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RE: **Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers**
CAG-00451N

Ms. Syrek Jensen and Drs. Szarama and Paserchia:

The American Society for Blood and Marrow Transplantation (ASBMT), the Center for International Bone and Marrow Transplant Research (CIBMTR) and the National Marrow Donor Program/Be the Match (NMDP) are grateful for the opportunity to submit comments in relation to the Centers for Medicare & Medicaid Services' (CMS') recently-announced decision to examine coverage for Chimeric Antigen Receptor (CAR) T-Cell therapies (CAR-T). Each of our organizations represents a different aspect of the cellular therapy community and we appreciate the collaborative history we have with CMS on issues related to cell therapy and hematopoietic cell transplantation (HCT) as the Agency strives to serve the needs of Medicare and Medicaid beneficiaries within the context of an evolving standard of cancer care.

The clinical teams in our community have spent considerable time over the last decade focusing on research involving antineoplastic immunotherapy. We were elated that two CAR-T therapies became FDA-approved this past year, though our enthusiasm was tempered by an understanding of the very real reimbursement hurdles associated with incorporating a costly innovative technology into the inpatient prospective payment system. As our programs began navigating the difficult reimbursement challenges, the welcome exception to the complexity we faced was coverage - we anticipated that Medicare beneficiaries would be afforded consistent access to CAR-T as a FDA-approved anti-cancer biologic. This theory was borne out in the months following approval; our organizations have received no reports of denials by Part A/B Medicare Administrative Contractors (MACS) for the approved CAR-T therapies.

We were both surprised and disappointed with CMS' decision to inject uncertainty into Medicare beneficiaries by opening the national coverage analysis (NCA) process. ***We do not support the establishment of a National Coverage Determination (NCD), as***

we anticipate it will cause significant and ongoing barriers to providing current and future CAR-T therapies to beneficiaries in need of breakthrough treatments. The comments provided in the remainder of this letter reflect our collective commitment to ensuring that cancer patients served by the Medicare program retain access to medically accepted cancer treatments, including CAR-T.

I. We urge CMS to issue immediate clarification to providers, Medicare Administrative Contractors (MACs) and Medicare Advantage (MA) Plans reflecting that Yescarta® (axicabtagene ciloleucel) and Kymriah™ (tisagenlecleucel) are covered for their medically-accepted uses.

The NCA request letter submitted by UnitedHealthcare (UHC) implied that an NCD is needed for Medicare to cover Kymriah and Yescarta. Specifically, UHC requested an NCD to *"clarify the circumstances under which the therapies will be covered and to create consistent patient access to the therapies across the country and financial sustainability in the Medicare Advantage program with regard to these therapies.*" Additionally, UHC stated: *"Absent a National Coverage Determination, providers and beneficiaries could get inconsistent treatment decisions and inconsistent MAC decisions, leading to inconsistent coverage determinations, depending on a beneficiary's location."*

Our organizations strongly believe that the circumstances under which CAR T anti-cancer therapies will be covered by Medicare are already known – Medicare covers medically accepted uses, i.e., FDA-approved indications and compendia-supported off-label uses. Due to CMS' long-standing policy of providing coverage of anti-cancer therapies without further restrictions, based on Section 1801 of the Social Security Act,[1] the Part A/B MACs have already provided consistent coverage for Yescarta and Kymriah for their FDA-approved indications and we have no current reason to believe this will not continue. Patient-specific decisions on medically accepted uses are inherently within the practice of medicine.

While not a part of the NCA process, we wish to raise a general concern about making the NCA process a vehicle to address the financial stability of the Medicare Advantage program. On the surface, the request letter appears to articulate concern with the potential for inconsistent coverage across MACs. However, as inconsistent coverage is purely hypothetical and not supported by program experience thus far, it appears the primary reason for the request is financial relief, as set out in footnote 1 of the request letter. We are aware of the statutory and regulatory provisions cited by United and suggest that the best way to address the associated financial concerns is by modifying MA plan payment policies – not through the NCD process. The introduction of cell and gene-based therapies will continue to challenge the MA plans, who are currently serving beneficiaries appropriately by providing access to therapies as they are approved. To create a situation in which the NCA process is initiated for each therapy whose

[1] Sec. 1801. [42 U.S.C. 1395] Nothing in this title shall be construed to authorize any Federal officer or employee to exercise any supervision or control over the practice of medicine or the manner in which medical services are provided, or over the selection, tenure, or compensation of any officer or employee of any institution, agency, or person providing health services; or to exercise any supervision or control over the administration or operation of any such institution, agency, or person.

cost is over a certain threshold will exhaust the resources of all stakeholders and potentially delay access to therapies for which there is no useful alternative. We ask that you send this comment to the appropriate component of the Center for Medicare (CM) for their consideration.

We are concerned that initiating the NCA process will create confusion regarding the current coverage status of CAR-T. We request that CMS issue clear and public guidance to MACs that they should continue to cover CAR-T therapies for their FDA approved and compendial supported indications. Similarly, we anticipate that some providers and patient advocacy organizations may express support for the NCD process or decline to comment due to the concern that without an NCD, CAR-T is not a medically-accepted treatment or that an NCD will alleviate the financial burdens providers currently face providing CAR-T within the MS-DRG system.

The stark reality is that patients whose clinical status meets the approved label parameters have no alternative treatment options and a very limited life-expectancy if they are unable to receive CAR-T. Unfortunately, it is likely that most of these individuals will die or progress past being a candidate for treatment while awaiting resolution of the current NCA process.

For patients and their families, a clarification from CMS is particularly important so that they do not face the extremely unfortunate situations in which providers decline to offer a treatment during the decision process or require a patient's agreement to self-pay her/his own costs in the event of a claim denial.

We urge CMS to make the necessary announcements and/or clarifications so that all stakeholders have a clear understanding that the Agency's decision to initiate the coverage process does not change the existing coverage requirements for medically accepted uses of Kymriah and Yescarta. An example of a simply-worded clarification is:

"CMS' initiation of the NCD process does not modify the existing requirement for coverage of these anticancer treatments for medically accepted uses, i.e., FDA-approved indications and compendia-supported uses."

II. Decisions on whether individual benefit may outweigh the associated risks of medically-accepted therapy should be made within the patient-physician relationship.

In the nearly two decades since CMS implemented its formal process for making national coverage decisions, Medicare has rarely moved toward restricting medically-accepted uses of anti-cancer drugs. CMS has consistently adhered to the principle that medical decisions involving medically accepted uses of anti-cancer treatments are firmly within the practice of medicine. We ask that CMS continue to maintain its longstanding commitment to noninterference with the practice of medicine, so that the promise of immunotherapy can be realized.

Patients falling within the indications for current CAR-T therapies represent an especially compelling case for individual, patient-directed decisions within the patient-physician relationship. CAR-T is a personalized therapy that offers a distinct approach to fighting cancer for a group of patients that have no other potentially curative options. Palliation-intended chemotherapy regimens are the only realistic alternative treatment for the indicated population of relapsed/refractory lymphoma patients. Both CAR-T products were approved based upon single-arm studies largely because the patients in the target indications had few, if any, treatment options available and their life expectancy without treatment was exceedingly short. The decision on whether to accept the risk of potentially severe, and even life-threatening, treatment side effects to have a chance at remission or cure belongs to the individual patient.

On the NCA tracking sheet, CMS noted the very common incidence of adverse events for individuals treated with CAR-T. Additionally, CMS expressed concerns that the clinical trials supporting FDA approval of Yescarta and Kymriah did not include a sufficient number of individuals over age 65 for CMS to assess the potential benefit to Medicare patients.

With respect to the safety concerns, FDA has placed significant constraints on distribution of these products to ensure that facilities administering CAR-T are qualified to do so safely. The companies require certification that a patient meets the labeled indication before they manufacture the product, which eliminates the current potential for off-label use outside of authorized clinical trials. The Risk Evaluation and Mitigation Strategies (REMS) system for both products were designed to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by ensuring that providers are extensively trained, certified for competence and that they have on-site, immediate access to tocilizumab. We note that both manufacturers have publicly stated that a limited number of facilities will be approved for participation in the cell collection and drug infusion process for CAR-T during the first several years due to the focus on site selection and certification.

Both manufacturers also require hospitals to be accredited by the Foundation for Accreditation in Cellular Therapy (FACT), which provides extensive standards for cell therapy facilities. Reports from ASBMT Administrative Directors indicate that the currently certified CAR-T centers are taking the potential side effects very seriously; programs report training an extensive number of staff, including several hundred pediatric and adult physicians and any providers and support staff that may come in contact with a patient before or after their stay (pharmacy, neurology, MICU/NICU, advance practice professionals, nursing, administrative staff and any individuals that could come into contact with a patient in the emergency department). Furthermore, the ASBMT is leading a national consensus project to standardize grading and management of CAR-T toxicity. This effort will bring together several stakeholders including experts in the immunotherapy/CAR-T field, transplant clinicians, pharmaceutical companies, CIBMTR, FDA, NIH and CMS. An in-person meeting is scheduled on June 21-22nd, 2018 in Washington, DC, and recommendations from this task force will be published in our society's peer-reviewed journal, *Biology for Blood and Marrow Transplantation*, shortly thereafter.

In addition to the distribution constraints, FDA has required post-marketing studies of both Kymriah and Yescarta. These 15-year observational studies require manufacturers of these

CAR-T products to assess long-term safety by following at least 1500 patients for 15 years after product administration. The primary endpoint of the study is time to development of secondary malignancies, while other endpoints include: rate of overall survival (OS), causes of death, time to relapse or progression of the primary malignancy and severity, time to onset, management, and clinical outcome of cytokine release syndrome. The CIBMTR will be collecting long-term data on patients receiving cellular therapy in the United States[2].

Given the intensive and specific focus on safety by FDA, the manufacturers, our organizations and the treatment centers and physicians themselves, the role for NCD in evaluating the safety of these products appears unfounded.

If CMS were to issue a Coverage with Evidence Development (CED) decision for CAR-T at the end of the NCA process, hospitals would be required to institute additional administrative processes and patient consents on top of those that will already be required for post-market studies and CIBMTR reporting. Adding repetitive layers of administrative processes through NCD/CED could cause some hospitals to opt-out of provision of the therapies under CED due to the time and expense associated with the process.

Similarly, while each of our organizations strongly believes that clinical trial participation can be the best option for many patients, we are concerned that placing a study-participation or data collection condition to coverage of the only potentially curative treatment option in individuals with an exceedingly short life expectancy could be problematic or viewed as coercion. If some centers opt-out of the CED for resource reasons, patients will face additional delays and personal expense in seeking out a treatment location that has decided to participate. Even for those centers that elect to participate, there will be a time gap during which the studies' administrative structure is built out, including approval through each center's Institutional Review Board (IRB) and site registration process; these are delays that patients eligible for these therapies have already borne during the approval-related clinical trial process and should not be subject to again. Our organizations believe that the distinguishing factors for CAR-T – a medically accepted and FDA-approved use of the only non-palliative treatment option for patients with a very limited untreated life expectancy – differentiate CAR-T from other treatments for which CMS has pursued CED. We firmly believe that any concerns that CMS might have with respect to data collection would be better managed through direct engagement with stakeholders than the national coverage process.

Next, we acknowledge the concern that a limited number of clinical trial participants over the age of 65 could create a level of uncertainty about the therapeutic benefit of CAR-T for this subpopulation Both product labels reflect the fact that approvals were based on clinical trials that did not include at least 100 individuals over age 65, but the geriatric use information provided on FDA-approved labeling is not a limitation on approved, medically accepted indications. It is intended to ensure that clinicians and their patients have the information necessary to make well-informed decisions as they assess the risks and potential benefits of a specific treatment for a particular individual.

[2] http://www.cibmtr.org/About/WhatWeDo/Pages/index.aspx

The facilities currently certified or authorized to offer CAR-T are among the nation's top cancer care providers and, due to the average age of diagnosis of most individuals with cancer, are very experienced in providing treatment therapies to seniors and Medicare beneficiaries. These facilities are early adopters of newly-approved therapies and often participate in clinical trial research as lead or supporting sites. Clinicians and facilities with expertise in treating cancer are accustomed to the duality of working with new treatments as part of the practice of medicine while keeping in mind the unique characteristics and needs of individuals over the age of 65.

In the NCA, CMS states that "Initial studies were also confined to the inpatient hospital setting." While Kite did initially restrict administration of Yescarta during its clinical trials, the current package insert does not restrict provision to the inpatient setting. For the Novartis product (Kymriah) approximately 25% of the pediatric participants in clinical trials were treated in an outpatient hospital setting and approximately 20% of adult patients were infused in the outpatient setting and remained outpatient for 3 or more days[3]. While we have been very clear in our communications with CMS that the vast majority of CAR-T patients are currently being treated in the inpatient setting, we do expect that some proportion of CAR-T administration will shift to outpatient care when providers feel they can safely care for and monitor patients in that setting. As indications and/or product safety profiles change with time, providers need flexibility in terms of where they choose to offer CAR-T. We reiterate that these decisions should be made between the patient and the provider based on the patient's health status and the provider's unique health system capabilities. CMS should not issue a National Coverage Determination to study or limit site of care appropriateness.

III. Creating an NCD for CAR-T will create barriers to patient access as new uses and product options are introduced.

The approval of Kymriah and Yescarta represents a profound change in how we approach cancer treatment for patients who previously had little hope of achieving remission. As CMS is likely aware, a substantial number of additional CAR-T or immune effector cell-based products are on the horizon for relatively near-term market entry. We would also expect that various subtypes of immunotherapy will evolve and become the standard of care for many cancers. A very limited number of the emerging therapies will fit under any NCD structures developed based on the current products, which would lead to the creation of an extensive, ongoing and potentially overlapping set of NCDs or CEDs to be navigated by providers and patients, which will most likely lag substantially behind the pace of therapeutic evolution.

Summary

In summary, we are concerned that the NCD that CMS is contemplating would limit beneficiary access therapies evaluated as safe and effective by FDA. We ask that CMS clarify the scope of

[3] B-ALL Trial information: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566168.pdf; JULIET (adult) trial information: https://www.novartis.com/news/media-releases/primary-analysis-results-from-novartis-pivotal-juliet-trial-show-kymriahtm-tisagenlecleucel-sustained-complete-responses-six-months-adults-rr-dlbcl-difficult

its intended CAR-T evaluation so that all stakeholders have an opportunity for meaningful participation.

We ask that the Agency ensure that stakeholders understand that:

- Kymriah and Yescarta are medically accepted treatments for on-label uses and compendia-supported uses. An NCD is not needed to "create" coverage;
- NCDs that apply to existing products and indications would prevent coverage for any other product or new use of current product until a reconsideration was completed;
- Requests for modification to an NCD would trigger the reconsideration or NCA process, which takes between 9-12 months to complete once initiated;
- Issuance of CED can place further coverage restrictions that would make it very difficult for some beneficiaries to gain access to CAR-T for the indication under review. Changes to study design, patient eligibility or data collection cannot be made without re-engaging the NCD process through a reconsideration and/or development, submission and approval of a new study; and
- The ordinary claims-based appeal processes available when a MAC would deny a claim is not available for NCD-based coverage denials. Beneficiaries would have to directly challenge the NCD and submit evidence showing that the NCD is inappropriate.

We understand the rationale and incentives that have triggered UHC's request for NCD and we acknowledge the high cost of including CAR-T within the current MA contracts with CMS. Collectively, our organizations do not endorse the price of these therapies. However, we reiterate our concerns with using NCD to resolve a financial contracting issue specific to the Medicare Advantage plans, as it has such strong potential to hinder access to CAR-T for those that need the therapy. We ask that CMS move quickly to provide clarification on the current requirements for coverage of medically accepted uses of CAR-T, as well as the intended scope and implications of the recently-initiated CAR-T NCD process.

For questions related to this letter, please contact:
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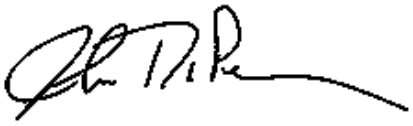

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About ASBMT
The American Society for Blood and Marrow Transplantation (ASBMT) is a professional membership association of more than 2,200 physicians, scientists and other healthcare professionals promoting blood and marrow transplantation and cellular therapy through research, education, scholarly publication and clinical standards. The ASBMT is dedicated to improving the application and success of hematopoietic cell transplants and other cellular therapies, such as CAR-T.

About CIBMTR
The CIBMTR® (Center for International Blood and Marrow Transplant Research) is a research collaboration between the National Marrow Donor Program® (NMDP)/Be The Match® and the Medical College of Wisconsin (MCW). The CIBMTR collaborates with the global scientific community to advance cellular therapy worldwide to increase survival and enrich quality of life for patients. The CIBMTR facilitates critical observational and interventional research through scientific and statistical expertise, a large network of centers, and a unique and extensive clinical outcomes database.

About National Marrow Donor Program/Be The Match
For people with life-threatening blood cancers such as leukemia and lymphoma, a cure exists. The National Marrow Donor Program(NMDP)/Be The Match connects patients with their donor match for a life-saving marrow or umbilical cord blood transplant, and works to identify and eliminate financial and other barriers faced by these patients. NMDP also provides patients and their families one-on-one support, education, and guidance before, during and after transplant.