



## VIA ELECTRONIC DELIVERY

July 23, 2023

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**RE: Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development.  
Docket No. FDA-2022-N-2480**

CLL Society has appreciated the Food and Drug Administration's (FDA's) stakeholder engagement to increase awareness and understanding of the Rare Disease Endpoint Advancement (RDEA) Pilot Program. We are pleased to submit our written comments to augment my brief statement during the June workshop conducted by the Duke-Margolis Center for Health Policy.

CLL Society is dedicated to addressing the unmet needs of the chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL, both diseases hereinafter referred to collectively as CLL) community through patient education, advocacy, support, and research. We are the largest nonprofit in the US focused exclusively on meeting the unmet needs of patients living with CLL.

Our patients live with a chronic rare cancer of the immune system. We strive to fulfill our primary mission of ensuring that patients have access to safe and effective treatment options, which includes informing patients and caregivers about the therapeutic landscape. We also stress the importance of clinical trials to those in our community, build and support patient networks, engage in research, and educate patients and their caregivers.

We are hopeful that the RDEA Pilot Program will help FDA, researchers, and patient advocacy organizations address the unique challenges associated with determining the appropriate efficacy endpoint(s) for clinical trials that are evaluating the effectiveness of CLL treatments. As we have noted in previously submitted comments, delays associated with the wait required to obtain overall survival data have already dampened research efforts and slowed patient access to potentially life-saving therapies. In addition, while we advocate for crossover in clinical trials to save lives, the strategy inherently compromises the "purity" of survival data.

The question of whether CLL patients will retain access to PI3K inhibitors as a remaining treatment option (after both BTK and BLCL2 inhibitors have failed to control their CLL) illustrates the inherent difficulties associated with studying this disease. Ideally, development of novel endpoints will



CLL SOCIETY

incrementally ease the heightened risk manufacturers must weigh when pursuing new therapeutic candidates. We are hopeful that FDA will continue to expand the role patients and their advocacy organizations have in FDA's drug development processes, including those related to approval, and when determinations are initiated to withdraw approval or modify a product's label.

## Background

CLL/SLL is a chronic blood cancer of the white blood cells known as B-lymphocytes where there is a progressive accumulation of too many mature B-lymphocytes. CLL is the most common type of adult leukemia in the United States, with around 21,000 cases diagnosed annually. It is classified as both a type of leukemia and a type of non-Hodgkin's Lymphoma (NHL). SLL is simply a different manifestation of the same disease and is best understood as a stage of CLL where there are not yet a significant number of cancer cells located in the bloodstream. As previously mentioned, we refer to the disease state collectively as CLL.

CLL is extremely heterogeneous, meaning each person's disease course and progression can vary considerably. Some patients have an aggressive form of the disease, experience rapid deterioration, and survive for as little as two years. Others have a less aggressive form of the disease, may never need treatment, and can expect to have a normal life expectancy. For most patients, CLL is indolent and incurable. There are, however, excellent choices for patients requiring front-line and even second-line therapy to help control the disease.

Taken together, the factors outlined above (heterogeneity, indolence, response to previous therapies) make overall survival a poor endpoint in clinical trials for CLL, particularly in early lines of therapy. Endpoints such as progression-free survival (PFS), time to next treatment (TTNT), duration of response (DoR), and measurable residual disease (MRD) may be more meaningful and pragmatic. Although MRD has not yet been included as an endpoint toward gaining approval of a CLL treatment, data suggests that it is predictive of overall survival.

A recent review on the use of MRD in CLL<sup>1</sup> concluded that, "[m]easurable residual disease (MRD) status in chronic lymphocytic leukemia (CLL), assessed on and after treatment, correlates with increased progression-free and overall survival benefit." Use of MRD as an endpoint would not only improve the breadth of data available to FDA but could significantly improve patient and clinician understanding of the treatment effects of emerging CLL product candidates. We expect that FDA acceptance of MRD data would also increase real-world use of MRD tools to guide and improve patient treatment plans, eventually enabling more patients to live longer while potentially spending less time and money treating their cancer.

---

<sup>1</sup> Fisher A, Goradia H, Martinez-Calle N, Patten P, Munir T. The evolving use of measurable residual disease in chronic lymphocytic leukemia clinical trials. *Front Oncol.* 2023 Feb 22;13:1130617. doi: 10.3389/fonc.2023.1130617. PMID: 36910619; PMCID: PMC9992794.



CLL SOCIETY

## Specific Comments and Recommendations

### FDA Staff Involved in RDEA Pilot Program

CLL Society appreciates that the FDA intends to include interdisciplinary FDA experts in endpoint development, as well as the review division associated with a particular research program. We agree that FDA should employ a flexible approach that matches team members with the nature of the proposed novel endpoint(s). We ask that FDA consider, on a case-by-case basis, inclusion of:

- Expert(s) in the science of rare diseases with specific expertise in challenges associated with small population studies.
- FDA staff with experience in Patient-Focused Drug Development (PFDD), particularly if the selection of the novel endpoint is based on patient preference data (or assumptions).
- Outside experts, including disease-specific clinicians and/or patient advocacy organizations to ensure that the novel endpoint (or data collection mechanism) is patient-centered.

### Program Eligibility

CLL Society supports FDA's decision to extend eligibility beyond those with an active drug development program to include sponsors initiating a natural history study. We ask that the Agency also consider:

- Requiring that sponsors proposing a development program for a common disease with a novel endpoint that is potentially applicable to a rare disease identify the specific rare disease(s), the justification for the novel endpoint, and likely timeline from adoption in the more common condition to its accepted use in the rare condition.
- Clarifying when an endpoint is considered "novel." The FDA suggests that the endpoint must be one that has "never been used to support drug approval" or is "substantially modified from previous use to support drug approval." CLL Society urges the FDA to determine whether an endpoint is novel within the context of the specific disease state. MRD, for example, would be a novel endpoint in CLL even if the concept were used in other blood cancers or conditions. Similarly, use of sensitive viral load testing tools in HIV to determine whether a treatment enabled patients to reach "undetectable" status should not make MRD any less novel in CLL and other blood cancers.



## RDEA Proposal Selection

CLL Society understands that the FDA will limit admission to the pilot program to a very limited number of proposals. With respect to the factors the Agency expects to consider in selecting proposals, we:

- Generally support FDA preference for proposals with the potential to impact drug development more broadly. However, this factor should not foreclose preference for a novel endpoint that might more reliably predict clinical benefit than existing endpoints in conditions that, like CLL, have a significant unmet need.
- Ask FDA to consider the extent to which the proposal and its sponsor have engaged patient stakeholders in selecting the novel endpoint and the proposed data collection mechanism(s). Incorporating the real-world experience of patients will maximize the extent to which clinical trials are able to increase the convenience and value of participation.
- Urge FDA to give preference to promising novel endpoints in life-threatening rare diseases for which existing treatments fail to impact outcomes in those in later stages of the disease.
- Ask that FDA consider novel endpoints, which can both speed patient access to new treatments and improve reliability of determinations that a drug is or is not safe and effective. This is particularly important for clinical trials in conditions, including CLL, that are either inappropriate for randomized controlled trials or that require cross-over to address ethical concerns.

## **Conclusion**

For patients with CLL and other generally incurable chronic diseases, developing new treatments is our lifeline. We welcome the opportunity to work with sponsors and FDA to identify and develop novel and emerging endpoints likely associated with clinical benefit and increased overall survival in an indolent cancer like CLL.

If you have any questions, please feel free to contact Saira Sultan, CLL Society's Director of Government Affairs and Public Policy at [ssultan@cllsociety.org](mailto:ssultan@cllsociety.org).

Sincerely,

Brian Koffman, MDCM, MSED  
Co-Founder, Chief Medical Officer, & Executive Vice President  
CLL Society