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 currently indicated 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 BLA Approval October 18, 2017. Review of this product was associated with the following clinical trial NCT023485216.
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. FDA BLA Supplement Approval March 5, 2021. The review of this supplement was associated with the following clinical trials: NCT03105336, NCT02348216, NCT03153462, NCT03761056.
  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).
- Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. FDA BLA Supplement Approval April 1, 2022. Review of this supplement was associated with the following clinical trial NCT033191466.

Yescarta is not indicated for the treatment of patients with primary central nervous system lymphoma.

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.

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.

Section 505-1 of the Federal Food, Drug and Cosmetic Act (FD&C Act) authorizes FDA to require a risk evaluation and mitigation strategy (REMS) for certain drugs if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks. The REMS consists of elements to ensure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The Yescarta REMS was originally approved by the FDA on July 24, 2020, and the most recent REMS modification was approved on June 12, 2024. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. On June 26, 2025, the FDA approved Kite Pharma's request to eliminate the Yescarta REMS.

Also on June 26, 2025, the FDA announced that it was eliminating the REMS for the following BCMA- or CD19-directed autologous CAR T cell immunotherapies: Yescarta, Tecartus, Kymriah, Carvykti, Breyanzi and Abecma, noting that the approved REMS for these six products must be eliminated because a REMS is no longer necessary to ensure that the benefits of the currently approved CAR T-cell immunotherapies outweigh their risks, and to minimize the burden on the healthcare delivery system of complying with the REMS.[1]

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 required.

Effective April 1, 2025, MassHealth transitioned the review and management of all APAD and APEC carve-out drugs, including Yescarta, to the MassHealth Drug Utilization Review (DUR) Program. Effective for dates of services on or after April 1, 2025, prior authorization requests for all APAD and APEC carve-out drugs, including Yescarta must be submitted to the DUR Program for review and approval prior to administration. NOTE: Only the prior authorization request for Yescarta and other APAD and APEC carve out drugs will be reviewed by the MassHealth DUR Program, Fallon Health is still responsible for reviewing prior authorization requests for the member's inpatient or outpatient hospital encounter.

Fallon Health Clinical Coverage Criteria

Fallon Health Clinical Coverage Criteria for Yescarta (axicabtagene ciloleucel) apply to Community Care members. For Medicare and MassHealth members, follow the applicable criteria described in the Medicare and MassHealth Variation sections below.

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)

[1] FDA Eliminates Risk Evaluation and Mitigation Strategies (REMS) for Autologous Chimeric Antigen Receptor CAR T cell Immunotherapies, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor.

- 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).

Medicare Variation

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)

MassHealth Variation

Effective April 1, 2025, MassHealth transitioned the review and management of all APAD and APEC carve-out drugs, including Yescarta, to the MassHealth Drug Utilization Review (DUR) Program. Effective for dates of services on or after April 1, 2025, all prior authorization requests for APAD and APEC carve-out drugs, including Yescarta must be submitted to the DUR Program for review and approval before administration. Note: Only prior authorization requests for the APAD and APEC carve-out drugs themselves will be reviewed by the MassHealth DUR Program. Fallon Health will still be responsible for reviewing prior authorization requests for the member's inpatient or outpatient hospital encounter.

Additionally, also effective for dates of services on or after April 1, 2025, MassHealth will pay claims for APAD and APEC carve-out drugs for MassHealth ACO enrollees consistent with Sections 5.B.8.b and 5.C.9 of the current MassHealth Acute Hospital Request for Applications (Acute Hospital RFA) for in-state acute hospitals and regulations at 130 CMR 450.233(D) for out-of-state acute hospitals. Fallon Health will continue to pay claims for the member's inpatient or outpatient hospital encounter.

Refer to the following MassHealth Bulletins for additional information*:* MassHealth Managed Care Entity Bulletin 125 March 2025, MassHealth Acute Inpatient Hospital Bulletin 201 March 2025, and MassHealth Acute Outpatient Hospital Bulletin 41 March 2025, available at: https://www.mass.gov/masshealth-provider-bulletins.

The MassHealth Acute Hospital Carve-out Drugs List is available at: https://masshealthdruglist.ehs.state.ma.us/MHDL/.

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 evaluated the efficacy of Yescarta 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 HSCT.

Results of ZUMA-7 are published by Locke et al., 2021. 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 in ZUMA-7 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.

Of the 437 patients screened, 359 underwent randomization between January 25, 2018, and October 4, 2019; a total of 180 patients were randomly assigned to the axi-cel group and 179 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 43.5) 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. The estimated progression-free survival at 4 years was 41.8% (95% CI, 34.1 to 49.2) with axi-cel and 24.4% (95% CI, 17.2 to 32.2) with standard care (Westin et al., 2023).

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.[2] 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. Results of ZUMA-1 are published by Neelapu et al., 2017.

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.

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

[2] 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)

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 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, we 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. Consensus is lacking 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). Results of ZUMA-5 are published by Jacobson et al., 2022).

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).

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

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

Code	Description
Q2041	Axicabtagene ciloleucel, up to 200 million autologous anti-CD19 CAR T Cells, including leukapheresis and dose preparation procedures, per infusion

Medicare and Community Care members
Medicare has provided 3 scenarios for how to bill the services described by CPT codes 38225, 38226, and 38227. These codes may be reported for tracking purposes but are non-payable (SE19009; Medicare Claims Processing Manual, Chapter 32, Section 400 - Chimeric Antigen Receptor (CAR) T-cell Therapy).

Scenario 1: CAR-T Dosing and Preparation Services and Viable T-cells Administered in Hospital Outpatient Setting
When CAR T-cell therapies are administered in the hospital outpatient setting, outpatient hospitals should report CPT code 38228 with revenue code 0874 for the administration and HCPCS code Q2042 with revenue codes 0891 for the biological. The procedures described by CPT codes 38225 (collection/handling), 38226(preparation for transport), and 38227 (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 Outpatient Prospective Payment System (OPPS) (under OPPS these codes have status indicator “B,” not paid under OPPS). Outpatient hospitals may report the charges for these various steps to allow tracking of these services when furnished in the outpatient setting, however, these steps are not reimbursed under OPPS.

Scenario 2: CAR-T Dosing and Preparation Services Administered in Hospital Outpatient Setting, but Viable T-cells Not Administered
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 38225, 38226, and 38227, as appropriate, and the charges associated with each code under the appropriate revenue code on the outpatient hospital claim, however, these steps are not reimbursed .

Scenario 3: CAR-T Dosing and Preparation Services Administered in Hospital Outpatient Setting, but Viable T-cells Administered in the Hospital Inpatient Setting

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.

Sources: MLN Matters®. Chimeric Antigen Receptor (CAR) T-Cell Therapy Revenue Code and HCPCS Setup Revisions SE19009. Article Release Date: March 17, 2022. Medicare Claims Processing Manual, Chapter 32, Section 400 - Chimeric Antigen Receptor (CAR) T-cell Therapy,

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

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) with HCPCS code Q2041.

Payment for the various steps required to collect and prepare CAR T-cell is included in payment for the CAR T-Cell.

Although HCPCS codes are not typically used on inpatient claims, the National Uniform Billing Committee (NUBC) allows drug and biologic HCPCS codes on inpatient claims. Fallon Health requires HCPCS codes on claims for CAR T-cell therapy along with revenue code 0891.

Outpatient CAR T-Cell Services

For Yescarta cell infusion use revenue code 0874 with CPT 38228.

For Yescarta product charges use revenue code 0891 with HCPCS code Q2041.

For cell harvesting, storage, and preparation use revenue codes 0871, 0872, or 0873, with CPT codes 38225, 38226 and 38227 respectively. These services are non-payable.

Revenue Code	Revenue Code Description	CPT/HCPCS Code	CPT/HCPCS Code Description
0871	Cell/Gene Therapy – Cell Collection	38225	Chimeric antigen receptor T-cell (CAR T) therapy; harvest of blood-derived T lymphocytes for

			development of genetically modified autologous CAR T-cells, per day
0872	Cell/Gene Therapy – Specialized Biologic Processing and Storage - Prior to Transport	38226	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	38227	Chimeric antigen receptor t-cell (CAR T) therapy; receipt and preparation of CAR Tcells for administration
0874	Cell/Gene Therapy – Infusion of Modified Cells	38228	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

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Policy history

Origination date:	07/01/2024
Approval(s):	Technology Assessment Committee: 05/28/2024 (introduced as a new policy), 07/22/2025 (annual review, under Policy, added information about the FDA elimination of the Yescarta REMS on June 26, 2025, added new sections for Medicare and MassHealth Variation). Utilization Management Committee: 08/19/2025 (annual review, approved with no changes to coverage criteria).

Instructions for Use

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).

Fallon Health generally 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.

For plan members enrolled in NaviCare, Fallon Health first follows 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.

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.

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