Targeted Therapy for Relapsed/Refractory Follicular Lymphoma: Focus on Clinical Utility of Tazemetostat

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Abstract: The management of follicular lymphoma (FL) in the relapsed and refractory setting is challenging and an area of ongoing investigation. Epigenetic dysregulation has recently been shown to be a hallmark of FL. Mutations in histone-modifying genes are likely early, driver events in FL pathogenesis, and so are attractive targets to drug. Gain-of-function mutations in the histone methyltransferase EZH2 are common in FL and maintained through disease evolution. With mounting data supporting a critical role for EZH2 as an oncogenic driver for FL, the small molecule inhibitor, tazemetostat, was developed. Tazemetostat has shown promising activity in preclinical models and early phase trials. Importantly, responses were seen in patients with high-risk features. Based on these data, tazemetostat was approved in the US in 2020 for EZH2mut patients with FL who had received at least two prior lines of systemic therapy, or for EZH2wt patients without alternative treatment options. Here, we will review the biology of FL as it pertains to tazemetostat, the available clinical trial data, and future directions for this new therapy.

Keywords: tazemetostat, follicular lymphoma, EZH2 mutation

Introduction

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin’s lymphoma (NHL) after diffuse large B-cell lymphoma (DLCBCL). Overall, FL accounts for about 12% of all NHLs, and predominantly affects older adults, with a median age of diagnosis of 60 years.1

Most patients with FL initially present with lymphadenopathy which can often wax and wane. Further workup often demonstrates the presence of widespread disease, with bone marrow involvement in up to 80% of cases, however, patients are often asymptomatic. Only 20% of patients will have B-symptoms of fatigue, night sweats, and weight loss at presentation.2 Initial treatment is primarily determined by the stage, grade, and symptoms of the patient at the time of diagnosis. Stage is assessed by the Lugano classification and can be categorized as limited (I–II) or advanced (III–IV). Grading of FL is determined by the ratio between centroblasts and centrocytes, with an increased number of centroblasts corresponding with a higher grade. While there does not appear to be a difference in survival between grade 1 and 2 FL, grade 3a disease is associated with significantly worse overall survival and increased rate of clonal evolution to transformed disease.3

Treatment for limited stage varies; observation, radiotherapy, and anti-CD20 monoclonal antibody with or without chemotherapy may be considered. In patients with advanced stage disease, the two commonly used criteria for treatment are those developed by the Groupe d’Etude des Lymphomes Folliculaires (GELF) and the British National Lymphoma Investigation (BNLI), and include cytopenias, presence of systemic B symptoms, bulky adenopathy, and compromise of organ function due to disease. The initial treatment of advanced stage FL varies, but typically involves combination chemo-immunotherapy consisting of an anti-CD20 antibody, either rituximab or obinutuzumab. Many patients will have an excellent response to front-line therapy and experience a lengthy progression-free survival (PFS). These patients can be treated intermittently over the course of decades. Approximately 20% of patients will have progression of disease
within 24 months (POD24) of first-line chemoimmunotherapy. POD24 has emerged as an important surrogate endpoint which correlates with poor survival. An additional population of concern is primary refractory, these patients also have a worse prognosis.

Management of relapsed and refractory (R/R) patients is much more challenging and an area of active investigation. The observational National Lymphocare study demonstrated markedly inferior PFS with subsequent lines of therapy, highlighting the unmet need for more effective therapies with unique mechanisms of action. There are few novel therapies currently approved for relapsed FL patients. These include the combination of rituximab and lenalidomide, phosphoinositide 3'-kinase (PI3K) inhibitors, and anti-CD19 directed CAR T-cell therapy. There are four PI3K inhibitors approved, including idelalisib, copanlisib, duvelisib, and most recently, umbralisib. The overall response rates (ORRs) with these agents range from 40–60%, with few complete responses, and median PFS of a year. These agents are associated with significant toxicity and often require discontinuation or dose reduction. In the ZUMA-5 study, axicabtagene ciloleucel produced an impressive ORR of 94% in multiply relapsed follicular lymphoma; the median PFS has not yet been reached. While quite effective, the durability of CAR T-cell therapy has not yet been defined and administration is associated with significant short-term and long-term adverse events.

More options are needed for patients with multiply relapsed follicular lymphoma, and in January 2020, tazemetostat, a small molecule inhibitor of the enhancer of zeste homolog 2 (EZH2) received US Food and Drug Administration (FDA) approval. In this review, we will discuss mechanism of action, the available data regarding the safety and efficacy, and future directions for tazemetostat for the treatment of FL.

**Mechanism of Action of Tazemetostat**

Epigenetic features such as DNA methylation, histone modifications, and chromatin structure regulation, are commonly dysregulated in cancer, and minor alterations in epigenetic regulators can have a cascade effect in promoting oncogenesis. DNA hypomethylating agents and histone deacetylation inhibitors have had remarkable efficacy in T cell lymphoma, myelodysplastic syndrome, acute myeloid leukemia, and multiple myeloma, however success with these agents in NHL have thus far been limited.

However, next-generation sequencing studies have shown that histone-modifying genes are especially common and highly selected for in follicular lymphoma, suggesting the importance of epigenetic factors in the genesis of this condition. Remarkably, one study of 22 FL tumor samples identified mutations in one or more chromatin modifier genes within 96% of FL tumors and two or more in 76% of tumors. While the clonal hierarchy is not completely understood, some of the somatic mutations involved in epigenetic pathways are likely early, driver events in lymphomagenesis and so are conceptually attractive and rational targets to drug. Unfortunately, the two most commonly mutated epigenetic regulators, CREBBP and KMT2D, are loss-of-function events and therefore challenging to target.

EZH2, the target of tazemetostat, is another commonly mutated protein in FL involved in epigenetic regulation. Gain of function mutations in EZH2 lead to alterations in substrate specificity and trigger vast reorganization in chromatin structure and in mouse models promote tumorogenesis. EZH2 encodes a histone methyltransferase responsible for trimethylating Lys27 of histone H3 (H3K27). EZH2 is highly expressed in germinal center B-cells (GCB), facilitating cell cycle progression and preventing terminal differentiation while inactivation leads to a profound impairment in germinal center responses and memory B-cell formation. EZH2 is then considered to be a master regulator of the germinal center, with persistent expression maintaining the GCB reaction.

Gain of function mutations in three recurrent hotspots (Y646, A682, A692) affecting the catalytic SET domain of the EZH2 molecule, are reported in 17–27% of patients with FL depending on the modality of assessment. Supporting the key role of EZH2 in maintaining the GC phenotype, EZH2 mutations are also observed in 22% of diffuse large B-cell lymphoma (DLBCL) in the GCB subtype, and not observed in the non-GCB subtype.

Sequential mutational studies show that EZH2 mutations are often maintained throughout FL evolution, although EZH2 mutations were observed to be gained or lost in some rare, paired cases of FL and transformed FL. Interestingly, EZH2 mutations are always heterozygous in patient tumors. This is thought to be due to cooperation observed between wild-type and mutant EZH2 to promote H3K27 methylation, as the mutant allele has reduced activity in catalyzing the addition of the first and second methyl groups.
In addition to its intrinsic role in B-cell differentiation, EZH2 is also critically important in regulating the tumor microenvironment. Disruption of EZH2 activity in intra-tumoral regulatory T-cells has been shown to promote cancer immunity. EZH2 mediated histone methylation also represses tumor production of chemokines which subsequently impairs effector T cell trafficking. In animal models of ovarian and colorectal cancer, epigenetic modulation of EZH2 activity increased effector T cell tumor infiltration and improved the efficacy of PD-L1 and CTLA-4 blockade. Mutant EZH2 in FL models also leads to profound alterations in T-follicular helper cells which further drives FL growth and tumorigenesis.

Given the mounting data supporting a critical role for EZH2 as a common oncogenic driver in follicular lymphoma, many groups worked to identify candidate small molecule inhibitors. From these efforts, a candidate compound EPZ-6438 (tazemetostat) was identified with good oral bioavailability with similar potency in inhibiting both mutant and wild type EZH2. Tazemetostat led to sustained and sometimes complete tumor regression in EZH2-mutant NHL xenograft-bearing mice. The best responses were seen in xenografts bearing the EZH2 A682G mutation. Slower tumor growth was seen in EZH2 wild type xenograft models, but otherwise tumor regression was not observed, suggesting a greater role for the compound in EZH2 mutated follicular lymphoma.

**Clinical Evidence for Tazemetostat**

Upon the results of these encouraging preclinical data, the first in human phase I clinical trial for tazemetostat was initiated in France in 2013. Sixty-four patients were enrolled from a variety of tumor types, including 21 patients with non-Hodgkin lymphoma, seven of whom had follicular lymphoma. The presence of an EZH2 mutation was not a requirement for enrollment. The most common grade 3 or higher adverse event was thrombocytopenia and was the primary dose-limiting toxicity. Four patients with FL had an objective response, two of which were a complete response (CR). The median time to response was about three months. EZH2 mutational analysis was performed retrospectively in using the PCR-based cobas EZH2 Mutation Test to assess for known gain-of-function mutations. One patient was identified with an EZH2 mutation and had a durable partial response before disease progression at 16 months. The investigators determined a recommended Phase 2 dose of 800 mg twice daily based upon pharmacodynamic and toxicity profiling.

Based on this efficacy and safety data, a single-arm phase 2 trial of tazemetostat in relapsed/refractory non-Hodgkin’s lymphoma was performed. This study included six cohorts. Patients with either EZH2mut or EZH2wt FL were enrolled into one of two FL cohorts. Patients with any grade FL, including histologically transformed FL were eligible. Patients were required to have relapsed/refractory disease following at least two standard prior systemic treatment regimens including at least one anti-CD20 based regimen. Those with central nervous system disease or grade 3 or higher cytopenias were excluded. The primary endpoint was ORR based on IWG-NHL 2007 criteria. Secondary endpoints were duration of response, PFS, and safety and tolerability. A total of 99 patients were enrolled, 45 patients were EZH2mut and 54 EZH2wt. There were several notable differences between the cohorts. The EZH2wt patient group was more heavily pre-treated (median three lines compared with two in the mutant group), and more likely to have previously received

| Trial ID    | Phase | EZH Status | n   | PFS | ORR (%) | Reference |
|-------------|-------|------------|-----|-----|---------|-----------|
| NCT01897571 | 1     | N/A        | 7   | N/A | 57      | [36]      |
| NCT01897571 | 2     | EZH2mut   | 45  | 13.8| 69      | [37]      |
|             |       | EZH2wt    | 54  | 11.1| 35      |           |
| NCT03009344 | 1     | N/A        | 4   | N/A | 75      | [38]      |
| NCT03456726 | 2     | EZH2mut   | 17  | N/A | 77      | [39]      |

**Abbreviations:** EZH2mut, EZH2 mutated; EZH2wt, EZH2 wildtype; PFS, progression-free survival; ORR, overall response rate.
a stem-cell transplant (39% versus 9%). The wild type group also contained three patients with transformed histology, compared with zero patients in the mutant group.

The objective response rate in the EZH2\textsuperscript{mut} cohort was 69% compared with 35% in the EZH2\textsuperscript{wt} cohort, including complete responses in 13% and 4% in mutant and wild type groups respectively. While EZH2\textsuperscript{mut} patients were more likely to respond, the response durability was similar between groups. Progression-free survival was relatively similar between groups, 13.8 months in EZH2\textsuperscript{mut} and 11.1 months in EZH2\textsuperscript{wt}. The median duration of response was 10.9 months in the EZH2\textsuperscript{mut} cohort and 13 months in the EZH2\textsuperscript{wt} cohort. Eleven patients completed two years of therapy and entered a roll-over study and continued treatment. Responses were also observed in high-risk subgroups, especially in the EZH2\textsuperscript{mut} group. For instance, in patients with POD24, 63% of patients harboring an EZH2\textsuperscript{mut} and 25% in the wild type cohort, had a response, with complete response rates of 11% and 3% respectively. The median time to first response was 3.7 months, similar to that seen in the Phase 1 trial. Tazemetostat was relatively well tolerated. Nine patients (9%) required dose reduction, and eight patients (8%) discontinued tazemetostat due to a treatment-emergent adverse event, five (5%) of which were considered to be treatment related. There were two secondary myeloid neoplasms seen in this trial; one case of myelodysplastic syndrome at 15.3 months and one case of acute myeloid leukemia at 25.8 months, both of which may have reflected prior chemotherapy exposure. Other events leading to drug discontinuation included oral fungal infection, prolonged QT interval, pneumonia, and thrombocytopenia. Based on the results of the results of this phase 2 trial, the FDA granted accelerated approval to tazemetostat for patients with EZH2 mutated R/R follicular lymphoma who had received at least two prior systemic therapies and for EZH2 wild type follicular lymphoma who have no satisfactory alternative treatment options.

There have been simultaneous studies performed with tazemetostat in Japan.\textsuperscript{38} In a phase I trial of seven patients, four of whom had R/R FL, no serious adverse events were observed. Three in four patients with FL had a response, one of whom had a detectable EZH2 mutation. In a multicenter phase 2 study of 17 patients with R/R follicular lymphoma with EZH2 mutations, the ORR was 76.5%, with six (35.3%) achieving CR.\textsuperscript{39} The median time to response was 3.64 months. The median PFS was not met. The most common adverse effects in this trial were dysgeusia (50%) and lymphopenia (25%); three patients discontinued the drug due to treatment emergent adverse events, namely atypical pneumonia, dysgeusia, and muscle spasticity.

Given the relatively encouraging safety signal and single agent activity, there have been several small studies examining tazemetostat in combination with other agents. Tazemetostat was combined with R-CHOP in a phase I study in older patients with newly diagnosed DLBCL with high-risk disease. This trial did not reveal any new concerning safety signals, and there was no significant additional hematologic toxicity. Patients tolerated the 800 mg twice-daily dose used for monotherapy.\textsuperscript{40} In another phase I study, tazemetostat was combined with the anti-programmed death-ligand 1 (PD-L1) atezolizumab in patients with R/R DLBCL. 35% of patients had a serious adverse event, most commonly anemia, neutropenia, or thrombocytopenia. The median PFS was 1.9 months, and the ORR was 16%. EZH2 mutations were identified in 17% of patients, and 60% of EZH2\textsuperscript{mt} did have a response.\textsuperscript{41}

Combination studies are also being conducted in R/R FL, including two trials that were presented at the American Society of Hematology 2021 annual meeting. Based on preclinical data demonstrating synergy between tazemetostat and lenalidomide and the well-established efficacy data with rituximab with lenalidomide, a phase 1b/3 study evaluating the triplet was performed in patients who had received at least one prior therapy.\textsuperscript{42,43} In the phase 1b portion of the study, three dose levels of tazemetostat were explored: 400 mg (n = 4), 600 mg (n = 4), and 800 mg (n = 6) twice daily. Patients received rituximab 375 mg/m\textsuperscript{2} on days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 2–5 and lenalidomide 20 mg on days 1–21 of cycles 1–12. Each cycle was 28 days. There were no dose-limiting toxicities. Grade 3 or higher adverse events were reported in 50% of patients; the most frequent was neutropenia in 21%. The most common all grade adverse events were nausea in 43% and headache in 36%. Of the 12 patients who were evaluable for response assessment, the ORR was 92% with a CR rate of 42%. The median duration of exposure was 17 weeks (range 8–28). The single arm phase II study of tazemetostat in combination with rituximab in R/R FL is also ongoing.\textsuperscript{44} As part of this single arm study, patients will receive rituximab 375 mg/m\textsuperscript{2} weekly during cycle 1 and on day 1 of cycles 3–6 for a total of 8 cycles and tazemetostat 800 mg twice daily for 24 cycles (28 days each).
Discussion

The novel EZH2 inhibitor, tazemetostat, is an important addition to the armamentarium for relapsed/refractory follicular lymphoma. By providing a mechanism of action distinct from other agents currently approved in this space, patients have an opportunity for improved outcomes, including those with high-risk features such as POD24 and double-refractory disease. The FDA granted accelerated approval based upon phase II data which demonstrate anti-tumor efficacy in patients refractory to two or greater lines of chemo-immunotherapy. This approval has been incorporated into the NCCN guidelines for treatment of R/R FL. It is important to note that there appears to be clinical benefit regardless of EZH2 status, providing disease control even in EZH2\textsuperscript{wt} patients.

Given the relatively comparable PFS curves between EZH2\textsuperscript{mut} and EZH2\textsuperscript{wt} FL, one may consider molecular testing to be primarily academic for these heavily pretreated patients. In addition, EZH2\textsuperscript{mut} appears to be a positive prognostic factor for response to cyclophosphamide-containing regimens such as CHOP/CVP as opposed to bendamustine regimens.\textsuperscript{45} Regardless, these trials were not designed to compare these cohorts and there were many differences in patient characteristics, and so we feel there is a role for EZH2 analysis to be useful in terms of patient education and expectations, especially in light of the disparate response rates.

The median time to response with tazemetostat was greater than three months, a finding which was reproduced in both phase 2 studies. Response assessments were undertaken every eight weeks, and so this result is unlikely to be an artifact of the trial design. As responses can often deepen with longer exposure, sufficient time should be permitted if clinically appropriate before changing regimens.

Further clinical investigation of tazemetostat is needed to better define its place in the increasingly complex landscape of the treatment of R/R FL. Given the modest PFS, questions remain regarding how best to sequence this agent and whether there is a role for combination with other agents. Although head to head trials are not available, the drug appears a reasonable option after chemoimmunotherapy and rituximab in combination with lenalidomide in patients who are not candidates for cellular therapy, including autologous stem cell transplant and/or CAR T-cell therapy. As tazemetostat is well tolerated, it may be considered over PI3K inhibitors in patients who are EZH2\textsuperscript{mut} or EZH2\textsuperscript{wt} patients with certain comorbidities. Given tazemetostat’s novel mechanism of action and tolerable safety profile, results from ongoing and future combination studies may allow for earlier administration. It is an ideal agent for combination with other targeted therapies.

Tazemetostat is the product of an improved understanding of the pathogenesis of follicular lymphoma over the past decade. The data for its use in patients with EZH2 mutations, especially in high-risk patients with few other options, are encouraging. Further studies are needed to define its impact on overall survival, its place in the sequence of therapies, and its role in combination with other agents.

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