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June 10, 2017

Administrator Seema Verma
Centers for Medicare & Medicaid Services,
Department of Health and Human Services,
CMS-1677-P 4; Mail Stop C4-26-05,
7500 Security Boulevard,
Baltimore, MD 21244-1850.

Administrator Verma:

The American Society for Blood and Marrow Transplantation (ASBMT) is an international professional membership association of more than 2,200 physicians, scientists and other healthcare professionals promoting blood and marrow transplantation and cellular therapy research, education, scholarly publication and clinical standards. ASBMT is dedicated to improving the application and success of blood and marrow transplantation, and ensuring access to all patients who need hematopoietic cell transplants.

Blood and marrow transplantation has several pseudonyms, including bone marrow transplantation, stem cell transplantation, cord blood transplantation, peripheral blood stem cell transplantation and hematopoietic cell transplantation. For purposes of simplification and scientific comprehensiveness, we will utilize hematopoietic cell transplantation (HCT) for the remainder of this document.

Hematopoietic cell transplantation is a medical sub-specialty comprised of physicians with Board Certifications in Internal Medicine, Medical Oncology, Pediatrics, Hematology and/or Immunology. Despite common misconceptions, HCT physicians are not surgeons and the introduction of hematopoietic cells into patients is performed via infusion, not open incision or other surgical procedures. HCT is a procedure that involves the infusion of either autologous (self) or allogeneic (donor) hematopoietic stem (progenitor) cells into a patient to reconstitute the patient's immune system as part of a larger treatment course for three primary clinical purposes: 1) treatment of malignancy, 2) replacement or modulation of an absent or poorly functioning hematopoietic immune system, 3) treatment of certain genetic diseases.[1] CMS recognized the

[1] National Institutes of Health, National Cancer Institute Hematopoietic Cell Transplantation Summary

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unique role and qualifications of HCT physicians by designating a unique code for Hematopoietic Cell Transplant and Cell Therapy (HCTCT) physicians in November 2016.[2]

HCT Utilization in the United States

By Federal mandate, the Center for International Blood & Marrow Transplant Research (CIBMTR) records data on each of the allogeneic HCTs performed within the United States each year. In 2015, the most recent verified data year, approximately 8,000 Allogeneic HCTs and 14,000 Autologous HCTs were performed on patients in the United States.[3] Of these, approximately 50% were performed in individuals 60 years of age or older. There has been substantial growth in the number of transplants performed in older individuals in the last 20 years due to advancements in preparative regimens and the ability to manage common age-associated co-morbidities. In the FY2018 Inpatient Prospective Payment System Proposed Rule, CMS data (Table 7A 7B NPRM) shows that there were 870 Allogeneic HCTs (MS-DRG 014) performed in Medicare Part A beneficiaries during FY16, with an average length of stay of 27.5 days. There are two Autologous HCT MS-DRGs (016, 017), differentiated by co-morbidity levels, that were reported a total of 2,110 times with lengths of stay of 18.8 (DRG 016 and 12.5 (DRG 017) days.

ASBMT Concerns with Proposed Changes to HCT and Cellular Therapy Reimbursement

The ASBMT welcomes the opportunity to comment on the CMS FY18 Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals Proposed Rule (Rule). There are several proposed changes in the FY18 Rule that will have significant effects on our hospital programs and our patients. A brief catalogue of these issues is listed below; detail on each item is provided later in the letter.

- The re-assignment of HCT cases into non-HCT MS-DRGs based on the proposed reclassification of ICD-10-PCS codes into Operating Room (OR) and Non-Operating Room (Non-OR) is extremely problematic for Autologous and Allogeneic HCT programs.

[2] CMS MLN Matters MM957
[3] D'Souza A, Zhu X. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2016. Available at: http://www.cibmtr.org

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- CMS should review and update its procedures for identifying and utilizing correctly coded HCT Claims.
- Current unclear CMS guidance on the appropriate site of care for HCT is causing local Medicare plans/contractors to inaccurately modify their HCT coverage policies.
- The ASBMT supports the application submitted for New Technology Add-on Payment status in relation to Axicabtagene Ciloleucel (KTE-C19, Kite Pharma), as well as the continuation of NTAP status for Defitelio (Jazz Pharmaceuticals).
- CMS should plan to adjust coding and reimbursement structures in a way that supports the adoption of CAR T and other Engineered T Cell therapies into use with the Medicare beneficiary population.
- CMS should understand the specialized clinical and structural needs associated with the safe delivery of CAR T and other Engineered T Cell Therapies.

I. O.R. to Non-O.R. Proposed Changes Negatively Impact HCT Reimbursement

Section D. II. F. 17a. Proposed Changes to Medicare Severity Diagnosis-Related Group (MS-DRG) Classifications and Relative Weights, Proposed Changes to Specific MS-DRG Classifications, Other Proposed Policy Changes: Other Operating Room (O.R.) and Non-O.R. Issues, O.R. Procedures to Non-O.R. Procedures

In Section D.II.F.17a, CMS outlines proposed reclassification of multiple Autologous and Allogeneic HCT codes from Operating Room (O.R.) status to Non-O.R. status. ASBMT concurs with CMS's assessment that these procedures do not take place in an O.R. setting but we ask that CMS review the unintended consequences this proposed change has on the MS-DRG Grouper Logic.

Table 6P.4o (below) lists the codes identified for re-classification from O.R. to Non-O.R. status.

TABLE 6P.4o--List of ICD-10-PCS procedure codes that relate to the percutaneous transfusion of bone marrow and stem cells

[4] ICD-10-PCS Procedure Codes Proposed to Change from O.R. to Non-O.R. Status	
ICD-10-PCS Procedure Code	**Code Description**
30233AZ	Transfusion of Embryonic Stem Cells into Peripheral Vein, Percutaneous Approach

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30233G0	Transfusion of Autologous Bone Marrow into Peripheral Vein, Percutaneous Approach
30233X0	Transfusion of Autologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach
30233Y0	Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach
30243AZ	Transfusion of Embryonic Stem Cells into Central Vein, Percutaneous Approach
30243G0	Transfusion of Autologous Bone Marrow into Central Vein, Percutaneous Approach
30243X0	Transfusion of Autologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach
30243Y0	Transfusion of Autologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach
30253G0	Transfusion of Autologous Bone Marrow into Peripheral Artery, Percutaneous Approach
30253G1	Transfusion of Nonautologous Bone Marrow into Peripheral Artery, Percutaneous Approach
30253X0	Transfusion of Autologous Cord Blood Stem Cells into Peripheral Artery, Percutaneous Approach
30253X1	Transfusion of Nonautologous Cord Blood Stem Cells into Peripheral Artery, Percutaneous Approach
30253Y0	Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Artery, Percutaneous Approach
30253Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Peripheral Artery, Percutaneous Approach
30263G0	Transfusion of Autologous Bone Marrow into Central Artery, Percutaneous Approach
30263G1	Transfusion of Nonautologous Bone Marrow into Central Artery, Percutaneous Approach
30263X0	Transfusion of Autologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach
30263X1	Transfusion of Nonautologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach
30263Y0	Transfusion of Autologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach
30263Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach

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This change has significant and directly negative consequences for the payment of Autologous and Allogeneic (noted as Nonautologous in the table) HCT, a policy change that was not otherwise noted or discussed in the Proposed Changes to the MS-DRG Classification and Weights section. **These proposed changes do not only modify the official classification of clinical setting for HCT procedures, but they effectively re-classify the procedures themselves into other MS-DRGs.**

Before discussing the financial impact of these changes, the ASBMT would like to highlight that there are numerous ICD-10-PCS codes on Table 6p.4o that are not utilized in the legitimate practice of HCT. The infusion of hematopoietic stem cells does not happen via an arterial approach; infusions for the purpose of HCT are only conducted through venous delivery. Additionally, embryonic cells are not utilized for the treatment of hematologic malignancies and/or immune reconstitution. The following subset of Table 6P.4o are the only codes that ASBMT views as legitimate descriptions of the HCT process.

ICD-10-PCS Procedure Code	Code Description
30233G0	Transfusion of Autologous Bone Marrow into Peripheral Vein, Percutaneous Approach
30233X0	Transfusion of Autologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach
30233Y0	Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach
30243G0	Transfusion of Autologous Bone Marrow into Central Vein, Percutaneous Approach
30243X0	Transfusion of Autologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach
30243Y0	Transfusion of Autologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach

In relation to the O.R./Non-O.R. issue, as noted by the National Marrow Donor Program/Be The Match, the proposed modification of the status of certain codes affects the grouper logic in a way that diverts the majority of Autologous HCT cases away from the clinically appropriate and CMS-designated MS-DRG.

MS-	AORv34 Cases	AORv35 Cases
014 Allogeneic Bone Marrow Transplant	869	844
016 Autologous Bone Marrow Transplant w/ CC/MCC	1953	4
017 Autologous Bone Marrow Transplant w/o CC/MCC	157	2

CMS notes on page 309 of the Proposed Rule that Autologous HCT MS-DRGs 016 and 017 are considered a Low Volume MS-DRG for the purposes of FY18 relative weight calculations. According to Table 7A (Grouper V34), Autologous HCT was performed 2,114 times (MS-DRG

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016 and 017) in FY2016, yet on Table 7B (Grouper V35) only 6 total cases map to these two MS-DRGs due to the new proposed grouper logic. The AOR/BOR Data Tables confirm this large-scale re-assignment of transplant cases and indicate that only 6 cases were used for the purpose of determining the relative weights for these MS-DRGs in FY18. **Discarding 99.7% of transplant cases for the purposes of relative weight calculation is numerically inaccurate and clinically unjustifiable.**

CMS has acknowledged the unique clinical requirements and intensity of HCT since October 1, 1990, when it created a unique DRG (009) for Bone Marrow Transplant. Since that time, CMS has further modified the payment system by first moving the DRG into a MS-DRG, an assignment driven by the presence of the ICD-9 code(s) for HCT, and then splitting the MS-DRG into more specialized sub-types. Throughout the process of these changes, CMS's own billing guidance manual has described the procedure in clinical detail, including that the procedure is performed via "intravenous infusion." Additionally, both Autologous and Allogeneic HCTs are recognized for their clinical uniqueness by being placed in the Pre-MDC section of the MS-DRG Definitions manual alongside solid organ transplants and specialized procedures that are driven by multiple diagnoses. **In this regard, CMS has always understood the process of HCT and has provided specific documentation acknowledging that neither Autologous nor Allogeneic HCT have been performed in the O.R. setting.**

As an example of the resource differences between the current and proposed MS-DRG assignment changes, we analyzed MS-DRG 016 - Autologous HCT w/ CC/MCC. For the 1,953 claims that were designated to be Autologous HCT in FY16, 1,606 (82%) of these would be reassigned to MS-DRG 840, Lymphoma and Non-Acute Leukemia, with the proposed changes to the grouper logic driven by the O.R./Non-O.R. policy modifications. In FY16, 8,262 claims were billed to CMS for MS-DRG 840. These claims had an Arithmetic Mean LOS of 9.7630, while MS-DRG 016 was analyzed to have an ALOS of 18.8. Only the 90th percentile of claims for MS-DRG 840 (20 days) surpasses the MS-DRG 016 ALOS, while the 90th percentile ALOS for 016 is 26 days. There are significant differences in the intent and clinical care provided in these two clinical episodes. For MS-DRG 840, individuals are admitted with the intent of providing intensive, episodic chemotherapy for the treatment of lymphoma. This treatment can be provided in a general hematology/oncology setting and may be performed at most hospitals with an inpatient oncology unit. For MS-DRG 016, the clinical intent of the care episode is to provide a one-time infusion of a patient's own cells for the purposes of immune reconstitution and anti-malignancy effect. HCT, both autologous and allogeneic, is performed in specialized,

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accredited clinical settings within a limited number of facilities in the United States and requires extensive teams of expert clinicians. Patients are typically within a dedicated unit within a hospital meant to protective individuals with compromised immunity due to the cell transplant process.

It is possible to calculate the predicted loss to HCT programs due to this proposed change in the grouper logic using the lowest value NPRM amounts provided by CMS in Tables 1A-1E (a base weight of $5,436.51). **In the MS-DRG 016 example provided, the re-assignment of 1,606 of the 1,953 cases from MS-DRG 016 (RW = 6.2657) to MS-DRG 840 (3.6284) would result in a loss of over $23 Million in reimbursement to the hospitals performing those services.**

MS-DRG	Weight	Cases	Base Total Reimbursement	**Loss to HCT Programs due to Reassignment**
016	6.2657	1606	$54,706,046.38	
840	3.6284	1606	$31,679,687.61	($23,026,358.76)

As CMS has long identified HCT procedures/clinical episodes to be clinically unique and intensive, and as the Agency has easily identifiable codes and specific MS-DRGs already in place, it should not move forward with grouper logic changes that reduce payment and dilute its ability to correctly gather data on clinically-similar care episodes. **We ask that CMS refrain from re-classification of the HCT procedure codes unless it modifies the associated changes in the grouper logic that drive the predicted reclassification.**

II. Updates to the Allogenic Claims Processing and Rate-Setting Calculations

New ICD-10-PCS donor source codes were approved and implemented for use by HCT programs in October 2016. Previous to the implementation of ICD-10 in 2014, codes to differentiate donor types were in place within the ICD-9 coding structure; these codes were inadvertently lost in the migration to ICD-10 in 2014 and could not be re-implemented until the coding freeze was lifted in 2016.

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Related Donor HCT	
30243G2	Allogeneic related bone marrow via percutaneous venous central line infusion
30243X2	Allogeneic related cord blood via percutaneous venous central line infusion
30243Y2	Allogeneic related peripheral stem cells via venous central line infusion
Unrelated Donor	
30243G3	Allogeneic unrelated bone marrow via percutaneous central line infusion
30243X3	Allogeneic unrelated cord blood via percutaneous central line infusion
30243Y3	Allogeneic unrelated peripheral stem cells via percutaneous central line infusion

The consistent use of these codes will be important for CMS and other interested parties to track the use and cost-effectiveness of various donor cell sources.

Also in 2016, the National Uniform Billing Committee established revenue code 0815 – Allogeneic Stem Cell Acquisition/Donor Services – for the purpose of specifically tracking the costs associated with identifying a donor and acquiring cells for use in Allogeneic HCT. CMS now has the tools to create a series of claims edits that will decrease the potential for non-HCT claims to be inappropriately billed and processed as an HCT episode of care. In the CY2017 OPPS Final Rule, CMS created C-APC 5224 (Level 4 Blood Product Exchange and Related Services) and placed CPT code 38240 (Hematopoietic progenitor cells; allogeneic transplantation per donor) within C-APC 5224. Additionally, CMS requires that C-APC 5224 contain both CPT Code 38240 and Revenue Code 0815 or it will be rejected through the MCE process. This allows the Agency to more accurately understand the cost to hospitals of performing these services and also reduces the potential for providers inaccurately utilizing the HCT reimbursement rate for non-approved services.

During the analysis of claims submitted as Autologous and Allogeneic HCT for the purposes of understanding the impact of the O.R./Non-O.R. reclassification, it became obvious that non-HCT procedures are being billed with the use of the HCT ICD-10 codes. As noted in the NMDP comment letter, there were numerous examples of claims that would be re-assigned to Cardiac or Orthopedic procedures. While there are very rare cases of necessary cardiac interventions that take place unexpectedly during HCT inpatient admissions, an elective orthopedic procedure such as a knee/hip replacement would never be planned in tandem with a HCT. These are likely inappropriately classified claims that should not be reimbursed as HCT procedures and should not be utilized for purposes of relative weight calculation and/or rate-setting.

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The ASBMT encourages CMS to 1) require that allogeneic transplant claims contain a non-zero dollar amount in Revenue Code 0815 AND utilize one of the newly instated donor source ICD-10-PCS codes. CMS should also update the Blood and Blood Products Cost Center Table (p.302 of the FY18 Proposed Rule) to reflect Revenue Code 0815. It is not currently included in the list of Revenue Codes used to develop the Cost Center statistics and the absence of this Revenue Code from the table may indicate an incomplete calculation of the products within this cost center, as the acquisition of allogeneic donor cellular products average approximately $50,000 per HCT.

Finally, we ask CMS to utilize these new coding tools to study the costs of Allogeneic HCT and, in particular, the acquisition costs associated with identifying, harvesting and transporting donor cells. The procedures and costs associated with this process mirror the living kidney donor process, for which CMS reimburses acquisition costs separately on a reasonable-cost basis. Based on repeated conversations with transplant center medical directors and administrators, the failure of CMS to directly address issues of donor cell product acquisition is likely over time to decrease the number of centers willing to provide access to allogeneic transplantation for Medicare beneficiaries, the standard of care and lifesaving therapeutic option for many otherwise fatal hematologic malignancies. **The ASBMT requests that CMS consider separate payment for acquisition costs associated with the HCT process based on the similarity to the solid organ donor process and the implementation of new codes that would allow CMS to accurately assess and track costs.**

III. MLN Matters Article SE1624 Creates Barriers for Medicare Advantage Patients

In February 2016, the Office of the Inspector General (OIG) issued a report entitled *"Medicare Did Not Pay Selected Inpatient Claims for Bone Marrow and Stem Cell Transplant Procedures in Accordance with Medicare Requirements."* The OIG report analyzed 132 inpatient HCT claims with lengths of stay significantly shorter than the Geometric Mean Length of Stay (GMLOS); most claims being reviewed reported stays of 1-2 days in comparison with the 10-21 day GMLOS for the various HCT transplant MS-DRGs. The audit performed on these 132 claims found that 120 stays should have been billed as Outpatient or Outpatient with Observation. We do not dispute that these claims may have been inappropriately coded or billed by the hospitals performing the procedure. However, the report did not specify whether the transplants analyzed were Autologous or Allogeneic. Allogeneic HCT is significantly more

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intensive clinical procedure and cannot be easily grouped in with Autologous HCT due to the additional clinical risks that must be managed for a patient. Given that the lengths of stay for the claims identified as inappropriately billed were 1-2 days, we believe that those care episodes were Autologous transplants. In November 2016, CMS issued MLN Matters Article SE1624, which summarized the OIG report, but also referenced outdated HCFA draft documentation and indicated that the typical site of service for HCT is in the outpatient setting.

In April 2017, the ASBMT was contacted by several transplant centers in the Southeastern United States in regard to a local Medicare Managed Care plan that had interpreted the MLN Matters article in such a manner that ***the Plan updated its Allogeneic HCT medical policy to require that AlloHCT be performed in the outpatient setting until special authorization was granted in advance.***

The Office of the Inspector General Report states (p.2, last paragraph) that *"according to an independent medical review contractor, stem cell transplantation is routinely performed as an outpatient procedure."* In addition to not providing any further detail about the credentials of the independent medical review contractor, this categorization of HCT being *"routinely"* performed in the outpatient setting is incorrect. A limited number of transplant programs do have the ability to perform HCT in the outpatient setting due to building the appropriate clinical setting and resources, including specialized physicians, nurses and other staff, to perform HCT and 24/7 emergency follow-up care for those patients who are appropriate candidates. Candidates for outpatient transplant are usually those otherwise healthy individuals receiving an autologous transplant for certain indications, such as Multiple Myeloma, and who live a short distance from transplant centers with 24/7 emergency department access. These types of transplants are typically relevant only to a minor subset of autologous stem cell transplants and an even smaller subset of allogeneic transplants in patients with few comorbidities and with decreased risk for opportunistic infections. Overall, these clinical transplant scenarios are a true minority of the total transplants performed and should not be considered the standard model for transplantation. The ability to offer outpatient transplantation to patients that may be clinically eligible does not exist in all transplant programs for a variety of valid reasons, including the lack of safe and affordable lodging options in close proximity to 24/7 urgent and emergent care facilities with transplant-experienced staff.

The CY2017 Medicare data reported in the 2017 NPRM Cost Statistics File shows that only 40 Allogeneic transplants were performed in the Outpatient setting during the previous data year.

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CMS reported 289 Autologous HCTs in the same year. The CIBMTR data for allogeneic transplants across adults of all ages reflects this proportion; approximately 1.2% of the allogeneic HCTs and 4.2% of autologous HCTs were performed in 2015 were within the outpatient setting.[4]

The ASBMT supports the use of the Outpatient Care setting when clinically appropriate to the patient, the disease being treated, the type of HCT being performed and the capacity and ability of the specific transplant center to perform and support care in that setting. For those patients and programs that can utilize the outpatient setting, maintaining that option is an important mechanism for meeting the needs of the growing Medicare HCT population.

Since the time of being contacted in regards to these issues, Medicare has issued an updated MLN Matters article on this topic. While the document corrected some of the shortcomings of the previous version, a statement that "stem cell transplants are routinely performed in the outpatient setting" remains in the document. This is factually incorrect and we respectfully ask that Medicare correct this documentation to reflect and support physician discretion in choosing and utilizing the site(s) of care most clinically appropriate for beneficiaries without the need for additional authorization activities. A failure to do so may encourage centers to perform transplants under less than optimal conditions, which will increase risks of morbidity, mortality and also overall costs due to increased rates of complications.

IV. New Technology Add-on Payments for HCT and Cellular Therapies

In Section H of CMS-1677-P, CMS asks for commentary on several drugs or devices pending renewed or initial acceptance as new technologies warranting add-on payment status. Per page 311 of the Proposed Rule, there are three criteria that a new medical service or technology must satisfy to be considered eligible "to receive the additional payment: (1) the medical service or technology must be new; (2) the medical service or technology must be costly such that the DRG rate otherwise applicable to discharges involving the medical service or technology is determined to be inadequate; and (3) the service or technology must demonstrate a substantial clinical improvement over existing services or technologies."

The ASBMT provides commentary on NTAP initial applications or annual continuations when the drug or device is immediately impactful to the clinical practice of HCT or other closely

[4] CIBMTR Comprehensive Report Form Data, ASBMT Request, May 2017; www.cibmtr.org

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related cellular therapies. Comments were solicited from the appropriate standing clinical committee(s) and/or individual subject matter experts and compiled in order to provide a response to CMS for the FY18 IPPS Proposed Rule Comment Period.

a. **Defitelio®:** CMS has proposed to continue new technology add-on payments for transplant cases utilizing Defitelio® for the treatment of veno-occulsive disease (VOD) through FY18. We support this extension and ask that CMS review all cases using the new ICD-10-PCS codes assigned to the infusion of defibrotide (XW03392 and XW04392) and consider a separate MS-DRG for cases with a VOD complication.

b. **Axicabtagene Ciloleucel (KTE-C19)**

In Section H.d. (pp. 389-401), CMS summarizes the application submitted by the manufacturer of KTE-C19 and asks for public comments on whether the product meets the criterion for both newness/substantial similarity and substantial clinical improvement. **The ASBMT feels that KTE-C19, and other Chimeric Antigen Receptor T Cell (CAR T) technologies, meet all criterion for New Technology status for the reasons outlined in the following sections.** Our comments pertain to Chimeric Antigen Receptor Cellular Therapies as a class of products, of which KTE-C19 is the first to apply for a New Technology Add-On Payment for an engineered T Cell-based treatment. If KTE-C19 does not gain FDA approval by the July 1 timeline requirement for FY18 IPPS NTAP status, we maintain our position on the qualification of CAR Cellular therapies for NTAP status as it would pertain to any subsequent product application(s).

Newness & Substantial Similarity: CMS evaluates technologies for NTAP status within the context of potential 'substantial similarity' to other treatments. Specifically, new services or technologies are evaluated for the following: "(1) whether a product uses the same or similar mechanism of action, (2) whether a product is assigned to the same or a different MS-DRG; and (3) whether the new use of the technology involves the treatment of the same or similar type of disease and the same or similar patient population" (p. 312). **The ASBMT feels definitively that KTE-C19, and similar engineered Cellular based therapies, should be considered a new technology and that they are not substantially similar to any other therapy currently available.**

Mechanism of Action: While CMS makes a correct assessment that KTE-C19 (CAR T) and bispecific T cell engager technology (BiTE) are both therapies that target CD19 antigens expressed by lymphoma and leukemia cells, they are wholly different compounds and different

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approaches to immunotherapy of CD19+ malignancies. There are significant differences between the technologies in both their mechanism of action and the logistics of their delivery to the patient; overall, CAR T (KTE-C19) is a novel therapy unlike any previously developed for patients with blood cancers. BiTE technologies, such as Blincyto, are constructed monoclonal antibodies, while KTE-C19 therapy is based on transferring a molecularly engineered receptor, or chimeric antigen receptor (CAR), into cells (autologous T cells), which are then infused into the patient. These cells are genetically altered to express the CAR molecule on their surface. They are grown (expanded) in culture over several days and prepared for infusion into the patient. The CAR T cells then circulate and when they come upon the target antigen present on tumor cells - CD19 - they activate, expand, produce cytokines, and destroy their tumor targets.

A CAR is a synthetic protein typically composed of three different domains, including (1) an antigen-recognition domain linked to (2) a transmembrane domain, and (3) an intracellular domain containing intracellular costimulatory molecules and a signaling molecule. To generate autologous CAR T cells, the patient undergoes a process, known as leukapheresis, in which blood is removed from the patient's veins in an outpatient procedure, similar to the process of donating platelets. The blood product, containing T cells, is sent to the product manufacturer for stimulation and growth in the laboratory, followed by genetic modification through the introduction of the CAR transgene into the T cells. After additional expansion over days to weeks, the T cells are shipped back to the site of care and reinfused into the patient. In the patient, the cells proliferate, recognize their target antigen on tumor targets, and perform effector functions characteristic of native T cells, resulting in tumor death.

The mechanism of action for KTE-C19 (CAR T) is distinctly different from BiTEs in the following ways:

- CAR T cells perform cell lysis on the targeted cancer cells. In contrast, BiTE technologies are antibodies designed to link a patient's T cells via CD3 to CD19 on their tumor cells. Following binding, the engaged T cells will react against the tumor. Without the BiTE present, the T cells do not recognize or destroy the target. Given the low molecular weight of BiTE, it must be continuously administered to have a therapeutic effect.
- BiTE therapies/technologies do not induce T cell co-stimulation, a foundational aspect of CAR T technologies.

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- As BiTE is a small protein molecule with a short half-life, it must be continuously administered to have a therapeutic effect and therefore does not have the same potential for long-term anti-tumor effects as CAR T cells. CAR T cells may persist for many months or even years, and provide continuous surveillance, protecting against relapse of tumor. In addition, they have the ability to expand in response to antigenic stimulation and are self-amplifying.
- CAR T also have a different volume of distribution to BiTE therapies as they can traffic through multiple tissue planes and access tumor deposits that may not be accessible to BiTE therapies.
- BiTE requires continuous intravenous infusion in 28-day cycles, while CAR T cells are typically delivered in one or two infusions. BiTE does not have the mechanistic ability to persist in the body in a manner that could be independently curative.
- BiTE technology is dependent on the fitness of the endogenous T cell population and does not generate new cells. CAR T therapy, including the KTE-C19, involves genetic modification or engineering the T cells, which are expanded *ex vivo*, and also expand *in vivo* following administration.
- BiTE is not a personalized medicine product and is manufactured through typical biologic pharmaceutical processes. As CAR T therapy is an autologous cellular product, it currently requires harvest, transport and laboratory modification of a patient's own cells, requiring entirely distinct product custody processes.
- CAR T allows for *ex vivo* modulation of the patient's T cell population with respect to phenotype and CD4:CD8 ratios, while BiTE, as a non-cellular product, does not allow for customization.

Assignment to Same MS-DRG*:* The Agency contends that KTE-C19 does not satisfy the MS-DRG assignment criterion because the patients who will utilize KTE-C19 map to the same MS-DRGs as those patients currently receiving non-KTE-C19 therapies for the same diagnoses. CMS uses a MS-DRG mapping system based on a patient's diagnosis within the Major Diagnostic Categories (MDCs). Aside from Autologous HCT (MS-DRGs 016/017), which is a Pre-MDC MS-DRG with an assignment driven by the use of the ICD-10-PCS code, there are no MS-DRGs that recognize a combination of a lymphoma diagnosis and a non-O.R. cellular therapy procedures like the infusion of KTE-C19. As CMS does not have other Cellular Therapy Pre-MDC MS-DRGs, all patients who are hospitalized for the treatment of their primary

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lymphoma diagnosis will be placed into one of the MS-DRGs with MDC 17 – Myeloproliferative Diseases & Disorders, Poorly Differentiated Neoplasms. Of the MS-DRGs within MDC 17, the applicant has correctly mapped potential KTE-C19 patient cases to all of the non-Surgical/O.R. lymphoma-diagnosis MS-DRGs available. It is unreasonable to expect that the patient population expected to be candidates for KTE-C19 would map to different MS-DRGs if those potential MS-DRGs do not currently exist.

Type of Disease and/or Patient Population: If FDA approved, KTE-C19 would be the first engineered autologous cellular immunotherapy indicated for the treatment of adult patients with relapsed/refractory aggressive B cell non-Hodgkin lymphoma (NHL) who are ineligible for autologous stem cell transplant (ASCT). Blincyto is currently indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Aggressive B cell non-Hodgkin lymphoma (NHL) is a distinct disease from ALL, with different genetic, pathologic, biochemical, epidemiologic, clinical, and therapeutic indicators. Although they are both derived from cells of the B cell lineage, and therefore both express CD19, they are very distinct diseases and require separate consideration as such. This would be the first and only FDA approved treatment for the relapsed/refractory aggressive B cell non-Hodgkin lymphoma patient population.

DRG Rate Inadequacy: The applicant provided an analysis that indicates that the vast majority of patient archetypes that would be potentially treated with KTE-C19 would be currently billed for MS-DRGs 840 (Lymphoma & Non-Acute Leukemia with MCC), 841 (Lymphoma and Non-Acute Leukemia with CC), 846 (Chemotherapy without Acute Leukemia as Secondary Diagnosis with MCC), and 847 (Chemotherapy without Acute Leukemia as Secondary Diagnosis with CC). The ASBMT does not have access to confidential information about pricing for KTE-C19 and other engineered T Cell Therapies, though public reports of anticipated price points for these therapies make it reasonable to expect product costs of more than $200,000 per patient. This product cost will be a true cost to the hospital providing the service, as the product's manufacturer is entirely separate from the healthcare organization. Additionally, there will be rare cases when a patient is not able to proceed with the infusion of the product due to death or other clinical complications. Of the potential MS-DRGs indicated by the applicant, MS-DRG 840 is at the highest relative weight. As noted earlier, MS-DRG 840 has a relative weight of 3.6284 and a base reimbursement of approximately $19,725. The lowest paying MS-DRG of the main potential MS-DRGs indicated by Kite Pharma is MS-DRG 847, with a RW of 1.2848 and an estimated corresponding reimbursement rate of $6,984.

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Separate from the cost of the product, the average length of stay for Medicare beneficiaries receiving KTE-C19 will likely deviate substantially from the range of ALOS numbers associated with MS-DRGs 840, 841, 846 and 847, which range from 4 to 11 days. As CMS notes, the applicant's supplied information about Study 1 indicated a median stay of 15 days. The subset of patients that develop one of known potential post-infusion complications, including Cytokine Release Syndrome (CRS) and/or treatment-associated neurotoxicity, will likely require hospitalization until symptoms fully resolve – potentially for up to 2-3 weeks. Additionally, in the Zuma-1 KTE-C19 study, 43% of patients experienced complications severe enough to need infusions of high doses of Tocilizumab, an expensive immunosuppressive drug. Given the expected price for the hospital to acquire the product, in conjunction with expected increases in ALOS and additional interventions during the inpatient stay, indicate that current MS-DRG rates are wholly inadequate.

Substantial Clinical Improvement: As CMS notes in the clinical summary, approximately 50% of newly diagnosed patients are successfully treated with CHOP/R-CHOP. For those patients with refractory or relapsed disease after first-line treatment, less than 50% of patients are eligible for second-line regimens and none of the current options will do more than temporarily halt progression of the disease. Medicare beneficiaries will be greatly impacted by the availability of this new technology, as the median age of diagnosis for non-Hodgkin Lymphoma is 67 years of age (NCI SEER Data).

In CMS's summary, the Agency notes that the study results submitted with the NTAP application had limitations in terms of numbers of individuals treated and post-treatment follow-up. Since the time of NTAP application submission and initial review (Q1 CY2017), additional study results have been publicly released and presented at clinical meetings. The primary analysis results of the pivotal Zuma-1 clinical trial evaluating KTE-C19 in patients with chemo-refractory aggressive B cell lymphomas (DLBCL, PMBCL, and TFL) was presented at the American Association for Cancer Research Annual Meeting on April 2, 2017.[5] Patients enrolled and treated on Zuma-1 had truly chemo-refractory disease defined as at best stable disease (no significant radiographic decrease in size of lymphoma tumors per standard criteria) to their last

[5] Locke FL, Neelapu N, Bartlett NL, Lekakis LJ, Miklos D, Jacobson CA, Braunschweig I, Oluwole O, Siddiqi T, Lin Y, Timmerman J, Friedberg JW, Bot A, Rossi J, Navale L, Jiang Y, Aycock J, Elias M, Wiezorek J, Go WY. Clinical Trials Plenary Session, Oral Presentation –Primary results from ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axicel; KTE C-19) in patients with refractory aggressive non-Hodgkin lymphoma. Clinical Trial Plenary Session. American Association for Cancer Research Annual Meeting. 20017/04/02: Abstract CT019

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line of chemotherapy or who had relapsed within 12 months of an autologous hematopoietic stem cell transplant. Of the 101 patients that had received KTE-C19 at the time of the data cut-off, the median follow-up was 8.7 months. Zuma-1 met the primary endpoint of improved Objective Response Rate (ORR) ($p<0.0001$) compared to historical control. The ORR was 82% and the Complete Response (CR) rate was 54% for treated patients, with 44% of patients remaining in response at the time of the data cutoff. These results compare favorably to outcomes with existing standard therapies evaluated in the SCHOLAR-1 study, an international meta-analysis of more than 600 patients in an analogous refractory patient population.[6] ORR was 82% in Zuma-1 compared to 26% in SCHOLAR-1; the CR rate was 54% in Zuma-1 compared to 8% in SCHOLAR-1; and the 6-month Overall Survival by Kaplan-Meier method was 80% in Zuma-1 compared to 55% in SCHOLAR-1. Importantly the median duration of response for patients achieving CR with KTE-C19 has not yet been reached. With 8.7 months of follow-up the lower bound of the 95% confidence interval for median overall survival is 10.5 months, and likely to be much longer, again comparing favorably to the SCHOLAR-1 with a median overall survival of 6.6 months. Three of the seven lymphoma patients treated with the same CAR T cell construct on the phase 1 trial of KTE-C19 remain in remission over 1 year after therapy[7] and patients treated at the National Cancer Institute remain in remission over 2 years after therapy.[8] These results clearly illustrate that KTE-C19 CAR T cell therapy is an improvement over existing standard of care therapies.

KTE-C19 also compares favorably to efficacy of BiTE antibody therapy for aggressive B cell NHL. Although the ORR to BiTE was 43% in a phase 2 trial of aggressive B cell lymphomas, it included patients with less aggressive disease than evaluated in Zuma-1 and SCHOLAR-1. For patients with truly chemo-refractory lymphoma treated with a CD19 BiTE, the ORR was a

[6] Crump, M., Neelapu, S.S., Farooq, U., Van Den Neste, E., Kuruvilla, J., Ahmed, M.A., Link, B.K., Hay, A.E., Cerhan, J.R., Zhu, L. et al. Outcomes in refractory aggressive diffuse large B-cell lymphoma (DLBCL): results from the international SCHOLAR-1 study. J. Clin. Oncol. 2016; 34

[7] Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM, Ghobadi A, Budde LE, Bot A, Rossi JM, Jiang Y, Xue AX, Elias M, Aycock J, Wiezorek J, Go WY. Phase 1 Results of ZUMA-1: A Multicenter Study of DTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. Mol Ther 2017 Jan; 25: (1) 285-295 PMID: 28129122, PMCD: PMC5363293.

[8] Brudno JN, Somerville RP, Shi V, Rose JJ, Halverson DC, Fowler DH, Gea-Banacloche JC, Pavletic SZ, Hickstein DD, Lu TL, Feldman SA, Iwamoto AT, Kurlander R, Maric I, Goy A, Hansen BG, Wilder JS, Blacklock-Schuver B, Hakim FT, Rosenberg SA, Gress RE, Kochenderfer JN. Allogeneic T Cells That Express an Anti-CD19 Chimeric Antigen Receptor Induce Remissions of B-Cell Malignancies That Progress After Allogeneic Hematopoietic Stem-Cell Transplantation Without Causing Graft-Versus-Host Disease. J Clin Oncol. 2016 Apr 1;34(10):1112-21. doi: 10.1200/JCO.2015.64.5929. Epub 2016 Jan 25.

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dismal 19%, which is not even close to the 82% ORR seen with KTE-C19 in this population and is similar to the 26% ORR seen with standard chemotherapies presented in SCHOLAR-1.[9]

In the FY2002 IPPS Final Rule, CMS states that a "new technology represents substantial clinical improvement when it reduces mortality, decreases the number of hospitalizations or physician visits or reduces recovery time compared to the technologies previously available" (66 FR 46902). As the previous comments outline, the reductions in mortality for relapsed/refractory patients being treated with KTE-C19 are pronounced. And while an extended study of comparative health care utilization is not yet available, KTE-C19's ability to create partial and complete remissions in a patient population will likely reduce otherwise on-going outpatient and inpatient visits and admission for chemotherapy and chemotherapy-induced complications.

CAR T therapy in general, and KTE-C19 specifically, should not be viewed as a better hammer, but an entirely new tool for a group of patients that do not have another option that would potentially induce remission. Palliation-intended chemotherapy regimens are the only realistic alternative treatment for the indicated population of relapsed/refractory individuals. The achievement of partial and complete remissions in these relapsed/refractory patients is not feasible with any other currently available therapy and is therefore extremely clinically remarkable. The ASBMT Committee on Cellular Therapy, comprised of leading experts in cellular therapies including hematopoietic transplantation, welcomes any further questions CMS staff may have on the technology, its intended uses and its clinically differentiating features.

V. Future Processing of Claims for Engineered T Cell Therapies

The ICD-10 Coordination & Maintenance Committee (C&M) recently approved ICD-10-PCS New Technology Codes XW033C3/XW043C3 – New Technology, Introduction, Engineered Autologous Chimeric Antigen Receptor T Cell Immunotherapy. As additional engineered T Cell therapies are developed and approved, we ask that CMS develop a comprehensive reimbursement structure for these therapies. As outlined elsewhere in this letter, these technologies are entirely new and will have costs and resource needs that are significantly different from either chemotherapy-oriented disease-specific MS-DRGs or from current cellular therapies like Autologous and Allogeneic HCT. CMS should plan to create separate MS-DRGs

[9] Viardot A, Goebeler ME, Hess G, Neumann S, Pfreundschuh M, Adrian N, Zettl F, Libicher M, Sayehli C, Stieglmaier J, Zhang A, Nagorsen D, Bargou RC. Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. Blood. 2016 Mar 17;127(11):1410-6. doi: 10.1182/blood-2015-06-651380. Epub 2016 Jan 11.

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for CAR T and other engineered T Cell therapies to ensure that the costs associated with the provision of these therapies does not impede access for Medicare beneficiaries. Use of the newly approved ICD-10-PCS code for CAR T, in combination with the product-specific J/Q indicator and National Drug Code will allow CMS and other Health Services Researchers to understand the resource utilization and cost-efficacy associated with these technologies.

While the first generation of CAR T therapies are autologous products, products currently in development include both individually-matched allogeneic and "universal donor" sourced cells. Requiring use of a code to indicate cell source and creating a specific table outside of the New Technology setting, similar to the Table 302 (Transfusion), dedicated to engineered T Cell therapies, will allow CMS and other stakeholders to capture the full detail on the variations in products as these technologies evolve.

VI. Facilities Appropriate for Implementation of Engineered T Cell Therapies

As discussed throughout this comment letter, the anticipated introduction of FDA-approved engineered T Cell Therapies will create a sea change within the practice of oncology for patients with the indicated diagnoses. While appearing to be very effective clinically, the processes required to successfully treat patients with CAR T Cell therapies are not trivial – they require sophisticated apheresis and cell laboratory capabilities, specialized training of all individuals involved with patient care, and multidisciplinary teams and care settings capable of quickly identifying and resolving post-infusion complications like CRS and treatment-associated neurotoxicity. HCT is similar in this regard, as the specialization needed to safely and effectively deliver it has resulted in centralized expert care teams within a limited number of hospitals/health care centers in the United States. Due to the need of payers and clinicians to be able to identify the clinical centers capable of performing this type of care, the Foundation for the Accreditation of Cellular Therapy (FACT) was founded as a joint effort between the ASBMT and the International Society for Cellular Therapy (ISCT) in 1996. An independent organization within the University of Nebraska, FACT has become the recognized leader in international standards and peer-accreditation for HCT programs. Due to the need for similar processes and structures for the delivery of the anticipated Engineered T Cell therapies, FACT has issued inaugural editions of Standards for Immune Effector Cells and an Accreditation Manual for programs hoping to provide these new therapies to their patients. We encourage the Agency to begin dialogue with FACT to better understand the need for these therapies to be delivered in

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facilities that have been vetted for their capabilities to safely and comprehensively care for patients receiving Engineered T Cell therapies.

Contact Information and Resources for CMS

The ASBMT greatly appreciates the opportunity to review the Agency's proposed changes to reimbursement for HCT and Cellular Therapy for the upcoming 2018 Fiscal Year. We understand that the requests that we have made throughout this comment letter are based on our expertise in a highly technical clinical sub-specialty area and we welcome the opportunity to dialogue with CMS staff in regard to these policy changes. ASBMT peer-elected leaders, member clinicians and policy staff are available as a resource for CMS staff when issues associated with HCT and other cellular therapies are raised internally in the future. Please do not hesitate to reach out whenever we may be of assistance.

Krishna Komanduri, MD
ASBMT President, 2016-2017

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