Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N)

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Decision Summary

A. The Centers for Medicare & Medicaid Services (CMS) covers autologous treatment for cancer with T-cells expressing at least one chimeric antigen receptor (CAR) when administered at healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and used for a medically accepted indication as defined at Social Security Act section 1861(t)(2) i.e., is used for either an FDA-approved indication (according to the FDA-approved label for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia.

B. The use of non-FDA-approved autologous T-cells expressing at least one CAR is non-covered. Autologous treatment for cancer with T-cells expressing at least one CAR is non-covered when the requirements in Section A are not met.

C. This policy continues coverage for routine costs in clinical trials that use CAR T-cell therapy as an investigational agent that meet the requirements listed in NCD 310.1.

See Appendix B for the language representative of Medicare's national coverage determination (NCD) for implementation purposes only.

Decision Memo

TO: Administrative File: CAG-00451N

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SUBJECT: National Coverage Determination for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers

DATE: August 7, 2019

I. Decision

A. The Centers for Medicare & Medicaid Services (CMS) covers autologous treatment for cancer with T-cells

expressing at least one chimeric antigen receptor (CAR) when administered at healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and used for a medically accepted indication as defined at Social Security Act section 1861(t)(2) i.e., is used for either an FDA-approved indication (according to the FDA-approved label for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia.

B. The use of non-FDA-approved autologous T-cells expressing at least one CAR is non-covered. Autologous treatment for cancer with T-cells expressing at least one CAR is non-covered when the requirements in Section A are not met.
C. This policy continues coverage for routine costs in clinical trials that use CAR T-cell therapy as an investigational agent that meet the requirements listed in NCD 310.1.

See Appendix B for the language representative of Medicare's national coverage determination (NCD) for implementation purposes only.

II. Background

Throughout this document we use numerous acronyms, some of which are not defined as they are presented in direct quotations. Please find below a list of these acronyms and corresponding full terminology:

AATB - American Association of Tissue Banks
ACT - Adoptive Cell Therapy
AEs - adverse events
AIDS - Acquired immune deficiency syndrome
ALL - Acute Lymphoblastic Leukemia
AHRQ - Agency for Healthcare Research and Quality
ARC - American Red Cross
ASBMT - American Society for Blood and Marrow Transplantation
ASCT - Autologous stem cell transplantation
ASFA - American Society for Apheresis
AYA - adolescent and young adult
BCMA - B-cell maturation antigen
BLA - Biologics Licensing Application
BOMC - Mini-Cog, Blessed Orientation-Memory-Concentration
CAP - College of American Pathologists
CAR - Chimeric Antigen Receptor
CAR-T - Chimeric Antigen Receptor T-cells
CARG - Cancer and Aging Research Group score
CD-19 - Cluster of Differentiation 19
CED - Coverage with Evidence Development
CHOP - Children's Hospital of Philadelphia
CIBMTR - Center for International Blood and Marrow Transplant Research
CMS - Centers for Medicare & Medicaid Services
CNS - central nervous system
CRASH - Chemotherapy Risk Assessment Scale for High-Age Patients
CR - complete response
CRi - complete response with incomplete hematologic/blood count recovery
CRS - cytokine release syndrome
DLBCL - diffuse large B-cell lymphoma
DLT - dose-limiting toxicity
DOR - duration of response

ECOG-PS - Eastern Cooperative Oncology Group Performance Status
ETASU - Elements To Assure Safe Use
FACT - Foundation for the Accreditation of Cellular Therapy
FDA - Food and Drug Administration
FL - Follicular Lymphoma
G8 - Geriatric-8
GA - geriatric assessment
GDS - Geriatric Depression Scale
HCT - allogeneic hematopoietic cell transplantation
HIV - human immunodeficiency virus
IADL - Instrumental activities of daily living
ICER - Institute for Clinical and Economic Review
ICU - Intensive Care Unit
ISCT - International Society for Cellular Therapy
MA - Medicare Advantage
MAC - Medicare Administrative Contractor
MEDCAC - Medicare Evidence Development and Coverage Advisory Committee
NCA - National Coverage Analysis
NCCN - National Comprehensive Cancer Network
NCD - National Coverage Determination
NCI - National Cancer Institute
NHL - Non-Hodgkin's Lymphoma
NMDP - National Marrow Donor Program
NOS - not otherwise specified
ORR - overall response/remission rate
OS - overall survival
PFS - progression-free survival
Ph - Philadelphia
PMR - postmarketing requirements
PR - partial response
PRO - Patient-Reported Outcome
REMS - Risk Evaluation and Mitigation Strategies
R/R - relapsed/refractory
SBRA - Summary Basis for Regulatory Action
SEER - Surveillance, Epidemiology, and End Results Program
TA - technology assessment
US - United States
VES-13 - Vulnerable Elders Survey-13

Background on Cancer

What is cancer?

Cancer is a collection of related diseases of dividing cells that can start almost anywhere in or on the body, evade the immune system, and invade nearby tissues. Categories of cancer are typically organized by the location in the body and specific type of cell. These categories may include carcinoma, sarcoma, leukemia, lymphoma, multiple myeloma, melanoma, and brain and spinal cord tumors. There are also changes to these cells that are not considered cancer. These changes include hyperplasia□□when a cell divides faster than normal□□and dysplasia□□a buildup of extra cells with abnormal shape and disorganization.

Lymphomas are cancers of lymphocytes (B cells or T cells) and consist of two main types. Hodgkin lymphoma arises usually from B cells and Non-Hodgkin lymphoma (NHL) can form from B cells or T cells. According to the American Cancer Society (2018), Hodgkin lymphoma is most common in early adulthood, with an average age of 39 at

diagnosis, while NHL accounts for about four percent of all cancers in the U.S. with an estimate that about 74,680 adult and children (41,730 males and 32,950 females) will be diagnosed with NHL and about 19,910 people will die from NHL (11,510 males and 8,400 females) during 2018. The most common sub-type of NHL is diffuse large B cell lymphoma (DLBCL) representing 30-40% of all cases worldwide and has a number of different cell subtypes of origin to divide cases into germinal centre B cell like subtypes and activated B cell like subtypes (Li et al., 2018). Additionally, follicular lymphoma, which arises from B cells, affects people over 50 years old, and comprises nearly 20-30% of NHL. While NHL can occur at any age, the risk increases with age; more than half of patients are 65 or older at the time of diagnosis (American Cancer Society, 2018).

In its 2018 guideline, The National Comprehensive Cancer Network (NCCN) noted that the incidence of NHL increased significantly between 1970 and 1995 but has moderated since the mid-1990s. While the increase was attributed partly to the human immunodeficiency virus (HIV) epidemic and the development of AIDS-related NHL, much of the increase in incidence has been observed in patients in their sixth and seventh decades. As a result, patients with NHL may also have significant comorbidities.

Leukemias are cancers that arise from blood-lineages of the bone marrow. The type of leukemia depends of the type of cell and cell growth. Acute lymphoblastic leukemia (ALL) is also a cancer of B-cell origin that is associated with immature B-cells in the bone marrow, blood, and other organs. The NCCN (2018a) notes that "the age-adjusted incidence rate of ALL in the U.S. is 1.58 per 100,000 individuals per year" (National Cancer Institute (NCI), 2016a), with approximately 5,970 new cases and 1,440 deaths estimated in 2017 (Swerdlow et al., 2008). The median age at diagnosis for ALL is 15 years (NCI, 2016b) with 57.2% of patients diagnosed at younger than 20 years of age (NCI, 2016c). In contrast, 26.8% of cases are diagnosed at 45 years or older and only approximately 11% of patients are diagnosed at 65 years or older (NCI, 2016c). ALL represents 75% to 80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast, ALL represents approximately 20% of all leukemias among adults (Jabbour et al., 2005; Esparza et al.,2005). Chronic lymphoblastic leukemia (CLL) is a more slowly progressing type.

Multiple myeloma begins in a different type of cell, the plasma cell. According to the Surveillance, Epidemiology, and End Results (SEER) Program Cancer Statistics Review (Noone et al., 2018) there were an estimated 124,733 people living with myeloma in the US and the lifetime risk of developing this cancer at some point is approximately 0.8 percent. Additionally, the number of new cases per year is 6.7 per 100,000 with 3.3 deaths per 100,000. In general, plasma cell neoplasms are most common in people who are at middle age or older. Treatment can be based on the stage of cancer, which is the result of a determination of combination of factors including the amount of cancer in the body and biomarkers such as albumin in the blood.

What are the treatment options for cancer patients?
Cancer has many treatments available, with some seen as the standard of care and others only available in the context of a clinical trial. For some patients, participation in a clinical trial may be the best process to access a new potential treatment. Surgery may be performed to remove certain cancerous tumors. Radiation therapy can be delivered externally or internally to disrupt cell division and keep cells from growing. Drugs, such as chemotherapy, stop cancer cell growth and division depending on the type and stage of cancer being treated. Targeted therapy works to attack a subset of cells by leveraging specific cellular processes, such as protein synthesis and degradation. Immunotherapy is a type of cancer treatment that involves strengthening a patient's own immune system. Different types of immunotherapy for cancer include biologicals such as monoclonal antibodies and cytokines, and drugs such as immune checkpoint inhibitors, and cancer vaccines. As one example, monoclonal antibodies identify and attach to substances on the cell surface to kill or keep cancer cells from spreading. Another method of rapidly-emerging immunotherapy is called adoptive cell transfer (ACT), which consists of the collection, alteration and then re-administration of a patient's immune cells to attack the patient's cancer. For example, in the case of stem cell transplantation, blood can be taken from the patient or a healthy donor, and these infused stem cells can restore the patient's normal immune system. Each treatment has specific and sometimes distinct side effects and the population

receiving a given treatment could be at risk for serious side effects or adverse events as a result.

Schuster et al. (2017), states that DLBCL "is successfully treated in about two thirds of patients with rituximab-based immunochemotherapy (Feugier et al., 2005; Pfreundschuh et al., 2006). When current frontline immunochemotherapy fails, high-dose chemotherapy with autologous stem-cell transplantation can lead to long-term disease-free survival (Gisselbrecht et al., 2010)." For patients with follicular lymphoma, there is "an excellent prognosis after receiving frontline rituximab- based therapies; however, in 20% of patients with follicular lymphoma, relapse occurs within 2 years after initial immunochemotherapy (Tan et al., 2013; Casulo et al., 2015). Among patients with relapsed follicular lymphoma that is refractory to rituximab and to alkylating-agent□based therapy, treatment with idelalisib or copanlisib, the only agents that have been approved by the Food and Drug Administration (FDA) for such patients, is associated with a median response duration of 10.8 and 12.2 months, respectively (Salles et al., 2017; Whippany et al., 2017)." (Schuster, 2017) Crump et al. 2017 reported on the results of a large, international, multi-cohort, retrospective study of patient's with NHL called SCHOLAR-1. The authors noted that "Published analyses of large-scale outcome data from patients with refractory DLBCL are limited" therefore the goal of the SCHOLAR-1 study was to evaluate the outcomes of currently available therapies for patients with refractory DLBCL in order to serve as a benchmark for future studies. The authors defined refractory DLBCL as "progressive disease (received ≥ 4 cycles of first-line therapy) or stable disease (received 2 cycles of later line therapy) as best response to chemotherapy or relapse ≤ 12 months after ASCT." Objective response rate, complete response rate and overall survival were estimated from the time of initiation of salvage therapy for refractory disease. The authors found "the objective response rate was 26% (complete response rate, 7%) to the next line of therapy, and the median overall survival was 6.3 months. Twenty percent of patients were alive at 2 years. Outcomes were consistently poor across patient subgroups and study cohorts."

Survival Rates from Cancer
Expected 5-year relative survival rates from 2008-2014 are derived from tables by socio-economic status, geography and race developed by the SEER program (Noone et al., 2018) and are available at https://seer.cancer.gov/csr/1975_2015/results_merged/topic_survival.pdf. The rates inclusive of both sexes and all races are reported here, while noticeable disparities are described in our analysis (see section VIII.). Survival rate in myeloma was 50.7%. Rates in lymphoma differed between Hodgkin (86.6%) and NHL (71.4%) as did rates in leukemia subsets between acute lymphocytic (68.1%) and chronic lymphocytic (84.2%).

According to the NCCN (2018a), the "The cure rates and survival outcomes for patients with ALL have improved dramatically over the past several decades, primarily among children (Ma et al., 2014). Improvements are largely owed to advances in the understanding of the molecular genetics and pathogenesis of the disease, the incorporation of risk-adapted therapy, the advent of new targeted agents, and the use of allogeneic hematopoietic cell transplantation (HCT). Data from the SEER database have shown a 5- year overall survival (OS) of 86% to 89% for children (Kenderian et al., 2013; Ma et al., 2014); however, AYA patients were reported to have a 5-year OS between 42% to 63% depending on the age range.

Adults have the poorest 5-year OS rate of 24.1% for patients between the ages of 40 and 59 and an even lower rate of 17.7% for patients between the ages of 60 and 69 (Pulte et al., 2014). Although the exact OS percentage can vary based on how the age range is defined for pediatric, AYA, and adult patients, the trend is nonetheless clear that OS decreases substantially with increased age. The exception is infants younger than age one, which is an age group that has not seen any improvement in survival over the last 30 years (Jabbour et al., 2005). The 5-year OS in this population is 55.8% (Ma et al., 2014). Cure rates for AYAs with ALL remain suboptimal compared with those for children, although substantial improvements have been seen with the recent adoption of pediatric treatment regimens (Stock et al., 2010). AYA patients represent a unique population, because they may receive treatment based on either a pediatric or an adult protocol, depending on local referral patterns and institutional practices." Schuster et al (2017) notes that "for most patients treated since the introduction of rituximab, the expected rate of 3-year event-free survival after autologous stem-cell transplantation is only approximately 20% (Gisselbrecht et al.,

2010)." "These patients with early relapse have a poor prognosis, with a rate of 5-year overall survival of only 50% when they are treated with currently available therapies (Tan et al., 2013; Casulo et al., 2015)."

Background on Chimeric Antigen Receptor T-cell Therapy
A person's immune system contains cells to help fight substances that are foreign to the body, such as bacterial and viral infections. These cells are called white blood cells, most of which are lymphocytes. The two main types of lymphocytes are B lymphocytes (B-cells) and T lymphocytes (T-cells). B-cells generate and release antibodies to fight infection, especially bacterial infections, while T-cells employ a number of other mechanisms to fight abnormal cells such as cancer. As previously described, one type of therapy that leverages the immune systemimmunotherapyis CAR T-cell therapy.

What is CAR T-cell therapy?
Chimeric Antigen Receptor T-cells (CAR T-cells) are T-cells that have been genetically altered in order to improve the ability of the T-cells to fight cancer. The genetic modification creates a new and special receptor on the surface of the T-cell. This special receptor is called a CAR and there are many CARs on the surface of the T-cell. CAR enhances the ability of the T-cell to recognize and attach to a specific protein, called an antigen, on the surface of a cancer cell. Currently there are two FDA-approved CAR T-cell products: tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta). These two CAR T-cell products have a CAR that recognizes a specific antigen on the surface of certain cells, called CD-19.

What are the toxicities associated with CAR T-cell therapy?
As with the administration of other types of cancer chemotherapy agents, administration of CAR T-cell therapy has associated toxicities. First, as a result of their normal duties, T-cells release cytokines in order to stimulate and direct an immune response. During administration of a CAR T-cell therapy, this significantly large number of T-cells present can lead to a massive release of cytokines, which leads to cytokine release syndrome (CRS)a potentially life-threatening toxicity that produces a systemic inflammatory disorder mainly characterized by fever, rapid pulse (tachycardia) and low blood pressure (hypotension). The severity of CRS has been correlated with the patient's cancer burden (Baruch et al. 2017) and has been managed with an FDA-approved drug called tocilizumab.

Another prominent toxicity associated with CAR T-cell therapy is neurotoxicity, which can include confusion or seizure-like activity. According to the NCI (2017d), "in nearly all patients the problem is short lived and reversible." Finally, a significant toxicity of some CAR T-cell therapy is B-cell aplasia, which is a mass die off of B-cells. Since a functional target of recently approved CAR T-cell products is also found on the surface of normal B-cells, this CAR T-cell therapy also destroys the normal B-cells, which leads to the decreased production of antibodies. To compensate, immunoglobulin therapy is administered in order to provide the patient with antibodies to fight off infections.

III. History of Medicare Coverage

CMS does not currently have an NCD on CAR T-cell therapy.

A. Current Request

CMS received a complete, formal request for a national coverage determination from Efrem Castillo, MD, Medicare & Retirement Chief Medical Officer, UnitedHealthcare. The formal request letter can be viewed via the tracking sheet for this NCA on the CMS website at https://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx? NCAId=291.

CMS initiated this national coverage determination (NCD) to consider coverage under the Medicare Program for CAR

T-cell therapy, a rapidly emerging adoptive cell transfer immunotherapy for select patients with relapsed or refractory cancers. Treatment protocols vary, but may be summarized in five steps:

1. lymphocyte harvesting from the patient with cancer;
2. creation of cancer-targeting lymphocytes in vitro using various immune modulators;
3. selection of lymphocytes with reactivity to cancer antigens using enzyme-linked immuno-assay;
4. depletion of the patient's remaining lymphocytes using immunosuppressive agents;
5. transfusion of the cancer-targeting lymphocytes back into the patient with cancer-this transfusion represents one treatment.

The scope of this review is limited to autologous transplant of T-cells expressing at least one CAR for treatment of patients with cancer.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories outlined in the Social Security Act (the Act). CAR T-cell therapy falls under the benefit categories set forth in section § 1861(b) "inpatient hospital services", § 1861(s)(2)(B) "hospital services," and § 1861(t) "drugs and biologicals". This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Date	Action
May 16, 2018	CMS opens an NCA for Initial 30-day public comment period begins.
June 15, 2018	First public comment period ends. CMS receives 53 comments.
August 22, 2018	Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) meeting to discuss CAR T-cell therapy and patient-reported outcomes.
February 15, 2019	Proposed Decision Memorandum posted. 30-day public comment period begins.
March 17, 2019	Second public comment period ends. CMS receives 93 comments.

V. Food and Drug Administration (FDA) Status

The existing CAR T-cell therapies on the market were approved as biologics and, therefore, provisions of the Medicare statute for biologicals apply. To date, two CAR T-cell products have been approved by the FDA. The first CAR T-cell product, tisagenlecleucel, received FDA approval on August 30, 2017 for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. A second FDA indication for tisagenlecleucel was granted on May 1, 2018 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large

B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

The second CAR T-cell product, axicabtagene ciloleucel received FDA approval on October 18, 2017 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL, not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Additional information about the FDA approval of tisagenlecleucel, including the Risk Evaluation Mitigation Strategy (REMS) program, is found at https://www.fda.gov/biologicsbloodvaccines/cellulargenetherapyproducts/approvedproducts/ucm573706.htm.

Additional information about the FDA approval of axicabtagene ciloleucel, including the REMS program, is found at https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel.

VI. General Methodological Principles

When making national coverage determinations, CMS generally evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public comments sometimes cite published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will be redacted or will not be made available to the public. CMS responds in detail to the public comments on a proposed national coverage determination when issuing the final national coverage determination.

VII. Evidence

A. Introduction

This section provides a summary of the evidence we considered during our review. The evidence reviewed to date includes the published medical literature on pertinent clinical trials of autologous transplant of T-cells expressing at least one CAR for treatment of patients with cancer.

For this NCD, CMS searched for and determined whether the current evidence on CAR T-cell therapy is adequate to draw conclusions about health outcomes, as well as whether the body of evidence is generalizable to the Medicare population. This NCA summarizes the clinical evidence relating to the administration of the two FDA-approved CAR T-cell products, tisagenlecleucel and axicabtagene ciloleucel, in patients with FDA indications. The evidence CMS examines has as its focus health outcomes, i.e., the benefits and harms of a particular treatment. Independently

assessed, validated instruments were most heavily weighted. Study endpoints should be clearly defined a priori to both improve the quality of clinical research and so as to allow comparison between clinical trials. In addition, we present evidence on non-FDA-approved uses, NCCN compendia recommendations, as well as evidence of promising Phase I/II clinical trials developing additional CAR T-cell products earlier in the product lifecycle.

Key outcomes of interest to CMS in the treatment of cancer were long-term overall survival (OS, at least one year), progression-free survival (PFS), objective response rate (ORR) including complete response (CR) and partial response (PR), duration of response to specify days to disease progression and/or days to disease recurrence, peri-administration and long- term risk of AEs (especially any and all life-threatening AEs such as CRS), 30-day hospitalization rate, as well as health- related quality of life and function after the administration of CAR T-cell therapy in Medicare beneficiaries.

B. Discussion of Evidence

1. Question(s)

1. *Is the evidence adequate to conclude that CAR T-cell therapy improves health outcomes for Medicare beneficiaries with relapsed or refractory large B-cell lymphoma?*
2. *Is the evidence adequate to conclude that CAR T-cell therapy improves health outcomes for Medicare beneficiaries with relapsed or refractory B-cell precursor acute lymphoblastic leukemia?*
3. *Is the evidence adequate to conclude that CAR T-cell therapy improves health outcomes for Medicare beneficiaries with other types of cancer?*
4. *If the answer to any of the questions above is positive, is the available evidence adequate to identify the characteristics of the patient, practitioner or facility that predict which beneficiaries are more likely to experience overall benefit or harm from CAR T-cell therapy?*

2. External Technology Assessments

CMS did not commission an external technology assessment (TA) on this topic. An English language TA was identified during our review and is summarized below.

On February 15, 2018, the Institute for Clinical and Economic Review (ICER), a self-proclaimed "independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs," published a TA titled Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value. As of this date, the TA is found at https://icer-review.org/material/car-t-final-report/.

In September, 2017, ICER performed a search of MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials from September 25 - 27, 2017. ICER noted that they "sought out head-to-head studies for these interventions, but none were identified. Recognizing the current state of the evidence base for CAR T-cell therapy, we included single-arm trials and compared outcomes with historical control data." ICER also held discussions with patients and patient groups. The ICER analysis was reported by FDA indication.

Acute Lymphoblastic Leukemia

The ICER analysis included the results from three single-arm clinical trials for tisagenlecleucel for patients with relapsed or refractory ALL. Information for two of the trials (B2101J and B2205J), which were Phase I/II trials that had yet to be published in the clinical literature, was obtained from the Novartis FDA Advisory Committee Briefing Document (2017). Information for the remaining trial, the Phase II ELIANA trial, was obtained from Maude et al. (2017). The primary clinical endpoint selected was cure of the cancer, for which ICER noted there is "no accepted

definition of a cure, as relapses can rarely occur more than 10 years after remission. A recent proposal is that children in remission four years after the completion of treatment could be considered cured (< 1% chance of relapse; Hunger and Mullighan, 2015; Pui et al., 2014). Thus, four-year event-free survival would be an ideal outcome."

ICER found the three clinical trials "to be of lower quality because they lack comparators. Furthermore, the studies are small and have short median follow-up, which adds to the uncertainty about long term outcomes with CAR-T therapy for pediatric B-cell ALL."

With regards to the primary clinical endpoint, four-year event-free survival, ICER noted that "none of the trials of CAR-T therapy have followed patients for that long. The reported overall remission rates for tisagenlecleucel in the three trials (from 69% to 95%) represents an optimistic presentation of the results that violates the intention to treat principle because they exclude patients who did not receive the therapy because of manufacturing failures, death prior to infusion, or adverse events (AEs). Table ES2 estimates the overall remission rates in the trials based on the number of patients enrolled in each trial (i.e., on an intention to treat basis)." Table ES2 is reproduced in its entirety.

Table ES2. Overall Remission Rates in Therapies for Relapsed or Refractory Childhood B-ALL

Trial	Therapy	Overall Remission*
B2101J18	Tisagenlecleucel	52/71 = 73% (61% to 83%)
B2205J18	Tisagenlecleucel	20/35 = 57% (39% to 74%)
B2202 / ELIANA1	Tisagenlecleucel	61/92 = 66% (56% to 76%)
Jeha 2006	Clofarabine	12/61 = 20% (11% to 32%)
Hijiya 2011	Clofarabine/etoposide/ cyclophosphamide	11/25 = 44% (24% to 65%)
Von Stackelberg 2016	Blinatumomab	27/70 = 39% (27% to 51%)
Locatelli 2017	Blinatumomab	25/40 = 63% (46% to 77%)

*Based on the number enrolled, not the number receiving the infusion with CAR-T cells

ICER also noted that while "this presentation suggests more modest benefits, the overall remission rates are higher with tisagenlecleucel than with the other therapies. Table ES3 below estimates the overall event-free survival in the trials based on the number of patients enrolled." Table ES3 is reproduced in its entirety.

Table ES3. Estimated Event-Free Survival at Six Months in Therapies for Relapsed or Refractory Childhood B-ALL

Trial	Therapy	Event-free Survival at 6	Overall Survival at 12

		Months*	Months
B2101J18	Tisagenlecleucel	58%	81%
B2205J18	Tisagenlecleucel	46%	62%
B2202 / ELIANA1	Tisagenlecleucel	60%	62%
Jeha 2006	Clofarabine	11%	20%
Hijiya 2011	Clofarabine/etoposide/cyclophosphamide	35%	35%
Von Stackelberg 2016	Blinatumomab	16%	38%
Locatelli 2017	Blinatumomab	NR	NR

*Based on the number enrolled, not the number receiving the infusion with CAR-T cells or the number responding to treatment

With regards to toxicity, ICER stated that the "key AEs experienced by the first 68 patients who received an infusion of tisagenlecleucel in the ELIANA trial were reported in the package insert and are summarized in Table ES4 below." Table ES4 is reproduced in its entirety.

Table ES4. Key Adverse Events in the ELIANA trial (n=68)27

Adverse Reaction	All Grades	Grade 3 or Higher
Cytokine Release Syndrome	79%	49%
Neurologic Toxicities	65%	18%
Fever	50%	15%
Encephalopathy	34%	10%
Headache	37%	3%
Acute Kidney Injury	22%	13%
Hypotension	31%	22%

Hypoxia	24%	18%
Infections/Pathogens/Unknown	41%	16%
Viral Infections	26%	18%
Bacterial Infections	19%	13%
Fungal Infections	13%	7%

ICER noted that "Additional important grade three or higher adverse events include disseminated intravascular coagulation (9%), histiolymphocytic hemophagocytosis (7%), heart failure (7%), cardiac arrest (4%), seizures (3%), and intracranial hemorrhage (1%). There were 11 deaths: 7 from disease progression, 3 from infections, and one from intracranial hemorrhage. An additional important toxicity is hypogammaglobulinemia due to B-cell aplasia. B-cells are the target of tisagenlecleucel in order to keep the leukemia in remission. Patients without the immunoglobulins produced by B-cells are at risk for infections and are typically treated with monthly intravenous infusions of pooled immunoglobulins (IVIG). The Novartis briefing document for the FDA Advisory Committee states that "responding patients experienced continued B-cell aplasia indicating the long-term effect of tisagenlecleucel" and notes "B-cell aplasia ongoing for > 3 years (FDA Advisory Committee, 2017)." For those who require IVIG, the typical duration of use is unknown."

The authors summarized that for the ALL indication, the "ELIANA trial demonstrated CR rates for tisagenlecleucel that were substantially higher than those observed in recent trials of other drug therapies for heavily pre-treated pediatric patients with B-cell ALL. In addition, the disease-free survival and OS were also greater than those observed with other therapies, particularly in the earlier Phase I trials that have longer follow-up. There are important harms that occur commonly with tisagenlecleucel therapy (CRS, neurotoxicity, B-cell aplasia), but they are manageable and perceived by clinicians as arguably no worse than the serious AEs associated with chemotherapy in this patient population. Thus, the estimated net health benefit is substantial ("B+" rating)." The "B+" rating indicates "Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit."

B-Cell Lymphoma

For the FDA indication of B-cell lymphoma, ICER analyzed four clinical trials including a Phase I/II trial (Kochenderfer et al., 2017) and the Phase II ZUMA-1 trial (Neelapu et al., 2017) for axicabtagene ciloleucel as well as a Phase I/II trial (Schuster et al., 2017) and the Phase II JULIET trial (Schuster et al., 2017b, abstract only) for tisagenlecleucel. All four trials studied adults. All four were single-arm. Therefore, ICER selected the SCHOLAR-1 study (Crump et al., 2017), which was an international, multi-cohort retrospective non-Hodgkin's lymphoma research study that retrospectively evaluated outcomes in patients with refractory DLBCL, as a comparator for their analysis. In SCHOLAR-1, Crump et al., 2017, included patients with refractory DLBCL that was defined as "progressive disease or stable disease as best response at any point during chemotherapy (> 4 cycles of first-line or 2 cycles of later-line therapy) or relapsed at &8805 12 months from autologous stem cell transplantation. SCHOLAR-1 pooled data from 2 phase 3 clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group LY.12) and two observational cohorts (MD Anderson Cancer Center and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence)." ICER noted that the SCHOLAR-1 trial used the same inclusion and exclusion criteria as the ZUMA-1 trial to select a subset of patients with aggressive DLBCL. With regards to the primary clinical endpoint, ICER selected event-free survival two years after the completion of treatment as "a reasonable surrogate outcome" based on the work published by Maurer et al. (2014).

ICER noted that the "The ZUMA-1 and JULIET studies as well as the two single site studies were considered to be of lower quality because they lack comparators. Furthermore, the studies were small and of short median follow-up, which adds to the uncertainty about long term outcomes with CAR-T therapy for adult aggressive B-cell lymphoma." In addition, both "the ZUMA-1 and JULIET studies of CAR-T therapies for lymphoma followed patients for less than a median of two years, which limits conclusions about long term impact. Complete remission is a marker for long-term survival, but the majority of patients with B-cell lymphoma who have failed prior therapy usually relapse even after achieving subsequent remission."

Axicabtagene ciloleucel

For axicabtagene ciloleucel, results of the ICER analysis showed:

"Table ES6. Objective Response Rates Reported for Axicabtagene Ciloleucel for Relapsed or Refractory Adult B-cell Lymphoma Compared with SCHOLAR-1

Trial	Therapy	ORR	CR
ZUMA-1	Axicabtagene ciloleucel	82%	54%
NCT00924326	Axicabtagene ciloleucel	73%	55%
SCHOLAR-1	Mix of salvage therapies	26%	7%

CR: complete remission, ORR: objective response rate

The complete remission rate for axicabtagene ciloleucel in ZUMA-1 (54%) shown in Table ES6 represents an optimistic presentation of the results that violates the intention to treat principle because it is based on patients who received the infusion of CAR T-cells and does not include the patients who enrolled in the trials but did not receive the therapy because of manufacturing failures, death prior to infusion, or AEs. Table ES7 below estimates the complete remission rate based on the number of patients enrolled in the trial." Table ES7 is reproduced in its entirety.

Table ES7. Estimated Complete Remission Rates for Axicabtagene Ciloleucel for Relapsed or Refractory Adult B-cell Lymphoma Compared with SCHOLAR-1s

Trial	Therapy	Complete Remission Rate*
ZUMA-1	Axicabtagene ciloleucel	52/111 = 47% (37% to 57%)
NCT00924326	Axicabtagene ciloleucel	12/NR = NR
SCHOLAR-1	Mix of salvage therapies	7% (3% to 15%)

*Based on the number enrolled, not the number receiving the infusion with CAR-T cells

NR: Not reported

ICER noted that "Even with this change, the complete remission rate is much higher with axicabtagene ciloleucel than with the other therapies. In SCHOLAR-1, the median overall survival was 6.3 months and the Kaplan-Meier estimates for one and two-year survival rates were 28% and 20% respectively. At six months, the Kaplan-Meier

estimates for overall survival were 80% in ZUMA-1 and 55% in SCHOLAR-1.

Neelapu and colleagues presented a propensity-score-matched analysis comparing the outcomes of ZUMA-1 to those of SCHOLAR-1 at American Society of Hematology (ASH) in December 2017 (Neelapu et al., 2017a). They reported that after matching, the ORR was 83% in ZUMA-1 and 33% in SCHOLAR-1 (treatment difference 49%, 95% CI 33% to 63%). Similarly, the estimated CR was 57% in ZUMA-1 and 12% in SCHOLAR-1 (treatment difference 46%, 95% CI 26% to 59%). The estimated HR for overall survival was 0.28 (95% CI 0.15 to 0.40) with 18-month OS estimated to be 47% in ZUMA-1 and 23% in SCHOLAR-1."

With regards to the toxicity of axicabtagene ciloleucel, ICER presented the following table:
"Table ES9. Key Adverse Events in the ZUMA-1 Trial (n=101)

Adverse Reaction	**All Grades**	**Grade 3 or Higher**
Cytokine Release Syndrome	94%	13%
Neurologic Toxicities	87%	31%
Fever	86%	16%
Encephalopathy	57%	29%
Headache	45%	1%
Renal Insufficiency	12%	5%
Hypotension	57%	15%
Hypoxia	32%	11%
Infections - Pathogens Unknown	26%	16%
Viral Infections	16%	4%
Bacterial Infections	13%	9%
Fungal Infections	5%	NR

Additional important grade 3 or higher adverse events include histiolymphocytic hemophagocytosis (1%), heart failure (6%), cardiac arrest (4%), seizures (4%) and pulmonary edema (9%). There were 44 deaths: 37 from disease progression, two from CRS, one from a pulmonary embolus, and four in patients with disease progression who were on subsequent therapies."

Tisagenlecleucel

The results of the ICER analysis of tisagenlecleucel for relapsed or refractory adult B-cell lymphoma showed:

"Table ES8. Objective Response Rates Reported for Tisagenlecleucel for Relapsed or Refractory Adult B-Cell Lymphoma Compared with SCHOLAR-1

Trial	Therapy	ORR	CR
JULIET	Tisagenlecleucel	53%	40%
NCT00924326	Tisagenlecleucel	64%	57%
SCHOLAR-1	Mix of salvage therapies	26%	7%

CR: complete remission, ORR: objective response rate

The complete remission rate for tisagenlecleucel in JULIET (40%) represents an optimistic presentation of the results that violates the intention to treat principle because it is based on patients who received the infusion of CAR-T cells and does not include the patients who enrolled in the trials but did not receive the therapy because of manufacturing failures, death prior to infusion, or AEs, nor does it include patients treated with tisagenlecleucel who had less than three months follow-up at the time of analysis. It was not possible to estimate a complete remission rate using an intent-to-treat analysis based on the data available from the public presentations. The reported CR and ORR in the JULIET trial (40% and 53% respectively) were slightly lower compared to the CR and ORR of the subset of patients with DLBCL in the ZUMA-1 trial (n=77) who were treated with axicabtagene ciloleucel (49% and 82%, respectively; Locke et al., 2017). However, the confidence intervals overlap extensively, and selection bias may also explain part of the differences. For example, the JULIET trial recruited patients from 10 different countries on 4 continents, while 21/22 sites for the ZUMA-1 trial were in the US (one in Israel). The complete remission rate (43%) among patients who received tisagenlecleucel was markedly higher than that observed in the SCHOLAR-1 trial (7%), which predominantly included adults with DLBCL (87% DLBCL). Given the paucity of the currently reported results for the ongoing JULIET trial, we were unable to project long-term outcomes for comparison with axicabtagene ciloleucel or the salvage regimens included in the SCHOLAR-1 study."

Below is a table showing the toxicity of tisagenlecleucel, as presented by ICER, as well as commentary by ICER:

"Table ES10. Key Adverse Events in the JULIET Trial (n=99)

Adverse Reaction	All Grades	Grade 3 or Higher
Cytokine Release Syndrome	58%	23%
Neurologic Toxicities	21%	12%
Infections	34%	20%
Cytopenias Not Resolved by Day 28	36%	27%
Febrile Neutropenia	13%	13%

Tumor Lysis Syndrome	1%	1%

There were no deaths or reported cases of cerebral edema.

Finally, there are theoretical concerns about mutagenesis from the insertion of the transgene into the patient's T-cells for both CAR-T therapies. The risk is likely to be quite low, but is an important long-term concern for further study."

For the B-cell lymphoma indication, the authors summarize that the "ZUMA-1 trial demonstrated CR rates for axicabtagene ciloleucel that were substantially higher than those observed in recent trials of other drug therapies for heavily pre-treated adults with B-cell lymphoma as reported in the SCHOLAR-1 study. In addition, the disease-free survival and OS appear to be greater than those observed with other therapies, but follow-up in the ZUMA-1 trial is short (median 15.4 months). There are important harms that occur commonly with axicabtagene ciloleucel therapy (CRS, neurotoxicity, B-cell aplasia), but they are manageable and perceived by clinicians as arguably no worse than the serious AEs associated with chemotherapy in this patient population. Thus, the estimated net health benefit is substantial ("B+" rating).

There are no head to head trials of axicabtagene ciloleucel and tisagenlecleucel for patients with relapsed/refractory B-cell lymphomas. The ORR and CR with axicabtagene ciloleucel are somewhat higher than those for tisagenlecleucel, but could easily reflect differences in the patient populations or chance. Patients treated with axicabtagene ciloleucel appeared to have fewer grade 3/4 CRS events, but more grade 3/4 neurologic events. Again, this may represent real differences in the two CAR-T therapies because of differences in their co-stimulatory domains, selection bias, or chance. The lack of head-to-head randomized trials and the small number of patients studied render such judgements premature. Given the level of uncertainty, the evidence is insufficient to judge whether one of the CAR-T therapies is superior to the other ("I" rating)." The "I" rating equals a rating of "Insufficient" and indicates "Any situation in which the level of certainty in the evidence is low."

ICER Summary: CAR T-cell Therapy
In summary, for both tisagenlecleucel and axicabtagene ciloleucel and for both FDA indications, ICER noted a number of uncertainties with regards to the results of the above clinical trials including that "the studies of CAR-T therapies are all single-arm trials. Given the possibility of selection bias in these trials, it is impossible to compare outcomes from these trials to those of other trials without considerable uncertainty." In addition, "the trials themselves are small and have short follow- up. The sample sizes with outcomes in the trials are less than 100 participants, and the median follow-up in the trials is less than two years. Thus, estimates of outcomes from the trials have wide confidence intervals; as such, both the benefits and duration of and long-term relapse-free survival is unknown at this point.

A related uncertainty is the long-term harms of therapy. In the intermediate term, there is insufficient data to estimate how many patients will continue to have clinically important hypogammaglobulinemia from B-cell aplasia. There are also theoretical concerns about complications from the viral vectors used in the manufacturing process and of secondary malignancies related to mutations in the T-cells due to the manufacturing process. Finally, there may be unanticipated harms that arise as larger numbers of patients are followed for several years."

3. Internal Technology Assessment

Literature Search Methods

On June 20, 2018, CMS searched PubMed for clinical trials that focused on tisagenlecleucel or axicabtagene ciloleucel

and were published in peer-reviewed journals. The literature search was limited by language (English), study population (human), article type (clinical trial) and timeframe (last ten years). Search terms included "chimeric antigen receptor," "CAR T," "T-cell," "CAR-T," "CART-19," "leukemia," and "lymphoma." Abstracts for the resultant citations were visually reviewed to find the clinical studies that focused on tisagenlecleucel or axicabtagene ciloleucel. From the PubMed search results, we found four relevant articles for lymphoma (Schuster et al., 2017; Neelapu et al., 2017; Kochenderfer et al., 2017; Locke et al., 2017) and two relevant articles for leukemia (Maude et al., 2014; Maude et al., 2018) that met our inclusion criteria. We reviewed articles submitted through public comment, and included any that met this search criteria.

We also searched the bibliography of each of the above articles, the citation list of clinical guidelines, professional society position statements and each public comment to find additional sources of clinical evidence for our review. We identified no new evidence from this search that met our criteria.

The full-text, peer-reviewed published literature articles that present the results of a clinical trial for tisagenlecleucel or axicabtagene ciloleucel are summarized below by FDA indication. Abstracts were excluded because they do not provide sufficient information about the clinical trial to support further review. Reviews, retrospective studies/case reports and commentaries were not included because they did not present the results of a data analysis (reviews), were of insufficient evidentiary weight compared to prospective clinical trials, or were subjective (commentaries). NCCN clinical guidelines and CMS approved compendia information were researched as part of this analysis. We include publicly accessible information, including the Summary Basis of Approval from the FDA website and professional society position statements as summarized in the Evidence Summary section that follows.

Evidence Summary

Tisagenlecleucel for Relapsed or Refractory ALL

Maude SL, Frey N, Shaw PA et al. Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. N Engl J Med 2014;371:1507-17.
The authors reported the two year outcomes of their Phase I/II clinical trial, which was a prospective, single arm, single center, open label, pilot study designed to assess the safety and feasibility of CART19 therapy (CTL019the precursor to tisagenlecleucel; Novartis) in children and adults with chemotherapy-resistant or refractory CD19+ leukemia. Conditioning chemotherapy with etoposide/cyclophosphamide, fludarabine/cyclophosphamide, methotrexate/eytarabine, or cyclophosphamide/vincristine/adriamycin was administered one week prior to CTL019 infusion unless medically contraindicated. The administration of tocilizumab was standard for all occurrences of severe CRS. Severe CRS was defined as hypotension requiring two or more vasopressors or respiratory failure requiring mechanical ventilation. The administration of immunoglobulin was standard for all occurrences of B-cell aplasia. A CR was defined by morphologic assessment of the bone marrow as M1 (< five percent leukemic blasts) with no evidence of extramedullary disease.

A total of 30 patients with relapsed or refractory ALL were treated. Twenty-five were five to 22 years of age (pediatric cohort: median age at infusion was 11 years; 56% male); five were 26 to 60 years of age (adult cohort: median age at infusion was 47 years; 80% male).

Median follow-up was seven months (range, 1 - 24). At one month, 27 of 30 (90%) patients achieved a CR. Nineteen of 27 patients remained in remission with 15 patients receiving no further treatment and four patients withdrawing from the study to receive further treatment. Seven of 27 patients relapsed between six weeks and 8.5 months after infusion; three relapses were associated with loss of CTL019 T-cells. The remaining patient with a CR developed myelodysplastic syndrome and withdrew from the study. The six-month event-free survival rate was 67% (95% confidence interval [CI], 51 ☐ 88). The six- month OS was 78% (95% CI, 65 ☐ 95). The probability that a patient

would have persistence of CTL019 at six months was 68% (95% CI, 50 ☐ 92). The probability that a patient would have relapse-free B-cell aplasia was 73% (95% CI, 57 ☐ 94).

No deaths related to the administration of CTL019 were reported. CRS developed in all 30 patients, who were hospitalized for treatment of the CRS. Severe CRS developed in eight (27%) patients, which was treated in the intensive care unit with tocilizumab with full recovery. Thirteen patients developed neurologic adverse events ranging from delirium associated with high temperatures to global encephalopathy. All symptoms were reported to be self-limiting and fully resolved over two to three days without need for treatment or apparent long-term sequelae. B-cell aplasia occurred in all patients who experienced a response to CTL019 infusion and was reported to persist for up to one year.

The authors concluded that the "complete remission rate of 90% and sustained remissions of up to 2 years that were seen in this study are encouraging."

Maude SL, Laetsch TW, Buechner J et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018;378:439-48.
Maude et al. reported the results of a single-arm, multi-center, global, open-label, Phase II clinical trial of single-dose tisagenlecleucel (formerly CTL019; Novartis) in patients with relapsed or refractory B-cell ALL. Patients had to be three years old or older at screening but no older than 21 years at diagnosis. There were 25 study sites in 11 countries (North America, Europe, Asia and Australia). The primary endpoint was ORR defined as the rate of a best overall response of either CR or CRi within three months. Responses were required to be maintained for at least 28 days. Secondary endpoints included the duration of remission, event-free survival (i.e., the time from infusion to the earliest of the following events: no response, relapse before response was maintained for at least 28 days, or relapse after having complete remission or complete remission with incomplete hematologic recovery), overall survival, cellular kinetics, and safety. An interim analysis was performed after 50 patients and the primary endpoint was met with an overall remission rate of 82% (95% CI, 69 ☐ 91; $p < 0.001$). This report presents results from an updated analysis of 75 patients who received tisagenlecleucel and had completed three months of follow-up or discontinued the study at an earlier point.

Ninety-two patients were enrolled and 75 patients received an infusion of tisagenlecleucel. Seventeen patients did not receive an infusion due to product-related issues (seven patients), death (seven patients) and AEs (three patients).

The median duration of follow-up after infusion was 13.1 months. Sixty-five (87%) of patients received bridging chemotherapy; 72 (96%) received lymphodepleting chemotherapy. For those who received an infusion, the median age was 11 years (range, 3 to 23). Forty three patients (57%) were male.

The ORR was 66% (95% CI, 56 to 76) in the intention-to-treat analysis (92 patients). For the 75 patients who received an infusion, 61 patients had a remission after at least 3 months of follow-up for an ORR of 81% (95% CI, 71 to 89). Forty-five of 75 patients (60%) had a CR and 16 (21%) had a CRi. None of the 61 patients reached a median DOR of 29 weeks as achieved with FDA-approved agents for relapsed B-cell ALL during the trial.

The OS for the 75 patients was 90% (95% CI, 81 to 95) 6 months after infusion and 76% (95% CI, 63 to 86) 12 months after infusion. The rate of relapse-free survival for patients who initially responded to the infusion was 80% (95% CI, 65 to 89) at six months and 59% (95% CI, 41 to 73) at 12 months. For those with an initial CR, 17 had a relapse before receiving additional anticancer therapy.

The median duration of persistence of tisagenlecleucel in blood was 168 days (range, 20 to 617 days; 60 patients) at data cutoff. No relationship between dose and expansion (measured as the geometric mean of the area under the

concentration-time curve in peripheral blood from time 0 to day 28) was observed among the 60 patients with a response of 28 days.

The most common AEs of any grade included CRS (77%), fever (40%) and febrile neutropenia (36%). Sixty-six of 75 patients (88%) had a grade three or four AE; 55 of 75 patients (73%) had a grade three or four tisagenlecleucel-related AE.

Fifty-eight of 75 patients (77%) developed CRS with a median time to onset of three days (range, 1 to 22) and a median duration of eight days (range, 1 to 36). Thirty-five of 75 patients (47%) received care in the intensive care unit, with a median stay of seven days (range, 1 to 34). Twenty-eight patients (37%) received tocilizumab.

Neurologic events occurred in 30 of 75 patients (40%) within eight weeks after infusion. Ten (13%) were grade three neurologic events; no grade four events were reported. The most common neurotoxicity of any grade were encephalopathy (11%), confusion (9%), delirium (9%), tremor (8%), agitation (7%), and somnolence (7%). The frequency of severe neurologic events increased as the severity of CRS increased; grade three neurologic events occurred more frequently in patients with grade four CRS than among those with lesser grades of CRS (32% [6 of 19] vs. 7% [4 of 56], respectively; 95% CI for the difference, -1 to 50 percentage points). Seventy-five percent of grade three neurologic events resolved within 18 days of infusion. Four episodes of grade three neurologic events were unresolved in three patients;one patient at the time of discontinuation from the trial for no response; one patient at the time of death due to leukemia progression; one patient at the time of death due to encephalitis. Two of these episodes of grade three neurologic events were thought to be related to tisagenlecleucel (one each of encephalopathy and delirium).

Nineteen deaths were reported after infusion. Two patients died within 30 days (one patient with CRS and cerebral hemorrhage; one patient from progressive B-cell ALL). Seventeen patients died more than 30 days after infusion and were reported to be due to B-cell ALL relapse or progression (12 patients), viral□induced encephalitis in association with prolonged neutropenia and lymphopenia (1), systemic mycosis associated with neutropenia (1), after new therapies for B-cell ALL and unknown causes (1).

All patients who responded to the infusion developed B-cell aplasia and most (exact number not reported) were treated with immunoglobulin. The median time to B-cell recovery was not reached during the trial. The probability of maintenance of B-cell aplasia at 6 months after infusion was 83% (95% CI, 69 to 91).

The authors noted the results of this clinical trial show "high response rates" and remissions that are "durable, with a 6-month relapse-free survival rate of 80%" in patients with relapsed or refractory B-cell ALL. The authors also noted that the "majority of neurologic events occurred concomitantly with CRS or shortly after its resolution" and were managed with supportive care.

The authors concluded that "tisagenlecleucel produced high remission rates and durable remissions without additional therapy in high-risk pediatric and young adult patients with relapsed or refractory B-cell ALL. The risks associated with tisagenlecleucel are substantial, leading to ICU-level care in some cases, but were mitigated in most patients with supportive measures and cytokine blockade."

Tisagenlecleucel for Relapsed or Refractory B-cell Lymphoma

Schuster SJ, Svoboda J, Chong EA et al. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. N Engl J Med 2017;377:2545-54.

The authors conducted a prospective, single-arm, single-center, Phase I/II clinical trial of single-dose CTL019

(precursor to tisagenlecleucel; Novartis) in patients with relapsed or refractory DLBCL or refractory follicular lymphoma. Refractory disease for DLBCL was defined as disease for which the best response to chemotherapy was progressive or stable disease (stable disease was defined as < 12 months in duration after at least four cycles of first-line therapy or two cycles of second- line or later therapy) or relapse within 12 months or less after ASCT. Double-refractory follicular lymphoma was defined as progressive disease within six months after the last dose of rituximab and the last dose of an alkylating agent. Lymphodepleting chemotherapy was selected by the investigator based on each patient's treatment history and clinical status. CTL019 was administered one to four days after lymphodepleting chemotherapy with cyclophosphamide, doxorubicin/etoposide/cyclophosphamide, bendamustine, radiation therapy/cyclophosphamide, or etoposide/cyclophosphamide. The primary endpoint was ORR at three months, which the authors did not define except to state that the response was evaluated by using the 1999 International Working Group response criteria as presented in Cheson 1999. Secondary endpoints were PFS, DOR and median survival time. The results of the analyses were not reported by age.

Thirty-eight patients were enrolled and 28 of these patients were infused with CTL019. Of the 10 enrolled patients who were not infused, four patients had rapid disease progression with clinical deterioration, five patients had an insufficient T-cell count for the manufacture of CTL019 cells and one patient withdrew consent. Of the 28 patients who were infused with CTL019, 14 (three women) had DLBCL and 14 (seven women) had follicular lymphoma. The median age was 58 years (range, 25 ☐ 77) for patients with DLBCL and 59 years (range, 43 ☐ 72) for patients with follicular lymphoma.

The median follow-up was 28.6 months. Three months after infusion with CTL019, 18 of the 28 patients had a response (64%; 95% CI, 44 to 81). By six months after infusion, 16 of 28 patients had a CR (57%; 95% CI, 37 to 76), including 6 of 14 patients with DLBCL (43%; 95% CI, 18 to 71) and 10 of 14 patients with follicular lymphoma (71%; 95% CI, 42 to 92). All patients with a CR at 6 months remained in remission for 7.7 to 37.9 months (median, 29.3 months).

Median PFS for patients with DLBCL was 3.2 months (95% CI, 0.9 to not reached); 43% of these patients were progression- free at the median follow-up of 28.6 months (95% CI, 18 to 66). For patients with follicular lymphoma, median PFS was not reached, and 70% (95% CI, 38 to 88) were progression-free at the median follow-up of 28.6 months.

For the median DOR, 86% of patients with DLBCL who had a response (95% CI, 33 to 98) and 89% of patients with refractory follicular lymphoma who had a response (95% CI, 43 to 98) had maintained the response by the median follow-up timepoint of 28.6 months.

Sixteen patients (57%) developed CRS; five of 16 had severe CRS. CRS resolved in all 16 patients with only one patient treated with tocilizumab. Eleven patients developed neurotoxicity ranging from mild cognitive disturbance to global encephalopathy. Three patients had grade three or higher encephalopathy. Neurotoxicity resolved fully within one week except for one patient with progressive neurologic deterioration and death.

The authors concluded that for patients with DLBCL or refractory follicular lymphoma and a poor prognosis, "our observed complete response rates of 43% for patients with diffuse large B-cell lymphoma and 71% for those with follicular lymphoma, with sustained remissions lasting up to 3 years after a single dose of CTL019 cells, support further development of this approach."

Axicabtagene ciloleucel for B-cell Lymphoma

Kochenderfer JN, Somerville RPT, Lu T et al. Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated With High Serum Interleukin-15 Levels. J Clin Oncol 2017;35:1803-1813.

Kochenderfer et al. conducted a prospective, single-arm, single-center, Phase I clinical trial of single-dose anti-CD 19 CAR- T-cells (precursor to axicabtagene ciloleucel; Kite Pharma) in patients with lymphoma. Lymphodepleting chemotherapy was administered prior to CAR T-cell therapy. The primary endpoint was ORR as defined by the revised International Working Group Table 2, Cheson 2007). Twenty-two patients were infused; 19 had DLBCL; two had follicular lymphoma and one had mantle cell lymphoma. All but five of the patients had refractory or relapsed disease. The age range was 26 to 67 years; six patients were 65 years old or older. Information about gender was not reported. The results of the analyses were not reported by age.

The ORR was 73%. Twelve of 22 (55%) achieved a CR with a median duration of 12.5 months without further chemotherapy. Four of 22 (18%) achieved a PR however no PRs were durable. The DOR range was seven to 24 months. The 12-month PFS for all patients was 63%. Fifty-five percent of patients developed severe neurologic toxicity. Rate of CRS was not reported. All acute toxicity was reported to resolve completely with one patient receiving steroids and two other patients receiving tocilizumab. The authors concluded that their "results should encourage further research aimed at developing CAR T-cell therapies with less toxicity and higher remission rates."

Locke FL, Neelapu SS, Bartlett NL et al. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. Molecular Therapy 2017;25:285-295.
Locke et al. reported the results of the Phase I portion of the Phase I/II ZUMA-1 clinical trial, which was a multicenter, single-arm, single-dose clinical trial of anti-CD 19 CAR T-cells (precursor to axicabtagene ciloleucel; now called KTE-C19; Kite Pharma) in patients with refractory DLBCL. Low-dose conditioning chemotherapy with cyclophosphamide and fludarabine was administered prior to KTE-C19 infusion. The primary endpoint was incidence of dose-limiting toxicity (DLT). Seven patients received an infusion of KTE-C19. The age range was 29 to 69 years; three patients were at least 65 years old. There were five men and two women.

ORR was 71% (5/7) within one month of the infusion; CR rate was 57% (n = 4/7). After at least 12 months of follow-up, three patients had an ongoing CR. One patient developed a DLT of grade four CRS and neurotoxicity. Grade three CRS and neurotoxicity developed in 14% (1/7) and 57% (4/7) patients, respectively. The authors concluded that this "regimen of KTE-C19 was safe for further study in phase 2 and induced durable remissions in patients with refractory DLBCL."

Neelapu SS, Locke FL, Bartlett NL et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017b;377:2531-44.
Neelapu et al. reported the Phase II results of the ZUMA-1 clinical trial, which was a multi-center (22 in the U.S.; one in Israel), single-arm clinical trial of KTE-C19 (axicabtagene ciloleucel (axi-cel); Kite Pharma) in patients with refractory DLBCL. Low-dose conditioning chemotherapy with cyclophosphamide and fludarabine was administered prior to KTE-C19 infusion. Bridging chemotherapy was not permitted. Patients who experienced disease progression at least three months after an initial response were permitted to receive another infusion of KTE-C19. The primary endpoint for the primary analysis was ORR (combined rates of CR and PR) at six months as defined by the revised International Working Group Response Criteria for Malignant Lymphoma (Table 2, Cheson 2007). Secondary endpoints were DOR, PFS and OS. An analysis of data pooled from the Phase I and Phase II portions of the clinical trial was also reported as an updated analysis.

A total of 111 patients were enrolled; 24 of these patients were ≥ 65 years old; 68 patients (67%) were male. One hundred and one (91%) patients were infused with KTE-C19; it was not reported how many were ≥ 65 years old. Reasons for not receiving an infusion included: unsuccessful manufacture of the CAR T-cell product (one); AEs (four); death due to disease progression (one); nonmeasurable disease before conditioning chemotherapy (two); sepsis after conditioning chemotherapy but before KTE-C19 infusion (one); death due to multiple factors with laboratory abnormalities suggestive of tumor lysis syndrome, gastrointestinal bleeding and perforation, and disease progression after conditioning chemotherapy but before KTE-C19 infusion (one).

The primary analysis was performed on data with a median follow-up of 8.7 months. The median age was 58 years (range, 23 to 76). Seventy-seven patients had DLBCL and 24 had primary mediastinal B-cell lymphoma or transformed follicular lymphoma.

For the 101 patients who received an infusion, ORR was 82% (95% CI, 73 to 89); the CR rate was 54%. For the 24 patients who were at least 65 years old, the ORR was 92% (95% CI, 73 ☐ 99%). The median time to response was one month (range, 0.8 to 6.0 months). The median DOR was 8.1 months (95% CI, 3.3 to yet to be reached). Response rates were consistent across age, disease stage, and use of tocilizumab or glucocorticoids. At the time of the primary analysis, 52 patients had disease progression, three patients had died from AEs during treatment, one patient started an alternative therapy before disease progression and 44 remained in remission (of whom 39 had a CR). Of the 52 patients who had disease progression after an initial response, nine were retreated with KTE-C19. Of these patients, five had a response (two CRs and three PRs).

Of the 101 patients who received an infusion, 95 (95%) developed a grade three or higher AE. The most common grade three or higher AEs were neutropenia (78%), anemia (43%), and thrombocytopenia (38%). AEs were not reported separately by age. CRS developed in 94 patients (93%); 37% were grade one and 44% were grade two. Thirteen percent were grade three or higher (9% grade 3; 3% grade 4; 1% grade 5). Fever, hypoxia, and hypotension were the most common symptoms of grade three or higher CRS. The median time from infusion to onset of CRS was 2 days (range, 1 to 12); the median time to resolution was eight days. Vasopressors were administered in 17% of the patients. All patients had full resolution of CRS except for one occurrence of grade five hemophagocytic lymphohistiocytosis.

Neurologic events developed in 65 patients (64%); 28% were grade three or higher. The most common grade three or higher neurologic events were encephalopathy (21%), confusion (9%), aphasia (7%), and somnolence (7%). The median onset of neurologic events occurred on day five (range, 1 to 17), with median resolution on day 17 after infusion. All neurologic events resolved except for four events that were present at the time of death (two deaths from progressive disease and two from AEs unrelated to the neurologic events). Forty-three percent of patients received tocilizumab and 27% received glucocorticoids for the management of CRS, the neurologic events, or both.

In an updated analysis of the pooled Phase I and Phase II data (108 patients), the median follow-up was 15.4 months with a minimum of 12 months. The ORR was 82% (95% CI, 73 ☐ 89%); (58% of this amount were CRs). For patients who did not have a CR by one month after infusion, 23 patients eventually had a CR as late as 15 months after infusion without additional therapies for cancer. Overall survival at 6 months was 78% (95% CI, 69 to 85), 59% (95% CI, 49 to 68) at 12 months and 52% (95% CI, 41 to 62) at 18 months. The median DOR was 11.1 months (95% CI, 3.9 to yet to be determined). The PFS at 6 months was 49% (95% CI, 39 to 58), 44% (95% CI, 34 to 53) at 12 months and 41% (95% CI, 31 to 50) at 15 months. Two patients who had a response underwent allogeneic stem-cell transplantation.

There were no new occurrences of CRS or neurologic toxicity to report compared to the primary analysis. There were 44 deaths (37 from disease progression; three from AEs, including the two deaths already reported during the primary analysis plus another death from a pulmonary embolism that was judged not to be due to axicabtagene ciloleucel, and four other deaths after disease progression and subsequent anti-cancer therapies that were judged not to be related to axicabtagene ciloleucel.

The authors stated that the 82% ORR and the 54% CR rate observed in their trial "compare favorably with the results of the recent SCHOLAR-1 study of existing therapies for this disease, which showed an objective response rate of 26% and a complete response rate of 7% (Crump et al., 2017). With a median follow-up of 15.4 months in our study, responses were ongoing in 42% of the patients, including in 40% who had a complete response, with the emergence of a plateau in the duration of the response curve at 6 months. Although most responses occurred in the

first month, 23 patients had a complete response as late as 15 months. It would be reasonable to monitor patients who did not have a complete response at the first disease assessment and allow for an opportunity for an improved response, since consolidation with allogeneic stem-cell transplantation comes with a high rate of treatment-related death and would also ablate CAR T-cells."

Neelapu et al. found that the "incidence of the cytokine release syndrome and neurologic events of grade 3 or higher decreased over the course of the study, possibly because of increased experience at the study centers and a protocol amendment allowing for earlier administration of tocilizumab or glucocorticoids (Neelapu et al., 2017c)." The "use of tocilizumab or glucocorticoids did not appear to affect the overall response among the patients in our study." In conclusion, the authors stated that their "findings support the use of axi-cel as an effective therapeutic option in adult patients with relapsed or refractory large B-cell lymphoma after at least two prior systemic therapies."

FDA Regulatory History and Review for CAR T-cell Therapy

The following excerpts from FDA materials obtained via the FDA website are included to provide the regulatory background of the two CAR T-cell therapies that are currently FDA-approved.

Tisagenlecleucel for ALL

In its August 30, 2017 Summary Basis for Regulatory Action (SBRA), the FDA recommended regular approval of tisagenlecleucel for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse. According to the FDA, "One clinical trial, CCTL019B2202 (B2202), conducted under a Special Protocol Assessment, provided the basis for the BLA submission for a regular approval for KYMRIAH.

The B2202 trial was adequate and well controlled and the review team concluded that the BLA contains substantial evidence to demonstrate effectiveness for the proposed indication. For the 63 patients in the efficacy analysis population, the CR rate was 63% (95% CI: 50%, 75%), and all patients in CR were MRD negative. With a median follow-up of 4.8 months, the median duration of CR was not reached.

The major risks of KYMRIAH include:

- Cytokine release syndrome, which occurred in 79% of the patients
- Transient neurologic toxicity which occurred in 65% of the patients
- Febrile neutropenia which occurred in 38% of the patients
- Cytopenias not resolved by day 28 which occurred in 53% of the patients
- Infections which occurred in 59% of the patients

Overall the benefit-risk profile for these heavily-pretreated pediatric and young adult patients with relapsed/refractory (R/R) B-cell precursor ALL is favorable with appropriate risk mitigation strategies in place. During the trial the applicant provided on-site training for participants, restricted study sites to transplant centers, and closely monitored safety events. This risk mitigation strategy was successful in reducing morbidity of KYMRIAH and will be continued in the Risk Evaluation Mitigation Strategy (REMS) with Elements To Assure Safe Use (ETASU) detailed later in this review.

The review team recommended approval of this BLA with postmarketing requirements (PMR) for a REMS with ETASU for the management of cytokine release syndrome and neurologic toxicity, training and assessment of sites and the use of tocilizumab and a postmarketing observational study to assess short and long-term toxicities of KYMRIAH (B2401). B2401 will include short-term CRS, neurologic, and other adverse event reporting as well as long-term observational follow-up for the potential of second malignancy with tumor assessment at the time of occurrence of a new (second) malignancy."

A meeting of the FDA Oncologic Drugs Advisory Committee was held on July 12, 2017 to discuss the product quality and safety, clinical safety and overall risk-benefit assessment for tisagenlecleucel. The FDA SBRA provided the following summary of the Advisory Committee discussion:

- "The Committee agreed that the risk-mitigation measures in the B2202 study were reasonable. The Committee did not express concern about testing for replication competent retrovirus. However, the Committee considered insertional mutagenesis to be a potential risk.
- Discussion of the planned 15-year follow-up centered on the B2401 postmarketing observational trial. The committee agreed that 15-year follow-up would be sufficient.
- The Committee voted 10 (Yes) to 0 (No) to the question, "Considering the efficacy and safety results of Study B2202, is the benefit-risk profile of KYMRIAH favorable for treatment of pediatric and young adult patients (age 3-25 years) with relapsed (second or later relapse) or refractory (failed to achieve remission to initial induction or reinduction chemotherapy) B-cell precursor acute lymphoblastic leukemia (ALL)"

Tisagenlecleucel for Lymphoma
In its April 13, 2018 SBRA, the FDA recommended regular approval of tisagenlecleucel for adult patients with relapsed or refractory (R/R) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. FDA included a limitation of use: tisagenlecleucel is not indicated for treatment of patients with primary central nervous system lymphoma. According to FDA, "CCTL019C2201 (C2201), a single arm, phase 2, multicenter, open-label trial was the data source used to assess the efficacy and safety of KYMRIAH for treatment of DLBCL. The recommendation for approval was based on the complete response rate and duration of response demonstrated in this study."

The SBRA stated a number of efficacy-related issues during the BLA review:

1) "Yescarta, another CD19-directed CAR T cell product, has already received regular approval for a similar clinical indication. The endpoints of CR and durability of CR are considered clinical benefit endpoints, hence KYMRIAH was reviewed for regular approval.

2) The applicant initially proposed earlier submission of this efficacy supplement based on less extended follow-up, but as described in greater detail in the Regulatory History in section 2, after discussions with the FDA, the applicant delayed submission until ≥ 6-month follow-up was available for all responders and could be provided to the FDA within 30 days after supplement submission.

3) As noted in the clinical efficacy assessment section above, 23 patients were excluded from efficacy assessment because the timing or therapeutic efficacy of bridging chemotherapy interfered with the documentation of baseline measurable disease after bridging chemotherapy needed to assess the independent contribution of KYMRIAH to patient's overall response. This methodologic decision was necessary for evaluation in a registrational single arm trial, but it does not imply any judgment concerning the benefits or risks of using bridging chemotherapy in association with KYMRIAH in the treatment of DLBCL. Clarification of this issue may require additional controlled prospective studies."

The risks of KYMRIAH can be linked to its mechanism of action, which involves the activation of T cells targeted to kill CD19+ cells. Cytokine release syndrome and neurotoxicity presumably linked to T cell activation-products occurred in 65% and 79% of patients respectively, and both complications can be life-threatening or fatal. Hypogammaglobulinemia resulting from CAR T cell attack on normal CD19+ B cells may persist for months requiring monitoring and replacement therapy. A potential risk of clonal mutagenesis or secondary malignancy associated with the use of a lentiviral vector cannot be excluded. In view of the grave prognosis of relapsed/refractory large B-cell

lymphoma after treatment with conventional chemo-immunotherapy, the review team concludes that the BLA efficacy and safety data indicate a favorable risk/benefit profile." The FDA review team recommended "issuing a regular approval (21 CFR 601.4 (a)) for KYMRIAH, implementing a REMS program, and requiring a long-term follow-up program as a PMR. The Prescribing Information (PI) will include a boxed warning for CRS and neurologic toxicity and a REMS with ETASU to ensure that the product's benefits outweigh the risks."

Axicabtagene ciloleucel for Lymphoma
In its October 18, 2017 SBRA, the FDA recommended the regular approval of axicabtagene ciloleucel for the "treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma." FDA included a limitation of use: axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system lymphoma. FDA stated that a "single clinical trial, ZUMA-1, provides the primary evidence of safety and effectiveness for the BLA submission. The recommendation for approval is based on the complete remission rate and duration of response demonstrated in the phase 2 portion of the study." The SBRA noted some initial BLA review issues including inadequate follow-up for efficacy, errors in the efficacy datasets and an excessive amount of early censoring for an efficacy endpoint that were adequately resolved by the submission of updated efficacy data.

The FDA risk/benefit assessment states that of "101 patients evaluated for efficacy, the objective response rate was 72%, with a CR rate of 51%, as determined by an independent review committee. With a median follow-up of 7.9 months, the estimated median duration of response was 9.2 months overall and was not reached in patients achieving CR. The risks of YESCARTA relate to its mechanism of action, which is the activation of T cells and the destruction of CD19+ B cells, both tumor cells and normal B cells. Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred in 94% of the patients. Neurologic toxicities, including fatal or life-threatening reactions, occurred in 85% of the patients. Hypogammaglobulinemia following YESCARTA occurred in 15% of patients and required monitoring and intervention.

The Prescribing Information (PI) includes a boxed warning for CRS and neurologic toxicity and a REMS with ETASU to ensure that the product's benefits outweigh the risks. The review of the BLA clinical and safety data provides a favorable risk/benefit profile considering the lack of available therapies for heavily pretreated patients with relapsed/refractory large B-cell lymphoma."

The review team recommended a PMR study, which is to be "a multicenter, prospective, observational safety study using a registry design. The study will include 1500 subjects who will be followed for 15 years after their YESCARTA infusion. The primary endpoint will be evaluation for secondary malignancy, which will include tissue work-up for these events."

4. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

A MEDCAC meeting entitled *CAR T-Cell Therapy and Patient Reported Outcomes* was convened on this issue on August 22, 2018. Additional information, including the voting questions, meeting agenda, invited presenters, speaker list, and panel members, is available at https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=76. Included with this decision is a summary of the background articles provided, and the overall recommendations of the panel:

Background Materials
In preparation for the MEDCAC, CMS provided the following background materials. These materials are summarized as part of the evidence for this decision.

Aaronson et al., for the European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI 1993; 85:365-376.
This international field study examined practicality, reliability, and validity of the EORTC-QLQ-C30. The EORTC-QLQ-C30 is a 30-item instrument which produces a health-related QoL summary score, a global health status score, five functioning scores including physical, role, emotional, social, and cognitive, and nine selected symptom item scores on a scale from 0 (worst) to 100 (best) based on the following characteristics: (1) standardization of assessment, (2) specific to cancer, (3) psychometrically robust, (4) concise for practical use in cancer clinical trials, (5) appropriate for self- administration, and (6) cross-cultural applicability. Participants included 305 nonresectable lung cancer patients of mean age (SD) 63 (10) years with 24% female. EORTC-QLQ-C30 was administered at baseline and one event dependent follow up during treatment (either on the last day of the first course of radiotherapy or the last day of the second cycle of chemotherapy). Completion rate was 88% and time was 11 minutes. Three approaches were taken to evaluate validity: (1) correlation among conceptually related scales, (2) known-group comparisons among patients of differing clinical status, performance status, and weight loss, (3) reliability between two questionnaires from same patient. Results showed all inter- scale correlations were statistically significant (p-value < 0.01). Statistically significant group differences in the expected direction were observed for all functional and symptom scores based on treatment performance status. Qualitatively, those patients whose performance status improved reported increased functioning and decreased symptoms. Conversely, patients whose performance status deteriorated reported decreased functioning and increased symptoms. The authors concluded that the level of detail provided by the EORTC-QLQ-C30 is appropriate for addressing research questions most commonly posed in phase III clinical trials.

Berry et al., Enhancing patient-provider communication with the electronic self-report assessment for cancer: a randomized trial. JCO 2011; 29:1029-1035.
This research team developed the Electronic Self-Report Assessment-Cancer (ESRA-C) to include patient-reported outcomes in oncology settings as promoted by federal agencies, clinicians, and research investigators. The purpose of this trial was to determine the effect of ESRA-C on the discussion of QoL between clinicians and patients with cancer in ambulatory clinic visits. Participants included cancer patients (n=765) with age range 18-89 years, 47% female, less than 10% minority representation. ESRA-C was collected at baseline before treatment and four to six weeks after treatment. Completion rate was 86%. Application of the ERSA-C resulted in a 29% increase in the odds of QoL discussed with the patient. There was no significant difference (p-value=0.35) between average length of clinic visit for those with ESRA-C results and those without. The authors concluded that including ESRA-C resulted in a greater likelihood of discussing the impact of cancer and/or treatment, and suggest that lack of attention to treatment adverse effects can be dangerous if not assessed reliably and systematically.

Berry et al., Electronic self-report assessment for cancer and self-care support: results of a multicenter randomized trial. JCO 2014; 32:199-205.
This prospective, randomized clinical trial assessed the impact of education, communication coaching, and QoL tracking on discussion of ESRA-C reported health-related QoL between clinician and patient. Participants included patients with any cancer diagnosis (n=779) with age range 19-88 years old, 46% female, and 7-9% minorities. ESRA-C was completed at baseline and at three follow up assessment points approximately (1) three to six weeks after starting treatment, (2) two weeks after first follow up, and (3) two to four weeks after treatment ended. The completion rate was 83%. Results comparing the ESRA-C to the Symptom Distress Scale-15 (SDS-15) suggest there was minimal impact in participants age < 50 years and evident impact among older participants age > 50 years. For older participants, ESRA-C score seemed stable in the intervention group and increased from baseline to end of study in the controls not introducing education, communication, and coaching. The authors concluded that reducing symptom distress with an engaging intervention that adds no time to a clinic visit is patient-centered care in action.

Cleeland et al., Assessing Symptom Distress in Cancer Patients: The MD Anderson Symptom Inventory (MDASI). Cancer. 2000; 89:1634-1646.
These authors designed the MDASI following the same developmental steps as in development of Brief Pain Inventory and Brief Fatigue Inventory to (1) choose the items from previous work, (2) consult with health care

professionals, (3) modify items based on preliminary data from patients. The MDASI combines the following scales with demonstrated utility in epidemiological studies, predicting survival, and aiding clinical care: Symptom Distress Scale, Memorial Symptom Assessment Scale, Rotterdam Symptom Checklist, and Edmonton Symptom Assessment System. Each symptom is rated on an 11-point interference scale from 0 (not present) to 10 (as bad as you can imagine) with 24 hour recall period. Validation study participants included three subgroups (n=527, 30, and 113) with mean age (SD) 55 (15), 47 (9.8), and 56 (13.4) years, and approximately 55% female, with 95% completion rate. Based on this study, the authors concluded that a 13-item model predicts symptom distress. Results showed the MDASI was determined to be sensitive to both disease severity and treatment status from a significant difference in mean severity (p-value<0.001) and mean symptom interference (p-value<0.001) between patients with high clinical performance status versus poor clinical performance status, and that both blood and bone marrow transplantation group as well as the chemotherapy group demonstrated significantly higher mean symptom interference relative to patients not currently receiving anticancer chemotherapy (p-value<0.01). Overall, the MDASI created a minimal set of common symptoms that can be rated by all cancer patients in less than five minutes when they begin treatment and throughout the course of their disease.

Anderson et al., Symptom burden in patients undergoing autologous stem-cell transplantation. Bone Marrow Transplantation. 2007; 39:759-766.
The objectives of this study were to assess symptom burden, intensity, and interference during the acute phase of autologous stem cell transplant and identify predictors of high symptom burden. Participants included patients scheduled for outpatient autologous transplant (n=100) with age range 24-75 years, 40% female and 81% white. MDASI and other QoL assessments were collected for comparison at baseline, during conditioning chemotherapy, at transplant, on day of nadir, and 30 days post-transplant. Completion rate was 82%. Results showed symptom severity and interference scores were only affected by time (p-value < 0.001), therefore the MDASI was not seen to be sensitive to demographics, diagnosis, or laboratory measures. Symptom-related interference was most intense at nadir and comparable to baseline at day 30. The intensities of nausea, lack of appetite, weakness, and feeling physically sick remained elevated compared to baseline levels. Analysis also showed significant time-by-cancer-diagnosis interactions for fatigue, sleep disturbance, lack of appetite, and pain severity (p-value < 0.05). The authors concluded that many patients may benefit from more aggressive symptom management during the acute phase of transplantation.

DeWalt et al., Evaluation of Item Candidates: The PROMIS Qualitative Item Review. Med Care. 2007; 45 (Suppl1):S12-S21.
The Patient Reported Outcome Measurement Information System (PROMIS) includes both quantitative and qualitative methods to inform the development and validation of health outcomes measurement. Using item response theory and computerized adaptive testing, PROMIS built on existing items in the Patient-Reported Outcome and Quality of Life Instruments Database with focus on the following characteristics (1) context: the instructions associated with answering the item, (2) stem: the part of the item that makes it unique from others in the same scale, (3) consistent response options, (4) time frame: time spent answering, (5) instrument of origin (6) domain-specific measurement. Ultimately the final set of items was designed to adequately represent the domains of physical, mental, and social health. Items were eliminated for consistency, applicability, and disease specificity. A seven day recall period was adopted as general convention and response levels were between four and six with questions targeted to the sixth-grade reading level. Patient input was included in development of item libraries through cognitive interviews. The authors concluded that this approach was consistent with FDA guidance for the development of patient-reported outcomes (Docket No. 2006D-0044).

Cook et al., PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrate clinical validity across a range of chronic conditions. J Clin Epi. 2016; 73:89-102.
The purpose of this clinical validity study was to evaluate PROMIS effectiveness in multiple clinical contexts. The hypothesis was that quantifying the impact of disease and health problems important to patients improves tracking the disease course. Participants included 218 patients (age range 55-59 years, 56% female, 85% white) with back or leg pain for six weeks and scheduled for spinal treatment, 310 individuals with cancer (age range 50-54 years, 61%

female, 81% white) beginning new treatment, 80 patients with severe chronic heart failure receiving a heart transplant (age range 50-54 years, 20% female, 86% white), 185 persons with chronic obstructive lung disease (age range 60-64 years, 40% female, 72% white), 512 individuals with rheumatoid arthritis (age range 65-69 years, 81% female, 88% white), 196 patients with major depressive disorder (age range 45-49 years, 74% female, 78% white). Measures included global ratings of change with recall to either the baseline, or most recent appointment, or past seven days. Responses were rated on a 1-7 scale from 1 (much better) to 7 (much worse). Follow-up ranged from weekly, 8 weeks post-treatment, 3 months, 6 months, and 12 months. Completion rates at baseline were between 95-100% and at follow-up between 79-95%. Cumulatively, the investigators report clinical validity for nine PROMIS measures in five PROMIS domains across six clinical conditions. Future directions include additional external anchors to clinician ratings, functional capacity and work status.

Dueck et al., Validity and Reliability of the US NCI's PRO-CTCAE. JAMA Oncol. 2015; 1(8):1051-1059.
To develop the patient-reported outcomes version of the NCI's Common Terminology Criteria for Adverse Events (PRO- CTCAE), 78 adverse events were selected for patient reporting with a standard recall period of seven days and software compliant with Section 508 of the U.S. Rehabilitation Act. This development was based on hypothesis that collecting information directly from patients improves the precision and reliability of symptomatic adverse event detection in trials and is feasible. This study tested validity (instrument accurately measures phenomenon), reliability (instrument produces similar scores on repeated measurements) and responsiveness (instrument shows change when phenomenon changes). Participants included 975 adult cancer patients with age range 19-91 years, 57% females, and 88% whites undergoing outpatient chemotherapy and/or radiation therapy. Validity was compared to the EORTC-QLQ-C30 and Global Impression of Change scales. Follow up was based on clinic visit schedule to avoid the necessity of extra clinic visits in this symptomatic population. Completion rate was 96% at baseline and 91% at follow up. Results showed 98% of PRO-CTCAE items were significantly associated in the expected direction with the QLQ-C30 summary score (p-value < 0.05). The authors concluded that the PRO-CTCAE can provide comprehensive data on symptomatic adverse events in cancer clinical trials from the patient perspective.

Rogers et al., The addition of mood and anxiety domains to the University of Washington quality of life scale. Head & Neck. 2002; 24(6):521-529.
This cross-sectional longitudinal survey reported the validity of version four of the University of Washington quality of life (UW-QOL) scale. The desired characteristics included (1) takes less than 10 minutes to complete, (2) simple to understand, and (3) measures health-related QoL longitudinally. This version included 12 domains, a single-item QoL question, a free- text section, and a recall period of the last seven days measured on a 100 point scale ranging from 0 (worst QoL) to 100 (best). The measures in these domains were compared to the EORTC-QLQ-C30 and EORTC head and neck measures. Study participants included 183 patients with head and neck cancer, with 35% female and approximately 40% over age 65 years. The completion rate was 79%. Results showed 42% of UW-QOL items were significantly associated in the expected direction with the EORTC-QLQ-C30 summary score (p-value < 0.05). Results also showed expected sensitivity to tumor size, radiotherapy, and type of surgery. The authors concluded that a high level of depressive symptoms before treatment is a good predictor of symptom severity and functioning after treatment.

Rogers et al., The patients' account of outcome following primary surgery for oral and oropharyngeal cancer using a "quality of life" questionnaire. Eur J Cancer Care (Engl) 2008; 17(2):182-188.
This data collection summarized UW-QOL scales collected from 1995-2006. The authors hypothesized that patients want an indication of long term outcomes, and health-related QoL information can give patients, caregivers, and clinical teams a much better understanding of outcomes following treatment to inform and aid shared decision-making. The investigators do not use clinical anchors and do not use a method for determination of meaningful change. Data were compiled at presentation, 6 months, and 12 months after treatment. Participants included 561 patients with mean age (SD) 63(12) years, and 39% female. Results found that patients who do best are those with the smallest tumors, therefore, the authors concluded that patients' questionnaire data can be used for the benefit of new patients.

Rogers et al., Screening for dysfunction to promote multidisciplinary intervention using the University of Washington Quality of Life Questionnaire. Arch Oto Head Neck Surg. 2009; 135(4):369-375.
This retrospective analysis of the UW-QOL investigates the potential to screen for further evaluation and intervention after cancer treatment, and to estimate how many patients a predetermined cutoff would identify at various times in various clinical subgroups. The authors aimed for a cutoff that would select not more than one in five patients. Compiled data showed considerable variation at around two years in cutoffs by age and gender. The authors found that applying cutoff criteria allows the patients reporting problems to be identified. In practice, the rates for final cutoffs ranged between 9% and 16%. When applied to a busy clinic, the authors found that 42% of patients with early disease had 1 or more domains that met the cutoff criteria compared with 81% of patients with advanced cancer. The authors concluded that UW-QOL helps provide structured feedback from the patient perspective and encourages further evaluation and intervention for complicated patients.

Schipper et al., Measuring the quality of life of cancer patients: the functional living index-cancer: development and validation. JCO. 1984; 5:472-483.
This validation study measured the Functional Living Index□Cancer (FLIC) against the following scales: Karnofsky, Beck Depression, Spielberger State and Trait Anxiety, and Katz Activities of Daily Living as well as the General Health Questionnaire and McGill/Melzack Pain Index. The goal was to design and validate an assay of the overall functional state of the patient with the following characteristics: (1) cancer specific, (2) functionally oriented, (3) designed for patient self- administration, (4) permit high compliance, (5) repeatable, (6) sensitive across the range of clinical practice to distinguish intensities of therapeutic intervention, (7) demonstrated face, content, construct, and concurrent validity and reliability. The FLIC adopts a Likert format, range one to seven, in four validation trials. As a result, the authors found that FLIC was insensitive to demographic variables. Construct validity was identified by the consistency of factor analysis across three clinical trials. The FLIC was strongly correlated with Karnofsky (0.693), General Health Questionnaire (0.765), and Beck Depression scale (0.773), and weakly correlated to Katz (-0.17). Stratification data showed validity across cancer illness by treatment stage. The authors concluded that FLIC measures a composite of distinct factors and would be additive to more traditional measures in cancer clinical trials so that the patient will be better able to participate in making an informed decision.

Kotronoulas et al., What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. JCO. 2014; 32:1480-1501.
This systematic review was to determine what evidence supports patient-reported outcome measures (PROMs) use in routine clinical practice. Trials were included if they comprise adult patients > 18 years old with cancer published in the English language with readily available abstracts. RCTs comprised 20 of 24 studies, 16 longitudinal designs, 17 interventional in the outpatient/ambulatory setting, 11 incorporated one PROM, seven incorporated two PROMs, and six used three or more instruments. EORTC-QLQ-C30 was most prevalent. Follow up assessments ranged from two to four months and up to 12 months after baseline. In two trials the PROM intervention was similar to usual care to address needs of patients. In the three trials, the positive effects included increased satisfaction with emotional support, follow-up, and communication with physicians in the outpatient setting compared with standard care. In four trials, health professionals felt obtaining an overall assessment of the patient was more helpful. Taken together, the studies identified overall satisfaction in at least 80% of patients. The authors suggest that patient physical symptoms and distress may be most amenable to improvement after PROM interventions. The authors concluded that the use of PROMs in clinical practice increases patient satisfaction, discussion of patient outcomes, and is associated with increased symptom control and supportive care.

Wildiers et al., End points and trial design in geriatric oncology research: a joint European organisation for research and treatment of cancer. Alliance for Clinical Trials in Oncology. International Society of Geriatric Oncology position article. JCO. 2013;31:3711-8.
This article discusses endpoints in cancer clinical trials and provides recommendations for application of critical endpoints for older individuals. The authors discussed disease-free survival (DFS) and overall survival (OS) as the most recognized and well accepted and recognized for metastatic solid tumors that progression-free survival (PFS),

time to tumor progression (TTP), time to treatment failure (TTF), response rate (RR) and OS are the most used endpoints. The authors assert these endpoints may not be the most appropriate in older patients with cancer, because older patients often die from comorbid disease, and relapse might not affect survival. If excluding older patients with comorbidities helps a trial determine whether a small benefit from treatment exists, but limits generalizability where patients are older, then the authors recommend larger sample sizes. In addition, the authors identify opportunities to take into account the role of toxicity as older patients are seen as less willing to continue treatment with severe toxicities or that limit health related QoL and independence. To this end, the authors recommend the following: (1) consideration for endpoints such as overall treatment utility and treatment failure- free survival, (2) application of the Balducci and Extermann (2000) definitions of fit, vulnerable, and frail patients, (3) single-arm phase II studies in older populations with toxicity as an end point, (4) large observational cohort studies and registries in the community.

Panel Recommendations
The panel roster is available at https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx? MEDCACId=76. The voting questions were presented to the audience prior to the presentation of evidence from invited presenters. Following the presentations from the five invited speakers, eight presentations from scheduled public commenters occurred. Following the scheduled public comments, members of the public were invited to speak. Many questions to the presenters were centered on clarification of the evidence presented. A videocast of the meeting is available at https://www.youtube.com/watch?v=_3SjVyw5v9g (Morning Session) and https://www.youtube.com/watch? v=8R0iY4W_eRU - (Afternoon Session).

The nine voting members on the panel voted on five questions using a scale of one to five, with one representing a low confidence vote and five representing a high confidence vote. An average voting score of 2.5 represented intermediate confidence. The scores of the voting panel members were recorded and the average was calculated. The MEDCAC recommended four out of seven PRO assessments (PRO-CTCAE, MDASI, EORTC-QLQ-C30, PROMIS) with greater than intermediate confidence, and believed that those assessments have available supporting evidence on almost all desired characteristics requested by CMS. One panelist noted that the desired characteristics were minimal standards that the recommended assessments exceeded. In addition, the MEDCAC suggested CMS consider additional disease-specific assessments, such as the FACT-Lymphoma and EORTC-disease-specific tools and recommended more stringent characteristics, such as incorporation of PRO assessment into Electronic Health Record systems.

This MEDCAC also sought greater public input by receiving and considering comments on the effectiveness of CAR T-cell therapy. We also obtained the perspective of affected patients, including the degree of perceived benefit, subjective assessment of risk, and burden of side effects through public comments and representatives on the panel. When the MEDCAC panel assessed whether scientific evidence supports specific study design characteristics, study duration, and suitable controls for applying PROs to health outcomes research, the recommendations were supportive of stringent requirements. The panel had more confidence in fixed time-dependent frequency interval of PRO assessment (i.e. weekly, monthly, or yearly; average = 4.0) than variable event-dependent intervals (average = 2.1). The panel had more confidence in longer study durations to identify a meaningful durable treatment effect with a valid PRO (average = 4.1). Finally, the panel was most confident in evidence of PRO assessments that compared usual care versus protocol-driven intervention (average = 3.9) and less confident when patients served as own controls (average = 3.8) or with use of historical controls (average = 2.0).

5. Evidence-Based Guidelines

The evidence-based guidelines are summarized below:

National Comprehensive Cancer Network (NCCN)

Three evidence-based clinical guidelines by NCCN that address CAR T-cell therapy were found and are summarized below by FDA indication.

B-cell Lymphomas

On March 6, 2019, NCCN released an updated U.S. evidence-based guideline (version 2.2019) for the management of patients with B-cell lymphoma. The sections of the guideline that are relevant to CAR T-cell therapy are reproduced below in their entirety with minor revisions of the tables for formatting reasons.

Axicabtagene ciloleucel[a]

- Patient selection
  - Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL, NOS; primary mediastinal large B-cell lymphoma; high grade B-cell lymphoma; and DLBCL arising from follicular lymphoma.[a]
  - Health care facilities that dispense and administer axicabtagene ciloleucel must be enrolled and comply with the Risk Evaluation and Mitigation Strategies (REMS) requirements.[a] See REMS for axicabtagene ciloleucel.
- Cytokine release syndrome (CRS) management - See CAR T-Cell-Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities
- Neurologic toxicity management - See CAR T-Cell-Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities
- Prolonged cytopenias
  - Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and axicabtagene ciloleucel infusion.
- Hypogammaglobulinemia
  - B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with axicabtagene ciloleucel.

Tisagenlecleucel[b]

- Patient selection
  - Tisagenlecleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL, NOS and high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.[b]
  - Health care facilities that dispense and administer tisagenlecleucel must be enrolled and comply with the REMS requirements.[b] See REMS for tisagenlecleucel.
- CRS management - See CAR T-Cell-Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities
- Neurologic toxicity management - See CAR T-Cell-Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities
- Prolonged cytopenias
  - Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and tisagenlecleucel infusion.
- Hypogammaglobulinemia
  - B-cell aplasia and hypogammaglobulinemia can occur in patients with a complete remission after tisagenlecleucel infusion.

[a]Prescribing information for axicabtagene ciloleucel is available at:
https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/

ApprovedProducts/UCM581226.pdf.
[b]Prescribing information for tisagenlecleucel is available at:
https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Acute Lymphoblastic Leukemia

- On March 12, 2018, the NCCN released a U.S. evidence-based guideline for the management of adolescent and young adult (AYA) patients with Philadelphia chromosome (Ph)□positive and Ph-negative ALL. The NCCN noted that due to "the complexity of ALL treatment regimens and the required supportive care measures, the NCCN ALL Panel recommends that patients be treated at a specialized cancer center with expertise in the management of ALL."
- In general, the NCCN stated that "The pre-treatment of patients with CAR T cells has served as a bridge for transplant, and patients who were formerly unable to be transplanted due to poor remission status have a CR and ultimately transplantation." In addition, the NCCN (2018a) noted that "Adverse events are attributed to CRS and macrophage activation that occur in direct response to adoptive cell transplant resulting in high fever, hypotension, breathing difficulties, delirium, aphasia, and neurologic complications. Improvement in patient monitoring has shown successful treatment of these symptoms with the monoclonal antibody tocilizumab, an antagonist of interleukin-6 (Davila et al., 2014). "For patients with relapsed or refractory Ph-positive or P-negative ALL, the NCCN (2018a) stated that tisagenlecleucel is "an option for patients up to age 25 years (age < 26 years) and with refractory disease or ≥ 2 relapses."

Management of Immunotherapy-Related Toxicities

- On November 14, 2018, the NCCN released a new clinical guideline for the management of immunotherapy-related toxicities, and that addresses CAR T-cell related toxicities in particular.

NCCN Guidelines Version 1.2019
Management of CAR T-Cell-Related Toxicities

PRINCIPLES OF PATIENT MONITORING

Before and During CAR T-Cell Infusion **Post-CAR** **T-Cell Infusion**	**Post-CAR T-Cell Infusion**
• Perform central venous access, preferably with double or triple lumen catheter, for intravenous IV fluid and other infusions in case of toxicities. • Perform cardiac monitoring at least at the onset of grade 2 cytokine release syndrome (CRS) until resolution to ≤ grade 1, and additionally as clinically indicated. • Tumor lysis precautions are recommended for patients with large	• Hospitalization or extremely close outpatient monitoring at centers with transplant or prior outpatient CAR T-cell transplant experience. Close monitoring in the hospital is preferable with current products used for adults; however, extremely close outpatient monitoring may be possible at centers with outpatient transplant experience. • Hospitalization for patients with CRS is warranted. • Monitor CBC, complete metabolic panel (including magnesium and phosphorus), and coagulation profile. • Baseline CRP and ferritin; recheck at least 3 times per week for 2 weeks post-infusion. Consider daily checks during CRS.

tumor burden and aggressive histologies, as per standard institutional guidelines. • Start seizure prophylaxis on the day of infusion for CAR T-cell therapies known to cause CAR T-cell-related neurotoxicity (eg, levetiracetam 500□ 750 mg orally every 12 h for 30 days). • Consider baseline brain MRI.	CRP can normalize prior to the onset of neurotoxicity. • Assessment for CRS should be done at least twice daily, or when the patient's status changes, during the peak window of CRS risk. • Neurotoxicity assessment should be done at least twice daily or when the patient's status changes, during the peak window of neurotoxicity risk. If neurologic concern develops, assess at a minimum of every 8 hours to include cognitive assessment and motor weakness.

Overview of CAR T-Cell Therapy-Related Toxicities (CART-2)
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

OVERVIEW OF CAR T-CELL THERAPY-RELATED TOXICITIES

	Axicabtagene ciloleucel[a] and tisagenlecleucel[b]
CAR CART-3	• Typical time to onset: 2-3 days • Typical duration: 7-8 days • Manifestation may include fever, hypotension, tachycardia, hypoxia, and chills. CRS may be associated with cardiac, hepatic, and/or renal dysfunction. • Serious events may include atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).
Neurologic Toxicity (CART-4)	• Typical time to onset: 4-6 days • Typical duration: 14-17 days • The most common neurologic toxicities include encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, anxiety, and autonomic neuropathy. Agitation, hyperactivity, or signs of psychosis can also occur. • Serious events including seizures, as well as fatal and serious cases of cerebral edema, have occurred.
Hemophagocytic Lymphohistiocytosis/Macrophage-Activation Syndrome (HLH/MAS) During CRS (CART-3)	• Criteria for considering HLH/MAS: ◦ Rapidly rising and high ferritin (> 5,000 ng/mL) with cytopenias in the context of CRS, especially if accompanied by *any of the following*: ◦ Grade ≥ 3 increase in serum bilirubin, AST, ALT ◦ Grade ≥ 3 oliguria or increase in serum creatinine ◦ Grade ≥ 3 pulmonary edema ◦ Presence of hemophagocytosis in bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 IHC.

Miscellaneous	• Patients may exhibit cytopenias for weeks to months following lymphodepleting chemotherapy and CAR T-cell therapy infusion. • Long-term B-cell aplasia and hypogammaglobulinemia can occur in patients with a complete remission after CAR T-cell therapy infusion.

[a] Axicabtagene ciloleucel: Median time to CRS onset of 2 days (range: 1-12 days), median duration of 7 days (range: 2-58 days). Median time to neurotoxicity onset of 4 days (range: 1□43 days), median duration of 17 days.

[b] Tisagenlecleucel: Median time to CRS onset of 3 days (range: 1-51 days), median duration of 8 days (range: 1-36 days). Median time to neurotoxicity onset of 6 days (range: 1□359 days); median duration of 14 days.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CYTOKINE RELEASE SYNDROME (CRS)[c]
Prompt and urgent intervention to prevent progression of CRS is required; however, other causes of systemic inflammatory response should be ruled out, including infection and malignancy progression. Empiric treatment for infection is warranted in the neutropenic patient. (CTCAE v5)

CRS Grade	Anti-IL-6 Therapy	Corticosteroids[d],[e]	Additional Supportive Care
Grade 1 Fever with or without constitutional symptoms	For prolonged CRS (> 3 days) in patients with significant symptoms and/or comorbidities, consider tocilizumab as per Grade 2	N/A	• Empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of organ toxicities
Grade 2 Hypotension responding to fluids; hypoxia responding to < 40% O2	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose)[d] .Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total	For persistent refractory hypotension after 1-2 doses of anti-IL-6 therapy: Dexamethasone 10 mg IV every 6 hours (or equivalent)[f]	• IV fluid bolus as needed • For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to intensive care unit (ICU), consider echocardiogram, and initiate other methods of hemodynamic monitoring • Manage per Grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy • Symptomatic management of organ toxicities
Grade 3	Anti-IL-6 therapy as per	Dexamethasone 10 mg IV	• Transfer to ICU, obtain

Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2	Grade 2d if maximum dose not reached within 24-hour period	every 6 hours (or equivalent)[f]. If refractory, manage as grade 4	echocardiogram, and perform hemodynamic monitoring • Supplemental oxygen including high-flow oxygen delivery and noninvasive positive pressure ventilation • IV fluid bolus and vasopressors as needed. • Symptomatic management of organ toxicities
Grade 4 Life-threatening consequences; requiring ventilator support or vasopressor-refractory shock	Anti-IL-6 therapy as per Grade 2d if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours (or equivalent)[f]. If refractory, consider methylprednisolone 1000 mg/day IV[g].	• ICU care and hemodynamic monitoring • Mechanical ventilation as needed • IV fluid bolus and vasopressors as needed. • Symptomatic management of organ toxicities

[c] For HLH/MAS during CRS, treat as per CRS with addition of steroids. If symptoms do not improve within 48 hours, consider etoposide and intrathecal cytarabine for neurotoxicity.
[d] After each dose, assess need for subsequent dosing.
[e] Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.
[f] Alternative steroids at an equivalent dose may be considered.
[g] For example, methylprednisolone IV 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 h for 2 days, and 60 mg every 12 h for 2 days.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CAR T-CELL-RELATED NEUROTOXICITY
Assessment and Supportive Care Recommendations (all grades)

- **Neurologic assessment and grading at least twice a day to include cognitive assessment and motor weakness**
  - **MRI of the brain with and without contrast (or brain CT if MRI is not feasible) for = grade 2 neurotoxicity**
  - **Conduct electroencephalogram (EEG) for seizure activity for = grade 2 neurotoxicity**
  - **Aspiration precautions; IV hydration**
  - **Use caution when prescribing medications that can cause central nervous system (CNS) depression (aside from those needed for seizure prophylaxis/treatment)**
  - **Neurology consultation at first sign of neurotoxicity**

Treatment by Grade	No Concurrent CRS	Additional Therapy if Concurrent CRS

Grade 1/ Mild impact on ADLs	• Supportive care	Tocilizumab 8 mg/kg IV over 1 h (not to exceed 800 mg/dose)[i]
Grade 2h 1 Moderate impact on ADLs	• Supportive care • Dexamethasone 10 mg IV x 1. Can repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 h if symptoms worsen.	Anti-IL-6 therapy as per Grade 1[i] Consider transferring patient to ICU if neurotoxicity associated with grade ≥; 2 CRS
Grade 3h Severe impact on ADLs; seizure; signs of elevated intracranial pressure (eg, papilledema, Cushing's triad, hypertension, bradycardia)	• ICU care is recommended. • Dexamethasone, 10 mg IV every 6 h or methylprednisolone, 1 mg/ kg IV every 12 [he] • Consider repeat neuroimaging (CT or MRI) every 2□3 days if patient has persistent grade ≥; 3 neurotoxicity.	Anti-IL-6 therapy as per Grade 1[i]
Grade 4h Patient in critical condition and/ or obtunded and cannot perform assessment of tasks; repetitive seizures without return to baseline or life-threatening seizures (non- convulsive or convulsive)	• ICU care, consider mechanical ventilation for airway protection. • High-dose corticosteroids[e,g] • Consider repeat neuroimaging (CT or MRI) every 2□3 days if patient has persistent grade ≥ 3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.	Anti-IL-6 therapy as per Grade 1[i]

[e] Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.

[g] For example, methylprednisolone IV 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 h for 2 days, and 60 mg every 12 h for 2 days.

[h] Diagnostic lumbar puncture for grade 3-4 neurotoxicity; consider for grade 2.

[i] Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient w l trials is especially encourage

6. Professional Society Recommendations / Consensus Statements / Other Expert Opinion

The Society for Immunotherapy of Cancer
In Boyiadzis et al. (2016), the Society for Immunotherapy of Cancer issued a consensus statement on immunotherapy for the treatment of hematologic malignancies. The consensus statement focused on multiple myeloma, lymphoma, and acute leukemia.

An expert panel met to consider issues related to patient selection, toxicity management, treatment cessation guidelines and current recommendations for treatment sequencing with the goal to provide a consensus statement on clinical use of immunotherapy for patients with hematological malignancies. Major emphasis was placed on FDA-approved agents through 2014, with the exclusion of HCT. Search terms included "lymphoma and chimeric antigen receptor" and "ALL and CAR or CART".

Regarding lymphomas, one key scientific question raised by the panel was why the response rates for lymphomas are so variable and not as high as observed in ALL. To provide suggestions on issues related to immunotherapy research in lymphoma, the lymphoma panel thought it was essential to try to learn as much as possible from every patient who enters a trial and it was emphasized the imperative for industry to share biologic data that result from such studies. The lymphoma panel stated that CAR T-cell therapy "is very promising as a salvage regimen. However, the immediate question is its role and timing among the many emerging choices for refractory and relapsed lymphomas. There will be increased utilization of this therapy and earlier consideration for it as a treatment option, as long as it proves to be safe (see toxicities), and especially if it is shown to be a "once and done" option, which has been observed in ALL." The leukemia panel also discussed CAR T-cells as an emerging immunotherapy, mainly in patients with B-cell ALL, and noted that "Adoptive transfer of T cells engineered to express a CAR has emerged as a powerful immunotherapy." The panel recommended the development of guidelines for management of complications with CAR T-cells. The Cancer Immunotherapy Guidelines Hematologic Malignancies Subcommittee is in the process of updating this guideline to address progress in the field of hematologic malignancies.

The myeloma panel noted that several CAR-modified T-cell approaches are in preclinical/early phase testing. The panel stated that evidence showed tumor regression in patients with relapsed or refractory multiple myeloma as well as melanoma. The myeloma panel recommended CAR T-cell therapy as a promising strategy for immunotherapy of multiple myeloma and identified patients with high-risk multiple myeloma or relapsed or refractory multiple myeloma as preferred clinical settings for evaluation of adoptive cellular therapies. The panel concluded that data were insufficient to deviate from preferred endpoints in multiple myeloma clinical trials, however PFS was not recognized as a consistent or reliable predictor of OS following immunotherapy.

Mohile SG, et al., Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. Journal of Clinical Oncology, 2018 Jun 22: JOP1800180.

The purpose of this guideline is to provide recommendations on the assessment and management of vulnerabilities in older patients undergoing chemotherapy based on an expert panel performing a systematic review of the medical literature. The panel recommends that geriatric assessment guided interventions be used to manage additional nononcologic problems.

ASCO believes that cancer clinical trials are vital to inform medical decisions for older patients with cancer and

improve cancer care and that all order patients should have the opportunity to participate. For the purposes of this guideline, comorbidity is defined as a medical condition that exists along with an index condition and geriatric assessment (GA) is a compilation of validated tools that assess specific domains known to be associated with adverse outcomes in older patients. A total of 68 studies met eligibility criteria and the age of 65 was used as the cutoff for the guideline recommendations. This ASCO clinical practice guideline recommends (Evidence quality = high; Recommendation strength = strong) GA for the evaluation of functional status, physical performance, falls, comorbid medical conditions, depression, social activity, social support, nutritional status, and cognition in older adults with cancer to predict adverse outcomes. To predict adverse outcomes, the guideline recommends (Evidence quality = high; Recommendation strength = moderate) the following GA tools based on evidence supporting their utility for predicting adverse outcomes and on ease of administration: Instrumental activities of daily living (IADL) for function, Geriatric Depression Scale (GDS), Mini-Cog, BlessedOrientation-Memory- Concentration (BOMC), Cancer and Aging Research Group score (CARG), Chemotherapy Risk Assessment Scale for High- Age Patients (CRASH), Geriatric-8 (G8), and Vulnerable Elders Survey-13 (VES-13). The authors suggest that managing toxicities and hospitalizations should not be considered more feasible than incorporating GA into clinical practice. The guideline also recommends (Evidence quality = high; Recommendation strength = strong) consideration of the following life expectancy data for community-dwelling patients to best inform treatment decision making for older patients with cancer: validated tools listed at ePrognosis, Schonberg Index, Lee Index. Such validated tools should determine if patients have adequate life expectancy beyond 4 years to expect benefits from specific cancer interventions, including chemotherapy. The panel strongly recommends that indices with "presence of cancer" as a relevant variable be indicated "no" if this is the patient's first cancer diagnosis, to consider competing risk of mortality. Finally, the guideline recommends (Evidence quality = moderate; Recommendation strength = moderate) using the GA to guide the following management activities: inform cancer treatment decisions, estimate risks for adverse outcomes, identify nononcologic problems, and select targeted interventions that could be implemented to address GA-identified vulnerabilities.

CMS received the following professional society position statements prior to issuing the proposed decision.

Circular of Information for the use of cellular therapy products. July 2016

This circular was prepared jointly by AABB, America's Blood Centers, the American Association of Tissue Banks (AATB), the American Red Cross (ARC), the American Society for Apheresis (ASFA), the American Society for Blood and Marrow Transplantation (ASBMT), the College of American Pathologists (CAP), the Cord Blood Association, the Foundation for the Accreditation of Cellular Therapy (FACT), ICCBBA, the International Society for Cellular Therapy (ISCT), the Joint Accreditation Committee of ISCT and EBMT, the National Marrow Donor Program (NMDP), and Netcord. The circular warns that because cellular therapy products are derived from human blood or tissues, they may carry a risk of transmitting infectious agents, malignant disease, and certain immunizing substances. To this end, the circular provides information and recommendations related to product sources, storage, administration, biohazards, and side effects. Recommendations include uniform donor history questionnaires, periodic patient monitoring, and uniform institutional policies and protocols to mitigate risks incurred in dosage, administration, and storage. One recommendation to facilitate these policies and protocols includes contact with manufacturing/processing facilities for handling and storage instructions. The circular notes that subsequent applications of any autologous products are limited to clinical trials and research protocols.

Foundation for the Accreditation of Cellular Therapy (FACT). Standards for Immune Effector Cell Administration. First edition, version 1.1. March 2018.

The objective of the Common Standards is stated to promote quality medical and laboratory practice in cellular therapies as an emerging and evolving field, and to represent basic intentions for cellular therapy from product

development through clinical trials. The Common Standards are developed through evidence-based consensus processes by experts active in the field of cellular therapy and require that quality management report and evaluate clinical outcomes of patients receiving cellular therapy. This consensus process also allows opportunity for public comment on draft editions. The basis for FACT accreditation is documented compliance with the current applicable set of Standards. Verifiable documentation of compliance by the organization with the Common Standards is necessary for application and continuation of accreditation.

These Common Standards apply to clinical program(s) of the organization involved in administration or evaluation of cellular therapy. Policies and procedures are outlined for cellular therapy collection, processing, labeling, shipping, clinical research, and data management. Policies identify key facility capabilities to make clear that the space, design, and location are adequate and appropriate for patient care or processing of patient materials. Procedures identify key personnel and responsibilities for each of the included protocol steps in advance of administration. Investigations into deviations from the Common Standards are a routine part of the clinical program(s) activities and are conducted to achieve the goal of planning for corrective and preventive actions to maintain quality patient care and safety.

7. Public Comment

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination.

CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. All comments that were submitted without excessive personal health information may be viewed by using the following link https://www.cms.gov/medicare-coverage- database/details/nca-view-public-comments.aspx?NCAId=291.

Initial Comment Period: 05/16/2018 - 06/15/2018

We received 53 public comments. One comment is not publicly posted because it contains excessive personal health information (PHI). Of the 53 public comments, three comments were from pharmaceutical manufacturers, six comments were from patients and patient-advocates, 18 comments were from hospitals, 23 comments were from physicians, clinical professionals, professional organizations and trade associations, and three did not self- identify. Below is a summary of the comments CMS received.

Several commenters asked that CMS update the benefit category section of the tracking sheet to either add section 1861(s) or remove reference to inpatient hospital services. A few commenters requested coverage consistent with FDA approval and labeling consistent with section 1861(t) of the Act, while a few other commenters recognized that the FDA standard of safe and effective is separate and distinct from the CMS standard of reasonable and necessary. A few commenters noted that there is a small population that has received CAR T-cell therapy and believe that this treatment will require more refining through clinical trials. One commenter asked that CMS clarify whether coverage will include bone marrow relapse specifically, given that the pivotal phase II trials on CAR T-cell therapy focused on bone marrow relapse. Another commenter asked that CMS consider coverage criteria based on which patients with progressive disease would benefit from coverage of CAR T-cell therapy.

A few commenters shared their experience that all patients who are treated with CAR T-cell products require inpatient care while a few other commenters noted that CMS must instead consider the side effects of each product and then determine the extent of care required. Many commenters identified hundreds of clinical trials registered on www.clinicaltrials.gov that are currently underway, and asked that CMS consider providing coverage for CAR T-cell

therapy for the Medicare population to support continued evidence collection. A few other commenters recommend that the NCA outline a process for shared decision-making. In contrast, several commenters stated that CMS should not require additional coverage criteria, and strongly encourage CMS to leverage product REMS programs and post-approval studies to the fullest extent possible. Several commenters requested that CMS rescind this NCA. A few other commenters raised concern that coverage of CAR T-cell therapy could vary unless additional clarification is provided in this NCA.

Second Comment Period: 02/15/2019 - 03/17/2019

CMS received 93 public comments on the proposed decision. Of the 93 public comments, 20 comments were from pharmaceutical manufacturers, 15 comments were from patients and patient-advocates, 60 comments were from hospitals, physicians, clinical professionals, professional organizations and trade associations, 4 comments from payers and 11 did not self-identify. Below is a summary of the comments CMS received.

Benefit Category

Comment: A few commenters asked that section 1861(s) be added or updated to include 1861(s)(1) and 1861(s)(2)(A), as the commenters believe that this section is not comprehensive. One commenter noted that under section 1861(s)(2)(B), the FDA approved CAR T-cell products qualify as a "medical and other health service" as a biological administered incident to a physician's service in the hospital outpatient department. A few commenters requested coverage consistent with FDA approval and labeling consistent with section 1861(t) of the Act

Response: We appreciate the comment. In this final decision, we indicate that CAR T-cell therapy also falls under the category of drugs and biologicals at section 1861(t) of the Act. We are maintaining the references to 1861(b) and 1861(s)(2)(B) to reflect the fact that per FDA requirements, the approved CAR T therapies are only available through healthcare facilities that are enrolled in the REMS requirements. We note that the list of benefit categories may not be an exhaustive list of all applicable Medicare benefit categories for the item or service

Comment: Commenters shared their support for the proposal to cover CAR T-cell therapy administered in the hospital. One commenter stated that hospitals as noted by the Foundation for the Accreditation of Cellular Therapy (FACT) are the providers currently equipped to ensure the safest and most efficacious delivery of CAR T-cell therapy.

Response: CMS is finalizing this NCD to provide for uniform national coverage consistent with section 1861(t) of the Act. Therefore, we are not requiring accreditation by FACT as a condition of coverage in our final decision. Per the FDA, hospitals and their associated clinics may administer CAR T if the facilities are enrolled in with the REMS requirements.

Coverage

Comment: Many commenters note that autologous CAR T-cell therapy is an evolving area of medicine and that this treatment is in its early phases and will require more refining through research and clinical trials, and that for many cancer patients, study participation is the best option for reaching patient goals of longer, high-quality life.

Response: We appreciate the comment. We agree that CAR T-cell therapies continues to evolve as research and clinical trials are ongoing.

Comment: A few commenters requested that CMS cover any FDA-approved CAR T-cell therapy in a manner consistent with its U.S. Food and Drug Administration (FDA) approval and labeling. Several commenters believe that

coverage for CAR T-cell therapy should not differ from coverage of all other FDA approved anti-cancer drugs.

Response: We agree and we are covering autologous CAR T-cell therapy for all medically accepted indications, including for FDA-approved indications on the FDA-approved labeling in this final decision.

Comment: A few commenters disagree with the scope of the NCD as they believe that CMS should not issue NCDs for a therapy that is still new and evolving, such as CAR T-cell therapy and contend that revising an NCD is burdensome.

Response: We agree the therapy is evolving and recognize the active ongoing research in the field. Under the final NCD, all FDA labeled indications and off-label uses recommended by CMS-approved compendia are coverable. We are issuing this NCD to ensure uniform national coverage consistent with 1861(t)(2) of the Act. See 42 C.F.R. 405.1060.

Medical Evidence

Comment: Many commenters requested that the NCD recognize new emerging technologies and not limit coverage to autologous CAR T-cell products. Commenters submitted additional evidence, including the updated Circular of Information for the Use of Cellular Products, which was released in October 2018, for CMS to consider including into a final NCD. A few commenters suggested the NCD should apply to all current and future FDA-approved CAR T-cell and similar targeted cellular therapeutic products regardless of origin of the effector cells (autologous or allogeneic), the subclass of effector cell, or the tumor cell target. One commenter noted that there is a small population that has received CAR T-cell therapy, and encouraged CMS to consider broadening the language in the NCD, so as not to limit manufacturing methods and referencing CAR T-cell and related immune effector cell therapies, rather than CAR T-cell therapy to enable the NCD to cover other novel cell-based therapies that are not derived from T-cells, such as newer products from Natural Killer (NK) Cells. This commenter is concerned that if the narrow language in the draft proposed decision memo is finalized, CMS will need to reopen the NCD each time a new CAR T-cell and related immune effector cell therapy becomes available.

Response: We appreciate the comment and recognize that CAR T-cell therapies are evolving with limited patient uses. This NCD is limited in scope to treatment with autologous T-cells. Allogeneic T-cell therapy is outside the scope of this final decision. CAR NK cells are outside the scope of this final decision. We are making this NCD in response to a formal request for an NCD from an outside party. We believe that a uniform national policy will be helpful to Medicare beneficiaries.

Patient Indications

Comment: Most commenters asked that CMS reconsider whether coverage will include patients in earlier stages of cancer. A few of these commenters offered the alternative proposal that CMS cover CAR T-cell therapy consistent with the FDA label, given that pivotal trials on CAR T-cell therapy are on-going and may evolve.

Response: We appreciate the comment. In this final decision, coverage is available to all medically accepted indications including FDA-approved autologous CAR T-cell therapy when used for an FDA-approved indication, or when such use is supported by a citation in one or more CMS-approved compendia.

Comment: Most commenters asked that CMS specify comorbidities that preclude patient benefit from CAR T-cell therapy. For example, one commenter suggested that CMS utilize NCCN guidelines to identify which comorbidities preclude patient benefit. Some commenters recognized that each CAR T-cell product could have specific

comorbidities that preclude patient benefit, and asked that CMS consider such unique manufacturing and mechanistic characteristics as it develops a final analysis. As an example, one commenter recommends language to read "is not currently experiencing any comorbidity that would otherwise preclude patient benefit as identified in the FDA-approved label of the prescribed CAR T-cell therapy."

Response: We appreciate the comment. In this final NCD, coverage is available to medically accepted indications including FDA-approved autologous CAR T-cell therapy when used for an FDA-approved indication. Another use of the FDA-approved product is also coverable if the use is supported by a citation in one or more CMS-approved compendia.

Comment: Many commenters suggested that the determination of comorbidities that would preclude patient benefit be based on discretion of the treating clinician. These commenters believe that because the benefits and risks of CAR T-cell therapy must be considered on an individual basis by the treating physician and the patient, the determination would be made at that time.

Response: We agree that the treating physician should take the individual patient's specific values and medical condition into consideration when recommending this treatment.

Comment: Commenters requested that CMS clarify whether additional doses of CAR T-cell therapy are covered.

Response: CAR T-cell therapy is provided as a single-dose for infusion containing a suspension of CAR-positive viable T cells. Additional doses of CAR T-cell therapy are not specified uses per the FDA-label.

Setting of Care

Comment: A few commenters shared their experience that all patients who are treated with CAR T-cell products require inpatient care. Additionally, a few other commenters noted that adverse events require patients to be admitted as inpatients for treatment. Therefore, these commenters believe that CMS must consider these side effects, the care required, and the setting associated in developing an appropriate coverage policy.

Response: CAR T-cell therapy is covered on-label and for use recommended in CMS-approved compendia. The FDA-approved labeling states that currently CAR T-cell therapy is available only through a restricted REMS program.

Comment: Commenters shared their support for the proposal to cover CAR T-cell therapy administered in the hospital. One commenter stated that hospitals as noted by the Foundation for the Accreditation of Cellular Therapy (FACT) are the providers currently equipped to ensure the safest and most efficacious delivery of CAR T-cell therapy.

Response: We finalize this NCD that provides for uniform national coverage consistent with section 1861(t) of the Act. Therefore, we are not requiring accreditation by FACT as a condition of coverage in our final decision. Per the FDA, hospitals and their associated clinics may administer CAR T if the facilities are enrolled in the REMS requirements.

Comment: One commenter noted that several academic centers have championed outpatient administration of CAR T-cells. Further, several commenters stated that CMS should permit providers to determine the appropriate setting of care for each patient who receives CAR T-cells.

Response: The FDA-approved labeling states that currently CAR T-cell therapy is available only through a restricted

REMS program at REMS participating sites. CMS covers all FDA-approved indications for use as well as other uses recommended by CMS-approved compendia. As of the date of publication, the compendia do not recommend other sites for administration of CAR T-cell therapy.

Comment: Many commenters expressed support for proposed standards of a hospital administering CAR T-cell therapy. Consistent with CMS' proposal, one commenter suggested this CAR T-cell care management team should have a documented protocol to ensure 24/7 communication and logistics for patient care coverage by members of the designated care team and provide continual oversight of the patient by the primary CAR T-cell physician. Another commenter suggested written guidelines when administering CAR T-cell therapy that address detailed discharge instructions for emergency and routine follow-up. These commenters believe that given the serious and non-serious adverse events that can occur following discharge, and to ensure the safety of Medicare beneficiaries after CAR T-cell therapy is administered, it is critical that the patient and caregiver receive detailed verbal and written instructions as to actions that should be taken should certain symptoms present.

Response: We appreciate the comments. We CMS is finalizing an NCD that provides for uniform national coverage consistent with section 1861(t) of the Act. The protocols suggested by these comments are not required under the FDA-approved label, and therefore we are not including such protocols as conditions of coverage. However, we note that while not required by our NCD, many hospitals and hospital associated clinics already perform these functions for the safety of Medicare beneficiaries after CAR T-cell therapy is administered.

Comment: A few commenters urged CMS to clarify the requirement of "at least one physician experienced in cellular therapy."

Response: We appreciate the comment and have removed the requirement as it is not part of the FDA-labeled indications for use.

Comment: A few commenters asked that CMS clarify whether accreditation of a treatment provider by the Foundation for the Accreditation of Cellular Therapy (FACT) or other nationally recognized organization(s) is sufficient for meeting the facility requirements for coverage.

Response: We appreciate the comment but have removed the requirement for administrative simplification and consistency with 1861(t)(2).

Comment: Several commenters questioned whether provider enrollment and anti-discrimination provisions in the conditions of participation require hospitals to furnish covered therapy (i.e., NCD covered therapies) to all patients to avoid any confusion amongst centers and address whether or not patients are required to sign either an Advanced Beneficiary Notice (ABN) or a Hospital Issued Notice of Noncoverage (HINN) acknowledging they have been advised that Medicare may not cover and pay for CAR T-cell therapy should a patient receive care at a hospital that chooses not to participate in data collection for the CED.

Response: We have removed the CED requirement from this decision. The NCD does not change any other Medicare rules, including hospital conditions of participation for hospitals, ABNs, or HINNs. Those rules apply to this therapy as a hospital would apply them in other situations for anti-cancer chemotherapy.

CED

Comment: We received many comments ranging from support for CED to others who believe that CED is not warranted for CAR T-cell therapy.

Response: We have removed the CED requirement in this final decision in order to provide Medicare coverage of CAR-T consistent with the language in section 1861(t)(2). We also recognize that there is important ongoing research by scientists and manufacturers and note that the routine costs of clinical trials where CAR T-cell therapy is an investigational agent would be covered per our existing Clinical Trial Policy [NCD 310.1]. We also note that FDA has required post-marketing studies. According to the FDA approval and labeling for two products, CAR T-cell therapy is indicated for very ill patients with certain relapsed or highly refractory cancers. In these rare cases, patients who have failed multiple lines of therapy may have limited remaining treatment options. CAR T-cell therapy has been shown to induce remission in carefully identified relapsed or refractory cancer patients in appropriate settings of care. Informed decision making between a physician and patient remains key to determining the best treatment.

Off-label CAR T-cell therapy

Comment: Many commenters expressed support for the coverage of off-label use of CAR T-cell therapy. Many commenters sought clarification on why the National Comprehensive Cancer Network (NCCN) was listed as the sole applicable compendium in the proposed decision memo when CMS recognizes others in the Medicare Benefits Policy Manual. A few commenters recommend that CMS allow Medicare Administrative Contractor (MAC) discretion to cover CAR T-cell therapy for non-relapsed/refractory indications.

Response: We appreciate the supportive comments. Additional uses of an FDA-approved CAR T-cell product are coverable when recommended for use by a citation in one or more CMS-approved compendia. As a result, coverage will be provided consistently on a national level and contractors local policies cannot supersede the NCD. In this final decision, off-label coverage will not be limited to uses recommended by NCCN.

Patient-Reported Outcomes (PROs)

Comment: We received many comments on PROs ranging from support of their collection to recommendations for additional assessment tools to request to remove PRO requirements.

Response: We appreciate these comments and understand that PROs are being incorporated into clinical studies by researchers and manufacturers. We reiterate that coverage is available for routine care items and services in clinical trials where autologous CAR T-cell therapy is administered as an investigational agent. CMS notes that the National Institutes of Health is co-funding the Center for International Blood and Marrow Transplantation Research (CIBMTR) database that currently collects health outcomes (and aims to collect patient reported outcomes in the future) on patients who have received CAR T-cell treatments. We encourage participation in ongoing research such as the CIBMTR.

Risk Evaluation Mitigation Strategy (REMS)

Comment: Several commenters expressed that CMS should require additional provider certification criteria since manufacturers of CAR T-cell products are required to be accredited by the Foundation for Accreditation in Cellular Therapy (FACT) as part of a Risk Evaluation and Mitigation Strategy (REMS) approved by the FDA. To this end, the commenters strongly encourage CMS to leverage product REMS programs to the fullest extent possible.

Response: We are not requiring additional provider certification requirements in our final decision. We note that FDA requires a REMS, which is on the FDA-approved label for the two currently approved FDA uses. We cover FDA-approved autologous CAR T-cell therapy when administered at healthcare facilities enrolled in with REMS and used for an FDA-approved indication. Additional off-label uses of the product are coverable if used for a medically accepted

indication as defined at section 1861(t)(2)(B) of the Act.

Comment: A few commenters noted that in addition to the REMS requirement, FDA also requires post-marketing studies of FDA-approved CAR T-cell products, specifically the 15-year observational studies to assess long-term safety by following at least 1500 patients for 15 years after product administration. To this end, the Center for International Blood and Marrow Transplant Research (CIBMTR®) has been identified to conduct such follow-up studies at the Medical College of Wisconsin Clinical Cancer Center.

Response: We appreciate the comment and recognize the post-marketing studies required by the FDA. We will continue dialogue with the FDA and emphasize the importance of this treatment for the Medicare population. For CAR T-cell therapies, there are potential commonalties in outcomes. We encourage that registries such as CIBMTR® consider the criteria for coverage to support ongoing research of CAR T-cell therapy. However, it is not a requirement of this NCD.

Oversight by the Physician

Comment: Several commenters requested that CMS include both the treating oncologist and hematologist as covered for the purposes of a final NCD. These commenters believe that hematologists are also specialists capable of managing patients eligible for treatment with CAR T-cell therapy.

Response: We agree. CAR T-cell therapy would be covered when prescribed by a treating oncologist and hematologist, as long as the therapy is used for a medically accepted indication in accordance with this NCD.

Comment: A few commenters noted that administration of CAR T-cell products can have tremendous benefits, but requires very close oversight by the treating physician during and following the treatment.

Response: We have removed the requirement for specific prescribers. CAR T-cell therapy is covered for FDA-approved indications and uses recommended by a citation in one or more CMS-approved compendia.

Comment: A few commenters noted that the treatment regimen is comprised of a single infusion. Therefore, commenters request that CMS clarify what is meant by the use of more than one therapeutic dose of a specific CAR T-cell product, as well as a new primary cancer diagnosis for repeated treatments.

Response: The decision includes coverage for FDA-approved autologous CAR T-cell therapy when used for an FDA-approved indication. Additional uses of the product are coverable if used for a medically accepted indication as defined at section 1861(t)(2)(B) of the Act.

Comment: One commenter shared their experience that pathologists are directly involved in the provision of CAR T-cell therapy clinical services, notably, the apheresis harvesting of blood-derived T-lymphocytes for development of genetically modified CAR T-cells.

Response: We appreciate the experience shared by the commenter, and remind all readers that this decision would not change the existing NCD for therapeutic apheresis (NCD 110.14).

8. Pending Clinical Trials

ClinicalTrials.gov

Using the terms and synonyms searched in our internal technology assessment identified 28 interventional studies currently recruiting patients aged 65 years or older in the United States without current results posted to www.clinicaltrials.gov (accessed August 8, 2018). In addition, a search for any interventional studies using CAR T-cell therapy currently recruiting patients aged 65 years or older in the United States identified 28 additional studies relevant to patients with any cancer. Information about these studies can be found in Appendix C.

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1869(f)(1)(B) of the Act). In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." (§1862(a)(1)(A) of the Act). With respect to coverage of drugs and biologicals used as part of an anticancer chemotherapeutic regimen, § 1861(t)(2) provides for uniform coverage when the product is used for a medically accepted indication - i.e., uses approved by the FDA, and other uses provided that the product is FDA-approved and the use is supported by one or more citations in certain compendia, unless the Secretary determines that such off-label use is not appropriate.

This section of the decision memorandum provides an analysis of the evidence we considered during our review. The evidence includes the published medical literature and guidelines pertaining to autologous transplant of T-cells expressing at least one CAR for treatment of patients with cancer. As we stated in our response to public comment, this decision did not consider other forms of transplant such as allogeneic T-cells, and did not consider additional cell types, such as Natural Killer (NK) cells. For details of each of the clinical trials, see the section VII.8. Pending Clinical Trials and Appendix C.

In this analysis, we addressed the question(s) below:

- *Is the evidence adequate to conclude that CAR T-cell therapy improves health outcomes for Medicare beneficiaries with relapsed or refractory large B-cell lymphoma?*
- *Is the evidence adequate to conclude that CAR T-cell therapy improves health outcomes for Medicare beneficiaries with relapsed or refractory B-cell precursor acute lymphoblastic leukemia?*
- *Is the evidence adequate to conclude that CAR T-cell therapy improves health outcomes for Medicare beneficiaries with other types of cancer?*
- *If the answer to any of the questions above is positive, is the available evidence adequate to identify the characteristics of the patient, practitioner or facility that predict which beneficiaries are more likely to experience overall benefit or harm from CAR T-cell therapy?*

CAR T-cell therapy is a new and rapidly-emerging treatment that was first FDA-approved in mid-2017. As a result, we found only a small number of published, peer-reviewed, full-text literature articles that presented the results of clinical trials for the two FDA-approved CAR T-cell products (tisagenlecleucel and axicabtagene ciloleucel) and the two FDA indications. Our review was based mostly on these publications combined with the FDA's regulatory reviews, a systematic review by ICER, and evidence-based clinical management guidelines by the NCCN. Our analysis is presented by FDA indication: ALL, B-cell lymphoma, and by other types of cancer.

<u>Relapsed or Refractory Acute Lymphoblastic Leukemia</u>

We found two published, full-text literature articles for the ALL indication. In Maude et al. 2014, the authors presented the results from a pilot study. Thirty patients with ALL received a single dose of tisagenlecleucel. None of these 30 patients were 65 years or older. The complete response (CR) at one month was 90% and the overall survival (OS) at six months was 78%. All 30 patients developed cytokine release syndrome (CRS), which was severe in 27% of the patients and treated with tocilizumab. The rate of neurotoxicity was in 43% of the patients.

Maude et al. 2018 reported the results of the ELIANA study, which was a single-arm, single dose Phase II clinical trial of tisagenlecleucel in 75 patients with ALL. None of the 75 patients were 65 years or older. The average age of the population was 11 years. The overall response rate (ORR) at three months was 81% with a 60% CR rate and the OS rate was 90% at six months and 76% at 12 months. In a systematic review of CAR T-cell therapy, ICER noted these ALL studies to be of lower quality due to the lack of a comparator, the small sample sizes and the short term median follow-up, which adds to the uncertainty about long term outcomes. ICER concluded that "there is at least a small net health benefit compared with current salvage chemotherapy, although the benefit may be substantial." Additionally, the NCCN (2018a) stated that CAR T- cell therapy "to treat ALL represents a significant advance in the field," recommended that tisagenlecleucel be "an option for patients up to age 25 years (age < 26 years) and with refractory disease or ≥; 2 relapses," and noted "that patients be treated at a specialized cancer center with expertise in the management of ALL."

The data from the ELIANA clinical trial served as the basis for FDA's approval of tisagenlecleucel for ALL. As part of the FDA review, a meeting of the FDA Oncologic Drugs Advisory Committee was held on July 12, 2017. Information regarding the key outcomes of this meeting is found in the Evidence Section of this NCA.

While acknowledging the significant risks of tisagenlecleucel due to adverse events (AEs), the FDA concluded that "the benefit-risk profile for these heavily-pretreated pediatric and young adult patients with relapsed/refractory (R/R) B-cell precursor ALL is favorable with appropriate risk mitigation strategies in place. During the trial the applicant provided on- site training for participants, restricted study sites to transplant centers, and closely monitored safety events. This risk mitigation strategy was successful in reducing morbidity of KYMRIAH and will be continued in the Risk Evaluation Mitigation Strategy (REMS) with Elements To Assure Safe Use (ETASU)." As a result of this strategy, the FDA approved tisagenlecleucel with postmarketing requirements for a REMS with ETASU for the management of CRS and neurologic toxicity, and required training and assessment of sites, and the use of tocilizumab and a postmarketing observational study, to assess the short and long-term toxicities of tisagenlecleucel.

Relapsed or Refractory B-cell Lymphoma

Both tisagenlecleucel and axicabtagene ciloleucel are FDA-indicated for B-cell lymphoma. Supporting evidence includes four published full-text literature articles. Kochenderfer et al. 2017 reported the results of a study of axicabtagene ciloleucel in 22 patients with relapsed or refractory B-cell lymphoma (19 with DLBCL). The age range was 26 to 67 years; six patients were ≥ 65 years old. Results were not reported by age. Complete response was 55% without further chemotherapy and the ORR was 73%. The rate of CRS was not reported, but 55% of patients developed severe neurologic toxicity.

Locke et al. (2017) reported the first results of seven patients in the Phase I/II ZUMA-1 clinical trial, which was a multicenter, single-arm, single-dose study of axicabtagene ciloleucel in patients with refractory DLBCL. The age range was 29 to 69 years; three patients were ≥ 65 years old. Results were not reported by age. Overall response rate (ORR) was 71% with CR rate 57% at one month and three patients had an ongoing CR at 12 months. Grade three CRS and neurotoxicity developed in 14% and 57% patients, respectively. Neelapu et al. (2017) reported the Phase II results of the ZUMA-1 clinical trial with 101 patients with B-cell lymphoma (77 with refractory DLBCL) who received axicabtagene ciloleucel. The median age was 58 years with a range of 23 to 76 years; however, the number of patients ≥ 65 years old who received axicabtagene ciloleucel was not reported. The ORR was 82%; for the 24 patients who were at least 65 years old, and response rates were consistent across age, disease stage, and use of tocilizumab or glucocorticoids. Analysis of the pooled data from 108 patients showed 58% CR and OS of 78% at six

months, 59% at 12 months, and 52% at 18 months.

Of note, in the ZUMA-1 trial, CRS developed in 93% of patients; 13% were grade three or higher, where grade three or higher CRS means that the complication was serious enough to require aggressive medical intervention. The median time from infusion to onset of CRS was 2 days with a range of one to 12 days; the median time to resolution was eight days. Neurologic events developed in 64%; 28% were grade three or higher. The median onset of neurologic events occurred on day five with a range of one to 17 days and a median resolution on day 17 after infusion. Adverse events (AEs) were not reported by age.

Schuster et al. (2017a) reported a single-dose Phase I/II study of tisagenlecleucel in 28 patients with relapsed or refractory DLBCL or refractory follicular lymphoma. The median age was 58 years with a range of 25 to 77 years for patients with DLBCL and 59 years with a range of 43 to 72 years for patients with follicular lymphoma. The number of patients = 65 years was not reported and the results of the analyses were not reported by age. Complete response (CR) was reported in 57% at six months. CRS developed in 57% of patients and 11 developed neurotoxicity ranging from mild cognitive disturbance to global encephalopathy.

In its systematic review of CAR T-cell therapy for B-cell lymphoma, ICER included all of the studies noted above (except Locke et al., 2017) as well as an abstract of the JULIET study results (Schuster et al., 2017b), which studied tisagenlecleucel. ICER found these studies to be of lower quality due to the lack of a comparator, the small sample sizes and the short median follow-up, which "adds to the uncertainty about long term outcomes with CAR-T therapy for adult aggressive B-cell lymphoma." The authors found that the "disease-free survival and OS appear to be greater than those observed with other therapies, but follow-up in the ZUMA-1 trial is short (median 15.4 months)." According to ICER the "follow-up in the JULIET trial design is shorter than that for the ZUMA-1 trial, but the earlier single-site trial of tisagenlecleucel provides evidence that the results are likely to be robust with longer follow-up."

For both CAR T-cell products, ICER noted common and significant AEs (CRS, neurotoxicity, B-cell aplasia), but that the estimated net health benefit is substantial. However, the level of certainty about the magnitude of the net health benefit was noted as low because there are no comparative trials, and the existing single-arm trial is small with short follow-up. Given these uncertainties, ICER assigned a "B+" rating for both axicabtagene ciloleucel and tisagenlecleucel. Additionally, the NCCN (2019) recommended the B-cell lymphoma use. Specifically, the NCCN stated that "Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL, NOS; primary mediastinal large B-cell lymphoma; high grade B-cell lymphoma; and DLBCL arising from follicular lymphoma" and that "Tisagenlecleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL, NOS and high grade B-cell lymphoma and DLBCL arising from follicular lymphoma." Of note, the NCCN (2018b) also acknowledged the toxicities associated with immunotherapies such as CAR T-cell products by recently publishing a new clinical guideline to address the management of these toxicities, which includes an overview of CAR T-cell therapy-related toxicities such as CRS and neurotoxicity as well as information about principles of patient monitoring.

The data from the ZUMA-1 clinical trial served as the basis for FDA's approval of axicabtagene ciloleucel. In its SBRA, FDA noted an ORR of 72% and a CR rate of 51%, which provided a "favorable risk/benefit profile." FDA mandated a REMS with ETASU and a 15-year, multicenter, observational safety PMR study in 1500 subjects using a registry design in order to evaluate the risk for secondary malignancy. Of note, FDA placed a limitation of use: axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system lymphoma. The data from the JULIET clinical trial (NCT02445248) served as the basis for FDA approval of tisagenlecleucel, for which we found neither a published, full- text article nor pending clinical trial because it is no longer recruiting. In its SBRA, FDA stated efficacy was "based on the complete remission (CR) rate and duration of response. In a population of 68 patients with relapsed or refractory disease, the objective response rate was 50% with a CR rate of 32%." The FDA review team concluded "a favorable risk/benefit profile" and noted a limitation of use: tisagenlecleucel is not

indicated for treatment of patients with primary central nervous system lymphoma. FDA mandated a REMS with ETASU and a long-term PMR study.

In its position statement from 2014, the Society for Immunotherapy of Cancer noted that CAR T-cell therapy has "emerged as a powerful immunotherapy" for patients with leukemia and "is very promising as a salvage regimen" with the potential for earlier use as a treatment option in patients with lymphoma if it "proves to be safe" and "especially if it is shown to be a 'once and done' option," while recommending the need for guidelines to management the complications associated with CAR T-cell administration. The Society also acknowledged the "promising" early phase development of CAR T-cell therapy for other types of cancer, particularly multiple myeloma and melanoma. (Boyiadzis et al., 2016)

The comments from the public comment periods focused on numerous issues and presented a wide range of opinions on those issues. For example, some commenters stated that coverage should be consistent with FDA approval and labeling while other commenters noted that only a small number of patients were studied during product development and, therefore, CAR T-cell therapy requires more study via post-marketing clinical trials. Similarly, many commenters noted the hundreds of clinical trials that are currently registered on www.clinicaltrials.gov and underway, and asked that CMS consider providing coverage for CAR T-cell therapy for the Medicare population to support continued evidence collection for not only the two FDA-approved products or for the two FDA indications but also for yet-to-be approved CAR T-cell products and for off-label uses. Several commenters raised concerns that coverage of CAR T-cell therapy could vary unless additional clarification is provided in this NCA.

For both tisagenlecleucel and axicabtagene ciloleucel, which are currently the only FDA-approved CAR T-cell products with an indication for relapsed or refractory large B-cell lymphoma, the evidence includes data from small, early-phase clinical studies and from a single Phase II clinical study served as the primary source of clinical evidence for each of the CAR T-cell products. Patients in the study by Schuster et al. (2017) had a median age of 58 years (though the number of patients ≥ 65 years of age was not reported). However, the number of Medicare patients is likely small since the study only had a total of 28 patients infused with tisagenlecleucel. For axicabtagene, 33 patients of 130 patients infused in three published studies were 65 years of age or older but results were not specifically reported for these patients. Hence, the clinical evidence base for each product is small, especially for patients 65 years or older. The lack of a control arm further weakened the clinical evidence from these studies. While the evidence shows a moderately-high rate of complete response, there is also evidence of significant risk of toxicity from cytokine release syndrome and neurotoxicity.

For tisagenlecleucel, which is the only FDA-approved CAR T-cell product to date that is FDA-indicated for B-cell precursor ALL, the evidence includes data from one small, early-phase clinical study and from a single Phase II clinical study served as the primary source of clinical evidence for tisagenlecleucel in patients up to 25 years of age. Hence, the clinical evidence base is small. The lack of a control arm further weakened the clinical evidence. While the evidence shows a moderately-high rate of complete response, there is also evidence of a significant risk of toxicity from cytokine release syndrome and neurotoxicity.

Also included in both FDA labels is a limitation of use, as these products are not indicated for treatment of patients with primary central nervous system lymphoma. It is important to note that these products have boxed warnings from the FDA, which state:

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

CRS, including fatal or life-threatening reactions, occurred in patients receiving this product. Do not administer to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids
Neurological toxicities, which may be severe or life-threatening, can occur following treatment with, including concurrently with CRS. Monitor for neurological events after treatment and provide supportive care as needed.
A Risk Evaluation and Mitigation Strategies (REMS) program is included on the FDA-approval and currently mandatory for tisagenlecleucel and axicabtagene ciloleucel due to the significant adverse effect profile of CAR T-cell therapy. The purpose of these REMS programs are to mitigate the risks of CRS and neurological toxicities by:
Ensuring that hospitals and their associated clinics that dispense therapy are specially certified and have on-site, immediate access to tocilizumab.
Ensuring those who prescribe, dispense, or administer therapy are aware of how to manage the risks of cytokine release syndrome and neurological toxicities.

In summary, CAR T-cell therapy is known to have a significant risk for toxicity, which is reflected in the FDA requirements for a REMS program and a boxed warning in the labeling for tisagenlecleucel and axicabtagene ciloleucel. Regarding the benefits of CAR T-cell therapy, the evidence from clinical studies for both tisagenlecleucel and axicabtagene ciloleucel is limited, especially for Medicare beneficiaries 65 years of age and older with a diagnosis of B-cell lymphoma, and weakened by the uncontrolled nature of the studies. The existence of gaps in the evidence due to these limitations are acknowledged in the FDA requirement for a 15-year post-marketing study, in the findings of an external technology assessment as well as in position statements and evidence-based clinical guidelines by professional organizations and the opinions provided by experts during the public comment period. CMS will continue to monitor the impact of this therapy in conjunction with the FDA for FDA-approved indications.

We recognize there may be cases where patients could benefit from expanded clinical use of an FDA-approved biological, such as for example in the case of an Investigational New Drug (IND) application for expanded use, as well as from CAR T-cell products still in development. As part of this final NCD, we re-affirm that this policy continues coverage for routine costs in clinical trials that meet the requirements listed in the Clinical Trial Policy (NCD 310.1) and use CAR T-cell therapy as an investigational agent. In addition, we identified over 50 cancer clinical trials currently recruiting patients who are 65 years old or older in the United States for applications of CAR T-cell therapy in cancers other than the currently FDA- indicated cancers (see Section VII.8 and Appendix C). Recommendations by professional organizations, such as the Society for Immunotherapy of Cancer, indicate that CAR T-cell therapy is an emerging immunotherapy.

Medicare Patient Population

Current FDA indications, and thus the current clinical evidence for CAR T-cell therapy, is limited to patients who have relapsed or refractory large B-cell lymphoma or relapsed or refractory B-cell precursor acute lymphoblastic leukemia. These patients have few treatment options, which influence their assessment and discussion of benefits and harms of options with their care provider. The evidence base for the B-cell lymphoma clinical studies is currently small especially for older adults where 33 patients who received axicabtagene ciloleucel and fewer than 28 patients who received tisagenlecleucel were 65 years old or older. Given that few clinical trials on CAR T-cell therapy have been performed and those data available have limited participation by Medicare beneficiaries, we performed an analysis of Medicare claims. We sought inpatient claims (see Appendix D) between October 2017 and November 2018 including

both ICD-10-PCS procedure codes XW033C3 and XW043C3 and a drug charge greater than $300,000. We identified approximately 100 Medicare inpatient recipients. Of the 100 Medicare patients we identified in our claims analysis, 20 of the attributed inpatients did not survive. The 6 month overall survival for those with follow-up available in our claims analysis was approximately 64%. The average survival time of those that died was less than 100 days, and the average length of stay in the hospital for all inpatients was approximately 18 days. Analyses like these may support patients and their clinicians making more informed treatment decisions. Additional analyses from commenters identified that our current understanding of the patient experience is limited, especially of those 65 and older.

We recognize there may be circumstances when a patient receives an FDA-approved CAR T-cell product for another use. We also note that the clinical review of the Bioligics Licensing Application(BLA) for axicabtagene ciloleucel states that, "Of the 101 subjects who had CRS events, seven subjects received a second treatment . . . these subjects were considered as separate subjects. Four of these subjects had CRS Grade 4 and three had CRS Grade 2." Furthermore, no conclusions were provided regarding the safety of the second administration and efficacy analyses based on second treatment were not reported. As of this publication the CMS-approved compendia do not provide recommendations for additional dosage of CAR T-cell products.

Practitioner and Provider Requirements

CAR T-cell therapy is associated with a significant risk of toxicity. Because of this, the FDA labeling for the two approved products restricts the availability of the therapy to programs that comply with REMS. Specifically, the labels provide that healthcare facilities that dispense and administer these products must be enrolled and comply with the REMS requirements, and must have on-site, immediate access to tocilizumab. Furthermore, FDA labelling requires certified healthcare facilities to ensure that healthcare providers who prescribe, dispense or administer the products are trained about the management of CRS and neurological toxicities.

Considerations for Further Research

As noted in the Comments and Responses, we recognize that CAR T-cell therapies are actively being developed and continue to evolve. In addition to the evidence that will be developed from the post marketing studies required by the FDA, there are ongoing studies and complete research results awaiting formal publication to help answer importance patient centered questions to inform patient treatment decisions. CMS notes that the National Institutes of Health is co-funding the Center for International Blood and Marrow Transplantation Research (CIBMTR®) database that currently collects health outcomes (and aims to collect patient reported outcomes in the future) on patients who have received CAR T-cell treatments. We encourage participation in ongoing research such as the CIBMTR®.

Health Disparities

In order to provide data on health disparities in CAR T-cell therapy, we performed a search on terms "CAR T-cell therapy health disparities" in PubMed for any publication type. This search resulted in one publication (Shah et al., 2018). The authors present a summary of the current literature in hematopoietic cell transplant (HCT) and cellular therapy with a focus on program structure, system capacity, coordination of care, institutional standardization, and diversity and disparity of care, and quality of life. The authors recognize that the improved health outcomes include broad consideration for both the operations and infrastructure of the health care system that provide processes of care, as well as the symptom burden experienced by the patient. To this end, the authors questioned the geographical distribution of HCT centers, with variability in annual transplant volume, outcomes, and resources. To this end, the authors recommend standardization through FACT or the Joint Accreditation Committee ISCT-European Society for Blood and Marrow Transplant, and discussed the importance of metrics to document the effectiveness of interventions as a basis for further improvement. The authors also recommend additional focused interventions to counterbalance the effects of outcome disparities due to race, gender and socioeconomic status. While data have not been systematically collected on the administration of CAR T-cell therapy, disparities seen in HCT are considered in part due to a delay in referral to a transplant center, barriers to access, ability to work before transplant, and

presence of support partner. While this data may be generalizable to other cancers, further research to identify the barriers that are unique to accessing and increasing the inclusion of a diverse population of patients in cancer clinical trials is warranted.

IX. Conclusion

A. The Centers for Medicare & Medicaid Services (CMS) covers autologous treatment for cancer with T-cells expressing at least one chimeric antigen receptor (CAR) when administered at healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and used for a medically accepted indication as defined at Social Security Act section 1861(t)(2) i.e., is used for either an FDA-approved indication (according to the FDA-approved label for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia.
B. The use of non-FDA-approved autologous T-cells expressing at least one CAR is non-covered. Autologous treatment for cancer with T-cells expressing at least one CAR is non-covered when the requirements in Section A are not met.
C. This policy continues coverage for routine costs in clinical trials that use CAR T-cell therapy as an investigational agent that meet the requirements listed in NCD 310.1.

See Appendix B for the language representative of Medicare's national coverage determination (NCD) for implementation purposes only.

APPENDIX A
General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to that group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is to the extent that differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well- designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of that have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e. g. , using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in that confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or

co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to that the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co- morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator?s lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one

of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology?s benefits and risk of harm to Medicare beneficiaries.

APPENDIX B
Medicare National Coverage Determinations Manual

Draft
This information is representative of Medicare's national coverage determination (NCD) for implementation purposes only. The information is subject to formal revisions and formatting changes prior to the release of the final NCD contractor instructions and publication in the Medicare National Coverage Determinations Manual.

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(Rev.)

Cancer is a collection of related diseases of dividing cells that can start almost anywhere in or on the body, evade the immune system, and invade nearby tissues. Categories of cancer are typically organized by the location in the body and specific type of cell. These categories may include carcinoma, sarcoma, leukemia, lymphoma, multiple myeloma, melanoma, and brain and spinal cord tumors. There are also changes to these cells that are not considered cancer. These changes include hyperplasia□□when a cell divides faster than normal□□and dysplasia□□a buildup of extra cells with abnormal shape and disorganization.

A person's immune system contains cells to help fight substances that are foreign to the body, including cancer. These cells are called white blood cells, most of which are lymphocytes. The two main types of lymphocytes are B lymphocytes (B-cells) and T lymphocytes (T-cells). B-cells generate and release antibodies to fight infection, especially bacterial infections, while T-cells employ a number of other mechanisms to fight abnormal cells such as cancer. One type of therapy that leverages the immune system□□immunotherapy□□is Chimeric Antigen Receptor (CAR) T-cell therapy.

CAR T-cells have been genetically altered in order to improve the ability of the T-cells to fight cancer. The genetic modification creating a CAR can enhance the ability of the T-cell to recognize and attach to a specific protein, called an antigen, on the surface of a cancer cell.

A. Effective for services performed on or after [Month/XX] [Day/XX], [20XX], the Centers for Medicare & Medicaid Services (CMS) covers autologous treatment for cancer with T-cells expressing at least one chimeric antigen receptor (CAR) when administered at healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and used for a medically accepted indication as defined at Social Security Act section 1861(t)(2) □i.e., is used for either an FDA-approved indication (according to the FDA-approved label

for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia.

C. Nationally Non-Covered Indications

The use of non-FDA-approved autologous T-cells expressing at least one CAR is non-covered. Autologous treatment for cancer with T-cells expressing at least one CAR is non-covered when the requirements in Section A are not met.

D. Other

Routine costs in clinical trials that use CAR T-cell therapy as an investigational agent that meet the requirements listed in NCD 310.1 will be covered.

APPENDIX C

Clinical trials of CAR T-cell products (CD19, CD20, CD22, CD123, BCMA, mesothelin, and EGFRvIII) currently recruiting patients with cancer aged 65 years or older in the United States.

NCT Number	Study Title	Sponsor/Collaborators	Outcome Measures
NCT02935543	CART19 in Patient With ALL	University of Pennsylvania	MRD+ ALL, OS, DOR
NCT03464916	Study to Evaluate the Safety and Efficacy of Anti-CD38 CAR-T in Relapsed or Refractory Multiple Myeloma Patients	Sorrento Therapeutics, Inc	MTD, CAR-T cell blood concentrations, Pharmocokinetics
NCT03089203	CART-PSMA-TFGBRDN Cells for Castrate-Resistant Prostate Cancer	University of Pennsylvania	AEs, anti-tumor effect
NCT03085173	A Trial of "Armored" CAR T Cells Targeting CD19 for Patients With Relapsed CD19+ Hematologic Malignancies	Memorial Sloan Kettering Cancer Center, Juno Therapeutics, Inc	MTD
NCT03434769	AntiCD19 Chimeric Antigen Receptor T Cells for Relapsed or Refractory Non Hodgkin Lymphoma	Case Comprehensive Cancer Center	Lymphoma response, DOR, disease-free survival

NCT03103971	huJCAR014 CAR-T Cells in Treating Adult Patients With Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma or Acute Lymphoblastic Leukemia	Fred Hutchinson Cancer Research Center, NCI	Toxicity, DLT, maximum concentration
NCT03126864	Study of Adoptive Cellular Therapy Using Autologous T Cells Transduced With Lentivirus to Express a CD33 Specific Chimeric Antigen Receptor in Patients With Relapsed or Refractory CD33-Positive Acute Myeloid Leukemia	MD Anderson Cancer Center, Intrexon Corporation, Ziopharm	Disease response, phase II dose of CD33-CAR-T cells
NCT03060356	Autologous T Cells Expressing MET scFv CAR (RNA CART-cMET)	University of Pennsylvania	AEs, objective overall response (CTCAE v4.03 and RECIST 1.1)
NCT02917083	CD30 CAR T Cells, Relapsed CD30 Expressing Lymphoma (RELY-30)	Baylor College of Medicine, Methodist Hospital, Texas Children's UNC Lineberger	DLT, ORR, number of T-cells transduced
NCT03016377	Administration of Autologous CAR-T CD19 Antigen With Inducible Safety Switch in Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia	Comprehensive Cancer Center	AEs, recommended phaseII dose, survival of CAR19 T cells
NCT03277729	A Phase I/II Study to Evaluate the Safety of Cellular Immunotherapy Using Autologous T Cells Engineered to Express a CD20-Specific Chimeric Antigen Receptor for Patients With Relapsed or Refractory B Cell Non-Hodgkin Lymphomas	Fred Hutchinson Cancer Research Center, NCI	DLT, complete remission, PFS

NCT02744287	Prostate Stem Cell Antigen (PSCA) -Specific CAR T Cells In Subjects With Non-Resectable Pancreatic Cancer	Bellicum Pharmaceuticals	MTD, DLTs
NCT02146924	Cellular Immunotherapy in Treating Patients With High-Risk Acute Lymphoblastic Leukemia	City of Hope Medical Center, NCI	Toxicity, DLT, assessed using CTCAE
NCT03049449	T Cells Expressing a Fully-Human Anti-CD30 Chimeric Antigen Receptor for Treating CD30-Expressing Lymphomas	NCI, NIH Clinical Center	Safety, feasibility, immunogenicity, in vivo persistence, antilymphoma activity
NCT02706392	Genetically Modified T-Cell Therapy in Treating Patients With Advanced ROR1+ Malignancies	Fred Hutchinson Cancer Research Center, NCI	AEs, persistence of T-cells, identification of migration sites
NCT03389230	Memory-Enriched T Cells in Treating Patients With Recurrent or Refractory Grade III-IV Glioma	City of Hope Medical Center, NCI	Grade 3 AEs, DLT, AEs
NCT03081910	Autologous T-Cells Expressing a Second Generation CAR for Treatment of T-Cell Malignancies Expressing CD5 Antigen for Patients With Glioblastoma	Baylor College of Medicine, Center for Cell and Gene Therapy, The Methodist Hospital System, Texas Children's Hospital	DLT
NCT02442297	T Cells Expressing HER2-specific Chimeric Antigen Receptors(CAR	Baylor College of Medicine, Center for Cell and Gene Therapy, The Methodist Hospital System, Texas Children's Hospital	DLT after admin of autologous T cells expressing transgenic (CAR) targeting the HER2 molecule
NCT01853631	Activated T-Cells Expressing 2nd or 3rd Generation CD19-Specific	Baylor College of Medicine, Center for Cell and Gene Therapy, The Methodist	DLT, CD19.CAR-ATLs, CD19.CAR-ATLs

	CAR, Advanced B-Cell NHL, ALL, and CLL (SAGAN)	Hospital System, Texas Children's Hospital	
NCT02663297	Administration of T Lymphocytes for Prevention of Relapse of Lymphomas	UNC Lineberger Comprehensive Cancer Center, NHLBI	AEs, survival of ATLCAR.CD30, PFS, OS
NCT01865617	Laboratory Treated T Cells in Treating Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia, Non- Hodgkin Lymphoma, or Acute Lymphoblastic Leukemia	Fred Hutchinson Cancer Research Center, NCI	Persistence of CAR T-cells, AEs, MTD
NCT02445222	CD19 CART Long Term Follow Up (LTFU) Study	Novartis, University of Pennsylvania	Incidence of new malignancy, new incidence of exacerbation of rheumatologic disorder, autoimmune disorder or hematologic condition, transgene levels, detectable RCL
NCT03483103	Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy (TRANSCEND- NHL-006)	Celgene Corporation, Juno Therapeutics	Antitumor activity, AEs, laboratory abnormalities
NCT02348216	A Phase 1-2 Multi-Center Study Evaluating Axicabtagene Ciloleucel in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1)	Kite, A Gilead Company	DLT, ORR, Safety
NCT02208362	Genetically Modified T-cells in Treating Patients With Recurrent or Refractory Malignant Glioma)	City of Hope Medical Center, NCI, Gateway for Cancer Research, Mustang Bio, Inc.	AEs (using CTCAE), DLT

NCT02706405	JCAR014 and Durvalumab in Treating Patients With Relapsed or Refractory B-cell Non-Hodgkin Lymphoma	Fred Hutchinson Cancer Research Center, AstraZeneca, Juno Therapeutics Inc.	AEs, DLT, MTD
NCT03310619	A Safety and Efficacy Trial of JCAR017 Combinations in Subjects With Relapsed/Refractory B-cell Malignancies (PLATFORM)	Celgene, Juno Therapeutics Inc.	DLT, complete response rate, AEs
NCT02631044	Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-cell Non-Hodgkin Lymphoma (TRANSCEND-NHL-001)	Juno Therapeutics Inc., Celgene	AEs using CTCAE, DLT, ORR
NCT03331198	Study Evaluating Safety and Efficacy of JCAR017 in Subjects With Relapsed or Refractory CLL or SLL (TRANSCEND- CLL-004)	Juno Therapeutics Inc., Celgene Corporation	AEs, laboratory abnormalities, recommended dose
NCT03262298	Anti-CD22 CAR-T cell therapy targeting B Cell Malignancies	Affiliated Hospital to Academy of Military Medical Sciences	AEs, Overall complete remission rate, disease response, CART cells persistance
NCT03233854	CD19/CD22 Chimeric Antigen Receptor T Cells and Chemotherapy in Treating Patients With Recurrent or Refractory CD19 Positive Diffuse Large B-Cell Lymphoma or B Acute Lymphoblastic Leukemia	Crystal Mackall, MD, Stanford University	DLTs, MTD, rate of successful manufacture and expansion of CD19/CD22 CAR T cells, OS, PFS, CR assessed by Response Criteria for Lymphoma and Response Criteria for ALL.
NCT03287817	CD19/22 CAR T Cells (AUTO3) for the Treatment of Diffuse	Autolus Limited	Phase I/II safety and overall response

	Large B Cell Lymphoma		
NCT03386513	Study of IMGN632 in Patients With Relapse/Refractory AML, BPDCN, ALL, Other CD123+ Hem Malignancies	ImmunoGen, Inc. Jazz Pharmaceuticals	MTD, AEs, ORR
NCT02730312	PH 1 Study to Evaluate Safety and Tolerability of XmAb14045 in Patients With CD123-expressing Hematologic Malignancies	Xencor Inc., Chiltern International Inc.	Safety, MTD, RD
NCT02152956	Safety Study of MGD006 in Relapsed/Refractory Acute Myeloid Leukemia (AML) or Intermediate-2/High Servier Risk MDS	MacroGenics, Institut de Recherches Internationales	DLT, AEs, occurrence of anti-drug antibody
NCT03203369	Study to Evaluate the Safety and Clinical Activity of UCART123 in Patients With BPDCN	Cellectis S.A.	AEs, anti-tumor activity
NCT03190278	Study Evaluating Safety and Efficacy of UCART123 in Patients With Acute Myeloid Leukemia	Cellectis S.A.	AEs, anti-leukemic activity
NCT02159495	Genetically Modified T-cell Immunotherapy in Treating Patients With NCI Relapsed/Refractory Acute Myeloid Leukemia and Persistent/Recurrent Blastic Plasmacytoid Dendritic Cell Neoplasm	City of Hope Medical Center, NCI	DLT, AEs, disease response
NCT03549442	Up-front CART-BCMA With or Without huCART19 in High-risk Multiple Myeloma	University of Pennsylvania, Novartis	AE, clinical outcomes, CART cell disposition
NCT03288493	P-BCMA-101 Tscm CAR-T	Poseida Therapeutics, Inc.	MTD, AEs, anti-

	Cells in the Treatment of Patients With Multiple Myeloma (MM)		myeloma effect
NCT03338972	Immunotherapy With BCMA CAR-T Cells in Treating Patients With BCMA Positive Relapsed or Refractory Multiple Myeloma	Fred Hutchinson Cancer Research Center, Juno Therapeutics Inc. NCI	DLT, AEs, duration of cell persistence
NCT03070327	BCMA Targeted CAR T Cells With or Without Lenalidomide for the Treatment of Multiple Myeloma	Memorial Sloan Kettering Cancer Center, Juno Therapeutics, Inc.	MTD
NCT03502577	BCMA-Specific CAR T-Cells Combined With a Gamma Secretase Inhibitor (LY3039478) to Treat Relapsed or Persistent Multiple Myeloma	Fred Hutchinson Cancer Research Center, NCI	MTD, incidence of general toxicities, objective response rate
NCT03287804	APRIL CAR T Cells (AUTO2) Targeting Autolus Limited Safety, anti-myeloma BCMA and TACI for the Treatment of Multiple Myeloma	Autolus Limited	AEs, Anti-myeloma response
NCT03548207	A Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against B-Cell Maturation Antigen (BCMA) in Participants With Relapsed or Refractory Multiple Myeloma	Janssen Research & Development, LLC	AEs, AEs by Severity, ORR
NCT03448978	Autologous CD8+ T-cells Transiently Expressing an Anti-BCMA CAR in Patients With Myeloma	Cartesian Therapeutics	Safety and Tolerability, treatment response

NCT03318861	A Study Evaluating the Safety and Efficacy of KITE-585 in Subjects With Relapsed /Refractory Multiple Myeloma	Kite, A Gilead Company	DLTs, ORR, DOR
NCT03274219	Study of bb21217 in Multiple Myeloma	Bluebird bio	AEs, DLTs, disease-specific response criteria
NCT03430011	Study Evaluating the Safety and Efficacy of JCARH125 in Subjects With Relapsed and/or Refractory Multiple Myeloma	Juno Therapeutics, Inc., Celgene Corporation	DLTs, AEs, Overall response rate
NCT02658929	Study of bb2121 in Multiple Myeloma	Celgene; bluebird bio	AEs, DLTs, ORR
NCT03361748	Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma (KarMMa)	Celgene	ORR, Complete response rate, time to response
NCT01583686	CAR T Cell Receptor Immunotherapy Targeting Mesothelin for Patients With Metastatic Cancer	NIH Clinical Center, NCI	AEs, response rate, In vivo survival of CAR cells
NCT02414269	Malignant Pleural Disease Treated With Autologous T Cells Genetically Engineered to Target the Cancer-Cell Surface Antigen Mesothelin	Memorial Sloan Kettering Cancer Center	AEs, change in mesothelin
NCT02792114	T-Cell Therapy for Advanced Breast Cancer	Memorial Sloan Kettering Cancer Center, US Department of Defense	MTD
NCT02664363	EGFRvIII CAR T Cells for Newly-Diagnosed WHO Grade IV Malignant	Gary Archer, PhD; Duke University	MTD, DLT

	Glioma		
NCT03283631	Intracerebral EGFR-vIII CAR-T Cells for Recurrent GBM	Gary Archer, PhD; Duke University; NCI, Duke Cancer Institute	MTD, T-cell trafficking
NCT01454596	CAR T Cell Receptor Immunotherapy Targeting EGFRvIII for Patients With Malignant Gliomas Expressing EGFRvIII	NCI, NIH Clinical Center	AEs, PFS, radiographic changes, engineered cell survival

APPENDIX D

Methods for claims analysis.

The Integrated Data Repository (IDR) is a high-volume data warehouse integrating Parts A, B, C, D, and DME claims, beneficiary and provider data sources, along with ancillary data such as contract information, risk scores, and many others. This retrospective claims analysis used administrative claims data from final action claims in the IDR to identify claims for CAR T-cell therapy administration and related services rendered from October 1, 2017, to November 9, 2018. To be considered within this analysis, claims with claim type code 60 and total charge amount greater than $300,000 associated with revenue center codes 025, 026, and 063 were considered. Average length of stay was calculated from all inpatient claims. Average time to death was calculated as the sum of days post-administration of CAR T-cell therapy for each patient who died divided by the total number of patients who died. Survival analysis is based on the method by Kaplan and Meier (1958). All results were approximated to the nearest ten. Technical assistance to researchers interested in the CMS Medicare and Medicaid data through the Chronic Conditions Data Warehouse (CCW) can be accessed through the Research Data Assistance Center (ResDAC). More information on accessing claims data is available at https://www.resdac.org/research-identifiable-files-rif-requests.

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