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September 6, 2017

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

Cc: Carol Blackford
Tiffany Swygert
Ryan Howe
NewTech@cms.hhs.gov

Re: CMS Payment Models for Chimeric Antigen Receptor T Cell (CAR-T) Therapy

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 and cellular therapies such as CAR-T.

Hematopoietic cell transplantation (HCT) is a medical sub-specialty comprised of physicians with Board Certifications in Internal Medicine, Medical Oncology, Pediatrics, Hematology and/or Immunology. CMS recognized the unique role and qualifications of HCT physicians by designating a unique code for Hematopoietic Cell Transplant and Cell Therapy (HCTCT) physicians in November 2016.[1] Due to their unique clinical expertise and training, ASBMT member clinicians and cellular therapy programs will be the primary individuals and teams initially providing Chimeric Antigen Receptor T Cell Therapy (CAR-T) to patients in need of

[1] CMS MLN Matters MM957

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treatment. We anticipate that CAR-T is the first of what is expected to be many engineered cellular therapies that are expected to outpace traditional oncology treatments in the coming decade. We concur with the expert commentary labeling cellular therapies as the key breakthrough therapy of the 21st Century, as discussed at the July 13, 2017 FDA Oncology Drugs Advisory Committee.[2] Due to the involvement of our membership and the coming wave of innovation that these cellular therapies represent, the ASBMT is keenly interested in the reimbursement models that will be applied to these technologies on behalf of our members.

Given the very recent approval of the Novartis CAR-T product, Kymriah, and the anticipated future approval of Kite Pharma's Axi-Cel, ASBMT has assessed the current reimbursement policies for anticipated impact to facilities providing CAR-T and we provide our commentary and suggestions to CMS throughout the remainder of this letter. On August 30, both Novartis and CMS issued public statements that the two organizations will be working together to develop innovative payment models for CAR-T. ASBMT acknowledges that new models for cellular therapy are likely necessary and we welcome any opportunity to engage with CMS on the development of these models. While most of the issues and proposed solutions in this letter are based on current payment policy tools vs. entirely new payment structures, they would be useful in serving as interim steps to assure access to CAR-T for Medicare beneficiaries while more complex methodologies are being developed. We have also received questions and comments from our members regarding the announcement of potential innovative payment methodologies, which are detailed later in this letter.

Summary of Request

On behalf of our membership, we request that CMS consider its authority to create off-cycle modifications to the inpatient payment system in order to ensure that CAR-T is available to Medicare beneficiaries. In addition, we ask that CMS create new codes in order to adequately describe services being provided and to track the associated costs, as well as issue interim billing and coding guidance for provider use during the period before new codes are approved and available.

[2] FDA ODAC Meeting, July 13, 2017

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Background Information on CAR-T

The most simplistic explanation of CAR-T is the following, as described by the National Institutes of Health:

"As its name implies, the backbone of CAR-T-cell therapy is T cells, which are often called the workhorses of the immune system because of their critical role in orchestrating the immune response and killing cells infected by pathogens. The therapy requires drawing blood from patients and separating out the T cells. Next, using a disarmed virus, the T cells are genetically engineered to produce receptors on their surface called chimeric antigen receptors, or CARs."[3]

From the patient treatment perspective, the process is as follows:

1) Patient is diagnosed with qualifying condition and is referred to treatment center.
2) Patient travels to treatment center for initial consultation and treatment planning; returns home or remains at treatment center for on-going treatment of disease.
3) Patient travels to treatment center to have cells removed through a process called autologous apheresis or leukapheresis; this may be conducted in either the inpatient or outpatient setting.
4) The hospital places order for production and ships patient cells to manufacturer; patient likely returns home for 2-3 weeks during the CAR-T production process.
5) Up until for infusion of CAR-T product, the patient will likely be receiving chemotherapy to control disease progression. This may be administered inpatient or outpatient.
6) Patient travels to treatment center for infusion of the CAR-T product after being notified of successful manufacturing and estimated arrival date.
7) ***Patient is admitted for preparatory lymphodepleting chemotherapy and CAR-T infusion.*** *The patient remains in the hospital for 7-10+ days, depending on the patient's individual response and until the treating physician team feels confident that the patient is not experiencing moderate to severe complications. Outpatient provision of CAR-T will likely be available in limited sites for specific patients but will not be common during the initial post-approval period.*
8) For approximately 15-30% of patients of patients, moderate to severe complications will result in staying in the hospital for up to 3 weeks as symptoms are being treated. Cytokine Release Syndrome (CRS) symptoms will begin appearing in affected

[3]

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individuals within 2-7 days after infusion with the product and neurotoxicity typically appears within 5-7 days of infusion.

9) Patient remains nearby the treatment center for an additional 1-2 weeks for monitoring.
10) Patient returns home for on-going monitoring with local clinical teams.

Complications: After infusion of the CAR-T product, patients have a moderate risk of complications that require additional inpatient care and support. CRS is a group of systemic reactions due to the high volume of cytokines released from cells targeted by the engineered T-cells; symptoms include fever, fatigue, and pulmonary and cardiac changes.[4][5] In addition to CRS, patients may experience neurotoxicity of varying degrees ranging from mild confusion to the inability to speak and unconsciousness. Uniform systems of grading these complications are forthcoming and complications vary by product and treatment population, but it is expected that somewhere between 15-30% of patients will experience Grades 3-4 CRS and/or neurotoxicity. To treat these symptoms, the clinical teams use various combinations of corticosteroids, supportive interventions and immunosuppressive medications, such as Tocilizumab. Prior to FDA approval of Actemra/Tocilizumab for treatment of CRS, hospital acquisition costs were reported by member pharmacists to be $5,000-10,000 per therapeutic dose, depending on the patient, and frequently needs to be administered 2-5 times. We anticipate this number will increase after the noted approval. Patients experiencing complications are frequently relocated to the Intensive Care Units at the first sign of these symptoms and are treated there until symptoms abate. These complication-driven additional therapeutic interventions will add additional costs to the inpatient episode that are not typical expenses for patients being treated for lymphoma.

Products and Timeline: There are two CAR-T products expected to receive FDA approval in the 2017 calendar year. Novartis' CTL019 product, Kymriah, was approved on August 30, 2017 for B-cell acute lymphoblastic leukemia (ALL) in patients up to age 25. Of more relevance to CMS and the Medicare beneficiary population is Kite Pharma's CAR-T product - axicabtagene ciloleucel **(**Axi-Cel) - expected to gain FDA approval in the third quarter of 2017. The initial clinical indications for Axi-Cel are Diffuse Large B Cell Lymphoma, Primary Mediastinal B Cell Lymphoma and Transformed Follicular Lymphoma, all sub-types of lymphoma most commonly diagnosed in older adults, including the Medicare beneficiary population.

[4] Cytokine Release Syndrome: Overview and Nursing Implications
[5] Neelapu et al, *Nature Reviews Clinical Oncology*, Fall 2017, publication in press

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Medicare Beneficiary Access to CAR-T Therapies

Predominantly Inpatient Care Setting Creates Reimbursement Concerns

We have received many reimbursement related questions from member clinicians and cell therapy programs undergoing financial planning exercises focused on the provision of CAR-T to beneficiaries. A poll of ASBMT member experts – those physicians that have been in charge of delivering CAR-T during the clinical trial process – indicates that all are planning to keep patients in the inpatient setting for at least 7 days after infusion to monitor for complications. Given the intensive use of the inpatient setting for this therapy, hospitals are rightly concerned about how CMS will reimburse for the provision of CAR-T. CAR-T is not presently eligible for a new technology add-on payment (NTAP) due to the annual cycle timeframe utilized by CMS. Additionally, the vast majority of costs, such as product costs, infusion cost, and post-treatment complication costs will likely be concentrated within the infusion inpatient stay. As it currently stands, this inpatient stay will be assigned to one of a few possible MS-DRGs, all of which have payment rates that will be grossly inadequate in their reimbursement of provider cost. **As outlined in more detail in the following sections, we are deeply concerned that the use of a very expensive new product without provision for additional new technology payment may result in limited beneficiary access.** Therefore, **we ask that CMS utilize its authority** under Section 1886(d)(5)(I) of the Social Security Act, which allows it to "provide by regulation for such other exceptions and adjustments to such payment amounts under [IPPS] as the Secretary deems appropriate" so that CMS may pay appropriately for this important new therapy in FY 2018. We strongly believe that a unique interim solution is necessary until such time as the agency has the opportunity to develop an innovative payment model or evaluate actual CAR-T claims data to determine the need for new/separate MS-DRGs. The ASBMT is prepared to work collaboratively with CMS to both present and discuss possible policy alternatives.

Limited Facilities for CAR-T Provision

Manufacturers have stated publicly[6] that only a very limited number of facilities – likely between 10-30 for the first year and up to 90 by the end of year 3 – will be approved for participation in the production and infusion process for CAR-T.[7] This means that patients from the entire United States will be directed to a relatively small number of facilities to receive treatment. Given the

[6] FDA ODAC Novartis Hearing, July 12, 2017; Kite Pharma 2nd Quarter Earnings Call, August 8, 2017
[7] Kymriah Treatment Sites, September 3, 2017

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intensive requirements needed for proper patient management and monitoring, it is clinically appropriate that only a limited number of facilities will offer this new therapy at the outset.

However, this also means that this limited group of facilities will be disproportionately impacted by the expected reimbursement deficits in a concentrated manner. If even a small percentage of these facilities decide that the financial burden of treating Medicare patients with CAR-T is more than they can sustain financially, then access could become a serious problem if patients seeking care begin to have fewer locations available. Therefore, we are asking CMS to carefully examine the access implications that its current reimbursement policies will likely have on the small number of facilities that will be administering this new therapy.

Problematic Acquisition Costs and FY2018 MS-DRG Groupings

CAR-T is expected to be an extremely cost-intensive therapy to provide, due to two key aspects of the treatment; 1) the cost of acquiring the personalized product from the manufacturer and 2) the cost of treating the complications that are expected to arise in a subset of patients. Novartis has announced the Kymriah will be priced at $475,000[8]. This pricing is just for the engineered cells (i.e., the product itself) and does not include any other patient care provision and expense. Other costs the facility incurs include inpatient nursing and infusion administration and if post-infusion complications occur, treatment costs will also be borne by the facility. Without a clear sense of which MS-DRG(s) these patients are likely to fall into, facilities are unsure what type of reimbursement they may receive.

Earlier in its 2017 response to the proposed new ICD-10-PCS codes, ASBMT requested CMS assign all CAR-T care episodes to MS-DRG 837 (Chemotherapy with Acute Leukemia as Secondary Diagnosis or with High Dose Chemotherapeutic Agent with MCC) and MS-DRG 838 (Chemotherapy with Acute Leukemia as Secondary Diagnosis with CC or High Dose Chemotherapeutic Agent), as these MS-DRGs could be considered clinically appropriate for the intensity of care being provided when administering CAR-T, even if they does not fully capture the resources used during these episodes of care. While the description of the MS-DRGs is not an exact match, it may be the nearest non-surgical comparator. As stated in our letter, CMS has precedent for making this kind of intensity-matched MS-DRG placement (see Addendum A).

[8] Bloomberg, August 31, 2017

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CMS did not provide additional commentary on this request in the proposed or final IPPS rule. In the FY18 IPPS Final Rule, the CAR-T new technology ICD-10-PCS code was identified as a non-Operating Room procedure (Table 6P.4o). While this categorization is clinically correct, the lack of O.R. designation subsequently results in lack of Pre-MDC direction to a specific set of MS-DRGs. Thus, CAR-T lymphoma cases will likely group to one of a few non-surgical MS-DRGs depending on the constellation of diagnosis and procedure codes reported on the claim. The use of a pre-MDC assignment mechanism for CAR-T cases would enable CMS to route these clinically complex and resource-intense cases to a specific set of MS-DRGs and is something we believe should be considered. The lack of clarity as to which MS-DRG a facility can expect to be assigned to its CAR-T creates unknown financial risk for hospital finance departments and executive staff to attempt to evaluate on their own. As the initial indications for the use of Axi-Cel are for subtypes of non-Hodgkin lymphoma and there will be no surgical procedure routinely provided during the care episode, our assessment of the most likely medical MS-DRG assignments for CAR-T cases are those listed below.

Table 1: Potential MS-DRG for CAR-T Inpatient Stays Based on Current Grouper Logic

MS-DRG	MDC	Type	Title	Weights	Approximate Base Reimbursement	Geo Mean LOS
840	17	MED	LYMPHOMA & NON-ACUTE LEUKEMIA W MCC	3.0786	$16,736	7
841	17	MED	LYMPHOMA & NON-ACUTE LEUKEMIA W CC	1.6201	$8,807	4.3
842	17	MED	LYMPHOMA & NON-ACUTE LEUKEMIA W/O CC/MCC	1.1241	$6,110	2.9

These MS-DRGs are not accurate matches for clinical provision of CAR-T, particularly when considering the expected length of stay for CAR-T patients, but they reflect the most likely assignment given CMS's DRG assignment process.

As mentioned earlier, ASBMT would like CMS to exercise its authority under Section 1886(d)(5)(I) of the Social Security Act, which allows CMS to "provide by regulation for such other exceptions and adjustments to such payment amounts under [IPPS] as the Secretary deems appropriate." We strongly believe CMS must make some sort of proactive adjustments for CAR-T payment for FY2018 given that one product has received FDA and another is expected to in the coming months. We believe CMS can either exercise its authority and create one or

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more new MS-DRGs for CAR-T for FY 2018 and/or implement another mechanism by which the product costs are evaluated and paid on a reasonable cost basis. ASBMT has identified one pathway that we outline below for CMS's consideration to take steps to protect access to care and financially protect hospitals using existing mechanisms, implemented in way specific to the current clinical requirements of CAR-T.

There is precedent for CMS to make a DRG grouping decision in advance of the FDA approval of a new technology. In 2003, CMS created new DRGs 526 and 527 at the time of introduction of drug-eluting stents (DES) in order to recognize the additional expense of this new technology, even prior to formal FDA approval. ASBMT asks that CMS mirror this policy initiative and create new MS-DRGs for the administration of CAR-T, including potential adjustment for the presence and severity of complications.

At the time of the off-cycle creation of new MS-DRGS for DES, they did not pass the cost threshold criterion for the NTAP, but the adoption of DES was expected to be so widespread that CMS created two new DRGs prior to the anticipated FDA approval of DES devices. Given that it would not be unique, we ask CMS to consider making a similar exception with CAR-T, particularly since it would meet the cost criterion for NTAP designation and separate MS-DRG assignment. While its initial use will not be widespread as DES, the expected clinical benefit is very large and the cost of product acquisition is such that we believe CMS should give this new technology special consideration.

New Technology Add-on Payment Essential for Initial Post-Approval Period

Kite Pharma applied for a New Technology Add-on Payment for Axi-Cel for the FY2018 cycle, as described in the FY18 IPPS Proposed Rule. ASBMT submitted comments in support of Axi-Cel qualifying as a new technology, which are included in Addendum B of this document. As noted in the FY18 IPPS Final Rule, Kite Pharma withdrew its application when its product did not receive FDA approval by CMS's July 1st procedural deadline. While we understand CMS's timeline, we are concerned about the significant financial losses expected for the facilities providing Axi-Cel as a therapy to beneficiaries in the future (FDA approval is expected in late Fall 2017). We expect losses in the range of multiple hundreds of thousands of dollars given the expected cost of the personalized product as well as the resources involved to infuse and care for the patient as outlined earlier.

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When appropriate to provide in the outpatient setting, our understanding is that providers would be reimbursed for Axi-Cel as a pass-through drug, at the standard payment level of ASP +6%. Given that much of the initial provision of CAR-T will take place in the IPPS setting, current CMS payment policy creates a reimbursement deficiency based on site of care, which the Agency has previously stated it is looking to minimize.

While cancer centers want to provide beneficiaries with the best possible care, centers may simply be unable to absorb the large financial losses that are likely for CAR-T under CMS' current reimbursement system. This is one reason why we ask CMS to exercise its authority and at a minimum, ***award Axi-Cel with NTAP status at the time of FDA approval*** despite this action being outside of its usual process timeline. While, as stated in our previous NTAP comments, we believe that Novartis's Kymriah would qualify as a substantially similar product, we understand and acknowledge that Novartis did not apply for NTAP in the FY2018 cycle. We believe CMS can exercise its authority and provide adequate reimbursement for a therapy which for beneficiaries who meet the clinical qualifications for treatment with Axi-Cel, there are no alternative therapies other than the provision of supportive care. We strongly believe Medicare beneficiaries should be afforded immediate access to CAR-T and ask CMS to find a way to support facilities that will be providing this care.

Charge Compression and Outlier Payment Implications

As cellular therapies are being touted as one of the most significant breakthrough medical advances in the 21st century, there has been and will continue to be much public and private scrutiny on the cost, reimbursement, and outcomes related to these therapies, beginning with CAR-T.

Combining the known product cost of $475,000 for Kymriah (and an assumed relative comparator for the Axi-Cel) and our knowledge of hospital coding, billing, and charging practices for high cost items/services such as drugs, devices, and cell acquisition costs for unrelated donor cells, we do not believe hospitals will mark up their invoice cost by their standard pharmacy or other cost-to-charge ratios (CCRs) when billing CMS or other payers.

CMS's current inpatient cost outlier and MS-DRG rate-setting method relies on hospital charges multiplied by cost-to-charge ratios (CCRs). For rate setting, CMS aggregates the cases into the MS-DRGs and groups the charges by revenue code and then reduces them to cost using one of 19 national CCRs. For CMS's methodology to yield an accurate estimation of cost from

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provider billed charges, providers must mark up their costs. Tthe cost to the provider for the CAR-T product is $475,000, as stated by Novartis. The provider will pay this cost to the manufacturer and will need to represent this cost to CMS on its claim in the form of a dollar charge. The best way to do this would be for the provider to mark-up the $475,000 cost by its own drug or overall CCR based on its cost report. For illustrative purposes, assume the provider's drug CCR is similar to the FY2018 IPPS national average CCR for the drug cost group (0.194). This means the hospital would have to mark-up (i.e., divide) its $475,000 invoice cost by 0.194 to report a line item billed charge of **$2,448,453** just for the product.

Without billing CMS this marked-up charge, providers will not see the costs of CAR-T reflected in future MS-DRG payment rates, nor will the provider be able to generate an appropriate outlier payment for this type of case at the point of current billing and reimbursement. The odds of providers reporting such an extraordinarily high single charge is extremely slim, given concerns that the patient, other payers, and CMS's own MACs might express. At best, such a high dollar charge might be seen as an error, and, at worst, as an egregious act of over-charging. Yet a hospital would be within its rights to apply such a mark-up if it reasonably relates to its costs and reflects CMS's current IPPS rate setting and cost outlier methodologies.

As hospitals are not likely to mark up their invoice costs in this a manner, they will likely not generate the type of outlier payment they might otherwise resulting in inadequate current reimbursement and in an incorrect picture of true cost to be factored into future reimbursement rates for this breakthrough therapy which is bound to create barriers to access. The charge compression we anticipate for CAR T is likely to be much worse than what we've experienced to date for implantable devices and the MRI, CT and cardiac catheterization cost centers.

Utilizing current reimbursement methodologies without the use of NTAP, a modification to the outlier formula, the creation of new MS-DRGs, cost reimbursement in the early years of CAR-T, or some other mechanism will create tremendous challenges to those providers who wish to bring this new technology to the appropriate subset of beneficiaries.

As noted above, only a small number of providers will be performing CAR-T from the start, and while some of these will be the PPS-exempt cancer centers, it should be noted that they will face a similar financial impact despite their exemption. This is because neither the NTAP nor IPPS cost outlier payment is available to them. These centers are paid for inpatient cases based on a TEFRA per case rate which is set at a specific period in time and periodically rebased. It is very

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likely that the provision of CAR-T could result in an exempt center exceeding their rate. While exemptions to the rate can be granted, these cannot be requested until after a full cost-report year is finalized and settled, which can be several years after the date of discharge for the case. Therefore, policy remedies as mentioned above are needed for all providers of CAR-T, including the PPS exempt cancer providers.

New Revenue Codes and Cost Center

In anticipation of the significant charge compression for CAR-T described previously, as well as successive cellular therapy products expected to be FDA approved in the coming years, ASBMT is planning to ask the National Uniform Billing Committee (NUBC) for a new, dedicated revenue code series for cellular therapy products. We believe this is necessary from the outset to clearly identify these products as unique from traditional drugs and antineoplastic agents. This is particularly important on inpatient claims where drug-specific HCPCS code and/or NDC code are not routinely billed to the Medicare program. Along with the new revenue code series, ASBMT is requesting CMS establish a dedicated cost center for cellular therapy products, beginning with CAR-T. Neither of the above is unlike what CMS recently did for stem cell transplants (i.e., new revenue code 0815 and new cost center line 77). We strongly believe this approach will help ensure that CAR-T and future cellular therapy products are protected from the outset from the well-known problems associated with charge compression and other rate setting anomalies.

Finally, the ASBMT strongly urges CMS to consider developing a 20th IPPS rate-setting cost group for cellular therapy using the information collected from the new revenue code and new cost center. This will enable CMS and the public to isolate this very new and extremely expensive therapy. CMS will have exercised considerable foresight if it anticipates these issues now and proactively plans to account for them in its rate-setting methodology from the outset.

New Codes Needed for Reimbursement and Tracking

The ASBMT has been working with providers and coding experts to identify the most appropriate ICD-10-PCS and CPT codes to describe the various steps involved in the use of CAR-T; namely the collection and infusion of cells, though there are also other steps that may be involved. Starting October 1, 2018, providers will be able to report CAR T infusion administration provided in the inpatient setting with a new ICD-10-PCS code. Until that time, facilities will have to exercise their judgement and report the next best code available.

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The following codes are not currently available:

- Collection of autologous cells for the purpose of CAR-T manufacturing (similar collection procedure codes are explicitly defined as for the purpose of HCT)
- Infusion/Administration of the CAR-T product into the patient
- Product specific J codes and/or temporary Q codes until J codes are available

We acknowledge there are codes that may work for an interim time period as substitutes for new and specific codes, but we believe this requires discussion with CMS and/or CPT to create clarity and consistency in the use of alternate codes so that these services do not inappropriately affect non-CAR-T APC calculations in upcoming years. In addition to clarifying interim codes for use, we believe it will be necessary for CMS to release G-codes to describe the various procedural steps involved in CAR-T due to the cost and unique aspects of care delivery associated with these products. We ask that CMS consider issuance G-codes very soon so they are available by January 1, 2018, as well as issuing guidance on interim coding procedures.

Innovative Payment Model for CAR-T

On August 30, 2017, Novartis and CMS issued public statements regarding alternative payment models for CAR-T in the Medicare beneficiary population. The ASBMT supports innovative thinking about reimbursement for the provision for CAR-T due to all of the reasons outlined in this letter. Novartis indicated that reimbursement would only be applicable in cases where the patient shows a response to Kymriah at 30 days after provision. Below, we summarize the comments and questions we have received from our member clinicians and administrative staff since the public commentary on this potential mechanism.

Response Determination:

- A third-party organization should be involved with the determination of response levels that would indicate payment is needed. Accurate and time-sensitive individual analyses will be needed. Publicly reported aggregate outcomes should be considered. The Center for International Blood and Marrow Transplant Research (CIBMTR) is a qualified potential resource for evaluating clinical responses.
- Historically, response assessment for therapies for hematologic malignancies have been assess at intervals well beyond 30 days. HCT is assessed for efficacy at 100 days, 6 months and 1 year after transplantation. We encourage open and public dialogue in determining the appropriate response timeline for CAR-T products.
- A certain percentage of CAR-T patients will relapse within a few months of treatment and will need to be either re-treated with CAR-T or receive HCT to attempt to gain a

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more secure remission or cure. In these cases, the valuation of the efficacy of the initial product, and corresponding payment, may need to be adjusted accordingly.

Financial Implications:

- Hospitals should not be held financially liable for the care provided to patients receiving CAR-T if the patient does not experience a response warranting payment for the product. A significant amount of resources will be utilized by the facility in advance of the Day 30 outcome evaluation and those services should be reimbursed by CMS.
- Hospitals should not be asked to pay for a product at the time of use if reimbursement for the product purchase will be determined at Day 30. Movement of significant dollars to and from the manufacturer in a short period of time will create financial reporting issues for facilities and may take the funds away from other patient care needs.

Summary and Contacts

ASBMT has gathered a cohort of provider, payer and manufacturer stakeholders that are helping to identify and resolve issues related to access, coding, billing, and reimbursement for CAR-T. We welcome the opportunity to discuss identified issues with CMS in hopes that the agency will choose to utilize its authority under the law to create appropriate reimbursement mechanisms outside of CMS's normal rate-setting schedule. CAR-T is a transformative therapy for the field of oncology and ASBMT is committed to making it available to beneficiaries that may benefit. ASBMT peer-elected leaders, member clinicians and policy staff are available as a resource for CMS staff when issues associated with HCT, CAR-T 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, 2017-2018

Health Policy Staff Contact: Stephanie Farnia, Director, Health Policy;
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Addendum A: Excerpt from Previous ASBMT Comment Letter on ICD-10-PCS Codes

CMS Precedent for Inclusion of High-Dose Interleukin Treatment in MS-DRG 837/838

As is described in the following excerpt from the Inpatient Prospective Payment System Fiscal Year 2008 Final Rule, CMS acknowledges this same issue during the early use of HD-IL-2 and clarifies that antineoplastic care episodes utilizing HD-IL-2 should be assigned to a MS-DRG more reflective of the resources utilized during the provision of care.

DEPARTMENT OF HEALTH AND HUMAN SERVICES Centers for Medicare & Medicaid Services 42 CFR Parts 411, 412, 413, and 489 [CMS-1533-FC] RIN 0938-AO70 Medicare Program; Changes to the Hospital Inpatient Prospective Payment Systems and Fiscal Year 2008 Rates https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/downloads/CMS-1533-FC.pdf

Administration of high-dose Interleukin-2 (HD-IL-2) is a hospital inpatient-based regimen that can produce durable remissions of metastatic renal cell cancer and metastatic melanoma in a subset of patients. In contrast to traditional cytotoxic chemotherapies which target cancer cells directly, HD-IL-2 enhances the body's natural cancer defenses by stimulating the growth and activity of cancer-killing white blood cells. HD-IL-2 therapy is associated with severe complications that can include: hypotension, metabolic acidosis, acute renal failure, arrhythmia, myocardial inflammation, coagulation defects, hyperthyroidism, psychosis, respiratory distress syndrome, catheter related septicemia, hyperbilirubinemia and thrombocytopenia. To safely administer HD-IL-2, the FDA-approved label states that HD-IL-2 "should be administered in a hospital setting under the supervision of a qualified physician experienced in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available." Strict nursing protocols must be followed in order to minimize adverse events such as cardiac arrhythmias as well as severe hypotension. Because it is associated with such severe side effects, HD-IL-2 therapy requires substantially greater resource utilization, including longer hospital stays and additional nursing support, than conventional chemotherapy. Conventional chemotherapy may be administered to patients either on an outpatient basis or through a series of short (that is, 1 to 3 day) inpatient stays.

In spite of the possibility of erroneous coding of low-dose IL-2 cases to procedure code 00.15 instead of the more appropriate code 99.28 as discussed above, the data do not currently suggest a problem with Medicare payment for most of the HD-IL-2 cases assigned to MS-DRGs 837, 838, and 839. However, the data do suggest that the costs of cases of IL-2 coded with 00.15

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currently assigned to MS-DRG 839 are closer to MS-DRG 838. Therefore, for FY 2008, we are assigning procedure code 00.15 (High-dose infusion of Interleukin-2 (IL-2)) to MS-DRG 837 (Chemotherapy with Acute Leukemia as Secondary Diagnosis or with High Dose Chemotherapeutic Agent with MCC) and MS-DRG 838 (Chemotherapy with Acute Leukemia as Secondary Diagnosis with CC or High Dose Chemotherapeutic Agent).

Addendum B: Except from ASBMT FY2018 IPPS Comment Letter

As submitted on June 10, 2017

I. 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."

a. 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).

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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 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.

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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.
- 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.

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- 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 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.

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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.

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

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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.[9] 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 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.[10] 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

[9] 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

[10] 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

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therapy[11] and patients treated at the National Cancer Institute remain in remission over 2 years after therapy.[12] 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 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.[13]

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

[11] 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.

[12] 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.

[13] 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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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.

II. 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 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.

III. 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

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