CLL SOCIETY

June 2, 2022

Dear Dr. Pazdur,

Thank you for your attention and concern surrounding the issue of toxicity and risks associated with PI3K inhibitors in chronic lymphocytic leukemia (CLL).

By way of introduction, CLL Society is the largest patient-centric nonprofit organization focused exclusively on the unmet needs of nearly 200,000 Americans living with CLL (SEER database, January 2018). We operate under the guidance of a Medical Advisory Board and Expert Medical Council, which are comprised of world-class experts in CLL research and patient care. Our interest is in ensuring that patients have access to safe and efficacious treatment options.

Despite significant progress with new BTK and BCL-2 inhibitors, CLL remains an unsolved and incurable cancer, with essentially all therapies being palliative. In addition, some patients may be poor candidates for BCL-2 inhibitors, particularly BTK inhibitors, due to comorbid conditions. Patients who progress after both BTK and BCL-2 inhibitors have a dismal prognosis[1]. PI3K inhibitors are currently their only approved targeted therapy option. Academic centers may offer promising new therapies and combinations of approved drugs via clinical trials. But many CLL patients will have either no access to clinical trials, be ineligible due to comorbidities or other issues, or prefer a different choice. This is particularly true for patients in underserved communities where participation in clinical trials remains low.

The use of PI3K inhibitors, their associated toxicity, and even their mortality risk should not be minimized. Their use and associated risks should be thoroughly discussed, and there should be shared decision-making between the patient and their healthcare provider. Powerful Risk Evaluation and Mitigation Strategy (REMS) programs, as well as explicitly clear product labeling, are critical. As experience with their use has grown, we are encouraged that adverse events which caught some physicians by surprise in the past are now better anticipated and managed.

It is important to recognize that PI3K inhibitors are highly effective agents for CLL, especially those in a high-risk genetic subset. Multiple opinion papers have been written outlining the utilization of PI3K inhibitors in CLL[2,3,4], as well as the management of associated toxicities. The real-world need that is being fulfilled by PI3K inhibitors is when they are used in patients that have no other good treatment options.

We see two critical roles in which properly managed PI3K inhibitor therapies should continue to be utilized:

1. Bridge therapy to reduce disease burden and increase success for other therapies, such as allogeneic hematopoietic stem cell transplants.
2. Long-term therapy for those who do not develop autoimmune and infectious complications, including those patients who are intolerant or not eligible for other approved therapies.

Going forward and looking more widely at the CLL therapeutic landscape, safety must never be compromised. But drug innovation should continue to be encouraged. We believe the FDA can leverage the power of electronic medical records and real-world data to further assess the safety of PI3K inhibitors. Delays associated with the wait for overall survival data have already started to dampen research efforts in CLL and have slowed patient access to potentially life-saving therapies. CLL is a chronic cancer, and patients are often exposed to multiple therapies over the span of their disease. Survival data will come too slowly for many patients and will never be "statistically pure." CLL Society and many others have pushed for crossover in clinical trials to ensure equipoise, which while further confounding the survival data, saves lives. In the opinion of CLL Society, clinical trial design focused on overall survival endpoints will ultimately delay or deny the best possible care to patients with CLL.

We collectively ask the FDA to ensure that all measures are taken to educate patients and providers about the risks associated with PI3K inhibitors but that the use of drugs already approved be a continued option for patients with CLL. Their use should be taken into careful consideration through informed and thoughtful shared decision-making between the patient and their healthcare provider. We would also like to see the FDA leverage its considerable expertise and knowledge to use real-world data both to assess the safety and as a way to expedite future drug development in CLL.

We would welcome the opportunity to schedule a ZOOM meeting with you and your team to discuss this important matter further.

Thank you again for all you are doing to help patients with CLL and other cancers.

Sincerely,

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