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June 15, 2018

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RE: National Coverage Analysis (NCA) Tracking Sheet for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N)

Dear Ms. Syrek Jensen and Drs. Szarama and Paserchia:

The American Society of Hematology (ASH) is pleased to offer comments on the National Coverage Analysis (NCA) for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers.

ASH represents over 17,000 clinicians and scientists worldwide, who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sick cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists were pioneers in demonstrating the potential of treating various hematologic diseases; and we continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients in diverse settings including teaching and community hospitals, as well as private practice.

CAR T-cell therapy is a newly approved treatment that is truly incomparable to existing forms of treatment for the approved indications (acute lymphoblastic leukemia and non-Hodgkin lymphoma). Patients receiving this therapy have typically exhausted all other treatment options, including chemotherapy, radiation, and stem cell transplant. Successful treatment with CAR T-cell therapy improves quality of life and increases survival for these patients. There are currently over 400 clinical trials of CAR T-cell therapies testing the effectiveness of these therapies across a wide variety of hematological and solid tumor cancers.

CAR T-cell therapy is the first of many innovative therapies to be approved for the patients treated by hematologists. It is critical that the Centers for Medicare and Medicaid Services (CMS) consider the precedent it is setting in this coverage process. Given the need for innovative coverage and reimbursement policy for this novel therapy, ASH is currently working closely with CMS as it develops a payment policy for CAR T-cell therapy through the Inpatient Prospective Payment System proposed rule and the Hospital Outpatient Prospective Payment System proposed rule.

First and foremost, CMS must clearly articulate to the Medicare Administrative Contractors (MACs) and Medicare Advantage (MA) insurers that they should continue to cover eligible beneficiaries until a final policy is released. Without this guidance, ASH has strong reason to believe that patients will not have access to this therapy based on what has occurred during previous coverage analyses, such as during the national coverage analysis for hematopoietic cell transplantation. Again, patients receiving CAR T-cell therapy are the sickest of the sick and have typically exhausted all other treatment options, including chemotherapy, radiation, or stem cell transplant. These patients cannot afford to delay treatment.

We also urge CMS to be cognizant of the impact the final coverage policy will have not only on CAR T-cell therapies, but on other innovative treatments, such as gene therapies for sickle cell disease and hemophilia, currently in the pipeline. The Society is working closely with the American Society of Blood and Marrow Transplantation (ASBMT) as well as other provider and patient groups and is available to work closely with CMS during this coverage review. We welcome the opportunity to help the agency identify experts in the field as well as point to the latest scientific literature.

Outlined below is information on the process of CAR T-cell therapy and on the associated adverse events. Ultimately, ASH does not believe initiating a National Coverage Determination (NCD) is appropriate at this point in time and we outline below why CMS should not proceed with this coverage analysis.

Background

Process of CAR T-cell Therapy

CAR T-cell therapy is currently approved for the treatment of patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. It is also approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Patients eligible for CAR T-cell therapy have typically exhausted all other treatment options, including chemotherapy, radiation, or stem cell transplant. Twenty to 50% of patients with DLBCL, the most common subtype of non-Hodgkin lymphoma, will be refractory to the standard treatment regimen or will relapse after achieving complete response. Even among patients with relapsed or refractory DLBCL who respond to salvage therapy and are able to undergo autologous stem cell transplantation (ASCT), about 50% will ultimately relapse after transplantation. The prognosis for these patients is poor, especially for those who have high-risk factors. Thus, most patients with refractory DLBCL have no curative treatment options.[1] CAR T-cell therapy truly is lifesaving for eligible patients.

Currently, each treatment is individual to the patient whose T-cells are genetically engineered to target a specific tumor-associated antigen. Cells are collected from patients via leukapheresis and then delivered to the manufacturer where the molecularly engineered receptors are inserted into the cells and then reproduced, a process that takes weeks. The new CAR T-cells are then returned to the hospital where they are infused into the patient. Most patients suffer from serious adverse events in the days following the infusion that may require

[1] Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood October 2017, 130(16) 1800-1808.

prolonged hospitals stays. The therapy can have tremendous benefits, as we have described, but requires very close oversight by the treating physician during and following the treatment.

Adverse Events

In the NCA, CMS notes the common incidence of adverse events for patients receiving CAR T-cell therapy. It is important to note that these adverse events are usually manageable but do increase the cost of this therapy as patients are typically required to be admitted as inpatients for treatment. The two most common adverse events are cytokine-release syndrome (CRS) and CAR T-cell-related encephalopathy syndrome (CRES). CRS, triggered by the T-cells engaging with the tumor cells, is the most common adverse event experienced by about 70 percent to 90 percent of patients. It manifests as a very severe case of the flu with high fever, fatigue and body aches, and can affect any organ system in the body. The onset of CRS usually occurs within the first week after CAR T-cell therapy, and typically peaks within one to two weeks of cell administration. In order to closely monitor for CRS, it is recommended that patients remain hospitalized for at least seven days after CAR T-cell infusion.[2] With CRES, patients can become confused and disoriented, experience language disturbance and impaired handwriting, and sometimes may not be able to speak at all for a few days.[3] This condition can also be managed and patients regain all of their neurological functions. As mentioned, these adverse events are common, yet manageable, but often require monitoring and treatment in the intensive-care setting. Appropriate management of both CRS and CRES depends on the severity. CMS must consider these side effects, the care required, and the costs associated in developing an appropriate coverage policy.

It is important to note that the Food and Drug Administration (FDA) has gone to great lengths to ensure that both the facilities and providers administering CAR T-cell therapy are qualified to do so safely. As noted in the NCA, both FDA-approved CAR T-cell therapies were approved with a Risk Evaluation and Mitigation Strategy (REMS), designed to mitigate the risks of CRS and neurologic toxicities. The FDA requires that providers are extensively trained, certified for competence and that they have on-site, immediate access to tocilizumab, which is FDA-approved to treat CRS. Additionally, the manufacturers require hospitals to be accredited by the Foundation for Accreditation in Cellular Therapy (FACT).

Concerns

National CAR T-cell Therapy Coverage Determination is Premature

The Society strongly recommends that CMS not proceed with a NCD at this time for the reasons we have outlined below.

<u>CAR T-cell Therapy is an Evolving Area of Medicine</u>

CAR T-cell therapy is an evolving area of medicine. With over 400 clinical trials in process, it is impossible to know what the ultimate applications of this therapy will be. The current approved applications to hematologic malignancies are just the first conditions to which CAR T-cell therapy will apply. The next CAR T-cell therapy targeting multiple myeloma is expected to be approved in 2019. There are numerous clinical trials underway for both blood cancers, including multiple myeloma and acute myeloid leukemia, and solid tumors, including ovarian, breast, pediatric neuroblastoma, and lung cancer.[3] Besides the likelihood that CAR T-cell therapy will be more broadly available within the next decade, ASH also wants the agency to understand that the science and its clinical application may change as well. Currently, CAR T-cell therapy is an incredibly personalized process, requiring products to be created individually for each patient. However, clinical trials are underway to develop allogeneic universal or "off-the-shelf" CAR T-cells.[4] CMS can find more information about the current pipeline here. Given the robust pipeline and the rapidly evolving science, a coverage determination at this time

[2] Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy – assessment and management of toxicities. *Nature Reviews Clinical Oncology* 15, 47-62 (2018).

[3] Juno Therapeutics. A Celgene Company. Our Pipeline. https://www.junotherapeutics.com/our-pipeline/

[4] Kenderian SS, Porter DL, Gill S. Chimeric Antigen Receptor T Cells and Hematopoietic Cell Transplantation: How Not to Put the CART Before the Horse. *Biology of Blood and Marrow Transplantation* 23 (2017) 235-246.

could potentially preclude coverage for certain conditions, which could have an unintended consequence of stifling innovation in this innovative area of research.

Concerns Related to Patient Access to Care

Additionally, ASH urges CMS to consider how this process and a final NCD will impact patient access to care. There are very few patients currently eligible for CAR T-cell therapy and as mentioned, these patients have exhausted all other courses of treatment. A NCD that restricts coverage for certain conditions has the potential to limit access to a life-saving therapy for patients. Allowing the Medicare Administrative Contractors (MACs) to address coverage at the local level as the science matures will help ensure patients, who have exhausted all other options, have continued access to this therapy. It is nearly impossible to get an accurate assessment of the applicability of this therapy given the rapidly evolving science and the hundreds of open clinical trials. It is standard practice for CMS to issue NCDs for well-established treatments, such as apheresis and PET scans for lymphoma, rather than a therapy that is still new and evolving, such as CAR T-cell therapy. It is too early to determine which conditions will be successfully treated by CAR T-cell therapy or to know the patient population that will be eligible once the science is more mature. This population will be continually changing over the next few years as more and more indications are approved.

Complex Nature of the National Coverage Process

The complex nature of the national coverage process, including the process of revising already existing NCDs, heightens our concerns about stifling innovation and limiting patient access. The science and practice of CAR T-cell therapy are immature at this point, and whatever coverage policy CMS finalizes may require frequent revisions to keep up with the science and its clinical translation. ASH members, both researchers and clinicians alike, feel it is premature to issue a NCD that many stakeholders agree will need to be reopened as new therapies and indications are approved, potentially as soon as 2019. United Healthcare states that "we believe there is an industry-wide need for at National Coverage Determination (NCD) to ensure a level playing field across Medicare Advantage plans." ASH respectfully urges CMS to address United Healthcare's concerns about MA plans outside of the national coverage process. Acceptance of an NCA request on this basis would set precedent that NCDs are a vehicle of opportunity for MA plans and driven by cost of care, rather than the need for a CMS determination to enable beneficiary access. Again, ASH recognizes the concern raised by United Healthcare, but recommends that CMS work closely with the insurers and other stakeholders to formulate a path to coverage and payment that is more flexible.

Conclusion

We appreciate the opportunity to comment on this NCA. ASH urges CMS not to proceed with this coverage analysis at this time because of the potential to stifle innovation and patient access to care. A NCD will be more appropriate once this area of medicine is more mature. For your reference, ASH has compiled a summary of the current scientific literature on CAR-T therapy. Please find that in Appendix A, sent separately to **CAGinquiries@cms.hhs.gov**.

ASH is available to serve as a resource, providing additional scientific literature and experts in the field as needed. If you have any questions or require additional information, please contact Leslie Brady, ASH Policy and Practice Manager, at lbrady@hematology.org or 202-292-0264.

Sincerely,

Alexis Thompson, MD, MPH
President