# Evolving Third-Line Treatment Options for Follicular Lymphoma

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**H&O** What led to the recent withdrawals of phosphoinositide 3-kinase (PI3K) inhibitors in the setting of follicular lymphoma?

**JB** In the past few months, several PI3K inhibitors have been withdrawn from the market for follicular lymphoma. I will summarize the events chronologically. In late November 2021, TG Therapeutics announced that they had halted the phase 3 UNITY-CLL trial of umbralisib (Ukoniq, TG Therapeutics) and ublituximab. Although this regimen improved progression-free survival (PFS) compared with obinutuzumab (Gazyva, Genentech) and chlorambucil in chronic lymphocytic leukemia (CLL), according to a press release, additional follow-up indicated that overall survival was worse with ublituximab/umbralisib. The decrease in overall survival was likely driven by a higher rate of deaths from COVID-19, likely because patients receiving ublituximab/umbralisib remained on continuous immunosuppressive therapy, whereas those patients on obinutuzumab/chlorambucil stopped treatment.

In early December 2021, the PI3K inhibitor duvelisib (Copiktra, Secura Bio) was withdrawn from the market for follicular lymphoma. The reason provided in the press release was that the current treatment landscape, plus the cost and logistics, made the conduct of the requisite confirmatory trial prohibitive. Duvelisib was left on the market for CLL.

In mid-January 2022, idelalisib (Zydelig, Gilead) was removed from the market for follicular lymphoma and small lymphocytic lymphoma but left on the market for CLL. Again, the manufacturers of idelalisib believed that it would not be possible to complete the confirmatory phase 3 trial that would allow full approval of the drug.

In mid-April 2022, TG Therapeutics announced that they were withdrawing their submission to the US Food and Drug Administration (FDA) for approval of umbralisib and ublituximab in CLL. They have also withdrawn umbralisib from the market for its approved indications of follicular lymphoma and marginal zone lymphoma. This decision was based on a follow-up analysis to the UNITY-CLL study described above.

Currently, the only PI3K inhibitor that remains on the market for follicular lymphoma is copanlisib (Aliqopa, Bayer).

**H&O** Do these withdrawals offer insight into the toxicities of PI3K inhibitors overall?

**JB** The toxicities of these drugs have been well known for a while. They include diarrhea, colitis, transaminase elevations, pneumonitis, opportunistic infections, and rash. PI3K inhibitors can suppress the immune system and lead to infections. What was not known was how these toxicities would impact patient outcomes during the COVID-19 pandemic. Based on the experience with umbralisib, it appears that continuous therapy with a PI3K inhibitor can increase the risk of an adverse outcome from COVID-19. This finding may also be true of other treatments that we use in hematologic malignancies, such as rituximab and obinutuzumab, which are used as maintenance therapy in follicular lymphoma, or Bruton tyrosine kinase inhibitors in CLL. It is likely that many immunosuppressive oncology drugs administered in a continuous fashion will have the same adverse effect on COVID-19 outcomes. This is a lesson that can be drawn from these withdrawals.

I will point out that idelalisib and duvelisib were not withdrawn from the market based on any new toxicity information; instead, they were withdrawn because the manufacturers believed that completion of the phase 3 confirmatory trials required for full approval would be difficult.

**H&O** How do the recent changes to the available PI3K inhibitors impact your treatment choices for relapsed/refractory follicular lymphoma?

**JB** These changes will not have a large impact on my selection of treatment. The use of PI3K inhibitors in follicular lymphoma was already limited based on their known toxicities as compared with the alternatives. Physicians and patients usually choose other treatments. Copanlisib is still an option for patients who are good candidates for a PI3K inhibitor.

**H&O** What type of drug is tazemetostat (Tazverik, Epizyme), and where does it fit into the management of follicular lymphoma?

**JB** Tazemetostat is a methyltransferase inhibitor that inhibits and reduces the activity of EZH2. *EZH2* is mutated in approximately 20% of patients with follicular lymphoma. When present, this mutation is a gain-of-function mutation. Even when the mutation is not present, EZH2 is still important for the growth and survival of follicular lymphoma cells. Therefore, inhibition of EZH2 activity has a strong rationale in follicular lymphoma.

In June 2020, the FDA granted accelerated approval to tazemetostat for the treatment of relapsed/refractory follicular lymphoma. The specific indications are for patients who have an *EZH2* mutation and have received at least 2 prior systemic therapies or for patients who have received at least 1 prior systemic therapy and now have no satisfactory alternative treatment options. The accelerated approval was based on response rate and duration of response. The manufacturer has committed to conduct a randomized trial to prove a clinical benefit, which is required to gain full approval.

**H&O** What are the efficacy and safety data that led to the approval of tazemetostat for these patients?

**JB** The approval was based on a phase 2 open-label, multinational trial that enrolled patients with relapsed/refractory follicular lymphoma who had received at least 2 prior therapies. The patients were divided into 2 cohorts: those without the *EZH2* mutation, referred to as wild-type *EZH2*, and those with the *EZH2* mutation. The primary endpoint of the study was the overall response rate as measured by an independent review committee. All patients received tazemetostat at a dose of 800 mg orally twice daily as continuous therapy. There were 45 patients with the *EZH2* mutation. Their median age was 62 years, and they had received a median of 2 prior therapies. Forty-nine percent of patients were refractory to their previous treatment, and 20% were double-refractory. Among the 54 patients who were *EZH2* wild-type, the median age was 61 years. These patients had received a median of 3 prior therapies, and 41% were refractory to their last regimen.

The efficacy results between the 2 cohorts differed slightly. In the *EZH2*-mutated cohort, the overall response rate was 69%, which included a complete response rate of 13%. The median duration of response was 11 months, and the median PFS was 14 months. The median time to response was 3.7 months. The median overall survival was not reached. The response rate was lower in the *EZH2*–wild-type patients, at 34%. The complete response rate was 4%, although approximately two-thirds of patients had at least some reduction in their tumor volume. The median duration of response was similar, at 13 months. The median PFS was fairly similar at 11 months. The median time to response was 3.9 months, and the median overall survival was not reached. Therefore, the response rate was not as high in the wild-type patients, but the duration of response was similar. Patients in the wild-type arm were more heavily pretreated, which might have contributed to their lower response rate.

The toxicities of the drug were relatively modest. Only 8% of patients discontinued treatment owing to side effects. The most common toxicities were fatigue, respiratory infection, musculoskeletal pain, nausea, and abdominal pain. Grade 3 and 4 toxicities were rare. No treatment-related deaths occurred. One patient developed myelodysplastic syndrome (MDS), and another developed acute myeloid leukemia (AML). Blood counts must be monitored in these patients. There should be a low threshold for performing a bone marrow biopsy if there is any suspicion that the patient might have AML or MDS.

**H&O** In what ways does tazemetostat differ from the other treatment options in this setting?

**JB** There are several other options in relapsed/refractory follicular lymphoma, with different routes of administration, efficacy rates, and toxicity profiles. Lenalidomide given with rituximab (so-called "R-squared") is commonly used as a second-line therapy. The lenalidomide/rituximab regimen achieves a median PFS of approximately 3 years in patients who are not refractory to rituximab. This treatment is administered for 1 year. Chemotherapy is another option in the third-line setting and beyond. Tazemetostat is quite different from chemotherapy. This drug is administered orally. It is less immunosuppressive, and it is associated with far fewer toxicities. The

chimeric antigen receptor (CAR) T-cell therapy axicabtagene ciloleucel (axi-cel, Yescarta, Kite) is now available for treatment in the third-line setting and beyond. Axi-cel has much higher rates of overall response and complete response. However, it is costly, requires hospitalization, and has a completely different side effect profile. Based on these features, in follicular lymphoma, axi-cel will probably be used more commonly in younger, fit patients and in those whose tumors have a more rapid growth rate. In contrast, tazemetostat might be a better fit for patients who are older or more frail, or those with slower-growing follicular lymphomas.

Bispecific antibodies are a promising treatment that may become available soon for patients with follicular lymphoma. Bispecific antibodies have excellent response rates. Compared with CAR T-cell therapy, bispecific antibodies may have a slightly lower rate of toxicities and may be easier to administer. They will likely be administered either intravenously or subcutaneously, depending on the product.

Based on the experience with umbralisib, it appears that continuous therapy with a PI3K inhibitor can increase the risk of an adverse outcome from COVID-19.

**H&O** What are the recent updates to the National Comprehensive Cancer Network (NCCN) guidelines regarding relapsed/refractory follicular lymphoma?

**JB** The NCCN guidelines for relapsed/refractory follicular lymphoma have removed all of the PI3K inhibitors except for copanlisib. Axi-cel was added last year. The guidelines now list tazemetostat as a category 2A recommendation for second-line therapy for the elderly or infirm who lack satisfactory alternative treatment options, in addition to its recommended use in the third-line setting consistent with its approved indication.

**H&O** Do you have any other observations regarding the treatment of relapsed/refractory follicular lymphoma?

**JB** The options include lenalidomide/rituximab, chemoimmunotherapy, axi-cel, tazemetostat, the PI3K inhibitor copanlisib, and the soon-to-come bispecific antibodies. These treatments differ in their efficacy, toxicities, routes of administration, risks, and benefits. They are all reasonable options in this setting, and it is great to have so many choices to fit individual patient needs. Physicians must be familiar with all of these treatments. They should be able to discuss the risks and benefits with each patient in the context of his or her age, comorbidities, preferences, and other factors. These considerations will help the physician and patient make the best choice.

***Disclosure***

*In the past 2 years, Dr Burke has served as a consultant for Kura, AbbVie, Genentech, MorphoSys, BeiGene, Seagen, Kymera, Bristol Myers Squibb, X4, AstraZeneca, TG Therapeutics, Epizyme, Lilly, and Nurix. He has served on speakers' bureaus for Seagen and BeiGene.*

## Suggested Readings


Gilead Statement on Zydelig® U.S. Indication for Follicular Lymphoma and Small Lymphocytic Leukemia. https://www.gilead.com/news-and-press/company-statements/gilead-statement-on-zydelig-us-indication-for-follicular-lymphoma-and-small-lymphocytic-leukemia. Posted January 14, 2022. Accessed May 2, 2022.

Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2020;21(11):1433-1442.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). B-cell lymphomas. Version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Updated April 25, 2022. Accessed April 29, 2022.

Secura Bio Announces Copiktra® (Duvelisib) Strategic Focus on T-cell Lymphoma and Voluntary U.S. Withdrawal of the Relapsed or Refractory Follicular Lymphoma Indication. https://www.prnewswire.com/news-releases/secura-bio-announces-copiktra-duvelisib-strategic-focus-on-t-cell-lymphoma-and-voluntary-us-withdrawal-of-the-relapsed-or-refractory-follicular-lymphoma-indication-301436834.html. Posted December 3, 2021. Accessed May 2, 2022.

TG Therapeutics Announces Extension of U.S. FDA BLA/sNDA PDUFA Date for Ublituximab Plus UKONIQ® (U2) to Treat Patients With CLL and SLLFDA Sets Updated PDUFA Goal Date of June 25, 2022. https://www.biospace.com/article/releases/tg-therapeutics-announces-extension-of-u-s-fda-bla-snda-pdufa-date-for-ublituximab-plus-ukoniq-u2-to-treat-patients-with-cll-and-sllfda-sets-updated-pdufa-goal-date-of-june-25-2022/. Posted March 3, 2022. Accessed May 2, 2022.

TG Therapeutics Announces Voluntary Withdrawal of the BLA/sNDA for U2 to Treat Patients With CLL and SLL. https://ir.tgtherapeutics.com/news-releases/news-release-details/tg-therapeutics-announces-voluntary-withdrawal-blasnda-u2-treat. Posted April 15, 2022. Accessed May 2, 2022.

TG Therapeutics Provides Regulatory Update. https://ir.tgtherapeutics.com/news-releases/news-release-details/tg-therapeutics-provides-regulatory-update. Posted November 30, 2021. Accessed May 2, 2022.