CLL SOCIETY

VIA ELECTRONIC DELIVERY

May 26, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2023-D-0110:
Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics

CLL Society appreciates the opportunity to submit its comments on the Food and Drug Administration's (FDA's) draft guidance to industry entitled "Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics."

CLL Society is dedicated to addressing the unmet needs of those within the chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) community through patient education, advocacy, support, and research. Our patients live with a chronic, rare cancer of the immune system. CLL Society is the largest nonprofit focused exclusively on the unmet needs of those living with CLL and SLL.

As a patient advocacy organization, we strive to ensure that patients have access to safe and effective treatment options by informing patients and caregivers about the therapeutic landscape, emphasizing the importance of clinical trials, supporting and building patient networks, engaging in research, and educating healthcare providers, patients, and their caregivers.

CLL Society strongly supports the need for early access to new therapies through accelerated approval while recognizing the need to ensure timely completion of any necessary studies to confirm clinical benefit. We appreciate that FDA seeks to ensure that the accelerated approval process remains available, and that it appropriately balances patient need for early access to promising treatments with FDA's mission to ensure the safety and efficacy of drugs marketed in the United States.

The accelerated approval mechanism has also been critical in facilitating the innovation and scientific progress that has driven hope for cancer patients and their families. The ability to utilize surrogate endpoints to gain approval is critical to ensuring there is a safe and expeditious path to early access to life-saving drugs and the resources available to complete studies that confirm clinical benefit.

Background: CLL and SLL

CLL is a chronic blood cancer of a type of white blood cell called the B-lymphocyte. In CLL there is a progressive accumulation of too many mature B-lymphocytes. CLL is the most common leukemia in adults in the United States, with around 18,000 cases diagnosed annually. Besides being a type of leukemia, it is also classified as a type of non-Hodgkin's Lymphoma (NHL). So CLL is both a leukemia and lymphoma. SLL is simply a different manifestation of the same disease and best understood as a different stage of CLL where there are not a significant number of cancer cells located within the bloodstream. When the cancer cells are only found in the lymph nodes it is called SLL. When the cancer is found in the bloodstream and possibly elsewhere, including the lymph nodes, it's called CLL.

CLL/SLL is very heterogeneous in that each person's disease type and the way the disease progresses can be extremely variable. Some individuals experience rapid deterioration due to having an aggressive form of the disease. Others have a less aggressive form of the disease and can expect to have a normal life expectancy without ever requiring treatment.

Although most CLL/SLL patients can expect a response to initial therapy, nearly all current treatment options are not considered curative. Most patients will experience one or more relapses during the course of their disease. It is also common for patients to either adjust their dosing due to side effects, take a "drug holiday," or completely discontinue a drug due to intolerance. Patients with relapsed/refractory disease or drug intolerance require individualized treatment planning based on prior therapies, prior response, the reason for discontinuation of previous therapy, comorbidities, biomarker characteristics, patient preference, and therapeutic goals.

Targeted therapies, such as BTK inhibitors and the BCL2 inhibitor known as venetoclax, offer substantial efficacy against CLL/SLL and have transformed care for those in our community affected by this disease. Patients now have more treatment options compared to ten years ago when the standard of care was chemoimmunotherapy, which did not necessarily work on all types of the disease, especially when used as second or later lines of therapy. Now, they can take an oral continuous BTK inhibitor, with or without a monoclonal antibody, until their disease progresses, or they develop intolerance. Alternatively, patients can choose a time-limited treatment approach that combines venetoclax (which is currently the only approved BCL-2 inhibitor) and a monoclonal antibody. The latter approach enables dose discontinuation until active monitoring reveals that the disease has again progressed to a degree that indicates a different treatment is needed.

The decision on which treatment should be used at any given time is extremely variable. Patients are living longer, meaning they will experience serial relapses over their lifespans, and many will be treated with all available agents at some point during the course of their disease. Patients who progress after both a BTK and BCL2 inhibitor fail them face a poor prognosis with few other approved treatment options besides PI3K inhibitors.

There is, therefore, a significant unmet need for new treatments and treatment combinations that improve the depth and duration of response, and/or are better tolerated, so that fewer of our patients experiencing serial relapses are without an approved therapeutic option. Unfortunately, the heterogeneity in disease burden and progression, combined with variability in initial and second-line treatment that patients receive in the real world, complicates research in CLL/SLL. Since CLL/SLL is not an ideal disease state from a research perspective, new treatments are often first approved for other types of cancer (many times through accelerated approval) and then later approved for CLL/SLL.

The accelerated approval pathway has generally worked as intended for CLL/SLL and has been vital in ensuring that CLL/SLL patients have timely access to promising new treatments, including:

- Venclexta (venetoclax), Abbvie
  - Accelerated approval 4/11/16
  - Treatment of patients with CLL with 17P deletion, as detected by an FDA approved test, who have received at least one prior therapy
  - Converted on 6/8/2018 (2 years, 2 months)
- Imbruvica (ibrutinib), Pharmacyclics
  - Accelerated approval 2/12/14
  - Treatment of patients with CLL who have received at least one prior therapy
  - Converted on 7/28/14 (5.5 months)
- Arzerra (ofatumumab), Novartis Pharmaceuticals ***(rarely used now)***
  - Accelerated approval 1/30/09
  - Treatment of patients with CLL refractory to fludarabine and alemtuzumab
  - Converted on 4/17/14 (5 years, 2.5 months)
- Campath (alemtuzumab) Genzyme ***(rarely used now)***
  - Accelerated approval 5/7/01
  - Treatment of B-cell CLL in patients who have been treated with alkylating agents and who have failed fludarabine therapy
  - Converted on 9/19/07 (6 years, 4 months)

The requirement that manufacturers complete confirmatory studies acts as an important guardrail against patient harm due to ineffective or unsafe treatments. Although we are unaware of any CLL/SLL accelerated approval treatments that have remained on the market for an extended period without completion of confirmatory studies, the application for Fludarabine Phosphate as monotherapy in CLL was withdrawn on December 31, 2011, approximately three years after its December 2008 accelerated approval.

FDA Recommendations: Randomized Controlled Clinical Trials to Support Accelerated Approval

CLL Society acknowledges that randomized controlled clinical trials (RCTs) are the recognized “gold standard” for determining whether a treatment is safe and effective. There is, unfortunately, an

inherent tension between the preference for RCTs and the accelerated approval requirement that a treatment address an unmet need in a serious/life-threatening condition. We urge FDA to examine the challenges associated with RCTs on a treatment and disease-specific basis and balance the Agency's interest in scientific "purity" with the underlying goal of the accelerated approval program—which is to ensure that patients with unmet needs have timely access to promising treatments. In CLL/SLL, challenges to conducting RCTs include:

- Newly diagnosed patients requiring treatment have FDA-approved treatments to induce a relatively durable remission. Patients will generally choose an effective, already-approved treatment, rather than be randomized to an investigational therapy making trials more difficult to accrue.

- Large study populations and observation over a significant time are required in order to demonstrate a treatment impact given the high variability in disease progression between newly treated patients and its often-indolent course.

- Patients without remaining viable treatment options are more interested in participating in clinical trials. For CLL/SLL, this means that studies of investigational treatments are more likely to include patients who have already had multiple relapses and have already exhausted all other approved treatment options.

- Challenges in designing and completing RCTs in patients who have relapsed after exhausting all other approved treatment options are challenging due to lack of a "control" standard of care that is effective and well tolerated.

- The relatively limited expected survival time for CLL/SLL patients who have relapsed after exhausting all other approved treatment options make the randomization to a placebo arm unethical. CLL Society recommends that all RCTs for CLL/SLL include a rescue or crossover contingency, even though these strategies may limit the validity of the data.

- Crossover is required due to ethical considerations in this vulnerable patient population. Data gleaned, therefore, may not capture the clinical benefit of the studied intervention.

CLL Society also urges FDA to clarify guidance, including:

- Providing greater detail on the acceptable clinical trial study design under the "one trial" approach outlined in FDA's discussion of RCTs, including whether FDA anticipates that the extended follow-up period after accelerated approval would be sufficient to enable confirmation of clinical benefit and, if not, what any other study design refinements FDA would consider acceptable.

- Outlining the options FDA would accept or propose if a standard of care control arm is not available.

- Identifying approaches to studies that incorporate real-world evidence and patient-reported outcomes, specifically for treatments that have been approved for a different indication as well as those that have not been previously approved.

- Providing a more detailed discussion on exactly how manufacturers can incorporate a patient-centered approach into their research and development programs.

FDA Recommendations: Single-Arm Trials to Support Accelerated Approval

As Sundeep Agrawal, MD noted in a recent JAMA Oncology article,[1] although RCTs are the preferred mechanism for evaluating treatments, single-arm trials "can provide substantial evidence of effectiveness and safety" when RCTs are infeasible. To date, FDA's approvals that have relied upon single-arm studies have reflected an interest in getting promising treatments to patients who urgently need them. 174 of the 176 approvals (116 accelerated; 60 traditional) based on single-arm studies were for locally advanced or metastatic disease. Most were for second-line or later treatment (49%), third-line or later treatment (20%), fourth-line or later treatment (4%), or fifth-line or later treatment (1%).[2] CLL Society urges FDA to preserve accelerated approval as a pragmatic mechanism that avoids delays in getting promising treatments to patients who need them.

We ask that FDA's final guidance include:

- Greater explanation on how FDA will evaluate feasibility of RCTs when considering acceptability of a single-arm trial that aligns with FDA's longstanding commitment to ensuring timely access to promising therapies.

- Clarification on whether or not FDA's guidance for industry entitled, "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision for Drug and Biological Products" applies to confirmatory studies of treatments granted accelerated approval based on single-arm trials.

- More information on FDA's expectations on timing for confirmatory studies, including the criteria the Agency will use in determining when those studies can be initiated after

[1] Sundeep Agrawal, MD, Agrawal S, Arora S, Amiri-Kordestani L, et al. Use of single-arm trials for US Food and Drug Administration drug approval in oncology, 2002–2021. *JAMA Oncol*. 2023; **9**(2): 266- 272. doi:10.1001/jamaoncol.2022.5985

[2] Nierengarten, M.B. (2023), Single-arm trials for US Food and Drug Administration cancer drug approvals. Cancer, 129: 1626-1626. https://doi.org/10.1002/cncr.34830

accelerated approval is granted and when approval might be withheld pending progress on confirmatory studies.

- Information on whether a "one study" concept could be applied to accelerated approvals based on single-arm studies.

- Consideration of the potential use of measurable residual disease (MRD) as a surrogate endpoint which is likely to reflect clinical benefit.
    - A recent review on use of MRD in CLL clinical trials[3] concluded that, "Measurable residual disease (MRD) status in chronic lymphocytic leukemia (CLL), assessed on and after treatment, correlates with increased progression-free and overall survival benefit."
    - There are a variety of techniques available for measuring MRD that cannot be directly compared across different trials. FDA guidance on including undetectable MRD reporting criteria would improve the utility of MRD data.
    - Greater use of MRD in clinical trials would facilitate its adoption in clinical practice and potentially enable CLL/SLL patients to maximize the benefits of their treatment regimens, while minimizing exposure to treatment toxicities.

Conclusion

CLL Society appreciates the opportunity to contribute the perspective of those living with CLL/SLL as FDA finalizes its guidance on clinical trials within the context of accelerated approval. We appreciate your consideration of our recommendations and welcome the opportunity to discuss our comments or the experience of CLL/SLL patients generally.

If you have any questions, please contact Saira Sultan, CLL Society's Director of Government Affairs & Public Policy at ssultan@cllsociety.org.

Sincerely,

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

[3] 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.