplish deeper and more durable responses.

To summarize, tazemetostat is another important addition to the armamentarium for the treatment of patients with relapsed FL; it is likely to contribute to the already-improving trajectory of the disease.

Conflict of interest statement
GS: Abbvie, Beigene, BMS/Celgene, Debiopharm, Genentech/Roche, Genmab, Incyte, Ipsen, Kite/Gilead, Miltenyi, Morphosys, Novartis, Velosbio GVK: Pharmaclicks, Morphosys, Incyte, Merck.

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