Yescarta (axicabtagene ciloleucel)
Clinical Coverage Criteria

Overview

Chimeric antigen receptor (CAR) T-cell therapies are immunotherapies that target specific types of cancer. CAR T-cell therapies are made are made by collecting T-cells from the patient and re-engineering them in the laboratory to produce proteins on their surface called chimeric antigen receptors, or CARs. The CARs recognize and bind to specific proteins, or antigens, on the surface of cancer cells and kill them. Since 2017, six CAR T-cell therapies have been approved by the Food and Drug Administration (FDA). All are approved for the treatment of blood cancers, including lymphomas, some forms of leukemia, and, most recently, multiple myeloma. The CAR T-cell therapies approved by FDA to date target one of two antigens on B-cells, CD19 or BCMA.

Yescarta (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

- Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.
- 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.
  Limitations of Use: Yescarta is not indicated for the treatment of patients with primary central nervous system lymphoma.
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Full prescribing information available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta. The Yescarta (axicabtagene ciloleucel) label has a boxed warning:

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGICAL TOXICITIES, and SECONDARY HEMATOLOGICAL MALIGNANCIES

See full prescribing information for the complete boxed warning.

- Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA 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 YESCARTA, including concurrently with CRS. Monitor for neurological events after treatment with YESCARTA. Provide supportive care as needed.
- T cell malignancies have occurred following treatment of hematological malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including YESCARTA.
- YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS.

Despite the therapeutic successes of CAR T-cell therapy, the intervention carries the risk of severe side effects. These include cytokine release syndrome (CRS), neurologic toxicities and B-cell aplasia, all of which can be life-threatening. On August 30, 2017, tocilizumab (Actemra) was FDA-approved to treat CAR T-cell induced CRS in in adults and in pediatric patients 2 years of age and older.

Because of the risk of CRS and neurological toxicities, Yescarta is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Yescarta REMS. The required components of the Yescarta REMS are:

- Healthcare facilities that dispense and administer Yescarta must be enrolled and comply with the REMS requirements.
- Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for administration within 2 hours after Yescarta infusion, if needed for treatment of CRS.
- Certified health care facilities must ensure that health care providers who prescribe, dispense, or administer Yescarta are trained in the management of CRS and neurological toxicities

Yescarta is only available at select treatment centers. Further information is available at https://www.yescartatecartusrems.com/.

Policy

This Policy applies to the following Fallon Health products:

☒ Fallon Medicare Plus, Fallon Medicare Plus Central (Medicare Advantage)
☒ MassHealth ACO
☒ NaviCare HMO SNP (Dual Eligible Medicare Advantage and MassHealth)
☒ NaviCare SCO (MassHealth-only)
☒ PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)
☒ Community Care (Commercial/Exchange)

Prior authorization by a Fallon Health Medical Director is required for Yescarta (axicabtagene ciloleucel). This prior authorization is separate from any prior authorization that may be required for the member's inpatient or outpatient encounter. Medical records from the providers who have diagnosed or treated the symptoms prompting this request are also required.

Medicare Advantage (Fallon Medicare Plus, Fallon Medicare Plus Central)
Fallon Health complies with CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations for Medicare Advantage members. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health may create internal coverage criteria under specific circumstances described at § 422.101(b)(6)(i) and (ii).

Medicare statutes and regulations do not have coverage criteria for Chimeric Antigen Receptor (CAR) T-cell therapy. Medicare has an NCD for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24), Version Number 1, Effective Date of this Version: 08/07/2019 (Medicare Coverage Database Search 05/27/2024).

Coverage criteria for CAR T-cell therapy are fully established by Medicare, therefore, the Plan's coverage criteria are not applicable.

Link: **NCD Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24)**

B. Nationally Covered Indications

Effective for services performed on or after August 7, 2019, Medicare 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
Effective for services performed on or after August 7, 2019, 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
Effective for services performed on or after August 7, 2019, 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.

MassHealth ACO
Fallon Health follows Medical Necessity Guidelines published by MassHealth when making medical necessity determinations for MassHealth members. In the absence of Medical Necessity Guidelines published by MassHealth, Fallon Health may create clinical coverage criteria in accordance with the definition of Medical Necessity in 130 CMR 450.204.

The MassHealth Drug List has medical necessity criteria for Yescarta (axicabtagene ciloleucel) (MassHealth website search 05/27/2024), therefore, the Plan's coverage criteria are not applicable.

Link: **Yescarta (axicabtagene ciloleucel)**

NaviCare HMO SNP, NaviCare SCO
For plan members enrolled in NaviCare, Fallon Health first follow's CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, or if the NaviCare member does not meet coverage criteria in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health then follows Medical Necessity Guidelines published by MassHealth when making necessity determinations for NaviCare members.

PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)
Each PACE plan member is assigned to an Interdisciplinary Team. PACE provides participants with all the care and services covered by Medicare and Medicaid, as authorized by the interdisciplinary team, as well as additional medically necessary care and services not covered by Medicare and Medicaid. With the exception of emergency care and out-of-area urgently needed care, all care and services provided to PACE plan members must be authorized by the interdisciplinary team.

Fallon Health Clinical Coverage Criteria

Fallon Health Clinical Coverage Criteria for Yescarta (axicabtagene ciloleucel) apply to Community Care members. For Medicare Advantage, MassHealth ACO, NaviCare and PACE plan members, follow the applicable criteria described in the Policy section above.

Relapsed or Refractory Large B-Cell Lymphoma after First-Line Chemoimmunotherapy
A single administration of Yescarta (axicabtagene ciloleucel) may be considered medically necessary when all of the following criteria are met:
1. The member is ≥ 18 years of age at the time of informed consent.
2. The member has histologically confirmed large B-cell lymphoma, including one of the following:
    - Diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS)
    - High-grade B-cell lymphoma, NOS
    - High-grade B-cell lymphoma with rearrangement of *MYC* and *BCL2* or *BCL6, or both* (double or triple hit)
    - DLBCL transformation from follicular lymphoma
    - T-cell or histocyte rich large B-cell lymphoma
    - Epstein–Barr virus–positive diffuse large B-cell lymphoma
    - Primary cutaneous diffuse large B-cell lymphoma
3. The member has relapsed or refractory disease after first-line chemoimmunotherapy:
    - Refractory disease is defined as no complete remission to first-line therapy (subjects who are intolerant to first-line therapy are excluded):
        - Progressive disease (PD) as best response to first-line therapy
        - Stable disease (SD) as best response after at least 4 cycles of first-line therapy (e.g., 4 cycles of R-CHOP)
        - Partial response (PR) as best response after at least 6 cycles and biopsy-proven residual disease or disease progression ≤ 12 months of therapy
    - Relapsed disease is defined as complete remission to first-line therapy followed by biopsy- proven disease relapse ≤ 12 months of initiating first-line therapy
4. The member received adequate first-line therapy including at a minimum:
    - A CD20 monoclonal antibody unless treating physician determines that the tumor is CD20-negative, and
    - An anthracycline containing chemotherapy regimen.
5. Treatment will be administered at a healthcare facility that is enrolled in the FDA Risk Evaluation and mitigation strategies (REMS) for Yescarta.

Patients have not yet received treatment for relapsed or refractory lymphoma and would otherwise be eligible to proceed to high-dose chemotherapy with autologous stem-cell transplantation.

Relapsed or Refractory Large B-Cell Lymphoma After Two or More Lines of Systemic Therapy
A single administration of Yescarta (axicabtagene ciloleucel) may be considered medically necessary when all of the following criteria are met:
1. The member is ≥ 18 years of age at the time of informed consent.
2. The member has histologically confirmed large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, or DLBCL arising from transformed follicular lymphoma.
3. The member has refractory disease, defined as progressive or stable disease as the best response to the most recent chemotherapy regimen or disease progression or relapse within 12 months after autologous stem cell transplantation.
4. The member must have received adequate prior therapy including at a minimum:
    a. A CD20 monoclonal antibody unless treating physician determines that the tumor is CD20-negative, and
    b. An anthracycline containing chemotherapy regimen.
    c. For individual with transformed FL must have chemorefractory disease after transformation to DLBCL.
5. Treatment will be administered at a healthcare facility that is enrolled in the FDA Risk Evaluation and mitigation strategies (REMS) for Yescarta.

Relapsed or Refractory Follicular Lymphoma
A single administration of Yescarta (axicabtagene ciloleucel) may be considered medically necessary when all of the following criteria are met:
1. The member is 18 years old or older at the time of informed consent.
2. The member has histologically confirmed follicular lymphoma or marginal zone lymphoma.
3. The member has relapsed or refractory disease after ≥ 2 lines of chemoimmunotherapy one of which an anti-CD20 monoclonal antibody combined with an alkylating agent.
4. Treatment will be administered at a healthcare facility that is enrolled in the FDA Risk Evaluation and mitigation strategies (REMS) for Yescarta.

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Exclusions

- Prior treatment with any anti-CD19-directed therapy.
- All other indications for Yescarta (axicabtagene ciloleucel) are considered experimental/investigational and not medically necessary.

Summary of Evidence

Relapsed or Refractory Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is an aggressive cancer of the lymphatic system. About 30% to 40% of people with DLBCL experience relapse and 10% are refractory to first-line treatment usually consisting of R-CHOP chemotherapy. Of those eligible for second line treatment, commonly consisting of salvage chemotherapy followed by autologous stem-cell transplantation, around 50% experience relapse. With a median overall survival of less than six to 12 months, the prognosis of individuals who relapse or are refractory to advanced lines of treatment or of those who are ineligible for autologous stem-cell transplantation, is very poor. With the introduction of chimeric antigen receptor (CAR) T-cell therapy, a novel treatment option for these people is available (Ernst et al., 2021).

U.S. Food & Drug Administration (FDA) Pivotal Trial
Relapsed or Refractory Large B-Cell Lymphoma after First-Line Chemoimmunotherapy
ZUMA-7 (NCT03391466) is a randomized, open-label, multicenter trial that evaluated the efficacy of axicabtagene ciloleucel (axi-cel) as second line treatment in adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after first-line chemoimmunotherapy that included rituximab and anthracycline. Patients had not yet received treatment for relapsed or refractory lymphoma and were potential candidates for autologous stem cell transplantation.

Eligible patients were at least 18 years of age and had histologically confirmed large B-cell lymphoma, according to the World Health Organization 2016 classification criteria, that was refractory to first-line treatment or that had relapsed from complete remission no more than 12 months after the completion of first-line chemoimmunotherapy including an anti-CD20 monoclonal antibody and anthracycline-containing regimen; patients intended to proceed to high-dose chemotherapy with autologous stem-cell transplantation. Refractory disease was defined as a lack of complete response to first-line therapy, and relapsed disease as biopsy-proven disease relapse occurring no more than 12 months after the completion of first-line therapy.

The primary end point was event-free survival (defined as the time from randomization to the earliest date of disease progression according to the Lugano classification, the commencement of new therapy for lymphoma, death from any cause, or a best response of stable disease up to and including the response on the day 150 assessment after randomization) according to blinded

central review. Key secondary end points were response and overall survival. Secondary end points included event-free survival as assessed by the investigator, progression-free survival (defined as the time from randomization to disease progression or death from any cause), and the incidence of adverse events.

Results of ZUMA-7 were published by Locke et al., 2022. Between January 25, 2018, and October 4, 2019, a total of 437 patients were screened and 359 underwent randomization. A total of 180 patients were assigned to the axi-cel group and 179 were assigned to the standard-care group. As of March 18, 2021, the median follow-up from randomization to the data-cutoff date was 24.9 months.

The median age of the patients was 59 years; 30% of the patients were 65 years of age or older. A total of 74% of the patients had primary refractory disease, 45% had a high second-line age-adjusted International Prognostic Index (IPI) (2 or 3 risk factors), 54% had an elevated lactate dehydrogenase level, 79% had stage III or IV disease, and 19% had high-grade B-cell lymphoma (including double- or triple-hit lymphomas) according to the investigator's assessment.

Among the patients in the axi-cel group, 178 (99%) underwent leukapheresis and 170 (94%) received axi-cel; 65 patients (36%) received bridging therapy with glucocorticoids. Axi-cel was successfully manufactured for all the patients who underwent leukapheresis. Among the 170 patients who received axi-cel, the median time from leukapheresis to product release (i.e., when the product passed quality testing and was made available to the investigator) was 13 days. Among the patients in the standard-care group, 168 (94%) received platinum-based salvage chemotherapy, and 64 (36%) received high-dose chemotherapy and underwent autologous stem-cell transplantation (including 2 patients who underwent autologous stem-cell transplantation outside the protocol).

The median event-free survival according to blinded central review was significantly longer in the axi-cel group (8.3 months; 95% confidence interval [CI], 4.5 to 15.8) than in the standard-care group (2.0 months; 95% CI, 1.6 to 2.8). The estimated event-free survival at 24 months was 41% (95% CI, 33 to 48) in the axi-cel group, as compared with 16% (95% CI, 11 to 22) in the standard-care group. The event-free survival curves show that treatment with axi-cel was superior to standard care (hazard ratio for event or death, 0.40; 95% CI, 0.31 to 0.51; P<0.001). The improvements in event-free survival with axi-cel as compared with standard care were consistent in all prespecified key subgroups.

The percentage of patients with a response in the axi-cel group was 1.66 times as high as that in the standard-care group (83% vs. 50%; difference, 33 percentage points; P<0.001). A complete response was observed in 65% of the patients in the axi-cel group and in 32% of those in the standard-care group.

The median overall survival, evaluated as an interim analysis, was not reached in the axi-cel group and was 35.1 months in the standard-care group (hazard ratio for death, 0.73; 95% CI, 0.53 to 1.01; P=0.054 [two-sided], statistical significance not reached). In the interim analysis, the estimated overall survival at 2 years was 61% in the axi-cel group and 52% in the standard-care group. Overall, 72 patients (40%) in the axi-cel group and 81 (45%) in the standard-care group died from any cause; 52 patients (29%) in the axi-cel group and 65 (36%) in the standard-care group died from progressive disease.

A total of 56% of the patients in the standard-care group received subsequent cellular immunotherapy. Results of a prespecified sensitivity analysis of overall survival, which was conducted to address the confounding effects of this treatment-switching in the standard-care group, showed a difference in overall survival in favor of axi-cel (stratified hazard ratio, 0.58; 95% CI, 0.42 to 0.81) with the rank-preserving structural failure time method. An additional analysis, which was conducted with the use of the inverse probability of censoring weights model, showed a stratified hazard ratio of 0.70 (95% CI, 0.46 to 1.05).

The median progression-free survival was 14.7 months (95% CI, 5.4 to could not be estimated) in the axi-cel group and 3.7 months (95% CI, 2.9 to 5.3) in the standard-care group (hazard ratio for progression or death, 0.49; 95% CI, 0.37 to 0.65). The estimated progression-free survival at 24 months was 46% (95% CI, 38 to 53) in the axi-cel group and 27% (95% CI, 20 to 35) in the standard-care group.

All the patients had at least one adverse event of any grade. Adverse events of grade 3 or higher occurred in 155 of 170 patients (91%) who received axi-cel and in 140 of 168 patients (83%) who received standard care. The most commonly reported adverse event of grade 3 or higher was neutropenia, which occurred in 69% of the patients who received axi-cel and in 41% of those who received standard care.

Serious adverse events of any grade occurred in 50% of the patients who received axi-cel and in 46% of those who received standard care. Various infections of any grade occurred in 41% of the patients who received axi-cel and in 30% of those who received standard care, with infections of grade 3 or higher occurring in 14% and 11%, respectively.

Prolonged cytopenias of grade 3 or higher that were present at or after 30 days after the initiation of definitive therapy (i.e., from receipt of the axi-cel infusion or first dose of high-dose chemotherapy) occurred in 49 patients (29%) who received axi-cel and in 12 of 62 patients (19%) in the standard-care group who underwent per-protocol autologous stem-cell transplantation.

Fatal adverse events occurred in 7 patients (4%) in the axi-cel cohort (of which only one event [hepatitis B virus reactivation] was considered by the investigators to be related to axi-cel) and in 2 patients (1%) in the standard-care cohort (both events [cardiac arrest and acute respiratory distress syndrome] were considered by the investigators to be related to high-dose chemotherapy).

Cytokine release syndrome occurred in 157 patients (92%) who received axi-cel, with an event of grade 3 or higher occurring in 11 patients (6%). No deaths related to cytokine release syndrome occurred. In the safety population, tocilizumab was administered to 65% of the patients, glucocorticoids to 24%, and vasopressors to 6%. The median cumulative use of tocilizumab, regardless of indication, was 1396 mg (range, 430 to 7200). The median time to the onset of cytokine release syndrome was 3 days (range, 1 to 10) after the infusion, and the median duration was 7 days (range, 2 to 43). All the events resolved. Neurologic events occurred in 102 patients (60%) who received axi-cel and in 33 (20%) who received standard care; neurologic events of grade 3 or higher occurred in 36 patients (21%) and 1 patient (1%), respectively. No deaths related to neurologic events occurred. In the axi-cel group, glucocorticoids were used in 32% of the patients for the management of neurologic events. The median time to the onset of neurologic events was 7 days in the axi-cel group and 23 days in the standard-care group, and the median duration was 9 days and 23 days, respectively. At the time of data cutoff, 2 patients had ongoing neurologic events; 1 patient who received axi-cel had grade 2 paresthesia and grade 1 memory impairment, and 1 who received standard care had grade 1 paresthesia.

The difference in overall survival between the two groups did not reach statistical significance. Patients who had disease progression or lack of response in the standard-care group could receive CAR T-cell therapy outside the protocol (which occurred in 56% of the patients), which may have confounded the analysis of overall survival, as suggested by the results of the prespecified sensitivity analyses.

Whereas the majority of patients with large B-cell lymphoma have a relapse less than 12 months after the receipt of induction therapy in the post-rituximab era, this trial did not enroll patients with large B-cell lymphoma relapse that occurred more than 12 months after the receipt of induction therapy. Relapses occurring later after induction therapy are generally associated with a greater probability of response to second-line therapy. However, the 2-year event free survival of 41%

among patients with refractory or early relapsed disease in the axi-cel group compares favorably with that in previous phase 3 trials involving patients receiving standard care who had received rituximab previously and had later disease relapse (>12 months after the diagnosis).

U.S. Food & Drug Administration (FDA) Pivotal Trial
Relapsed or Refractory Large B-Cell Lymphoma After Two or More Lines of Systemic Therapy

ZUMA-1 (NCT02348216) is a single-arm, open-label, multicenter trial evaluated the efficacy of a single infusion of Yescarta in adult patients with histologically confirmed B-cell non-Hodgkin lymphoma.[1] Eligible patients had refractory disease defined as no response to the most recent line of therapy or relapse within 1 year after autologous hematopoietic stem cell transplantation (HSCT). The study excluded patients with prior allogeneic HSCT, any history of central nervous system lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/µL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection.

The primary end point in ZUMA-1 was the rate of objective response (calculated as the combined rates of complete response and partial response), as assessed by the investigators according to the International Working Group Response Criteria for Malignant Lymphoma. Secondary end points included the duration of response, progression-free survival, overall survival, incidence of adverse events, and blood levels of CAR T-cells and serum cytokines.

Results of ZUMA-1 are published by Neelapu et al., 2017. The primary analysis was conducted at the point when 92 patients could be evaluated 6 months after the axi-cel infusion. Efficacy and safety analyses were reported in the modified intention-to-treat population of all the patients who had received axi-cel. The authors also performed an updated analysis of all the patients who had been treated in phase 1 and phase 2 of ZUMA-1.

A total of 111 patients were enrolled in the study. Axi-cel was manufactured for 110 patients (99%) and administered to 101 patients (91%); the latter population was included in the modified intention-to-treat analysis. Patients included 77 with diffuse large B-cell lymphoma and 24 with primary mediastinal B-cell lymphoma or transformed follicular lymphoma. The date of data cutoff for the primary analysis was January 27, 2017; the median follow-up was 8.7 months. The cutoff date for the updated analysis was August 11, 2017, which resulted in a median follow-up of 15.4 months.

The median time from leukapheresis to delivery of axi-cel to the treatment facility was 17 days. Of the 10 patients who did not receive axi-cel, 1 had unsuccessful manufacture of the CAR T-cell product, 4 had adverse events, 1 died from disease progression, and 2 had nonmeasurable disease before conditioning chemotherapy. After conditioning chemotherapy but before axi-cel infusion, 1 patient had sepsis and 1 died from multiple factors with laboratory abnormalities suggestive of the tumor lysis syndrome, gastrointestinal bleeding and perforation, and disease progression.

Among the patients who were treated with axi-cel, the median age was 58 years (range, 23 to 76). Most of the patients (85%) had stage III or IV disease; 77% had disease that was resistant to

[1] ZUMA-1; NCT02348216 Key Inclusion Criteria
https://clinicaltrials.gov/study/NCT02348216?a=11#participation-criteria
Histologically confirmed:

- Diffuse Large B Cell Lymphoma (DLBCL)
- Primary Mediastinal Large B Cell Lymphoma (PMBCL)
- Transformation Follicular Lymphoma (TFL)
- High grade B-cell lymphoma (HGBCL)

second-line or later therapies, 21% had disease relapse after transplantation, 69% had received at least three previous therapies, and 26% had a history of primary refractory disease.

Efficacy Primary Analysis
At a minimum of 6 months of follow-up, the objective response rate among the protocol-specified 92 patients was 82% (95% confidence interval [CI], 72 to 89; P<0.001 for the comparison with a 20% historical control rate); among these patients, the complete response rate was 52%. An additional 9 patients were enrolled and awaiting treatment at the time that the 92nd patient received the axi-cel infusion. Among the 101 patients who received axi-cel, the objective response rate was 82% (95% CI, 73 to 89), with a 54% complete response rate.

Best Overall Response Based on Investigator Assessment of the Primary Analysis Population (at a minimum of 6 months of follow-up):

Response	**DLBCL N = 72**	**PMBCL/TFL N = 20**	**All Patients N = 92**
Objective response rate	58 (81%)	17 (85%)	75 (82%)
Complete response	34 (47%)	14 (70%)	48(52%)
Partial response	24(33%)	3(15%)	27(29%)
Stable disease	9(13%)	2(10%)	11(12%)

The median time to response was rapid (1.0 month; range, 0.8 to 6.0). The median duration of response was 8.1 months (95% CI, 3.3 to could not be estimated). Response rates were consistent across key covariates, including age, disease stage, International Prognostic Index score at enrollment, presence or absence of bulky disease, cell-of origin subtype, and use of tocilizumab or glucocorticoids. Responses were also consistent in 26 patients who had a history of primary refractory disease (response rate, 88%) and in 21 patients who had a history of autologous stem-cell transplantation (response rate, 76%). The response rates did not appear to be influenced by biologic covariates, such as the prevalence and intensity of CD19 expression, or by product characteristics, such as the ratio of CD4 cells to CD8 cells and T-cell phenotypes.
At the time of the primary analysis, 52 patients had disease progression, 3 patients had died from adverse events during treatment, 1 patient started an alternative therapy before disease progression, 44 remained in remission (of whom 39 had a complete response), and 1 had stable disease. Of the patients who had disease progression after an initial response, 9 were retreated with axi-cel, according to the protocol. Of these patients, 5 had a response (2 complete and 3 partial), and 2 of these patients had an ongoing response.

Efficacy Updated Analysis
To evaluate the durability of response with axi-cel, the authors performed an updated analysis when the 108 patients in the phase 1 and 2 portions of ZUMA-1 had been followed for a minimum of 1 year. The objective response rate was 82%, including a complete response rate of 58%. Of the patients who did not have a complete response at the time of the first tumor assessment (1 month after the infusion of axi-cel), 23 patients (11 of 35 with a partial response and 12 of 25 with stable disease) subsequently had a complete response in the absence of additional therapies as late as 15 months after treatment. At the data cutoff, 42% remained in response, including 40% with a complete response. Of the 7 patients in phase 1 of the study, 3 had an ongoing complete response at 24 months.

Ongoing response rates were consistent across key covariates, including the use of tocilizumab or glucocorticoids. The median duration of response was 11.1 months (95% CI, 3.9 to could not be estimated). The median duration of progression-free survival was 5.8 months (95% CI, 3.3 to could not be estimated), with progression-free survival rates of 49% (95% CI, 39 to 58) at 6 months, 44% (95% CI, 34 to 53) at 12 months, and 41% (95% CI, 31 to 50) at 15 months. The median overall survival was not yet reached (95% CI, 12.0 months to could not be estimated) (Fig. 2C), with overall survival rates of 78% (95% CI, 69 to 85) at 6 months, 59% (95% CI, 49 to

68) at 12 months, and 52% (95% CI, 41 to 62) at 18 months. A total of 56% of patients remained alive at the time of the data cutoff. Two patients who had a response underwent allogeneic stem-cell transplantation.

Safety Primary Analysis
During treatment, all 101 patients who had received axi-cel had adverse events, which were grade 3 or higher in 95% . The most common adverse events of any grade were pyrexia (in 85% of the patients), neutropenia (in 84%), and anemia (in 66%). The most common adverse events of grade 3 or higher were neutropenia (in 78%), anemia (in 43%), and thrombocytopenia (in 38%). The cytokine release syndrome occurred in 94 patients (93%). Most cases were of low grade (37% of grade 1 and 44% of grade 2), with 13% of grade 3 or higher (9% of grade 3, 3% of grade 4, and 1% of grade 5).

The most common symptoms of the cytokine release syndrome of grade 3 or higher were pyrexia (in 11% of the patients), hypoxia (in 9%), and hypotension (in 9%). Vasopressors were used in 17% of the patients. The median time after infusion until the onset of the cytokine release syndrome was 2 days (range, 1 to 12), and the median time until resolution was 8 days. All the events associated with the cytokine release syndrome resolved except for one event of grade 5 hemophagocytic lymphohistiocytosis. Another event of grade 5 cardiac arrest occurred in a patient with the cytokine release syndrome.

Neurologic events occurred in 65 patients (64%); 28% were grade 3 or higher. The most common neurologic events of grade 3 or higher were encephalopathy (in 21% of the patients), confusional state (in 9%), aphasia (in 7%), and somnolence (in 7%). The median onset of neurologic events occurred on day 5 (range, 1 to 17), with median resolution on day 17 after infusion. One patient had ongoing grade 1 memory impairment that resolved after the data cutoff for the primary analysis. All the other neurologic events resolved except for four events, which were ongoing at the time of death (two deaths from progressive disease and two from adverse events unrelated to neurologic events). Rates of the cytokine release syndrome and neurologic events decreased over the course of the study. Forty-three percent of patients received tocilizumab and 27% received glucocorticoids for the management of the cytokine release syndrome, neurologic events, or both, with no apparent effect on overall or ongoing response rates.

Safety Updated Analysis
Ten patients had serious adverse events (including nine infections in 8 patients) after the data cutoff for the primary analysis. There were no new events associated with the cytokine release syndrome or neurologic events related to axi-cel treatment. Forty-four patients (44%) died from causes that included disease progression (in 37 patients), adverse events (in 3 patients, including 2 with the above-mentioned axi-cel–related events associated with the cytokine release syndrome and 1 with pulmonary embolism that was not related to axi-cel), and other causes after disease progression and subsequent therapies that were not related to axi-cel (in 4). One death that was not associated with axi-cel was previously reported in phase 1 of ZUMA-1 (Locke et al., 2017). There were no new deaths from adverse events after the primary analysis. No cases of replication-competent retrovirus or axi-cel treatment-related secondary cancers were reported.

Relapsed or Refractory Follicular Lymphoma

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma, representing 17% to 35% of all NHL cases in the United States and Europe. Relapsed follicular lymphoma is generally considered incurable. There lacks consensus in treatment guidelines for FL, resulting in substantial variability in therapeutic regimens for relapsed/refractory FL patients. Moreover, relapsed/refractory FL patients are heterogeneous in terms of response and duration of response to available therapies, functional status, and prognostic risk factors. Limited data have been published on the outcomes of patients treated with multiple lines of therapy, with reported median progression-free survival to second-line and third-line of ~18 and 12 months, respectively. A

recent systematic literature review confirmed that median overall survival and progression free survival decreased with each passing line of therapy (Kanters et al., 2021).

U.S. Food & Drug Administration (FDA) Pivotal Trial
ZUMA-5 (NCT 03105336) is a single-arm, open-label multicenter, phase 2 trial. Patients were eligible if they were aged 18 years or older, with histologically confirmed indolent non-Hodgkin lymphoma (follicular lymphoma or marginal zone lymphoma), had relapsed or refractory disease, previously had two or more lines of chemoimmunotherapy (including an anti-CD20 monoclonal antibody with an alkylating agent).

The primary endpoint was overall response rate (complete response and partial response) assessed by an independent review committee per Lugano classification. The primary activity analysis was done after at least 80 treated patients with follicular lymphoma had been followed up for at least 12 months after the first response assessment at week 4 after infusion. The primary analyses were done in the per-protocol population (i.e., eligible patients with follicular lymphoma who had 12 months of follow-up after the first response assessment and eligible patients with marginal zone lymphoma who had at least 4 weeks of follow-up after infusion of axicabtagene ciloleucel).

Results of ZUMA-5 are published by Jacobson et al., 2022). Between June 20, 2017, and July 16, 2020, 153 patients were enrolled and underwent leukapheresis, and axicabtagene ciloleucel was successfully manufactured for all enrolled patients. As of data cutoff (Sept 14, 2020), 148 patients had received an infusion of axicabtagene ciloleucel, 124 (84%) who had follicular lymphoma and 24 (16%) who had marginal zone lymphoma.

The median follow-up for the primary analysis was 17.5 months (IQR 14.1-22.6). Among patients who were eligible for the primary analysis (n=104, of whom 84 had follicular lymphoma and 20 had marginal zone lymphoma), 96 (92%; 95% CI 85-97) had an overall response and 77 (74%) had a complete response.

The most common grade 3 or worse adverse events were cytopenias in 104 of 148 patients (70%) and infections in 26 of 148 patients (18%). Grade 3 or worse cytokine release syndrome occurred in ten (7%) patients and grade 3 or 4 neurological events occurred in 28 (19%) patients. Serious adverse events (any grade) occurred in 74 (50%) patients. Deaths due to adverse events occurred in four (3%) patients, one of which was deemed to be treatment-related (multisystem organ failure).

Analysis of Evidence (Rational for Determination)

The development of CAR T-cell therapy has been a decades-long journey from when the technology was first proposed in the late 1980s to the U.S. Food and Drug Administration (FDA) approval of Novartis's tisagenlecleucel in 2017. Research to further optimize CAR T-cell design and delivery raises the hope of a cure for many more people with malignancies and heralds an exciting new era in cancer treatment. Data continue to accumulate supporting the efficacy of responses to anti-CD19 CAR-T cell therapy in B-cell malignancies.

Despite promising early response rates in trials, applying this data to real-world patients is challenging, partly as inclusion criteria favor better prognosis groups. Durability of remissions and incidence of long-term adverse events are critical factors determining the utility of anti-CD19 CAR T-cell therapy, but long-term follow-up of patients treated with anti-CD19 CAR T-cells is limited.

A 2021 Cochrane Review (Ernst et al., 2021) found that the evidence on CAR T-cells in the treatment of relapsed or refractory DLBCL was very uncertain, mainly because of the absence of comparative clinical trials. The overall risk of bias was high for all studies. The certainty of evidence was very low for all outcomes. The evidence is very uncertain about the effect of CAR T-cell therapy on overall survival. The evidence is very uncertain about the effect of CAR T-cell therapy on quality of life. CAR T-cell therapy may increase the risk of cytokine release syndrome,

but the evidence is very uncertain about the exact risk. The evidence is very uncertain about the effect of CAR T-cell therapy on progression free survival. The evidence is very uncertain about the effect of CAR T-cell therapy on complete response rates. The authors caution that the results presented should be regarded in light of this limitation and conclusions should be drawn very carefully.

The majority of clinical trials using CAR-T cells are early phase studies. Randomized controlled clinical trials will better establish the place for CAR-T cells in relation to existing potentially curative therapies in B-cell malignancies. The selection of suitable patients for the application of CAR T-cells is important. The factors that drive the curative potential of CAR T-cell therapy may be fundamentally different than the factors that drive outcomes with autologous stem cell transplantation, which are predominantly related to chemotherapy sensitivity.

Coding

Medicare and Community Care members
Per CMS instructions (SE19009), when CAR T-cell therapies are administered in the inpatient setting, the hospital reports CAR T-Cell therapy using revenue code 0891 – Special Processed Drugs – FDA (U.S. Food and Drug Administration) Approved Cell Therapy – Charges for Modified Cell Therapy. Payment for the various steps required to collect and prepare CAR T-cell is included in payment for the CAR T-Cell.

Per CMS instructions (SE19009), when CAR T-cell therapies are administered in the hospital outpatient setting, outpatient hospitals should report CPT code 0540T with revenue code 0874 for the administration and HCPCS code Q2042 with revenue codes 0891 for the biological. Payment for the procedures described by CPT codes 0537T (collection/handling), 0538T (preparation for transport), and 0539T (receipt and preparation) represent the various steps required to collect and prepare the genetically modified T-cells, and these steps are not paid separately under the OPPS (under OPPS these codes, not separately paid, status indicator = B). Outpatient hospitals may report the charges for these various steps to collect and prepare the CAR T-cells separately to allow tracking of these services when furnished in the outpatient setting. However, the claim lines will reject as Medicare does not pay for these services under the OPPS.

In instances when CAR T-cell therapy is not ultimately administered to the member, but the preparation services are initiated or performed, the provider may not report the Q-code (which only applies when the T-cells are administered). Outpatient hospitals may report CPT codes 0537T, 0538T, and 0539T (as appropriate) and the charges associated with each code under the appropriate revenue code on the outpatient hospital claim. Medicare OPPS will reject these codes.

When the CAR T-cell preparation services occur in the hospital outpatient setting, but the administration of the CAR T-cells occurs in the inpatient setting, the outpatient hospital cannot report the drug Q code (which only applies when the T-cells are administered). Per CMS instructions (SE19009), inpatient hospitals may report the charges associated with the various steps for the collection and preparation of the CAR T-cells on the inpatient claim separately using revenue codes 0871, 0872, or 0873.

Alternatively, the hospital may include the charges for these various steps in the charge reported for the CAR T-Cell therapy using revenue code 0891 – Special Processed Drugs – FDA (U.S. Food and Drug Administration) Approved Cell Therapy – Charges for Modified Cell Therapy.

When the CAR T-cells are collected in the hospital outpatient setting and the CAR T-cell is administered in the hospital inpatient setting, inpatient providers should report the date that the CAR-T administration took place and not the date the cells were collected.

Source: MLN Matters®. Chimeric Antigen Receptor (CAR) T-Cell Therapy Revenue Code and HCPCS Setup Revisions SE19009. Article Release Date: March 17, 2022.

Procedure codes
The following codes are included below for informational purposes only; inclusion of a code does not constitute or imply coverage or reimbursement.

Use the following revenue codes for billing inpatient CAR T-cell therapy services:

Revenue Code	Revenue Code Description
0871	Cell/Gene Therapy – Cell Collection
0872	Cell/Gene Therapy – Specialized Biologic Processing and Storage - Prior to Transport
0873	Cell/Gene Therapy – Storage and Processing after Receipt of Cells from Manufacturer
0874	Cell/Gene Therapy – Infusion of Modified Cells
0891	Special Processed Drugs – FDA (U.S. Food and Drug Administration) Approved Cell Therapy – Charges for Modified cell therapy

Use the following revenue and CPT codes for billing outpatient CAR T-cell Services:

Revenue Code	Revenue Code Description	CPT/HCPCS Code	CPT/HCPCS Code Description
0871	Cell/Gene Therapy – Cell Collection	0537T	Chimeric antigen receptor t-cell (car-t) therapy; harvesting of blood-derived t lymphocytes for development of genetically modified autologous cart cells, per day
0872	Cell/Gene Therapy – Specialized Biologic Processing and Storage - Prior to Transport	0538T	Chimeric antigen receptor t-cell (car-t) therapy; preparation of blood-derived t lymphocytes for transportation (eg, cryopreservation, storage)
0873	Cell/Gene Therapy – Storage and Processing after Receipt of Cells from Manufacturer	0539T	Chimeric antigen receptor t-cell (car-t) therapy; receipt and preparation of car-t cells for administration
0874	Cell/Gene Therapy – Infusion of Modified Cells	0540T	Chimeric antigen receptor t-cell (car-t) therapy; car-t cell administration, autologous
0891	Special Processed Drugs – FDA (U.S. Food and Drug Administration) Approved Cell Therapy – Charges for Modified cell therapy	Q2041	Axicabtagene ciloleucel, up to 200 million autologous anti-CD19 CAR T Cells, including leukapheresis and dose preparation procedures, per infusion

MassHealth ACO members
In accordance with MassHealth Managed Care Entity Bulletin 42, Fallon Health requires hospitals to take the following actions with respect to drugs and biologics (including CAR T-cell therapies) on the MassHealth Acute Hospital Carve-Out List for MassHealth ACO plan members:

1. Drugs and biologics on the MassHealth Acute Hospital Carve-Out Drugs List require prior authorization. The hospital must obtain prior authorization for the drug or biologic from Fallon Health or our designated pharmacy vendor. This prior authorization is separate from any prior authorization that may be required for the member's inpatient or outpatient encounter.

2. A drug or biologic designated by MassHealth as a carve-out drug must not be included on the facility/institutional claim that the hospital submits for the plan member's inpatient or outpatient encounter.
3. The hospital must instead submit a separate claim for the carve-out drug on a facility/institutional claim form (i.e., UB-04). (In other words, the drug is the only item on the UB-04 claim.) The charge reported on the claim must be the "hospital's actual acquisition cost" for the drug.*
4. The claim for the carve-out drug must be reported with revenue code 0636 (Drugs requiring detailed coding), the HCPCS code for the drug, the National Drug Code (NDC) for the drug, and number of units administered.
5. The hospital must also include the following as separate attachments to the claim:
    a. A statement of the hospital's actual acquisition cost of the carve-out drug (as defined below) used to treat the member; and
    b. A copy of the invoice(s) for the carve-out drug from the drug manufacturer, supplier, distributor, or other similar party or agent; and
    c. Other additional documentation that the Plan deems necessary to evidence the hospital's actual acquisition cost of the carve-out drug.

* For purposes of this requirement, the "hospital's actual acquisition cost" of the carve-out drug is defined as follows:
"…*the hospital's invoice price for the drug, net of all on-or-off invoice reductions, discounts, rebates, charge backs and similar adjustments that the hospital has or will receive from the drug manufacturer or other party for the drug that was administered to the member including any efficacy, outcome, or performance-based guarantees (or similar arrangements), whether received pre-or post-payment*."

The MassHealth Acute Hospital Carve-out Drugs List is available at: https://masshealthdruglist.ehs.state.ma.us/MHDL/. This list may be updated from time to time.

Drugs Designated for Exclusion from 340B Coverage
Effective for dates of service on or after July 1, 2024, MassHealth has designated certain high-cost drugs as nonpayable when purchased through the 340B drug pricing program and provided to MassHealth ACO members. Each of these drugs is listed on the MassHealth Acute Hospital Carve-Out List discussed in the section above.

Yescarta (axicabtagene ciloleucel) is included in the list of high-cost drugs that are nonpayable when purchased through the 340B drug pricing program and provided to MassHealth ACO members. Accordingly, claims for Yescarta (axicabtagene ciloleucel) must not be submitted with modifier UD.

Note: This policy affects only the method by which specific high-cost drugs may be purchased when provided to MassHealth ACO members and does not impact the use of 340B drugs for other members. The Plan currently pays the actual acquisition cost for such drugs regardless of whether the drug is acquired through the 340B Drug Pricing Program or not. The Plan will continue to pay providers the actual acquisition cost for such drugs after this policy is implemented.

Sources:
- MassHealth All Provider Bulletin 366 (May 2023), as updated by MassHealth All Provider Bulletin 390 (April 2024).
- MassHealth Managed Care Entity Bulletin 114 (April 2024).

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Policy history

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Approval(s):	Technology Assessment Committee: 05/28/2024 (introduced as a new policy).

Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully-insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans. For Medicare and Medicaid members, this policy will apply unless Medicare and Medicaid policies extend coverage beyond this policy.