CLL SOCIETY

SUBMITTED ELECTRONICALLY

June 10, 2025

Mehmet Oz, MD
Administrator
Centers for Medicare & Medicaid Services
U.S. Department of Health and Human Services
7500 Security Blvd
Baltimore, MD 21244

Re: Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2026 Rates; Requirements for Quality Programs; and Other Policy Changes [CMS-1833-P]

Dear Administrator Oz:

CLL Society appreciates the opportunity to submit its comments on the Centers for Medicare & Medicaid Services' (CMS') Proposed Rule updating and refining the hospital inpatient prospective payment system (IPPS). We remain committed to working with the Administration as it strives to deliver on its goals of improving the health and lives of America's elderly and disabled citizens, including Medicare beneficiaries living with chronic, incurable, life-threatening conditions such as chronic lymphocytic leukemia and small lymphocytic lymphoma (collectively referred to as CLL.

Our organization is the largest nonprofit focused exclusively on the unmet needs of patients living with CLL. We strive to fulfill our primary mission of ensuring that patients have access to safe and effective treatment options by informing patients and caregivers about the rapidly changing therapeutic landscape and the importance of clinical trials, supporting and building patient networks, supporting and engaging in research, and educating providers and patients. As an organization, we also recognize that the healthcare landscape extends beyond science, clinical care, and patient support.

The Medicare program is critical for our patients given that the average age for individuals newly diagnosed with CLL is 65-70 years. Although CLL is currently incurable, the advances in therapeutic options over the past decade have enabled patients to live longer, healthier lives. This means that

even patients diagnosed at younger ages can expect to rely on Medicare as they age and move through the set of existing treatment options.

Our comments provide a brief background on CLL, unmet needs in treating patients as their cancer progresses, and challenges research sponsors face in developing new treatment options. We urge CMS to recognize the importance of ensuring patient access to all treatment options and focus primarily on the Proposed Rule's provisions related to New Technology Add-On Payments (NTAPs) and application of the NTAP criteria to CLL.

Background

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 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 different stage of CLL where there are not a significant number of cancer cells yet located in the bloodstream. When the cancer is only found in the lymph nodes it is classified as SLL. When it is found in the bloodstream and possibly elsewhere, including lymph nodes, it is referred to as CLL.

CLL is extremely heterogeneous, and each person's disease course and progression can be extremely variable. Some individuals have an aggressive form of the disease, experience rapid deterioration, and may not survive beyond two years. Individuals with a less aggressive form of CLL may never need treatment and can expect to have a normal life expectancy. It is common for clinicians to recommend that newly diagnosed CLL patients be actively monitored without treatment until CLL symptoms emerge.

Targeted therapies such as BTK inhibitors and the BCL2 inhibitor known as venetoclax offer substantial efficacy against CLL/SLL and have transformed care for our patient community. Patients now have more treatment options compared to just years ago when the standard of care was chemoimmunotherapy. Although most CLL patients can expect a response to their initial therapy, most will experience one or more relapses during the course of their disease. In addition to treatment changes due to relapse, many patients are forced to change treatments, take a "drug holiday," or adjust dosing due to drug intolerance. Patients with relapsed or refractory disease (or treatment intolerance) require individualized treatment plans based on prior therapies, prior

response, the reason for discontinuation of previous therapy, comorbidities, biomarker characteristics, patient preference, and therapeutic goals.

The unfortunate reality for our patients is that CLL remains incurable despite significant progress in treatments. The set of treatment options for CLL are not interchangeable alternatives for individual patients as they move through treatment, response, relapses, and progression. Over time, patients can progress through each available treatment option and be left with the poor prognosis associated with cancer progression. There is, therefore, a significant unmet need for new treatments and treatment combinations that can improve the depth and duration of response, and/or are better tolerated, so that patients experiencing serial relapses are not left without an approved therapeutic option.

Unfortunately, the heterogeneity in disease burden, biomarker characteristics, comorbidities, and progression, combined with the real-world variability in initial and subsequent-line treatments that patients receive complicates research in relapsed/refractory CLL. For example, designing and completing randomized, controlled clinical trials (RCTs) in patients who have relapsed after exhausting all other approved treatment options is a challenge due to lack of a "control" standard of care that is effective and well tolerated. Moreover, the limited expected survival time for CLL patients who have relapsed after exhausting all other approved treatment options make the randomization to a placebo arm unethical. Although crossover can marginally mitigate this issue, any data gleaned can fail to fully capture clinical benefit of the studied intervention.

New Technology Add-on Payment (NTAP) for BREYANZI®

CLL Society appreciates CMS' careful review of the submission requesting the Agency assign an NTAP for BREYANZI® administration in the hospital inpatient setting. Throughout the stakeholder engagement events associated with the Medicare Drug Price Negotiation Program (MDPNP), CMS has heard from CLL patients. Each patient's experience with CLL, including the treatments they have received and the impact their cancer has on their daily lives, is unique. Common threads, however, emerged in CMS' discussions during the two negotiation cycles – (1) patients need access to all available options; (2) the available lines of treatment for CLL are best viewed as options that can be utilized first, second, etc., based on clinical judgment and shared decision making rather than as a pure choice between one and another; and (3) patients have significant concerns that they might utilize, and progress through, each available line of therapy and be left without an effective treatment.

BREYANZI® Meets the "Newness" Criterion for an NTAP

In discussing the "newness" requirement as applied to BREYANZI® CMS acknowledged the manufacturer's argument that it is the only CAR-T approved for relapsed/refractory CLL. The Agency, however, expressed the concern that:

> [T]here are other existing (non-CAR T-cell) treatments for patients with R/R CLL/SLL who have received two or more prior LOTs including a BTKi and a BCL2i, such as noncovalent BTKis, PI3Kis, or allogeneic HSCT, and therefore, we question whether BREYANZI® treats a different type of disease or patient population than existing technologies."

CLL Society urges CMS to place significant weight on the "newness" of an FDA-approved CAR-T option in treating CLL. This is not the case of a new product joining an existing class of therapies for relapsed/refractory CLL or a new option that might be chosen to the exclusion of other treatments approved for this CLL subpopulation. CMS has heard from CLL patients who have exhausted (or are not appropriate candidates for) all the treatments CMS discussed as existing treatments for the same addressable population. The nuanced point we urge CMS to consider is that whether a patient receives BREYANZI® as their first treatment after progressing on two or more lines of therapy or after a noncovalent BTKi and/or a PI3Ki, it is added to the set of tools available to address the significant unmet need for additional lines of therapy in CLL. Any incremental gain in survival is "new" in that it is added to that achieved by both previous and subsequent treatments.

BREYANZI® Meets the "Substantial Improvement" Criterion for an NTAP

CMS expressed several concerns on whether BREYANZI® represents a substantial improvement for relapsed/refractory CLL patients:

- CMS asked whether there is a particular subpopulation "for which BREYANZI® offers a treatment option that is unresponsive to or ineligible for other existing therapies." The Agency specifically noted that "being the first CAR T-cell therapy for a particular indication relates to mechanism of action and is not relevant to the demonstration of substantial clinical improvement."

  - As detailed more fully above, part of the clinical improvement BREYANZI® offers by virtue of being the only approved CAR-T option is the additional survival from a new line of treatment for patients with few available options. Unlike a second generation covalent BTKi, which is unlikely to be effective after progression on another treatment in its class, BREYANZI® and its incremental benefit are best viewed as additions to that accrued by both prior and subsequent treatments.

- CMS also relayed its concern that the pivotal study for BREYANZI® was a single-arm trial.
  - 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.
  - A 2023 article assessing the use of single-arm studies noted that 174 of the 176 approvals identified (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] The FDA's acceptance of single-arm studies reflects both the challenges research sponsors face in designing RCTs in these patient populations and FDA's interest in getting promising treatments to patients who need them.

- CMS similarly questioned how BREYANZI® "represents a substantial clinical improvement, given the higher values with respect to the existing therapies for particular outcome results."
  - During CMS' MDPNP Town Hall for IPAY 2027, CLL researchers and clinician experts emphasized that the treatment goal for CLL is to prolong survival without compromising quality of life. Patients may remain in a "wait and see" period after diagnosis and may delay second and subsequent lines of treatment to delay or avoid progression through available treatments. The "time to next treatment" endpoint,

[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

therefore, is highly relevant to CLL. According to the manufacturer of BREYANZI® "median time to next therapy was considerably longer than that observed in a real-world study of patients with CLL/SLL after prior treatment with a BTKi and B-cell lymphoma 2 inhibitors (6.6 months [95 percent CI, 3.6–10.a]." From both a patient and clinician perspective, this is an important clinical improvement for this patient population.

- Clinicians and researchers also noted that patients tend to prefer treatment regimens that are of fixed duration and offer remission with shorter times on treatment. The option of receiving a course of therapy through a single infusion is an important BREYANCE® benefit.
- Patients receiving BREYANCE® or Jaypirca are not choosing between the median PFS of 18/11.9 months for BREYANCE® and the 16.9-month median PFS for Jaypirca®. As detailed above, the decision is one of sequencing rather than picking one to the exclusion of another. The incremental benefit in terms of PFS and/or overall survival is additive and significant.

CLL Society urges CMS to assign an NTAP for BREYANCE® as a new line of treatment addressing unmet medical needs and offering significant improvement in terms of net gain in PFS.

Conclusion

CLL Society appreciates the opportunity to submit its comments to the Proposed Rule. If you have any questions, please feel free to contact me or Saira Sultan, CLL Society's Director of Government Affairs and Policy at ssultan@cllsociety.org

Sincerely,

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