



March 16, 2019

Tamara Syrek-Jensen, JD
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Department of Health and Human Services
7500 Security Blvd.
Baltimore, MD 21244

Cc: Katherine B. Szarama, PhD, Lead Analyst
Lori Paserchia, MD, Lead Medical Officer

Re: National Coverage Decision (NCD) for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N)

Dear Mrs. Syrek-Jensen:

The Alliance for Regenerative Medicine (ARM) appreciates the opportunity to comment on the recently issued National Coverage Decision (NCD) for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers.¹ ARM is comprised of more than 300 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. ARM takes the lead on the sector's most pressing and significant issues, fostering research, development, investment, and commercialization of transformational treatments and cures for patients worldwide. Our diverse membership is united around a singular goal of improving the health and outcomes of patients. Because of this goal, ARM's members have significant experience in clinical trial development, efficient data collection, and safety monitoring activities. As a result of these experiences, ARM provide the following concerning comments on these issues to CMS' proposed NCD.

As of year-end 2018, ARM estimates there are 906 regenerative medicine and advanced therapies developers worldwide sponsoring 1,028 clinical trials across dozens of indications, including oncology, cardiovascular, central nervous system, musculoskeletal, metabolic disorders, ophthalmological disorders, and more.²

¹ <https://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=291&bc=ACAAAAAAQAAA&>

² https://www.alliancerm.org/wp-content/uploads/2019/03/ARM_AR2018_Web_FINAL.pdf

A subset of these clinical trials focuses on the power of chimeric antigen receptor (CAR T) therapies. These therapies are the first in a wave of new and exciting advanced therapies and technologies that are the next frontier in the fight against some of humankind's most devastating diseases and disorders. CAR T therapy is a type of treatment in which a patient's T cells (a type of immune system cell) are changed in the laboratory so they will attack cancer cells. T cells are taken from a patient's blood, as it flows through a tube to an apheresis machine, which removes the white blood cells, including the T cells, and sends the rest of the blood back to the patient. Then, the gene for a special receptor called a chimeric antigen receptor (CAR) is inserted into the T cells in the laboratory. Millions of the CAR T cells are grown in the laboratory and then given to the patient by infusion. The CAR T cells are able to bind to an antigen on the cancer cells and kill them.³ ARM is currently tracking the outcomes of the approximately 158 ongoing clinical trials using the CAR T technology in a variety of stages of cancer and cancer types. ARM believes that this new and promising technology provides the possibility that most future treatments for many types of cancer at its many stages will focus on using the power of the patient's own immune system to fight their particular cancer.

ARM believes that we are at the beginning of our scientific journey to curing many of these diseases and urges CMS to work with all stakeholders in order to streamline and ensure broad and safe beneficiary access on the date the NCD is finalized, reduce duplicative data collection efforts for sites of care, and implement a patient reported outcome tool that allows for the agency to appreciate the full breadth and depth of the patient experience. With this focus, CMS' Coverage with Evidence Development (CED) program will hopefully balance immediate broad access to CAR T technologies while generating the necessary data to further determine the full range of the technology's clinical power.

I. Regenerative Therapies Represent the Future of Health Care

In addition to CAR T therapies, ARM provides the following primer on the other powerful technologies under clinical development.

- Cell therapy is broadly defined as the administration of viable, often purified cells into a patient's body to grow, replace, or repair damaged tissue for the treatment of a disease. A variety of different types of cells can be used in cell therapy, including hematopoietic (blood-forming) stem cells, skeletal muscle stem cells, neural stem cells, mesenchymal stem cells (adult stem cells that differentiate into structures as connective

³ <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/CAR-T-cell-therapy>

tissues, blood, lymphatics, bone, and cartilage), lymphocytes, dendritic cells, and pancreatic islet cells.

- Cell therapies may be autologous, meaning that the patient receives cells from their own body, or they may be allogenic, meaning the patient receives cells from a donor. Allogeneic cell therapies are often referred to as “off-the-shelf” therapies, as they are derived from a donor who is not the patient, enabling advance preparation and available to the patient immediately at the time of need.
- Many cell-based therapies currently being developed utilize induced pluripotent stem cells (iPSCs). Unlike embryonically-derived pluripotent stem cells, these are adult cells that have been genetically reprogrammed back into a pluripotent state, capable of becoming one of many types of cells inside a patient’s body. This technology may enable the development of an unlimited type of a specific type of human cells needed for therapeutic purposes.
- ARM members are currently developing cell therapy approaches to treat diseases and disorders that include chronic heart failure, Crohn’s disease, ALS, ischemic stroke, diabetes, Parkinson’s disease, degenerative disc disease, and more.
- Tissue engineering combines scaffolds, cells and biologically active molecules into functional tissues to restore, maintain or improve damaged tissues. Biomaterials are medical devices designed to interact with living systems, providing physical structures and support for engineered tissues. ARM members are currently developing tissue-engineered products and biomaterials to treat cartilage damage and degeneration, wound repair, spinal cord injury, hernia repair, and more.
- Gene therapy seeks to modify, replace, inactivate or introduce genes into a patient’s body with the goal of durably treating, preventing or even curing disease. Gene therapy techniques include genetically modifying a patient’s cells outside of their body, which are then re-introduced to deliver a therapeutic effect, an approach known as gene-modified cell therapy. ARM members are currently developing gene therapy and genome editing approaches to treat inherited blood disorders beta-thalassemia and sickle cell diseases, blood cancers leukemia and lymphoma, inherited retinal disease, Huntington’s disease, and more.

What is critical about all these technologies is that many of the therapies are transformative – they provide a durable therapeutic benefit or even a cure with a single administration of therapy.

ARM is concerned that based on the details presented in the proposed NCD, beneficiary access to current and future therapies could be limited or delayed and therefore offers its suggestions below on how to improve overall access to these transformative therapies.

II. Current Data Suggests that Trials Used to Support FDA Approval are Generalizable to Medicare Population

ARM agrees with CMS that the CAR T therapies currently on the market and those in the pipeline show great promise for patient populations that have limited options and very poor outcomes with continued chemotherapy. Prior to the approval of the two CAR T therapies, these patient populations had a very short life expectancy. These same patient populations are now being treated with CAR T technology and are experiencing durable responses with some patients in a complete response several years after treatment, specifically those from the original clinical trials.

ARM understands CMS' desire to collect additional data on Medicare beneficiaries, and believes strongly that these data will continue to demonstrate the promise of CAR T cell therapy for Medicare beneficiaries. For example, Kite/Gilead's two year follow up of its ZUMA 1 trial included a sub group analysis of Medicare aged population. That analysis confirmed that at the two year follow up, Medicare aged patients treated with YESCARTA had similar clinical and safety outcomes as the younger patient population. Similarly, in the pivotal trial for tisagenlecleucel in DLBCL, the overall response rate was consistent in patients over 65 years of age with those below 65.

Given the strength of the currently available data, ARM believes that CMS should include the data from both clinical trials and post market in its CED analysis as this will help the agency conclude that the data used to support FDA approval is also appropriate for determining coverage because it is generalizable to the Medicare population.

III. Much of the Proposed Data Collection in The NCD Is Ongoing and Should be Leveraged and Not Duplicated by CMS

CMS proposes the collection of certain clinical data elements that are already being collected as part of an existing cellular therapy registry. Therefore,

ARM urges CMS to leverage the existence of this registry and the lessons learned from this registry when developing the registry for the CED. ARM believes that selecting a centralized registry to coordinate data collection, from an organization with relevant experience, will make the synthesis of data more efficient, as compared to allowing new individual registries to collect data. Further, allowing new individual registries, without previous experience in capturing cellular therapy outcomes data, will create an additional administrative and financial burden to administering sites.

CMS proposes the collection of certain clinical data elements that are already being collected as part of an existing cellular therapy registry. Specifically, the proposed CED requires the furnishing site of care to track the following data elements at baseline, at treatment, and at follow-up 3 months, 6 months, 12 months, and 24 months after the treatment is administered: age, gender and comorbidities; specifics of cancer diagnosis (e.g., sub-classification, stage); number(s) or line(s) of previous therapies, therapeutic agents previously administered; days to disease progression; days to recurrence; overall survival; and progression-free survival.

ARM notes that the overwhelming majority of these requisite CED data elements are already being tracked, at the above specified intervals, by the Center for International Bone & Marrow and Transplant Research (CIBMTR) Cell Therapy Registry. In addition, the manufacturers of both CAR T products are working with CIBMTR to capture data on safety and efficacy consistent with the FDA requirement of a 15-year post-marketing observational study. The Cell Therapy Registry captures data, including many of the proposed CED requisite data elements, from the FDA-required observational studies for both approved CAR T therapies by following at least 1500 patients for 15 years after CAR T administration.

As part of the final NCD, ARM urges CMS to clarify how it will work with the organization/s operating the registry (e.g., CIBMTR) to establish a process for the organization to share the aggregate clinical data collected on Medicare beneficiaries at set intervals and engage the provider and researcher communities on the CED questions specified in the proposed decision memo. Under this approach, as more data is collected, CMS can adjust, if necessary, the NCD quicker than under a CED.

Finally, ARM reminds CMS that each CAR T cell therapy includes a safety monitoring program through an FDA Risk Evaluation and Mitigation Strategy (REMS), which is in place to ensure hospitals are certified to treat with CAR T and ensure providers are trained on adverse event monitoring. ARM believes that monitoring the safety and adverse event profile of any given therapy is within the jurisdiction of the FDA, as demonstrated by the REMS,

which is already driving the collection of much of the proposed CED data elements.

Therefore, ARM urges CMS to leverage current data collection efforts and not duplicate them within the CED.

IV. Patient Inclusion Criteria Must Mirror Current Beneficiary Access to Other Anti-Cancer Treatments.

The promise of cell therapy is uniquely exciting for the patients and their families that have limited effective cancer treatment options and otherwise poor survival outcomes. These patients deserve the same access to cancer treatments as all other Medicare beneficiaries under the law.

The NCD only permits coverage to patients who have relapsed or refractory cancer (R/R). There is no discretion at the local level, and even worse, no consideration of all current therapies being studied in other indications/disease states. ARM believes that CMS must expand its eligibility criteria to create equal access for Medicare beneficiaries to future regimens and those therapies supported in all of CMS' recognized compendia.

A. NCD Must Provide Access to Future Indications of CAR T Technology

The proposed NCD specifically limits coverage to R/R, but as mentioned above, many current clinical trials are currently investigating the value of CAR T in many types of cancer at many different stages. For example, there are ongoing trials in evaluating CAR T cell therapy's front-line potential to treat various aggressive cancer subtypes such as glioblastoma, multiple myeloma, and aggressive B-cell lymphomas.⁴ If any one of these trials is successful, there does not seem to be a path to coverage for these patients as the proposed NCD precludes access for Medicare beneficiaries to anything but a R/R indication. ARM believes that this fundamentally discriminates against future Medicare beneficiaries because the agency is denying them coverage to an FDA approved therapy. Specifically, ARM asks the agency to clarify how it will cover future FDA approved CAR T therapies?

As such, in order to preserve access to future FDA approved indications, ARM recommends that CMS amend the NCD to account for and be flexible

⁴ Clinicaltrials.gov: Study evaluating efficacy and Safety of Axicabtagene CiloleuceL as First-Line Therapy in Participants With High-Risk Large B-Cell Lymphoma, available at <https://clinicaltrials.gov/ct2/show/NCT03761056?term=NCT03761056&rank=1>; A study evaluating EGFRvIII CAR T Cells for Newly-Diagnosed WHO Grade IV Malignant Glioma (ExCeL), available at <https://clinicaltrials.gov/ct2/show/NCT02664363?term=NCT02664363&rank=1>; A study evaluating Up-front CART-BCMA With or Without huCART19 in High-risk Multiple Myeloma, available at <https://clinicaltrials.gov/ct2/show/NCT03549442?term=NCT03549442&rank=1>

enough to include future CAR T therapies. If a therapy is FDA approved, this NCD must not preclude Medicare patients from access to that therapy.

B. CMS Should Expand Coverage Beyond the NCCN Compendia

The Social Security Act (SSA) states that the term drug includes drugs or biologicals used in an anticancer chemotherapeutic regimen for a medically accepted indication, which is further defined as any use which has been approved by the FDA for the drug and such use is supported by one or more citations which are included in one or more of a CMS approved compendia with certain levels and types of evidence.⁵ ARM is concerned that the agency narrowed coverage to only NCCN guidelines thereby ignoring the statute and Congress' intent to provide broader coverage to anticancer therapies that are included in a CMS approved compendia. As such, ARM urges CMS to remain consistent with its current coverage policy related to compendia and fully cover all appropriately listed indications in CMS approved compendia.

V. Site of Care Should Focus on The Ability to Safely Administer a CAR T Versus Designation as a Hospital

CMS proposes to cover CAR T-cell therapy in a hospital that meets certain requirements consistent with a nationally accredited Cellular Therapy Program and other site of care requirements including:

- a. A Cellular Therapy Program consisting of an integrated medical team that includes a Clinical Program Director, a Quality Manager, and at least one physician experienced in cellular therapy, and demonstrates that protocols, procedures, quality management, and clinical outcomes are consistent from regular interaction among all team members;
- b. a designated care area that protects the patient from transmission of infectious agents and allows for appropriate patient isolation as necessary for evaluation and treatment; and,
- c. written guidelines when administering CAR T-cell therapy for patient communication, monitoring, and transfer to an intensive care unit.⁶

ARM supports robust safety criteria for sites delivering CAR T cell therapy across the inpatient and outpatient settings of care and appreciates and understands that this is a primary focus for CMS. In particular, written protocols for ensuring patient communication, monitoring and transfer to an

⁵ SSA §§1861(t)(2)(A) & (B).

⁶ NCD at page 51.

intensive care unit are essential to both recognize and manage the unique side effects and adverse events that some CAR T patients experience.

At the same time, ARM understands that there clinical trials underway to demonstrate that, depending upon the characteristics of the individual patient, his or her underlying disease, and the profile of the CAR T cell therapy itself, patients can safely and effectively receive CAR T cells as outpatients, even in non-hospital settings.⁷ ARM therefore has concerns that CMS appears to have unnecessarily limited the site where a CAR T patient can be infused to just the hospital setting.

ARM believes that the safety criteria outlined by CMS should determine the setting in which CAR T cell therapy may be delivered, not a statutorily defined entity. In fact, there are current trials The safety criteria themselves, along with the amount of staff, coordination, and infrastructure required to set up a CAR T cell therapy program, create a natural limitation on the sites where CAR T cell therapy may be delivered. Arbitrary restrictions, such as limiting coverage to sites licensed or billing as hospitals that go beyond these safety criteria are not necessary and could create patient access barriers for patients in certain geographic areas as CAR T cell therapies evolve and provider comfort level with managing these adverse events also evolves.

ARM therefore believes that narrowing the site of care to only hospitals unnecessarily limits beneficiary access to CAR T therapy. ARM believes that rather than confining the CED to just hospitals, the agency should defer to only the requirements above as a condition for administration and not further limit access by also requiring the site of care to be a hospital.

VI. ARM Urges CMS to Clearly State How a Patient Reported Outcome Tool Will be Implemented and Utilized as Part of the CED

CMS proposes that either the National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS®) or Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) patient-reported outcome assessment tool be used to

⁷ Clinicaltrials.gov: A Safety Trial of Lisocabtagene Maraleucel (JCAR017) for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL) in the Outpatient Setting, available at <https://clinicaltrials.gov/ct2/results?cond=&term=NCT03744676&cntry=&state=&city=&dist=>; Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy (TRANSCEND-NHL-006), available at <https://clinicaltrials.gov/ct2/show/NCT03483103?term=NCT03483103&rank=1> See also, . <https://clinicaltrials.gov/ct2/show/NCT03744676?term=juno&draw=2&rank=5>; <https://clinicaltrials.gov/ct2/show/NCT03448978?term=cartesian&rank=1>

address CED questions on health-related quality of life. ARM appreciates that CMS wants to understand the patient experience but is concerned about the impact that including patient reported outcomes (PROs) could have at this juncture on access to the CAR T therapy.

As stated above, ARM's members have significant experiences with collecting a wide range and types of clinical data. ARM therefore appreciates that establishing and maintaining a registry is a time consuming exercise especially PRO data because of the amount of resources needed to maintain an exhaustive registry that relies on the patient experience. ARM understands from its members' current registry partners and other stakeholders that implementing a PRO requirement by the expected NCD completion date many not be practicable and therefore urges the agency to only include PROs if the agency is confident that this process will not hamper or delay access to the CAR T therapy.

VII. Should the Agency Proceed with a PRO Tool, ARM Recommends the PROMIS Tool

ARM believes that should CMS proceed with PROs the PROMIS tool is best structured to fully capture the beneficiary's CAR T experience and is more user friendly than the PRO-CTCAE tool. Specifically, the PROMIS tool is designed to enhance communication between clinicians and patients in a wide range of clinical settings. Given the nature of the proposed CED it is important that communications amongst and between sites of care are efficient and accurate. Further, the PROMIS tool was created to be relevant across all conditions for the assessment of symptoms and functions, is available in multiple formats and is easily integrated into diverse data collection tools. Regardless of the PRO tool utilized, ARM urges CMS to clarify how the agency will cover a CAR T administration under this CED if the patient PRO data is incomplete?

VIII. Consistent with the NCD Completion Date ARM Urges CMS to Ensure that Beneficiary Access Continues to be Available on May 17, 2019

As discussed above, CMS proposes to cover autologous treatment with T-cells expressing at least one chimeric antigen receptor through a CED that includes various types of data collection from both beneficiaries and from the site of care. ARM appreciates that CMS wants to establish a registry and collect PROs. ARM, however, urges CMS to prioritize maintaining beneficiary access as of May 17 over any other procedural aspect of the CED. Unfortunately, many stakeholders are already confused regarding coverage status of CAR T therapies and any other further delay will only further add to

this misinformation. ARM believes that Medicare beneficiaries should be able to access a CAR T as of the NCD's scheduled completion date.

IX. Conclusion

In conclusion, ARM believes that the field of regenerative medicine has the potential to heal people and bend the health cost curve toward lower long-term costs and higher quality outcomes. This trend is already evidenced by several approved and marketed first-generation regenerative medicine products that are demonstrating both clinical and cost reduction value in relation to current "standards of care". Specifically, by reducing hospital care, the need for physician, clinical and professional services, nursing and home healthcare, we could substantially reduce overall healthcare expenses. ARM is confident that meaningful improvements in clinical outcomes and cost reduction can be accomplished through regenerative medicine technologies.

Much of the dialogue around healthcare in recent years has focused on the issues of broadening access (through insurance reforms) and controlling costs through Medicare and Medicaid reimbursement reforms such as payment cuts to health providers. Clearly, reducing expenditures alone will not enable us to improve clinical outcomes and achieve enhanced patient quality of life if it hampers innovation.

It is critical for CMS to develop and implement policies and programs that support beneficiary access to new technologies when they are deemed most clinically appropriate and stimulate their continued development. This is particularly true for regenerative medicine and other advanced therapies that hold the promise of durably treating and potentially even curing chronic or life-threatening diseases.

In light of this goal, ARM asks CMS to ensure Medicare patients who can benefit from CAR T therapies are covered under the NCD, allow CAR T to be administered in certified, trained, experienced facilities and not limit access to hospitals, and certify a registry to be in place by May 17 to ensure continued access to CAR T by Medicare beneficiaries.

Sincerely,



Director, U.S. Policy and Advocacy