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Refining the Management of Relapsed or Refractory Follicular Lymphoma

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Abstract: In patients with follicular lymphoma, the prolonged clinical course consisting of multiple relapses is a fundamental challenge that requires clinicians to consider how to best balance treatment efficacy while minimizing toxicity and preserving quality of life. The treatment approaches and decisions regarding therapy are largely driven by the unique clinical features evident in each patient. The traditional treatment approaches for relapsed follicular lymphoma include chemoimmunotherapy regimens, targeted agents, radioimmunotherapy, and, occasionally, immunotherapy alone. The primary targeted agents used in the relapsed or refractory follicular lymphoma setting are the phosphatidylinositol 3-kinase (PI3K) inhibitors idelalisib, copanlisib, and duvelisib. PI3K inhibitors can have a significant toxicity profile. Radioimmunotherapy remains an underutilized option. The newest agent that has gained regulatory approval in the treatment of follicular lymphoma is tazemetostat, a methyltransferase inhibitor that inhibits and reduces the activity of EZH2. In June 2020, tazemetostat was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with relapsed or refractory follicular lymphoma who have tumors that are positive for an *EZH2* mutation (as detected by an FDA-approved test) and who have received at least 2 prior systemic therapies, or patients who have no satisfactory alternative treatment options. Data from a phase 2 study demonstrated that tazemetostat can produce clinically meaningful and durable responses, with a favorable safety profile, in heavily pretreated patients with or without an *EZH2* mutation.

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Unmet Needs in the Management of Relapsed or Refractory Follicular Lymphoma

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Overview of Follicular Lymphoma

Follicular lymphoma is the second most common form of lymphoma in the United States, and the most common type of indolent non-Hodgkin lymphoma (NHL).[1] It is considered an incurable disease. However, the prognosis of patients with follicular lymphoma has significantly improved over a span of decades.[2,3] The improvement in prognosis may be a result of several factors, including the introduction of anti-CD20 monoclonal antibodies, the development of new chemotherapy agents like bendamustine, the discovery of new targeted agents like lenalidomide and the phosphatidylinositol 3-kinase (PI3K) inhibitors, improvements in diagnostic imaging and staging, and improvements in supportive care. Lead time bias may also be a factor suggesting improved outcomes, as earlier detection occurs with the increased use of computed tomography (CT) scans.

Approximately 90% of patients with follicular lymphoma will require treatment. In the other 10% of patients, treatment may be deferred for at least a decade and may not be required at all. In patients who do receive treatment, initial remissions may last for well over a decade. Approximately half of patients will eventually require second-line therapy.[4] Some patients may die of other causes when they are in remission. Another feature of follicular lymphoma is its propensity to transform into diffuse large B-cell lymphoma (DLBCL). This transformation, which occurs in approximately 2% to 3% of patients annually, renders the lymphoma more aggressive and difficult to treat.[5]

In patients with a history of follicular lymphoma who experience recurrence of lymphadenopathy, a repeat biopsy should generally be performed at least once for the purposes of confirming that the diagnosis is correct and checking for transformation to aggressive lymphoma. Often, many years have elapsed since the initial therapy, and new malignancies can arise that mimic the original follicular lymphoma.

Progression-free survival becomes progressively shorter with each subsequent line of therapy. For example, after the first line of therapy, the median progression-free survival is measured in many years. Subsequent second-line therapy leads to a median progression-free survival that is shorter, ranging between 1 and 2 years. Beyond that, subsequent lines of therapy tend to achieve a median progression-free survival of 1 year or less. These observations were confirmed in a retrospective analysis of 1088 patients with grade 1 through 3A follicular lymphoma who received treatment between 1998 and 2009 at a single institution.[4] The median progression-free survival was 4.73 years after first-line treatment. Following successive lines of treatment, the median progression-free survival was 1.5 years (after second line), 1.1 years (after third line), 0.9 years (after fourth line), 0.6 years (after fifth line), and 0.5 years (after sixth line). A similar pattern was observed in median overall survival, as well.

The prognosis of patients with relapsed or refractory disease depends greatly on the duration of their first remission.[6] The association between disease progression within 24 months of frontline chemoimmunotherapy initiation and patient outcomes was demonstrated by data from the prospective, observational National LymphoCare Study.[7] This study included 588 patients with follicular lymphoma who were treated with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) between 2004 and 2007 at more than 200 community and academic sites in the United States. The analysis excluded patients with mixed or transformed histology, those who could have undergone watchful waiting or received other forms of treatment, and those who had disease progression before starting first-line R-CHOP. The patients were grouped into 2 cohorts: those with disease progression or who died within 2 years of diagnosis (defined as the early progressor group, n=110), and those without progression or who did not die within 2 years (defined as the reference group, n=420). Overall, disease progression within 2 years of R-CHOP occurred in

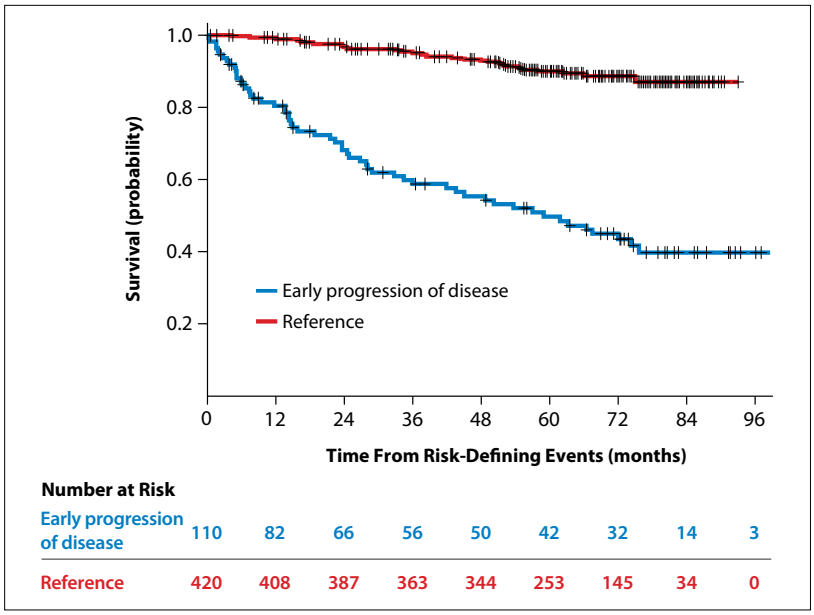

Figure 1. Overall survival from a risk-defining event after diagnosis among patients treated with R-CHOP in the National LymphoCare Study group. R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. Adapted from Casulo C et al. *J Clin Oncol.* 2015;33(23):2516-2522.[7]

approximately 20% of patients and was significantly associated with inferior overall survival (Figure 1). The 5-year overall survival was 50% among the early progressors compared with 90% in the reference group. Even after controlling for the Follicular Lymphoma International Prognostic Index (FLIPI) score, patients who experienced an early relapse had an increased risk for death (hazard ratio [HR], 6.44; 95% CI, 4.33-9.58). These results have subsequently been confirmed in several different patient cohorts.[8-10]

Physicians must consider a number of factors before deciding upon what therapy, if any, is appropriate for a particular patient, whether as initial treatment or in the relapsed setting. For example, in previously untreated patients with advanced stage but low–tumor burden disease, a strategy of watchful waiting avoids potential toxicities of drug therapy and does not compromise overall survival. Other patients in that situation could reasonably choose treatment with rituximab therapy alone. Previously untreated patients with high–tumor burden disease are usually treated with chemoimmunotherapy. However, if such patients have a strong preference to avoid chemotherapy, the combination of lenalidomide and rituximab has data supporting its use. Elderly or frail patients, even with high–tumor burden disease, might be treated only with immunotherapy in an attempt to achieve disease control with a minimum of toxicity. In the relapsed setting, factors that may impact choice of therapy include the presence or absence of symptoms, the stage and bulk of disease, the rate of disease progression, the time from their prior therapy to relapse, the type of previous therapy, age, comorbidities, the patient's goals, and the patient's personal preferences.

Traditional Treatment Approaches for Relapsed Disease

The first-line treatment strategy for patients with follicular lymphoma who require therapy generally consists of chemoimmunotherapy. The preferred chemotherapy options are CHOP; cyclophosphamide, vincristine, and prednisone (CVP); and bendamustine. The preferred immunotherapy options are rituximab or obinutuzumab.

The traditional treatment approaches for patients with relapsed follicular lymphoma include the same and other chemoimmunotherapy regimens, targeted agents such as lenalidomide and PI3K inhibitors, radioimmunotherapy, and, occasionally, immunotherapy alone. In the relapsed setting, chemoimmunotherapy regimens generally consist of alternate chemotherapy agents that the patient has not yet received, plus an anti-CD20 antibody. For example, patients treated with R-CHOP or rituximab plus CVP (R-CVP) in the first-line setting might receive bendamustine plus obinutuzumab as second-line treatment. This approach is supported by the GADOLIN trial, a randomized phase 3 study that evaluated bendamustine plus obinutuzumab or bendamustine alone among patients with relapsed indolent NHL who were refractory to rituximab.[11] The combination of obinutuzumab and bendamustine improved progression-free survival and overall survival. The median progression-free survival was not reached with obinutuzumab plus bendamustine vs 14.9 months with bendamustine monotherapy (HR, 0.55; 95% CI, 0.40-0.74; *P*=.0001). The most frequent grade 3 or higher adverse events were neutropenia (33% in the chemoimmunotherapy arm vs 26% in the bendamustine monotherapy arm), thrombocytopenia (11% vs

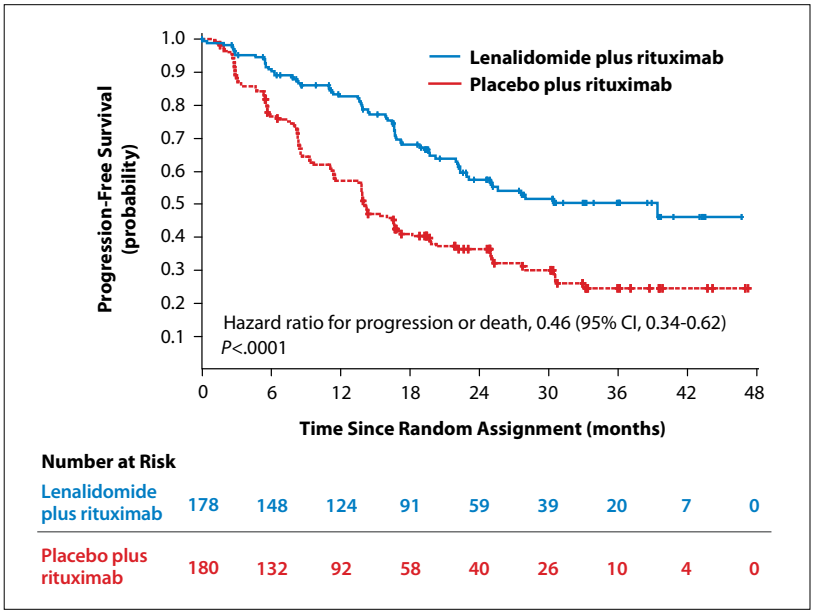

Figure 2. Progression-free survival, as assessed by an independent review committee, in the intention-to-treat population of a randomized phase 3 trial of lenalidomide plus rituximab or placebo plus rituximab in patients with relapsed or refractory indolent non-Hodgkin lymphoma. Adapted from Leonard JP et al. *J Clin Oncol.* 2019;37(14):1188-1199.[12]

16%), anemia (8% vs 10%), and infusion-related reactions (11% vs 6%).

Several studies have evaluated the combination of lenalidomide plus an anti-CD20 antibody. This combination led to response rates of nearly 70%, with complete response rates approaching 30% to 40%, and a median progression-free survival exceeding 1 year. These earlier studies ultimately culminated in the AUGMENT study, a randomized phase 3 trial in which patients received either lenalidomide plus rituximab or placebo plus rituximab.[12] A total of 358 patients with relapsed or refractory indolent NHL were randomly assigned to treatment. The median progression-free survival was significantly improved with lenalidomide plus rituximab vs placebo plus rituximab (39.4 vs 14.1 months; HR, 0.46; 95% CI, 0.34-0.62; *P*<.001; Figure 2). Grade 3 or 4 adverse events that were more common in the combination arm compared with the control arm included neutropenia (50% vs 13%) and leukopenia (7% vs 2%). All-grade adverse events that were more common with lenalidomide plus rituximab included infections (63% vs 49%), neutropenia (58% vs 23%), and cutaneous reactions (32% vs 12%). Thus, the combination of lenalidomide and rituximab is now commonly used as a therapy in the second-line setting and beyond.

An additional category of targeted agents used in relapsed or refractory follicular lymphoma is the PI3K inhibitors. Currently, there are 3 agents in the PI3K class available for use in follicular lymphoma: idelalisib, copanlisib, and duvelisib. These agents have activity against the delta isoform of the PI3K; additionally, copanlisib also inhibits the alpha isoform of PI3K, whereas duvelisib additionally inhibits the gamma isoform.[13] The activity of each of these agents has been supported by phase 2 clinical trials, with response rates ranging between 42% and 59% in patients with follicular lymphoma, and a median progression-free survival from 9.5 months to 12.5 months.[14-16] Toxicities of PI3K inhibitors include diarrhea, colitis, pneumonitis, elevated liver function studies, infections, and cytopenias. In addition, copanlisib also has some unique toxicities—including transient hyperglycemia after infusions and hypertension—but it has lower rates of some of the other toxicities typically associated with this class of agents.

Radioimmunotherapy is an often-forgotten treatment modality in patients with relapsed or refractory follicular lymphoma. The radiolabeled agent ibritumomab tiuxetan consists of an anti-CD20 monoclonal antibody conjugated to the radioisotope yttrium-90.[17] Trials of this agent were conducted several years ago. A pooled analysis that included patients with relapsed follicular lymphoma demonstrated objective response rates of 72% and 86%, with the latter outcome associated with treatment in first relapse.[18] The median time to progression ranged from 12.6 months after first relapse to 7.9 months in patients with multiple relapses, although some patients who respond well can have remissions lasting for many years. Toxicities include cytopenias, infusion reactions, rash, and, potentially, myelodysplastic syndrome. Radioimmunotherapy is not commonly incorporated into patient management in community settings, as it is fairly complex to coordinate the care that is required to deliver it.

High-dose chemotherapy and stem cell transplant have a role in selected patients with relapsed or refractory follicular lymphoma. Several studies have demonstrated high rates of overall response and 5-year survival in

approximately three-quarters of patients. This treatment is relatively toxic compared with some of the other modalities in use, and therefore it is generally reserved for younger and more fit patients with aggressive disease.

Why Are New Treatment Strategies Needed?

The prolonged clinical course consisting of multiple relapses in patients with follicular lymphoma is a fundamental challenge that requires clinicians to consider how to best balance treatment efficacy while minimizing toxicity and preserving quality of life.[19] It goes without saying that there is always a need for more effective and less toxic cancer treatments. For example, although PI3K inhibitors can be lifesaving for some patients, they have a significant toxicity profile. Patients frequently must discontinue treatment owing to severe colitis and diarrhea, as well as occasional cases of pneumonitis and infections. The immunomodulatory agent lenalidomide can cause cytopenias, rash, and other toxicities that can limit use in elderly patients or those with renal insufficiency. Some patients with relapsed or refractory follicular lymphoma have difficulty tolerating available treatments and thus may have a poor prognosis, ultimately succumbing to their disease.

Selecting the most appropriate treatment for an individual patient at a particular time can be a challenge for physicians managing patients with relapsed or refractory follicular lymphoma.[19] Although the availability of novel therapies for follicular lymphoma has greatly expanded in recent years, the optimal approach to selecting and sequencing these treatments for an individual patient is not well defined. An important area of research remains the identification of predictive biomarkers of progression, response, and resistance to specific therapies, with the aim of improving patient selection for both observation and intervention.

Management of patients with follicular lymphoma that is high-risk—defined as those who have relapsed within 2 years of their initial therapy—represents another important unmet need in this field.[19] In particular, there is a general lack of consensus regarding how to manage these patients, which is further complicated by the lack of a foolproof tool to identify patients, prior to initiation of therapy, who are destined for early relapse and poor survival. An ongoing clinical trial is investigating the roles of conventional chemotherapy and targeted agents in the early relapsing population.

Preventing death from follicular lymphoma in these high-risk patients, and preventing transformation of follicular lymphoma to aggressive lymphomas, should be the top priorities for investigators in this field. In order to achieve these goals, therapies with novel mechanisms of action are likely to be required. Mechanisms of action that are currently being explored include EZH2 inhibition, bispecific antibodies that recruit T cells to attack malignant B cells, and chimeric antigen receptor (CAR) T-cell therapy.

New Treatment Options

The newest agent that has gained regulatory approval in the treatment of follicular lymphoma is tazemetostat, a methyltransferase inhibitor that inhibits and reduces the activity of EZH2. EZH2 is an epigenetic regulator of B-cell identity in the germinal center.[20] EZH2 represses the expression of gene sets that allow for germinal center exit and terminal differentiation, and its activity is important in both normal B cells and follicular lymphoma cells.[21] *EZH2* may become mutated. Regardless of the oncogenic mutation, follicular lymphoma tumors have a critical dependence on EZH2 for growth and survival. Inhibition of EZH2 activity may allow for the expression of genes involved in terminal differentiation and germinal center exit in B cells.

In June 2020, tazemetostat was approved by the US Food and Drug Administration (FDA) for the treatment of relapsed/refractory follicular lymphoma.[22] Specifically, this indication for tazemetostat is for the treatment of adult patients with relapsed or refractory follicular lymphoma who have tumors that are positive for an *EZH2* mutation (as detected by an FDA-approved test) and who have received at least 2 prior systemic therapies, or patients who have no satisfactory alternative treatment options.[23] These indications in relapsed/refractory follicular lymphoma were approved under the FDA's accelerated approval program, based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.

The approval was based on results of an open-label, single-arm, multicenter, phase 2 trial referred to as Study E7438-G000-101.[24] This trial was conducted in 38 centers throughout France, the United Kingdom, Australia, Canada, Poland, Italy, Ukraine, Germany, and the United States. Patients with follicular lymphoma were enrolled into 1 of 2 cohorts. One cohort included 45 patients with *EZH2*-mutated disease. The second cohort included 54 patients with *EZH2*–wild-type disease. *EZH2* mutation status was centrally determined using a real-time, allele-specific polymerase chain reaction test. Although the specific tissue type was not protocol-mandated, most *EZH2* testing was performed with formalin-fixed paraffin-embedded tissue from a resection or excisional lymph node biopsy.

The primary endpoint of this phase 2 study was

objective response rate according to an independent radiology committee; investigator assessments were considered supportive in nature. Tumor responses were assessed per the International Working Group Criteria for Non-Hodgkin Lymphoma (IWG-NHL) response criteria by CT or magnetic resonance imaging administered every 8 weeks for the first 6 months, and then every 12 weeks thereafter. Secondary efficacy endpoints included duration of response and progression-free survival. Safety and tolerability were also evaluated as secondary endpoints. Prespecified exploratory endpoints were overall survival, disease control rate, and time to first response.

Eligibility criteria that spanned both cohorts included histologically confirmed follicular lymphoma (grades 1, 2, 3a, or 3b) that had relapsed or was refractory to 2 or more standard systemic therapies.[24] The study permitted enrollment of patients with transformed follicular lymphoma, which was defined as evolution of a clinically indolent follicular lymphoma to a clinically aggressive lymphoma (eg, DLBCL). In addition, measurable disease per the IWG-NHL was required, and patients had to have sufficient tissue available for central testing of *EZH2* mutation status. Other inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, and adequate renal, bone marrow, and liver function. Patients were enrolled into both cohorts between July 2015 and May 2019.

Patients received 800 mg of tazemetostat twice daily, administered orally in continuous 28-day cycles.[24] Dose modifications, including reductions and interruptions of tazemetostat, were permitted per the study protocol. Treatment was continued for up to 2 years or until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. Patients who received 2 years of tazemetostat were eligible to continue treatment in the TRuST rollover study. A total of 11 patients (3 from the *EZH2*-mutated cohort and 8 from the *EZH2*–wild-type cohort) completed 2 years of treatment and entered the rollover study.

In the *EZH2*-mutated cohort, the median age was 62 years (interquartile range [IQR], 57-68), and 42% of patients were male.[24] All patients in this cohort had an ECOG performance status of 0 (47%) or 1 (53%). The median time from diagnosis was 4.7 years (IQR, 1.7-6.4). Patients in this cohort had received a median of 2 prior therapies; 16% had received 5 or more. Approximately half of patients in this cohort (49%) were refractory to their last regimen, and 20% were double refractory.

In the *EZH2*–wild-type cohort, the median age was similar (61 years; IQR, 53-67), and 63% of patients were male.[24] Although most patients in this cohort had an ECOG performance status of 0 (48%) or 1 (43%), 7% had an ECOG performance status of 2. (Information was missing for 1 patient.) The median time from diagnosis for patients in this cohort was 6.3 years (IQR, 3.4-9.0). Patients in this cohort had received a median of 3 prior therapies; 30% had received 5 or more. Slightly less than half of the patients in this cohort (41%) were refractory to their last regimen, and 28% were double refractory. Among the 3 patients in the study who had transformed follicular lymphoma, all had *EZH2*–wild-type disease.

The median follow-up was 22.0 months (IQR, 12.0-26.7) for patients in the *EZH2*-mutated cohort and 35.9 months (IQR, 24.9-40.5) in the *EZH2*–wild-type cohort.[24] At the time of data cutoff (August 9, 2019), 31 patients in the *EZH2*-mutated cohort had a response; the objective response rate according to the independent radiology committee was 69% (95% CI, 53%-82%).[24] Of these responses, 6 (13%) were complete; the remaining 25 (56%) were partial. All but 1 patient (98%) in the *EZH2*-mutated cohort showed evidence of a reduction in tumor volume.

A total of 19 patients in the *EZH2*–wild-type cohort had a response; the objective response rate per the independent radiology committee was 35%.[24] There were 2 (4%) complete responses and 17 (31%) partial responses. Approximately two-thirds (65%) of patients in the *EZH2*–wild-type cohort showed evidence of a reduction in tumor volume.

Of the 42 patients who achieved a partial response across the 2 cohorts, 8 patients (4 in each cohort) had ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) scans.[24] All 8 of these patients remained in the partial response classification per the ^{18}F-FDG PET scan assessment. Concordance between the objective response rates as assessed by the independent radiology committee and by the investigators was high (87%).

Among the 3 patients with grade 3b follicular lymphoma in the *EZH2*-mutated cohort, all achieved a partial response.[24] Two of the 6 patients with grade 3b or transformed follicular lymphoma in the *EZH2*–wild-type cohort achieved a response (both were partial responses).

The median duration of response was 10.9 months (95% CI, 7.2 to not estimable [NE]) in the *EZH2*-mutated cohort and 13.0 months (95% CI, 5.6-NE) in the *EZH2*–wild-type cohort.[24] In the *EZH2*-mutated cohort, the response lasted 6 months or longer in 19 patients (61%), 12 months or longer in 7 patients (23%), and 18 months or longer in 6 patients (19%). In the *EZH2*–wild-type cohort, the response lasted 6 months or longer in 10 patients (53%), 12 months or longer in 27 patients (37%), and 18 months or longer in 4 patients (21%).

The secondary endpoint of median progression-free survival was 13.8 months (95% CI, 10.7-22.0) in

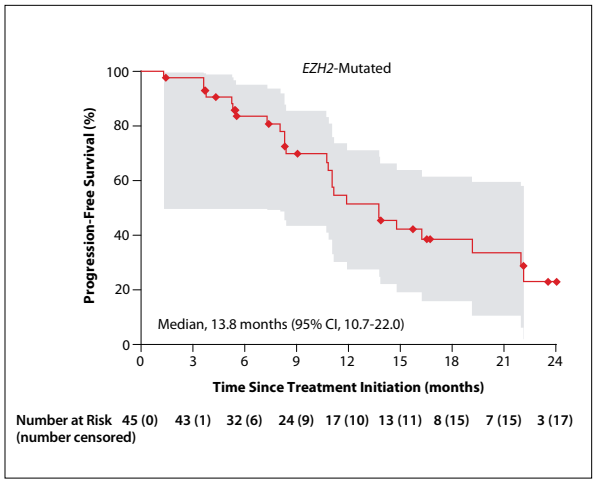

Figure 3. Progression-free survival according to an independent radiology committee among patients with follicular lymphoma treated with tazemetostat in a phase 2 trial. Data are shown for patients with the *EZH2* mutation. The shaded area indicates the 95% simultaneous confidence bands. Adapted from Morschhauser F et al. *Lancet Oncol.* 2020;21(11):1433-1442.[24]

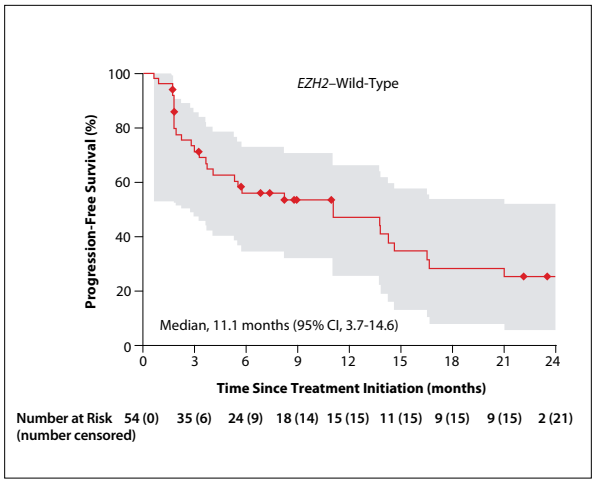

Figure 4. Progression-free survival according to an independent radiology committee among patients with follicular lymphoma treated with tazemetostat in a phase 2 trial. Data are shown for patients with *EZH2*–wild-type disease. The shaded area indicates the 95% simultaneous confidence bands. Adapted from Morschhauser F et al. *Lancet Oncol.* 2020;21(11):1433-1442.[24]

the *EZH2*-mutated cohort and 11.1 months (95% CI, 3.7-14.6) in the *EZH2*–wild-type cohort (Figures 3 and 4).[24] In prespecified exploratory analyses, the median time to first response was 3.7 months (IQR, 1.9-5.5) in the *EZH2*-mutated cohort and 3.7 months (IQR, 2.2-8.3) in the *EZH2*–wild-type cohort. The median overall survival was not reached in either cohort (95% CI, NE-NE in the *EZH2*-mutated cohort and 95% CI, 24.9-NE in the *EZH2*–wild-type cohort; Figures 5 and 6).

Patients from both cohorts were pooled for safety analyses.[24] Among the 99 patients across both cohorts, 27% experienced a serious treatment-emergent adverse event. The most common of these events were sepsis, general physical health deterioration, and anemia (each with 2 cases). Most treatment-emergent adverse events were grade 1 or 2 in severity. The most frequent treatment-emergent adverse events reported across both cohorts were nausea (23%), diarrhea (18%), asthenia (18%, with grade 3 cases in 3%), alopecia (17%), and cough (16%).

Treatment-emergent adverse events led to dose reductions of tazemetostat in 9% of patients and to dose interruptions of tazemetostat in 27%.[24] A total of 8% of patients discontinued tazemetostat owing to a treatment-emergent adverse event. Myelodysplastic syndrome was reported in 1 patient at 15.3 months after starting treatment, and acute myeloid leukemia was reported in another patient at 25.8 months after starting treatment. Although 4 patients died within 30 days of the last dose of study treatment, no deaths were considered treatment-related.

The study authors concluded that this phase 2 study demonstrated that tazemetostat can produce clinically meaningful and durable responses, and is associated with a favorable safety profile.[24] Notably, these responses occurred in heavily pretreated patients, including those with and without an *EZH2* mutation.

Given the favorable toxicity profile associated with tazemetostat, coupled with the potential immunomodulating properties that have been attributed to this agent, combination regimens are being explored in the setting of relapsed or refractory follicular lymphoma. One such regimen is the combination of tazemetostat with lenalidomide and rituximab, which is being evaluated in a double-blind, randomized phase 3 trial with a 3-stage, biomarker enrichment design.[25] Another potential combination partner for tazemetostat is the PI3K inhibitors, with the thought that the PI3K signaling pathway is known to promote oncogenesis by regulating the epigenome.[26]

In addition to tazemetostat, other new categories of novel therapies are under investigation for the treatment of patients with relapsed or refractory follicular lymphoma. CAR T-cell therapy was shown to be successful as salvage treatment in the setting of other advanced hematologic malignancies.

Two CAR T-cell products, both of which target the CD19 antigen, have recently reported promising clinical data. Axicabtagene ciloleucel, which is currently FDA-approved for DLBCL (including cases arising from follicular lymphoma),[27] is now being studied in patients with relapsed or refractory indolent NHL. An interim analysis from the multicenter, single-arm, phase 2 ZUMA-5 trial was reported at the 2020 American Society of Clinical

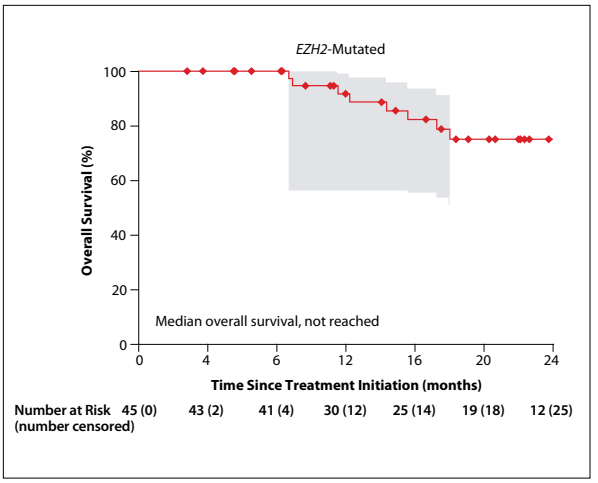

Figure 5. Overall survival according to an independent radiology committee among patients with follicular lymphoma treated with tazemetostat in a phase 2 trial. Data are shown for patients with the *EZH2* mutation. The shaded area indicates the 95% simultaneous confidence bands. Adapted from Morschhauser F et al. *Lancet Oncol.* 2020;21(11):1433-1442.[24]

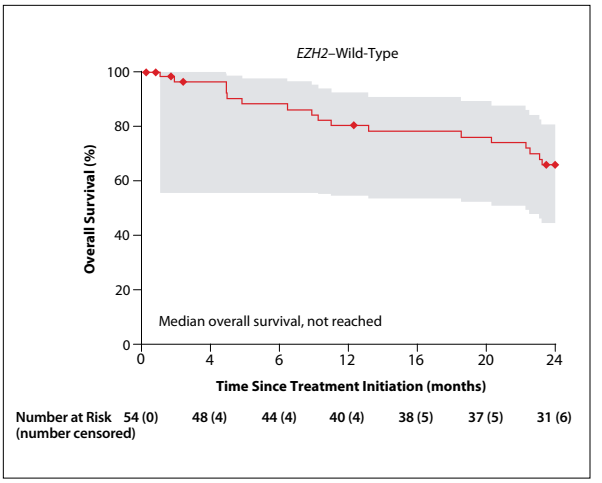

Figure 6. Overall survival according to an independent radiology committee among patients with follicular lymphoma treated with tazemetostat in a phase 2 trial. Data are shown for patients with *EZH2*–wild-type disease. The shaded area indicates the 95% simultaneous confidence bands. Adapted from Morschhauser F et al. *Lancet Oncol.* 2020;21(11):1433-1442.[24]

Oncology meeting. Patients had high-risk follicular lymphoma (n=80) or marginal zone lymphoma (n=16).[28] The overall response rate among patients with follicular lymphoma was 95%, and 81% had a complete response. The median duration of response was 20.8 months, and the median progression-free survival was 23.5 months. After a median follow-up of 16 months, the median overall survival was not reached. Toxicities were consistent with those known to occur from axicabtagene ciloleucel in aggressive lymphomas.

Promising data for a second CAR T-cell therapy, tisagenlecleucel, were reported in relapsed or refractory follicular lymphoma. Tisagenlecleucel is also currently FDA-approved for DLBCL (including cases arising from follicular lymphoma).[29] In an interim analysis of the phase 2 ELARA trial presented at the 2020 American Society of Hematology (ASH) meeting, the rate of complete response was 65.4%, and the overall response rate was 82.7%.[30] The median duration of response, progression-free survival, overall survival, and time to next anti-lymphoma treatment were not reached. The study investigators reported no severe cytokine release syndrome (CRS) and very few neurologic events, allowing limited use of anticytokine therapy.

Several bispecific antibodies are in development. These agents have an arm targeting CD20 on B cells and an arm targeting CD3 on T cells. The crosslinking that occurs is thought to activate T cells to kill the malignant B cells. Antibodies in this category include mosunetuzumab, glofitamab, odronextamab (formerly known as REGN1979), and epcoritamab. Each of these bispecific antibodies has a unique structure. They are associated with overall response rates in relapsed or refractory follicular lymphoma ranging from 63% to 95%, and complete response rates between 43% and 77%.[31-34] These agents can cause CRS and neurotoxicity, but these toxicities tend to be milder than those that arise after CAR T-cell therapy.

Disclosures

Dr Burke has received consulting fees from Roche/Genentech, AstraZeneca, Verastem, MorphoSys, Adaptive Biotechnologies, Epizyme, Kura, and BeiGene, and he has served on speakers' bureaus for Seagen and BeiGene.

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Treatment Selection in Patients With Relapsed or Refractory Follicular Lymphoma

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There are several different options for the treatment of patients with relapsed or refractory follicular lymphoma. They tend to be utilized differently in individual patients and across unique circumstances. It is known that patients with follicular lymphoma should not be treated unless there is a clinical indication. When treatment is needed, frontline therapy often consists of a standard chemoimmunotherapy regimen (typically, bendamustine plus rituximab, R-CHOP, or R-CVP).

A nonchemotherapy strategy has been explored as an alternative for older or unfit patients. The RELEVANCE study was a multicenter, international, phase 3 trial that compared rituximab plus lenalidomide vs a standard rituximab-based chemoimmunotherapy regimen (1 of 3 as selected by the investigator).[1] This study was conducted in 1030 patients with previously untreated follicular lymphoma. It demonstrated similar rates of confirmed/unconfirmed complete response at 120 weeks (a primary endpoint): 48% with rituximab plus lenalidomide and 53% with rituximab plus chemotherapy (P=.13). The interim 3-year rate of progression-free survival (a co–primary endpoint) was 77% and 78%, respectively. The rates of grade 3/4 neutropenia (32% vs 50%) and any-grade febrile neutropenia (2% vs 7%) were higher in the rituximab-plus-chemotherapy arm. Grade 3 or 4 cutaneous reactions were more frequent with rituximab plus lenalidomide (7% vs 1%). Therefore, this trial clearly showed that this nonchemotherapy regimen had similar clinical activity and acceptable tolerability compared with the standard frontline chemoimmunotherapy regimens. Although this study did not achieve its primary endpoint, the encouraging data suggest that the combination of rituximab plus lenalidomide may be an emerging frontline regimen for older or unfit patients.

Relapsed/Refractory Follicular Lymphoma

Treatment approaches and decisions regarding therapy are largely driven by each patient's unique clinical features. Factors to consider when selecting treatment include the patient's goals and tolerability for therapy based on performance status, age, and disease burden. The older age of these patients often also remains an important consideration. Among patients with follicular lymphoma, the median age at diagnosis is approximately 63 years, and 27.0% of diagnoses are made when the patient is between the ages of 65 and 74 years (Figure 7).[2] Thus, once patients have relapsed, they are not uncommonly in their mid-70s, and they may have developed significant comorbidities. By age 70 years, at least 90% of patients with follicular lymphoma have a comorbidity; in at least half of these patients, the comorbidity is considered major (eg, coronary artery disease, chronic obstructive pulmonary disease, or chronic kidney insufficiency).

All of these factors must be taken into account when choosing a therapy for patients with relapsed or refractory follicular lymphoma. Perhaps even more importantly, clinicians must recognize that the current treatment options are palliative, and not administered with curative intent using standard approaches. (There may be a potential for cure with some investigational methodologies, such as the CAR T-cell therapies or bispecific antibody therapies.)

Third-Line Treatment Options

The options for third-line therapy are relatively limited in this patient population. Most of the treatments approved in the third-line or later settings are drawn from the class of agents known as PI3K inhibitors. Three PI3K inhibitors are FDA-approved for these patients: idelalisib, duvelisib, and copanlisib. However, these agents are largely underutilized in this setting, primarily because they are associated with immune-mediated toxicities, as well as potential significant morbidity.

The combination of rituximab plus lenalidomide as second-line or later treatment was also validated in the

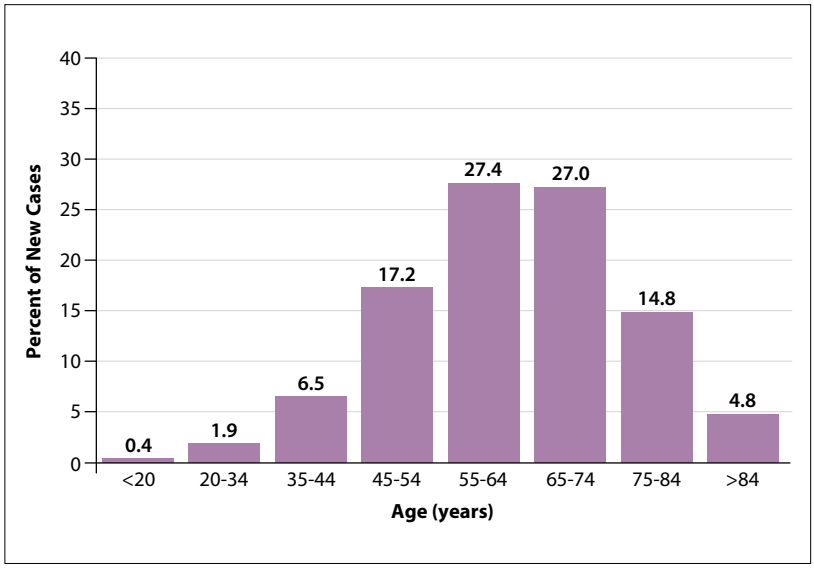

Figure 7. Age of diagnosis among patients with follicular lymphoma. Adapted from the National Cancer Institute. Cancer Stat Facts: NHL—Follicular Lymphoma.[2]

AUGMENT study.[3] The median progression-free survival was 39.4 months with lenalidomide plus rituximab vs 14.1 months with rituximab plus placebo (HR, 0.46; 95% CI, 0.34-0.62; *P*<.001). This regimen is now widely used in the second-line setting and beyond for patients with relapsed follicular lymphoma.

Tazemetostat as an Alternative Therapy in the Third-Line Setting

Tazemetostat targets EZH2, which is an epigenetic regulator of gene transcription and regulation. Specifically, EZH2 methylates histone H3. This histone methylation leads to repression of genes for cell cycle checkpoints and differentiation. EZH2 is required for germinal center formation. Most *EZH2* mutations, which occur in approximately 20% of cases of follicular lymphoma, are gain-of-function mutations that lead to dysregulation of the cell cycle. They block differentiation, thereby locking B cells in the germinal state, which can then lead to transformation into cancer.[4]

Tazemetostat is an oral agent that targets both wild-type and mutant *EZH2*, and appears to be very well tolerated in the relapsed or refractory follicular lymphoma setting. In the phase 2 trial of single-agent tazemetostat in the third-line or later settings, significant response rates were seen in patients with or without an *EZH2* mutation.[5] As previously discussed, the objective response rate was 69% (95% CI, 53%-82%) among patients with the *EZH2* mutation and 35% among patients with *EZH2* wild-type disease. It is important to note that the *EZH2*-mutated and *EZH2*–wild-type cohorts differed in several high-risk clinical features. For example, the median number of prior therapies was 2 in the mutated patients vs 3 in the wild-type patients. Nonetheless, in both *EZH2*–wild-type and *EZH2*–mutated patients, these responses can be extremely meaningful, with durations of remission lasting approximately 1 year in these pretreated patients. Perhaps more importantly, this agent has an extremely well-tolerated adverse event profile. There were very few, if any, grade 3/4 adverse events. The grade 1/2 adverse events were mild. In clinical practice, tazemetostat-mediated toxicities appear to be self-limited, if evident at all. This low toxicity profile is further supported by the observation that few patients discontinue tazemetostat, even in this later line of treatment. In the phase 2 study, 8 of 99 patients discontinued tazemetostat owing to a treatment-emergent adverse event; 5 of these discontinuations were deemed to be treatment-related.[5] Treatment-emergent adverse events leading to tazemetostat dose reductions were reported in 9 patients, and treatment-emergent adverse events leading to dose interruptions of tazemetostat occurred in 27 patients. It is notable that these low rates of discontinuation and dose reductions are quite different from those seen with other agents in this treatment space.

Tazemetostat is approved in patients with relapsed or refractory follicular lymphoma who have an *EZH2* mutation and whose disease had failed to respond to 2 or more lines of therapy.[6] Tazemetostat is also, importantly, approved for any patients with relapsed or refractory follicular lymphoma who have no other satisfactory alternative options, regardless of their *EZH2* mutation status. For example, it might therefore be possible to administer tazemetostat after first relapse in patients who have significant comorbidities or cytopenias, who might not be candidates for cytotoxic chemotherapeutic agents

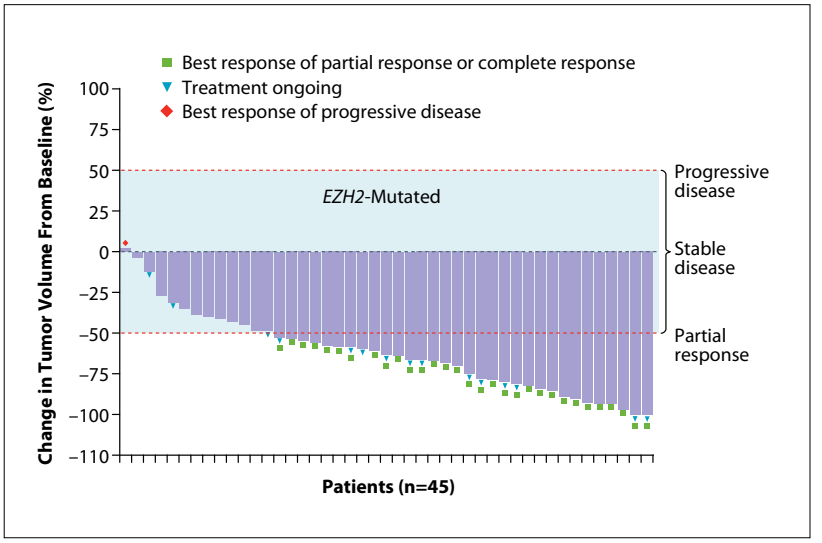

Figure 8. Changes in tumor volume from baseline according to an independent radiology committee among patients with follicular lymphoma treated with tazemetostat in a phase 2 trial. Data are shown for patients with *EZH2*-mutated disease. The dashed red lines indicate thresholds for progressive disease (≥50% increase in tumor volume) and partial response (≥50% reduction in tumor volume). The shaded area represents tumor volume changes that correspond to stable disease (<50% increase or decrease in tumor volume). Adapted from Morschhauser F et al. *Lancet Oncol.* 2020;21(11):1433-1442.[5]

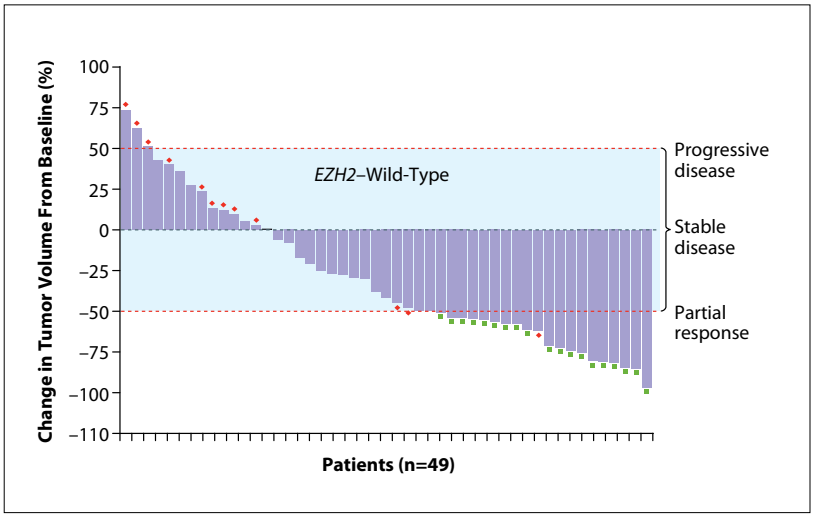

Figure 9. Changes in tumor volume from baseline according to an independent radiology committee among patients with follicular lymphoma treated with tazemetostat in a phase 2 trial. Data are shown for patients with *EZH2*–wild-type disease. The dashed red lines indicate thresholds for progressive disease (≥50% increase in tumor volume) and partial response (≥50% reduction in tumor volume). The shaded area represents tumor volume changes that correspond to stable disease (<50% increase or decrease in tumor volume). Adapted from Morschhauser F et al. *Lancet Oncol.* 2020;21(11):1433-1442.[5]

or lenalidomide.

Not surprisingly, patients will eventually relapse after treatment with tazemetostat. However, as demonstrated in the phase 2 clinical trial, the median progression-free survival was 13.8 months among patients in the *EZH2*-mutated cohort and 11.1 months in patients with *EZH2*–wild-type disease.[5] Given the population, even if responses do not meet the objective categorization of a partial response, many patients can benefit from tumor reductions that are classified as stable disease (Figures 8 and 9). Stable disease may still be an important outcome for these patients because controlling their symptoms may help them feel well for a relatively long period.

When choosing treatment with tazemetostat, it is not necessary to know the patient's *EZH2* mutation status. However, there is an option to assess for the *EZH2* mutation in this setting. There is a companion diagnostic test available for the *EZH2* mutation. In addition, status can be assessed through a next-generation sequencing approach or via *EZH2* hotspot mutation testing that could be available. The test requires lymph node or lymphatic tissue, which can be archival tissue. Unfortunately, the test cannot be performed with a peripheral blood specimen, which lacks circulating follicular lymphoma cells. It may take a few weeks until the test results are available. The scenario may arise in which a patient needs to begin treatment before the results are available. For this situation, it is important to remember that the FDA has approved tazemetostat in patients with or without the mutation.[6] Scenarios in which testing might be considered appropriate could be during early relapse or perhaps even at the time of diagnosis. The results might influence the clinician's selection of the line of therapy in which to use tazemetostat compared with other available agents. In

later lines of therapy, given the tolerability of tazemetostat, it is likely that testing may be less important because the drug might be utilized regardless of the patient's *EZH2* mutation status.

Tazemetostat represents a major advance for this difficult patient population because it can be active even in high-risk patient subgroups. These high-risk patients include those with progression of disease within 24 months after upfront chemoimmunotherapy, as well as those who were refractory to a rituximab-containing regimen or even double-refractory to an alkylating agent and an anti-CD20 antibody therapy. Patients with high-risk features are typically considered to have a major unmet need for adequate, well-tolerated therapies. Tazemetostat may help address this unmet need.

Given the extremely favorable adverse event profile of tazemetostat, in the future, it may be possible to administer tazemetostat as part of novel combination regimens. An ongoing randomized phase 3 trial is exploring the use of lenalidomide and rituximab with or without tazemetostat.[7] The results of this study have the potential to improve outcomes, providing longer progression-free survival in particular, without significantly increased toxicity. The future use of tazemetostat certainly has great potential to benefit patients with relapsed or refractory follicular lymphoma.

Disclosures

Dr Pagel is a consultant for AstraZeneca, Seagen, Loxo Oncology, Gilead, BeiGene, Incyte, and Epizyme.

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Clinical Use of Emerging Therapies in Relapsed or Refractory Follicular Lymphoma

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Optimizing Treatment Administration

It is an exciting time in the management of relapsed or refractory follicular lymphoma, and efforts continue to develop novel, better-tolerated, and more effective treatment options. As a result, there are an increasing number of factors to consider when selecting treatment for a patient with relapsed/refractory follicular lymphoma, and the importance of personalized care is becoming increasingly apparent.

Treatment regimens in the relapsed/refractory follicular lymphoma space include options administered via oral, subcutaneous, intravenous, and combination routes. Regardless of the treatment type and route of administration, adverse events can be managed by adding supportive care, holding the therapy, and/or adjusting the dose. Selection of the intervention depends on the severity and types of adverse reactions a patient experiences. Since the presence of comorbid conditions and the use of concomitant medications with potential for drug-drug interactions may increase the likelihood of adverse events, a baseline dose adjustment may be warranted. Patients at increased risk of adverse events should be monitored more frequently.

Monitoring for Relapse

A common question from patients with follicular lymphoma is how to monitor for signs and symptoms of relapse. The health care provider should assess the patient's general health status and perform routine physical examination, blood work, and radiographic surveillance. Patients should be encouraged to self-monitor for any potential signs or symptoms of relapse, including enlarging lymph nodes and development of B symptoms (unintentional weight loss, drenching night sweats, fever, and fatigue out of proportion to daily activities). Self-monitoring should be balanced with encouragement for patients to live their lives without constant fear of relapse, which can be a challenging balance to achieve.

Radiographic surveillance, typically performed with CT scans or occasionally PET scans, tend to be administered more frequently soon after completion of frontline or subsequent therapy, and become less frequent with time. In cases of long-term remission, radiographic surveillance is superseded by clinical surveillance.

Discussing the Next Treatment Approach With Patients

When discussing the next line of treatment for relapsed or refractory follicular lymphoma with patients, there are several key factors to consider. Because this treatment space is rapidly changing, clinicians should gauge the patient's interest in participating in the available clinical trials. If the patient is not interested or suitable for enrollment in a clinical trial, then the focus should shift to selecting the most appropriate standard-of-care choices.

When considering the standard-of-care choices, assessment of the patient's fitness and details of prior treatment(s) are key. What types of treatment have been administered? What were the mechanisms of action? What was the depth and duration of response? How did the patient tolerate the treatment? What is the patient's performance status, and are there any comorbid conditions that need to be taken into consideration? Furthermore, logistical considerations and impact on quality of life should be considered. Does the patient have a preference

for oral vs intravenous therapy? Is adherence a concern? How far does the patient live from the treatment center? Does the patient work or have other responsibilities that complicate scheduling?

It is important to consider all of these factors because they are often predictive of response to the next line of therapy. For example, if a patient was treated with rituximab monotherapy and responded, but experienced symptomatic relapse soon after, retreatment with rituximab monotherapy is not recommended—even if treatment was well-tolerated—based on the short duration of response. Similarly, if a patient was treated with chemoimmunotherapy, but experienced a relatively short remission (<2 years), then treatment with a novel agent or a nonchemotherapeutic approach should be pursued owing to the relatively short duration of response to chemoimmunotherapy. In the second-line setting, whether the first-line treatment consisted of CD20 monotherapy or chemoimmunotherapy, the standard options to discuss with patients could include participation in a clinical trial or administration of lenalidomide plus rituximab, as evaluated in the AUGMENT study.[1]

The patient's insurance coverage is also an important consideration in the current treatment landscape. Sometimes coverage is different for an oral drug as compared with an intravenous drug. The patient must be able to afford and obtain coverage for the treatment. Fortunately, there are several societies, including the Leukemia & Lymphoma Society and the Lymphoma Research Foundation, as well as drug-specific treatment-assistance programs, that can help assist patients who are unable to afford or access therapy.

Discussion of the side effect profile should include events that are potentially serious but rare, as well as those that are more common. What should the patient expect during treatment? What are the rates of these side effects? For oral regimens, are there any restrictions regarding timing around meals? What are the potential drug interactions? Does starting the follicular lymphoma therapy warrant adjustment of other medications?

Finally, it is important to discuss the expectation for response to the chosen treatment. What is the expected depth of response? Is the treatment administered for only a certain period, or is it used indefinitely? Patients often want to know how a particular treatment might impact their routine daily activities.

It is always important to educate patients. The oral drugs available in this setting, including tazemetostat, lenalidomide, idelalisib, and duvelisib, have excellent patient-support references, websites, and printed information that can enhance and augment the provider-directed educational efforts. It is imperative to review instructions regarding a missed dose. Clinicians should also advise patients to avoid any new or unprescribed medications, including herbal supplements or other vitamins, without first consulting a health care provider.

Novel Therapies Used in the Clinic

Tazemetostat

There are now several novel therapies in the clinic. The most recently approved agent is tazemetostat, an oral EZH2 inhibitor dosed at 800 mg twice daily.[2] Tazemetostat is administered continuously until a patient develops unacceptable toxicity or progression. This agent was granted accelerated approval by the FDA in June 2020 for 2 indications: (1) patients with relapsed/refractory follicular lymphoma who have received at least 2 prior lines of treatment and have the *EZH2* mutation; and (2) patients with follicular lymphoma and no other satisfactory alternative treatment options. The second part of the indication does not specify a required minimum number of prior lines of therapy, and includes patients with both *EZH2*-mutated and *EZH2*–wild-type tumors. The clinical data demonstrate that tazemetostat shows activity in both *EZH2*–wild-type and *EZH2*–mutated patients, although response rates were higher in patients with the *EZH2* mutation. In a phase 2 study of tazemetostat administered at 800 mg orally twice daily in patients with relapsed/refractory follicular lymphoma, the objective response rate was 69% (95% CI, 53%-82%) among patients with the *EZH2* mutation and 34% (95% CI, 22%-48%) among those with *EZH2* wild-type disease.[3]

Typically, when patients begin treatment with an oral agent such as tazemetostat, they undergo routine blood work and office visits to assess toxicity. These assessments are more frequent when treatment begins, and then become less frequent with time, assuming therapy is well-tolerated. This monitoring strategy provides an opportunity to evaluate patients for some of the more common—and typically mild—symptoms associated with tazemetostat, including fatigue, gastrointestinal disturbance, respiratory tract infection, and myalgias. These events are usually grade 1/2, with a low incidence of grade 3 or higher. In the phase 2 trial, 17% of patients developed treatment-emergent grade 1/2 alopecia, a potential side effect that is relatively uncommon with oral nonchemotherapeutic agents.[3]

Tazemetostat is associated with a relatively low rate of gastrointestinal disturbance, including diarrhea and liver function test abnormalities (Table 1).[3] Cases of treatment-related and treatment-emergent grade 1/2 diarrhea were reported in 12% and 18% of patients, respectively. No cases of diarrhea were grade 3 or higher. This low rate is particularly important against the background of the many other orally available agents used in the treatment of

Table 1. The Most Common Adverse Events in a Phase 2 Trial of Tazemetostat in Relapsed or Refractory Follicular Lymphoma

	Treatment-Emergent Adverse Events			Treatment-Related Adverse Events		
	Grade 1/2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 1/2 (%)	Grade 3 (%)	Grade 4 (%)
Nausea	23 (23)	0	0	19 (19)	0	0
Diarrhea	18 (18)	0	0	12 (12)	0	0
Alopecia	17 (17)	0	0	14 (14)	0	0
Cough	16 (16)	0	0	2 (2)	0	0
Asthenia	15 (15)	3 (3)	0	13 (13)	1 (1)	0
Fatigue	15 (15)	2 (2)	0	11 (11)	1 (1)	0
Upper respiratory tract infection	15 (15)	0	0	1 (1)	0	0
Bronchitis	15 (15)	0	0	3 (3)	0	0
Abdominal pain	12 (12)	1 (1)	0	2 (2)	0	0
Headache	12 (12)	0	0	5 (5)	0	0
Vomiting	11 (11)	1 (1)	0	6 (6)	0	0
Back pain	11 (11)	0	0	0	0	0
Pyrexia	10 (10)	0	0	2 (2)	0	0

Adapted from Morschhauser F et al. *Lancet Oncol.* 2020;21(11):1433-1442.[3]

relapsed or refractory follicular lymphoma, which tend to show both early and delayed gastrointestinal disturbance as one of the main potential side effects. These characteristics make tazemetostat unique compared with some of the other available oral medications in the relapsed or refractory follicular lymphoma space.

Other Treatments

Several other treatments are now available in the management of relapsed or refractory follicular lymphoma. Lenalidomide is an immunomodulatory agent that was approved by the FDA for patients with relapsed or refractory follicular lymphoma in November 2019 based on the AUGMENT study. Progression-free survival was 39.4 months with lenalidomide plus rituximab vs 14.1 months with placebo plus rituximab, for an HR of 0.46 (95% CI, 0.34-0.62; $P<.001$).[1] Before this formal approval, lenalidomide had been included in treatment guidelines for relapsed/refractory follicular lymphoma, with various levels of supporting evidence. Lenalidomide is administered orally for 21 days of a 28-day cycle, and typically given together with a rituximab product either intravenously or subcutaneously each month for the first 6 months of the 12-month treatment program, which is commonly referred to as the R-squared regimen. A primary benefit of this regimen is that it is mostly oral, with infrequent office visits for intravenous or subcutaneous therapy. Although the R-squared regimen is typically administered for 12 cycles, this can be adjusted depending on the patient's response and tolerance of therapy.

Gastrointestinal disturbance (primarily early- or late-onset diarrhea) is one of the more common potential side effects. Muscle cramping, cytopenias, and blood chemistry abnormalities can also occur. Lenalidomide is teratogenic, and therefore patient education must accompany the prescription. Lenalidomide is available only through a Risk Evaluation and Mitigation Strategy program.[4] Other rare but potentially serious adverse reactions include both arterial and venous thromboembolism, as well as risk of secondary malignancies. Patients typically require more frequent blood work when first starting treatment. As they continue therapy longer, the frequency of blood work decreases. In my personal practice, I typically check patients at least monthly to ensure they are not experiencing any side effects or dose-limiting cytopenias before resuming each new cycle of lenalidomide with or without rituximab.

There are 3 PI3K inhibitors approved for the treatment of third-line follicular lymphoma. Idelalisib and duvelisib are oral agents, and copanlisib is administered intravenously. The study populations vary across the trials of PI3K inhibitors in relapsed/refractory follicular lymphoma. In general, however, the objective response rates for these agents range from approximately 40% to 60%.[5-7] The toxicity profiles are distinct for the orally available agents vs copanlisib. Idelalisib and duvelisib

Table 2. The Most Common Adverse Events That Occurred During Treatment With Idelalisib in a Phase 2 Trial

	Any Grade (%)	Grade ≥3 (%)
Adverse Event	103 (82)	68 (54)
Diarrhea	54 (43)	16 (13)
Nausea	37 (30)	2 (2)
Fatigue	37 (30)	2 (2)
Cough	36 (29)	0
Pyrexia	35 (28)	2 (2)

Adapted from Gopal AK et al. *N Engl J Med*. 2014;370(11):1008-1018.[5]

have a toxicity profile that includes immune-mediated toxicities that are predominantly gastrointestinal in nature (eg, diarrhea of early or later onset, colitis, and hepatitis or liver function test abnormalities; Tables 2 and 3).[5,6] Another potential immune-mediated adverse event is pneumonitis, which can be challenging to distinguish from infectious pneumonia caused by bacterial, viral, or opportunistic pathogens.[8] The toxicity profile of the intravenous PI3K inhibitor copanlisib is more metabolic in nature and includes infusion-related hyperglycemia and hypertension.

In young or very fit patients with aggressive disease or an early relapse, consolidation with autologous stem cell transplant may be an option. Allogeneic stem cell transplant could be a consolidation option for select young, fit patients with aggressive disease.

The best available option may be participation in a clinical trial, including studies evaluating combinations of well-tolerated, single agents with modest activity and nonoverlapping toxicity profiles. For example, although single-agent activity is disappointing for ibrutinib (objective response rate, 21%; complete response, 11%) and venetoclax (objective response rate, 38%; complete response, 14%) in relapsed/refractory follicular lymphoma, synergy without overlapping toxicity has been demonstrated.[9,10] Trials evaluating combination therapy are ongoing.

At the 2020 ASH meeting, results from the phase 2 trial evaluating the combination of venetoclax and ibrutinib in relapsed/refractory follicular lymphoma were updated.[11] The objective response rate was 83% (complete response, 33%) at the recommended phase 2 dose level. Another appealing combination currently being studied is lenalidomide plus rituximab in combination with tazemetostat for relapsed/refractory follicular lymphoma.[12] When combining novel agents, it is important to perform a thorough evaluation, starting with data from phase 1 clinical studies, as there is the potential for unexpected toxicities to emerge. For example, a phase 2 study of the PI3K delta inhibitor idelalisib plus the spleen tyrosine kinase (Syk) inhibitor entospletinib in 66 patients with relapsed/refractory NHL was aborted owing to an unexpectedly high rate of pulmonary toxicity.[13] In this study, 13 patients overall (24%) experienced pneumonitis, with 11 patients developing grade 3 or higher cases, including 2 fatal events.

The next major advancements in the field of relapsed or refractory follicular lymphoma are CAR T-cell therapy and bispecific antibody therapy. CAR T-cell therapy has been approved by the FDA in acute lymphoma, relapsed or refractory diffuse large B-cell lymphoma, and mantle cell lymphoma. Hopefully, CAR T-cell therapy will be approved in the relapsed or refractory follicular lymphoma setting based on results from the ZUMA-5 study. The primary analysis of this study was reported at the 2020 ASH meeting.[14] With a median follow-up of 17.5 months, the objective response rate was 92%, including a complete response rate of 76%, for the entire cohort, which included 104 evaluable patients with indolent NHL and at least 12 months of follow-up. For the 84 patients with relapsed/refractory follicular lymphoma, the objective response rate was 94% (with a complete response rate of 80%). For the 20 patients with marginal zone lymphoma, the objective response rate was 85% (with a complete response rate of 60%). Of note, based on the smaller number of patients with marginal zone lymphoma—and the fact that the independent review committee deemed that 15% did not have measurable disease after enrollment—the rates of objective response and complete response are challenging to interpret and may be artificially decreased. Responses seem durable, with a 12-month estimated duration of response in 72%. The rate of progression-free survival was 74%, and the rate of overall survival was 93%. Any-grade adverse events occurred in 99% of patients, and grade 3 or higher adverse events occurred in 86%, most commonly cytopenias. Grade 3 or higher CRS (per the Lee 2014 criteria) occurred in 7% of patients, and grade 3 or higher neurologic toxicity occurred in 19% of patients. One patient experienced grade 5 CRS attributed to axicabtagene ciloleucel.

CD20-targeted bispecific antibodies are another exciting option in the advanced stages of development for patients with relapsed/refractory follicular lymphoma. One example is odronextamab, a first-in-class CD3 × CD20 bispecific antibody that demonstrated efficacy and safety across B-cell NHL subtypes. At the 2020 ASH meeting, updated safety and efficacy results were presented from a phase 1/1b study.[15] Among the 28 patients with relapsed/refractory grade 1 to 3a follicular lymphoma treated with 5 mg or more of odronextamab, the objective response rate was 92%, with a complete response rate of 75%.

Table 3. The Most Common TEAEs in a Phase 2 Study of Duvelisib in Patients With Refractory Indolent Non-Hodgkin Lymphoma

	Any Grade (%)	Grade ≥3 (%)
Number of patients	129	129
Patients with ≥1 TEAE	128 (99.2)	114 (88.4)
Diarrhea	63 (48.8)	19 (14.7)
Nausea	38 (29.5)	2 (1.6)
Neutropenia	37 (28.7)	32 (24.8)
Fatigue	36 (27.9)	6 (4.7)
Cough	35 (27.1)	0
Anemia	34 (26.4)	19 (14.7)
Pyrexia	32 (24.8)	0

TEAEs, treatment-emergent adverse events.

Adapted from Flinn IW et al. *J Clin Oncol.* 2019;37(11):912-922.[6]

The median duration of response was 7.7 months (range, 0-20.9 months and ongoing). Among the 21 patients who achieved a complete response, 13 (61%) had an ongoing response at the last assessment. Overall, 127 patients with relapsed/refractory B-cell NHL were included in this evaluation. The maximum tolerated dose was not reached, at doses up to 320 mg weekly. A common adverse event was CRS, which occurred in 62% of patients, with 7% experiencing grade 3 to 4 CRS. Treatment-related grade 3 neurologic adverse events occurred in 3 patients, and there were no grade 4 neurologic adverse events. None of these events led to discontinuation of therapy.

Disclosure

Dr Leslie is a member of the speaker bureaus of Seagen, Celgene/BMS, Kite Pharma, BeiGene, Pharmacyclics/Janssen, AstraZeneca, Epizyme, and Karyopharm. She is an advisory board member and/or a consultant for Bayer, Seagen, ADC Therapeutics, AbbVie, Janssen, Pharmacyclics, Kite, AstraZeneca, Epizyme, and TG Therapeutics.

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Refining the Management of Relapsed or Refractory Follicular Lymphoma: Case Scenarios

John M. Pagel, MD, PhD, John M. Burke, MD, and Lori A. Leslie, MD

John M. Pagel, MD, PhD In follicular lymphoma, it is not uncommon to treat elderly patients (even in their late 70s or early 80s), either at initial presentation or in the relapsed or refractory setting. Of course, their goals are quite different from those for someone who is younger, perhaps in their 40s or 50s. For the older population, rituximab monotherapy is also often relied upon because of the patients' comorbidities. When patients relapse, tazemetostat might be an appropriate palliative therapy—even in the second-line setting—given its favorable tolerability profile.

An example of this kind of patient could be a 75-year-old man who received upfront rituximab monotherapy. He achieved a good partial remission that led to a duration of remission of approximately a year and a half. However, inevitably, the patient will relapse. The goal then is to keep him doing well clinically. This patient might also have relatively fragile blood counts, which is not uncommon among elderly people. An aggressive therapy that may cause cytopenias would not be warranted in this case. In the second-line setting, there might not be another satisfactory alternative therapy. In this case, tazemetostat might be an appropriate choice.

John M. Burke, MD I agree completely. I often see elderly patients such as this one, with some comorbidities, who received rituximab monotherapy as initial therapy. These patients might achieve a remission of a year and a half, or perhaps up to 2 years, but then come back with symptomatic progressive disease. One option in this situation is to repeat the rituximab. However, there is now another very reasonable option with tazemetostat. Given the very favorable toxicity profile of tazemetostat, I would feel comfortable using it in the elderly patient population because it should be tolerable, which is particularly advantageous among older patients with comorbidities.

John M. Pagel, MD, PhD What are your thoughts about testing for *EZH2* mutations?

John M. Burke, MD I order this testing on a case-by-case basis. For example, in the case we were just discussing, in which an elderly patient has comorbidities and lacks good treatment alternatives, I do not order a test. That type of patient is not a great candidate for other options, such as chemotherapy, the R-squared regimen, or PI3K inhibitors. I would likely just proceed with using tazemetostat in the absence of *EZH2* mutational data.

In contrast, let's consider a reasonably fit patient in her 60s. Perhaps she was initially treated with R-CHOP 10 years earlier, and then 5 years ago had a relapse that was observed until progression, and then treated with bendamustine plus obinutuzumab. She has received 2 prior chemoimmunotherapy regimens. This patient would probably best be served by either aggressive treatment (eg, with autologous transplant) or with targeted therapies (eg, lenalidomide plus rituximab or obinutuzumab, or PI3K inhibitors). If an *EZH2* mutation test indicates that she does have the mutation, I might consider tazemetostat over the other options, given the high response rate observed in the *EZH2*-mutated cohort in the phase 2 clinical trial, as well as the good tolerability. Therefore, there are scenarios where the treatment choice might be swayed by the results of the test.

John M. Pagel, MD I agree with that. Even in this patient, though, the options are still somewhat limited given the tolerability profile of PI3K inhibitors.

John M. Burke, MD, PhD Yes. I think there is a very clear difference in the tolerability between tazemetostat and the PI3K inhibitors. In my experience, there are not many patients who can stay on PI3K inhibitors for more than a year. Usually, they must discontinue therapy within less than a year of starting treatment.

Lori A. Leslie, MD I have treated a 68-year-old man who initially presented with mild diarrhea. He went to several different gastroenterologists, and was given a diagnosis of probable inflammatory bowel disease of late-onset. After CT scans revealed an enlarging mesenteric lymphadenopathy, he underwent lymph node biopsy, which resulted in a diagnosis of grade 1/2 follicular lymphoma. The pathology report indicated a low Ki-67 level (<10%). He additionally had diffuse, nonbulky adenopathy in the abdomen. Based on these symptoms and the volume of disease, he was deemed symptomatic. The provider recommended initiation of treatment. After reviewing the

options in the frontline setting, the patient proceeded with bendamustine and rituximab. He achieved a complete response.

The provider and patient discussed maintenance therapy, but observation alone was selected. Approximately 22 months later, the patient underwent a routine surveillance CT scan, which showed recurrence of lymphadenopathy. Soon after, while a biopsy was being scheduled, he further developed gastrointestinal symptoms, including diarrhea reminiscent of his initial presentation. There was no high uptake on a PET scan. The biopsy showed that he still had grade 1/2 follicular lymphoma.

This relapse occurred relatively early, within 2 years of the upfront chemoimmunotherapy. Lenalidomide and rituximab were recommended. The patient received 12 months of treatment and again achieved a complete remission. During treatment, he had some diarrhea that required dose modification of the lenalidomide. Overall, his therapy was well tolerated. However, within 12 months, the patient again progressed in the same manner, with onset of diarrhea and recurrence of lymphadenopathy on CT scan. A repeat biopsy again showed low-grade follicular lymphoma. Molecular testing at this time revealed an *EZH2* mutation.

A variety of treatment options were discussed. The patient was adverse to receiving chemotherapy or infusional therapy. Additionally, given that diarrhea was his primary disease symptom and occurred with the previous line of therapy, he was concerned about any further gastrointestinal issues as a potential side effect associated with some of the other available treatment options. The patient had also become a caretaker for his wife, so he was worried about flexibility and trying to minimize his exposure to the health care environment (particularly in light of the current COVID-19 pandemic). As a result, the patient opted to proceed with tazemetostat. As we initiated treatment, we reviewed the potential toxicity profile and dosing schedule. The patient has been doing well thus far, and has tolerated treatment.

Disclosures

Dr Burke has received consulting fees from Roche/Genentech, AstraZeneca, Verastem, MorphoSys, Adaptive Biotechnologies, Epizyme, Kura, and BeiGene, and he has served on speakers' bureaus for Seagen and BeiGene. Dr Pagel is a consultant for AstraZeneca, Seagen, Loxo Oncology, Gilead, BeiGene, Incyte, and Epizyme. Dr Leslie is a member of the speaker bureaus of Seagen, Celgene/BMS, Kite Pharma, BeiGene, Pharmacyclics/Janssen, AstraZeneca, Epizyme, and Karyopharm. She is an advisory board member and/or a consultant for Bayer, Seagen, ADC Therapeutics, AbbVie, Janssen, Pharmacyclics, Kite, AstraZeneca, Epizyme, and TG Therapeutics.

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Treatment of Follicular Lymphoma

- Approximately 90% of patients with follicular lymphoma will require treatment
- Approximately half of patients will eventually require second-line therapy[1]
- Follicular lymphoma transforms into DLBCL in approximately 2% to 3% of patients annually, rendering the lymphoma more aggressive and difficult to treat[2]

DLBCL, diffuse large B-cell lymphoma.
1. Batlevi CL et al. *Blood Cancer J.* 2020;10(7):74. 2. Tan D et al. *Blood.* 2013;122(6):981-987.

Progression After Therapy

- Progression-free survival becomes shorter with each subsequent line of therapy
- After the first line of therapy, the median progression-free survival is measured in many years
- Subsequent second-line therapy leads to a median progression-free survival from 1 to 2 years
- Subsequent lines of therapy tend to achieve a median progression-free survival of 1 year or less

Relapsed/Refractory Follicular Lymphoma: Prognosis

- The prognosis of patients with relapsed or refractory disease corresponds to the duration of their first remission
- The association between disease progression within 24 months of initiation of frontline chemoimmunotherapy and outcome was demonstrated by data from the prospective, observational National LymphoCare Study[1]
  - The 5-year overall survival was 50% among early progressors (those with disease progression or who died within 2 years of diagnosis) compared with 90% in the reference group

1. Casulo C et al. *J Clin Oncol.* 2015;33(23):2516-2522.

Unmet Needs in Third-Line Treatment of Relapsed/Refractory Follicular Lymphoma

- The prolonged clinical course consisting of multiple relapses is a fundamental challenge that requires clinicians to consider how to best balance treatment efficacy while minimizing toxicity and preserving quality of life
- Although PI3K inhibitors can be lifesaving for some patients, they have a significant toxicity profile. Patients frequently must discontinue treatment owing to severe colitis and diarrhea, as well as occasional cases of pneumonitis and infections
- The immunomodulatory agent lenalidomide can cause cytopenias, rash, and other toxicities that can limit use in elderly patients or those with renal insufficiency

PI3K, phosphatidylinositol 3-kinase.

Monitoring for Signs of Relapse

- The health care provider should assess the patient's general health status and perform routine physical examination, bloodwork, and radiographic surveillance
- Patients should be encouraged to self-monitor for any potential signs or symptoms of relapse, including enlarging lymph nodes and development of B symptoms (unintentional weight loss, drenching night sweats, fever, and fatigue out of proportion to daily activities)
- Self-monitoring should be balanced with encouragement for patients to live their lives without constant fear of relapse, which can be a challenging balance to achieve

Selection of Third-Line Treatment for Relapsed/Refractory Follicular Lymphoma

- The treatment approaches and decisions regarding therapy are largely driven by each patient's unique clinical features
- Factors to consider when selecting treatment include the patient's goals and tolerability for therapy based on performance status, age, and disease burden
- The older age of these patients often also remains an important consideration

Newer Treatment Options for Relapsed/Refractory Follicular Lymphoma

- Management of patients with high-risk follicular lymphoma—defined as those who relapsed within 2 years of initial therapy—represents an important unmet need
- Preventing death from follicular lymphoma in high-risk patients and preventing transformation of follicular lymphoma to aggressive lymphomas should be the top priorities for investigators in this field
- In order to achieve these goals, therapies with novel mechanisms of action are likely to be required
- Mechanisms of action that are currently being explored include EZH2 inhibition, bispecific antibodies that recruit T cells to attack malignant B cells, and chimeric antigen receptor T-cell therapy

Tazemetostat in Follicular Lymphoma

- A methyltransferase inhibitor that inhibits and reduces the activity of EZH2
- Approved by the FDA for the treatment of adult patients with relapsed or refractory follicular lymphoma in 2 settings:
  - Patients with tumors that are positive for an *EZH2* mutation (as detected by an FDA-approved test) and who have received at least 2 prior systemic therapies
  - Patients who have no satisfactory alternative treatment options

FDA, US Food and Drug Administration.

Tazemetostat in Follicular Lymphoma: Phase 2 Data

- The follicular lymphoma cohort included 45 patients with *EZH2*-mutated disease and 54 patients with *EZH2*–wild-type disease
- The objective response rate according to the independent radiology committee was 69% in patients with *EZH2*-mutated disease and 35% in those with *EZH2*–wild-type disease
- The median duration of response was 10.9 months and 13.0 months, respectively
- The median progression-free survival was 13.8 months and 11.1 months, respectively

Morschhauser F et al. *Lancet Oncol*. 2020;21(11):1433-1442.

Tazemetostat: Adverse Events

- Tazemetostat is associated with a relatively low rate of gastrointestinal disturbance, including diarrhea and liver function test abnormalities
- In the phase 2 trial, treatment-related and treatment-emergent grade 1/2 diarrhea was reported in 12% and 18% of patients, respectively.[1] There were no cases of grade 3 or higher diarrhea
- Early and delayed gastrointestinal disturbance is a main side effect of other orally available agents used in this setting[2,3]

1. Morschhauser F et al. *Lancet Oncol*. 2020;21(11):1433-1442. 2. Gopal AK et al. *N Engl J Med*. 2014;370(11):1008-1018. 3. Flinn IW et al. *J Clin Oncol*. 2019;37(11):912-922.

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