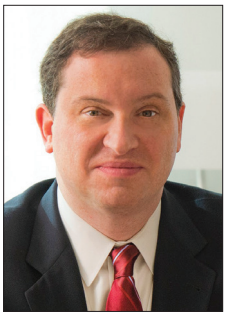
I Think the FDA Got It Wrong ...



We have experienced a string of great successes in clinical therapeutics for CLL over the past several years, both in the number of novel therapies approved or entering clinical development and in the durability of their efficacy. CLL remains an incurable disease, however, with a subset of patients experiencing aggressive disease and multiple relapses. The mainstays of treatment at this time are BTK inhibitors and venetoclax, which can be used alone, in combination, or in combination with anti-CD20 monoclonal antibodies. Despite the availability of these regimens as treatment of frontline and relapsed disease, we still have patients who need additional therapies.

On April 21, 2022, the FDA convened an Oncologic Drugs Advisory Committee meeting to "discuss the observed toxicity of the PI3K inhibitor class and whether randomized data are warranted with an assessment of overall survival (OS) to support the evaluation of benefit-risk in patients with hematologic malignancies." After their discussion, the Committee recommended (by a 16 to 0 vote, with 1 abstention) that future approvals of PI3K inhibitors should require randomized data. On the surface, this decision appears reasonable. It might even be considered a testament to the successes seen with CLL therapies—suggesting that the bar for approval needs to be moved higher because such great advances have been made in this setting. The intent of this decision could not be further from that, however. The FDA has issued so many Safety Alerts, limitations of use, and requests for additional data and follow-up regarding PI3K inhibitors that the continued marketing of these agents has been hampered, leading to several market withdrawals. I worry that hematologic oncologists are now paying for the FDA's missteps regarding aducanumab for Alzheimer's disease.

Three PI3K inhibitors are currently approved in hematologic malignancies, all targeting the delta isoform of PI3K. Immune-mediated adverse events, which are the stereotypical adverse events caused by delta isoform–directed PI3K inhibitors, are hypothesized to result from a greater sensitivity of the regulatory T cells than the helper T cells to delta inhibition, leading to autoimmunity. The FDA Safety Alerts have focused on an increase in deaths in the PI3K inhibitor arm in several studies of idelalisib, duvelisib, and umbralisib. Of course, overall survival is the most important endpoint for our patients, but circumstances exist in this case that render the analysis less clear-cut.

For example, we have now learned about a deleterious interaction between PI3K inhibitors and bendamustine. In the UNITY-CLL study, the FDA raised concerns regarding an increase in deaths resulting from adverse events with umbralisib plus ublituximab (U2) compared with chlorambucil plus obinutuzumab (Chl-Obi). Because U2 was administered continuously (until disease progression or withdrawal for another reason) and improved progression-free survival, patients receiving U2 remained on treatment longer than those receiving Chl-Obi. Further complicating this study was COVID-19, which arrived after most of the Chl-Obi patients had completed treatment, whereas many U2 patients were still receiving treatment. These events are typical of situations in which longer progression-free survival allows for more time for adverse events. Furthermore, the FDA cited a hazard ratio of 1.23 for risk of death for patients on U2 compared with those on Chl-Obi as demonstration of possible harm. The FDA ignored the fact that the confidence interval crossed 1.0, however, and therefore was not statistically significant. Additionally, when a sensitivity analysis was conducted to exclude the effect of COVID-19 deaths, the hazard ratio fell to 1.03. By contrast, the CLL14 trial that served as the basis for the approval of venetoclax plus obinutuzumab in treatment-naive CLL demonstrated a hazard ratio for death of 1.24 (Fischer K. *NEJM*. 2019). Additionally, Barr and colleagues presented data at the 2019 ASH annual meeting with U2 plus venetoclax that demonstrated excellent safety and efficacy when ublituximab was limited to 6 cycles.

I am not looking for a statement that PI3K inhibitors are the best treatment for our patients with CLL, because they are not. PI3K inhibitors are less efficacious and more toxic than BTK and BCL2 inhibitors, and there is a learning curve for managing the adverse events of patients on PI3K inhibitors. Still, the FDA could have better served our patients by educating physicians and guiding additional research on better optimizng the use of these agents before writing them off. After all, we have data demonstrating a worse survival with FCR than with ibrutinib plus rituximab (Shanafelt T. *Blood*. 2022), yet physicians still elect to use FCR. I believe that PI3K inhibitors still have an important role to play in patients with CLL who have progressed through other agents, and need to be preserved as part of the therapeutic armamentarium.

Sincerely,

Richard R. Furman, MD