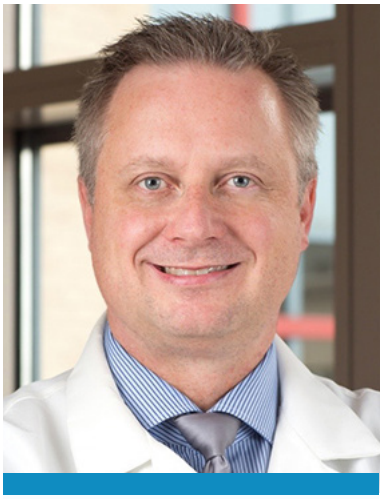
# Advancements in Follicular Lymphoma Treatment: Where We Are and Where We Are Going

***A Q&A With Andrew M. Evens, DO, MSc***



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***AJMC®*: What is your assessment of the treatment landscape in follicular lymphoma (FL)?**

**EVENS:** FL is, generally speaking, a fairly heterogeneous cancer. It is classified is an indolent lymphoma, meaning slow growing. We meet some patients for the first time with newly diagnosed FL, and it was an incidental diagnosis, whether they had a hernia repair or there was a lymph node that a surgeon biopsied, etc. For patients like this with small amounts of disease and who are asymptomatic, we would say they have a low tumor burden. Patients with low burden often do not need to be treated right away. We still do something called watchful waiting or close observation, and some patients will go many years without needing therapy. For the slight majority of patients we meet for the first time, their disease is more advanced, with higher tumor burden. The lymphoma can cause symptoms—local symptoms from a mass, such as pain, or there may be systemic symptoms, such as severe fatigue or B symptoms, which can [include] drenching night sweats, high fevers, [and] weight loss, all caused by the lymphoma. The good news is that if patients need treatment, the initial treatment platforms are very effective. This includes rituximab as a single agent or more commonly for the high tumor burden patient, rituximab combined with chemotherapy. There is a new second-generation anti-CD20 monoclonal antibody that was FDA approved, called obinutuzumab, which can be combined with chemotherapy, as well. In addition, it is not FDA approved for newly diagnosed FL, but there are also favorable data using lenalidomide combined with rituximab in the frontline setting.

A majority of patients treated with one of the aforementioned platforms will go into remission and remain disease-free for a number of years. In fact, in examining several of the recent frontline studies combining CD20 antibody with chemotherapy, the median first remission is approximately 10 years. However, at some point, most patients will relapse and eventually warrant subsequent treatment. As alluded to, the time to relapse can vary. It can uncommonly happen in 12 months, and sometimes it may last for more than 15 years. At the time of relapse, especially if there are symptoms due to the disease, a different or new treatment plan needs to be devised.

***AJMC®*: What is the impact of targeted therapy on the treatment of FL, in initial treatment and in the relapsed/refractory setting?**

**EVENS:** Targeted therapies have significantly enhanced the FL treatment landscape. We still use chemotherapy, but adverse events [AEs] occur due to chemotherapy, such as pancytopenia, low blood counts, anemia, increased risk of infection, etc. Very often, these are manageable in many patients. But targeted therapies may potentially avoid many of those typical chemotherapy AEs. That is not to say targeted therapies don't have AEs, but they are different and usually manageable.

***AJMC®*: Could you discuss the phosphoinositide 3-kinase (PI3K) pathway and its role in treating relapsed/refractory cases of FL?**

**EVENS:** The PI3K pathway plays a significant role in FL. Interestingly, we have known for a number of years that the PI3K pathway is part and parcel of what we call lymphomagenesis. It is among the many pathways that [we believe] cause FL and its growth. It may be abnormally mutated and hyperregulated. Thankfully, investigators and pharmaceutical companies have translated the bench science to the bedside in targeting this pathway. There now are 3 FDA-approved PI3K inhibitor agents; 2 are oral, and 1 is intravenous [IV]. There are many similarities across these 3 agents; however, there are also several key differences. These agents each target different PI3K isoforms. The initial agent FDA approved was a more pure delta inhibitor. And now we have a delta-gamma and a delta-alpha inhibitor approved as well. Scientifically speaking, whether that has a meaningful difference at the bedside for patients, we're actually not sure. When we look at all 3 of these agents, even though they've not been compared head-to-head, they appear to have overall similar efficacy. These agents induce a remission of disease [combined partial and complete remission] between 50% and 60% of the time, which, frankly, is nearly as good as many chemotherapy regimens.

***AJMC®*: Do the PI3K inhibitors and the trials that led to their approval have any particular nuances?**

**EVENS:** All 3 PI3K inhibitors are clinically efficacious. In terms of study design, the key differential comes more along the lines of tolerability. They each have slightly different and, in some cases, very different AE panels. The oral agents tend to have some associations (uncommonly) with increased liver function tests, irritation of the lung (or pneumonitis), and they may also lead to irritation of the gastrointestinal [GI] tract (or colitis). Thankfully, the majority of AEs are lower grade and manageable. The AEs with the IV agent have a different [adverse] effect panel with acute elevations in blood glucose and sometimes blood pressure (ie, hypertension) that are seen. These appear to be related to the infusion. Once the infusion has stopped, the patient is managed supportively and those AEs subside. Often, in choosing among agents, it's considering these aforementioned differences and also the patient's history and preferences. If I had a patient with brittle diabetes and/or who had blood pressure problems, I would not consider the agent that causes those AEs. Conversely, if I had a patient who had prominent liver issues and/or significant pulmonary or GI disturbances, I would likely not choose oral agents. In addition, some patients may prefer oral over IV agents or vice versa; thus, it is always important in a disease like FL—which is remitting and relapsing—that patient preference be an important part of the consideration in choosing therapy.

***AJMC®*: What are some challenges and/or opportunities of having several available options for the treatment of relapsed/refractory FL?**

**EVENS:** Generally, having more therapies to choose from is better. Not only does it let you have a [more] competitive landscape, potentially with drug pricing, but it allows you to analyze differences among the agents to try to tailor therapy most optimally to the individual patient. Not to minimize the AEs related to these and other agents, but it is important to appreciate that the better we are treating patients and, hopefully, achieving remission, the higher the likelihood they're staying out of the clinic and hospital and not needing additional care services. We want the patient to be in remission and have as optimal quality of life as possible.

***AJMC®*: What do you think the future might look like over the next few years with these agents? Do you expect guidelines and/or formularies to evolve and potentially integrate PI3K inhibitors earlier in treatment?**

**EVENS:** As exciting as it is to have these targeted therapies available for FL, we are actually a little behind in comparing with other lymphomas, such as mantle cell lymphoma or diffuse large B cell with CAR [chimeric antigen receptor] T-cell therapy approved. Outside of 2 monoclonal antibodies and a treatment that unfortunately is not used nowadays (ie, radioimmunotherapy), PI3K inhibitors (and lenalidomide, most recently) are the only nonchemotherapy agents FDA approved in FL. With that said, there is a lot of ongoing research, including trying to move these agents up earlier in the disease setting. In addition, there is significant translational and clinical research examining what are the most optimal combinations of agents to use, including "novel-novel" combinations. It is important to note these new combinations should always be done in the context of a clinical trial. We cannot assume that combining a targeted agent with another targeted is always going to be effective and safe.

Another point is that we can continue to do a better job as [investigators] in terms of finding predictive biomarkers for all targeted drugs. We don't currently

have any clinical or scientific-based markers (tissue or blood based) or other clinical factors that may predict who is going to respond or not. It would be ideal to have a lab test or even a genetic test (eg, host single nucleotide polymorphism) to enrich the potential efficacy and who [may] experience potential severe toxicity. So, instead of a 50% to 60% response rate in an unselected FL patient population, we could conceivably improve that to 80% or higher with a validated biomarker.

**_AJMC®_: What particular areas of FL research and treatment should be addressed in the next several years?**

**EVENS:** We need continued research and collaboration among pharmaceutical companies, academia, the NIH [National Institutes of Health], the FDA, the CTEP [Cancer Therapy Evaluation Program], payers, cancer foundations, and all stakeholders across the board. Hopefully, more and newer targeted therapies [will be] studied and approved by the FDA for patients with FL. Furthermore, we need to continue to find ways to collaborate more with community oncologists for increased clinical trial enrollment and also novel methods of clinical collaboration and patient care, such as telementoring or telemedicine. [Also,] in a relatively chronic disease that is remitting and relapsing, we need to more robustly study and incorporate quality-of-life end points into treatment decisions. Altogether, outcomes have improved considerably for FL, especially over the last decade; this means not just longer remission but overall survival that is significantly prolonged. Patients, thankfully, are living longer based in part on these novel therapies; that's the good news. However, we still have a lot of work to do. Many patients will still die prematurely or suffer toxicities to treatment, or suffer undue symptoms due to the disease. Ultimately, our goal is to discover a cure for FL. In the meantime, we must continue to identify highly effective therapies that have low and manageable AEs so patients can stay out of the doctor's office and the hospital and maintain a high quality of life. ◆