Kymriah (tisagenlecleucel)
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.

Kymriah (tisagenlecleucel) is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of:

- Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.
- Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
  Limitations of Use: Kymriah is not indicated for 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 and duration of response. 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/kymriah. The Kymriah (tisagenlecleucel) 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 KYMRIAH. Do not administer KYMRIAH 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 KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. 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 KYMRIAH
- KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH 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, Kymriah is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Kymriah REMS. The required components of the KYMRIAH REMS are:

- Healthcare facilities that dispense and administer KYMRIAH 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 KYMRIAH infusion, if needed for treatment of CRS.
- Certified health care facilities must ensure that health care providers who prescribe, dispense, or administer KYMRIAH are trained in the management of CRS and neurological toxicities

Kymriah is only available at select treatment centers. Further information is available at www.kymriah-rems.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 Kymriah (tisagenlecleucel). 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 Kymriah (tisagenlecleucel) (MassHealth website search 05/27/2024), therefore, the Plan's coverage criteria are not applicable.

Link: **Kymriah (tisagenlecleucel)**

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 Kymriah (tisagenlecleucel) 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.

Pediatric and Young Adult Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia (ALL)

A single administration of Kymriah (tisagenlecleucel) may be considered medically necessary when all of the following criteria are met:
1. The member is < 26 years old on the date of infusion.
2. The member meets one of the following criteria:
   a. Philadelphia chromosome negative (Ph-) that is refractory or in second or later relapse.
   b. Philadelphia chromosome positive (Ph+) that is refractory or in second or later relapse following therapy that has included 2 tyrosine kinase inhibitors (TKIs).
3. Treatment is administered at a healthcare facility that is enrolled in the FDA Risk Evaluation and mitigation strategies (REMS) for Kymriah.

Any relapse following allogeneic stem cell transplant must be ≥ 6 months from stem cell transplant at the time of Kymriah (tisagenlecleucel) infusion.

Adult Relapsed or Refractory Large B-cell Lymphoma
A single administration of Kymriah (tisagenlecleucel) may be considered medically necessary when all of the following criteria are met:

1. The member is 18 years old or older on the date of infusion.
2. The member has a confirmed diagnosis of large B-cell lymphoma, including any of the following:
   a. Diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), or
   b. DLBCL that has transformed from follicular lymphoma, or
   c. High grade B-cell lymphoma with *MYC* rearrangement plus rearrangement of *BCL2*, *BCL6*, or both genes.
3. The member has relapsed or refractory disease after ≥ 2 lines of chemotherapy and either failed autologous stem cell transplantation or was ineligible for or did not consent to autologous stem cell transplantation.
4. Treatment is administered at a healthcare facility that is enrolled in the FDA Risk Evaluation and mitigation strategies (REMS) for Kymriah.

Limitations of Use: Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma.

Adult Relapsed or Refractory Follicular Lymphoma
A single administration of Kymriah (tisagenlecleucel) may be considered medically necessary when all of the following criteria are met:
1. The member is 18 years old or older on the date of infusion.
2. The member has a confirmed diagnosis of relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.
3. Treatment is administered at a healthcare facility that is enrolled in the FDA Risk Evaluation and mitigation strategies (REMS) for Kymriah.

This indication is approved under accelerated approval based on response rate and duration of response. 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 Kymriah (tisagenlecleucel) are considered experimental/investigational and not medically necessary.

Summary of Evidence

Pediatric and Young Adult B-cell Precursor Relapsed or Refractory Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) can be of B or T cell origin. Approximately 80-85% of pediatric ALL diagnoses are B cell precursor in origin and CD19 positive (CD19+). CD19 is an antigen on the membrane of the cell, not only at initial diagnosis, but at relapse. This made CD19 a natural target for immunotherapy. The strategy with Kymriah was to produce genetically modified chimeric antigen receptor (CAR) T-cells transduced with a lentiviral vector encoding the chimeric antigen receptor genes to target CD19 exclusively.

Kymriah is composed of autologous T-cells that are genetically modified with a lentiviral vector encoding a chimeric antigen receptor (CAR). The CAR specifically recognizes the CD19 protein present on CD19+ B lineage tumor cells as well as normal B cells.

ALL is predominantly a childhood disease, however, the disease demonstrates bimodal incidence, with the second peak occurring after age 60 years. Overall survival for ALL in children exceeds 85%. Improved survival primarily stems from decreased incidence of relapse, with very little improvement for more than 20 years in survival rates for children who relapse. In contrast, overall survival for adults with ALL is quite poor and relapsed ALL remains particularly challenging for all age groups, making it a leading cause of cancer deaths in children and carrying a dismal prognosis in adults. Most children in first relapse will achieve a second complete remission (CR2), in contrast to the adult population, in which CR2 rates are 50% at best. Even for patients who achieve CR2, those remissions are frequently not sustained. With each subsequent relapse, achieving remission is harder and long-term survival is extremely poor. Refractory ALL is also challenging, with long-term survival close to 30%. For those who do not achieve a remission, options are limited (Maude et al., 2015).

The goal of therapy in relapsed and/or refractory (R/R) ALL is to induce a subsequent remission and then to consolidate that complete response (CR) with an allogeneic hematopoietic cell transplant (HCT) on the basis of a significant survival benefit seen with an allogeneic HCT. Fifteen to 20% of pediatric B-cell precursor ALL patients relapse after their initial remission. Survival after relapse is dependent on the timing of the relapse and the type of the relapse. Those patients who relapse on therapy, or have relapsed multiple times, have a poor prognosis. With more aggressive therapies for front-line treatment, salvage therapy has become less effective. Relapsed ALL remains a leading cause of cancer deaths in children in the US (Maude et al., 2015).

U.S. Food & Drug Administration (FDA) Pivotal Trial
ELIANA was a single-arm, open-label, multicenter, international phase 2 study of tisagenlecleucel in children and young adults with CD19+ relapsed or refractory B-cell ALL. Results of ELIANA (NCT02228096) were published by Maude et al., 2018. To be eligible for participation in the study, patients had to be at least 3 years of age at screening and no older than 21 years of age at diagnosis and to have at least 5% lymphoblasts in bone marrow at screening. The primary end point was an overall remission rate higher than 20%. The overall remission rate was defined as the rate of a best overall response of either complete remission or complete remission with incomplete hematologic recovery within 3 months, as assessed by an independent review committee on the basis of the results of laboratory testing of blood, bone marrow, and cerebrospinal fluid (CSF), as well as physical examination. Responses were required to be maintained for at least 28 days. Secondary end points included the rate of complete remission or complete remission with incomplete hematologic recovery with undetectable minimal residual disease.

Between April 8, 2015, and the data cutoff on April 25, 2017, a total of 107 patients were screened, and 92 were enrolled. A total of 75 patients received an infusion of tisagenlecleucel. The median duration of follow-up among patients who received a tisagenlecleucel infusion was 13.1 months. At enrollment, patients who received tisagenlecleucel had a median age of 11 years (range, 3 to 23), a median of 3 previous therapies (range, 1 to 8), and a median marrow blast percentage of 74% (range, 5 to 99); 46 patients (61%) had undergone previous allogeneic hematopoietic stem-cell transplantation.

Before tisagenlecleucel infusion, 72 of 75 patients (96%) received lymphodepleting chemotherapy, which was not given at investigator discretion if a patient had leukopenia.
In an intention-to-treat analysis of the full enrolled population (92 patients), which included patients who discontinued participation in the study before tisagenlecleucel infusion, the overall remission rate was 66% (95% CI, 56 to 76). In subgroup analyses that included patients with or without previous transplantation, with high-risk genomic lesions, or with Down's syndrome, the overall remission rate ranged from 79% to 83%.

Among the 75 infused patients, 61 patients (81%) (95% CI, 71 to 89); 45 patients (60%) had complete remission, and 16 (21%) had complete remission with incomplete hematologic recovery. All patients who had a best overall response of complete remission with or without complete hematologic recovery were negative for minimal residual disease.
Among the 61 patients with complete remission with or without complete hematologic recovery, the median response duration was not reached. The rate of relapse-free survival among patients with a response to treatment was 80% (95% CI, 65 to 89) at 6 months and 59% (95% CI, 41 to 73) at 12 months. Among patients with complete remission, 17 had a relapse before receiving additional anticancer therapy. Relapse also occurred in 3 patients who proceeded to receive new cancer therapy for the emergence of minimal residual disease or loss of tisagenlecleucel persistence and in 2 patients who had already been classified as not having a response to treatment because remission was not maintained for at least 28 days. No patients were found to have relapses in the central nervous system (CNS) during primary follow-up; 1 CNS relapse was reported after new anticancer therapy. Characterization of CD19 status at the time of relapse showed that 1 patient had a CD19+ recurrence and 15 patients had CD19− (3 with concomitant CD19+ blasts); 6 patients had unknown CD19 status.

The rate of event-free survival was 73% (95% CI, 60 to 82) at 6 months and 50% (95% CI, 35 to 64) at 12 months; median event-free survival, defined as the time from tisagenlecleucel infusion to the earliest of the following events: no response, relapse before response was maintained for at least 28 days, or relapse after having complete remission or complete remission with incomplete hematologic recovery, was not reached. Eight patients underwent allogeneic hematopoietic stem-cell transplantation while in remission, including 2 patients with minimal residual disease–positive bone marrow and 2 with B-cell recovery within 6 months after infusion. All 8 patients were alive at the time of manuscript submission — 4 with no relapse and 4 with unknown disease status. The rate of overall survival among the 75 patients who received tisagenlecleucel was 90% (95% CI, 81 to 95) at 6 months after infusion and 76% (95% CI, 63 to 86) at 12 months after infusion.

The safety analysis set included all 75 patients who received an infusion of tisagenlecleucel; the median time from infusion to data cutoff was 13.1 months (range, 2.1 to 23.5). Eighteen patients (24%) received their infusions in an outpatient setting. A total of 66 of 75 patients (88%) had a grade 3 or 4 adverse event; 55 of 75 patients (73%) had a grade 3 or 4 tisagenlecleucel-related adverse event.

The cytokine release syndrome occurred in 58 of 75 patients (77%); the median time to onset was 3 days (range, 1 to 22), and the median duration was 8 days (range, 1 to 36). A total of 35 of 75 patients (47%) were admitted to the intensive care unit (ICU) for management of the cytokine release syndrome, with a median stay of 7 days (range, 1 to 34). Nineteen patients (25%) were treated with high-dose vasopressors, 33 (44%) received oxygen supplementation, 10 (13%) received mechanical ventilation, 7 (9%) underwent dialysis, and 28 (37%) received tocilizumab for management of the cytokine release syndrome.

Nineteen deaths occurred after tisagenlecleucel infusion. Within 30 days after infusion, 1 patient died from cerebral hemorrhage in the context of coagulopathy and resolving cytokine release syndrome (15 days after infusion), and 1 patient died from progressive B-cell ALL. More than 30 days after infusion, 17 patients died; the causes of death were B-cell ALL relapse or progression

(12 patients), HHV-6–positive encephalitis in association with prolonged neutropenia and lymphopenia (1), systemic mycosis in association with prolonged neutropenia (1), and unknown causes (1); in 2 patients, death occurred after new therapies for B-cell ALL (1 from pneumonia and 1 from hepatobiliary disease).

Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma. Although in the majority of patients the condition responds well to first-line immunochemotherapy combinations containing rituximab, 10 to 15% have primary refractory disease within 3 months after treatment initiation, and another 20 to 35% have a relapse. Approximately 40 to 60% of patients with relapsed or refractory DLBCL have a response to second-line chemotherapy; 50% of these patients proceed to undergo autologous hematopoietic stem-cell transplantation, and of these, approximately 30 to 40% remain progression-free 3 years after transplantation. For patients who are unable to proceed to high-dose chemotherapy and hematopoietic stem-cell transplantation as second line therapy, the prognosis is poor, with a median overall survival of 4.4 months and 1-year and 2-year overall survival rates of 23% and 16%, respectively. For a small, highly select group of chemotherapy sensitive patients who have a relapse after autologous transplantation, allogeneic hematopoietic stem-cell transplantation is possible if the patient has a response to chemotherapy and a donor is available; however, the procedure has a high associated risk of therapy-related complications, and the associated rate of death unrelated to disease relapse is 23% at 1 year (Schuster et al., 2019).

U.S. Food & Drug Administration (FDA) Pivotal Trial

ELIANA was a single-arm, open-label, multicenter, international phase 2 study of tisagenlecleucel in adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Results of ELIANA (NCT02228096) were published by Schuster et al., 2019. To be eligible for enrollment, patients had to be 18 years of age or older and to have previously received at least two lines of therapy, including rituximab and an anthracycline. Patients had either had a relapse after or were ineligible for autologous transplantation. The study also included patients who had DLBCL that had transformed from follicular lymphoma, as well as patients who had high-grade B-cell lymphoma with *MYC* rearrangement plus rearrangement of *BCL2*, *BCL6*, or both genes (i.e., double or triple-hit lymphoma). Patients were excluded if they had previously received CD19-directed therapy, had primary mediastinal DLBCL, had previously received an allogeneic transplant, or had active central nervous system involvement of their DLBCL.

Before infusion, patients received one cycle of lymphodepleting chemotherapy (not required for patients whose white-cell count was ≤1000 cells per cubic millimeter within 1 week before tisagenlecleucel infusion). For lymphodepletion, patients could receive either fludarabine (25 mg per square meter of body-surface area) and cyclophosphamide (250 mg per square meter) daily for 3 days or bendamustine (90 mg per square meter) daily for 2 days.

The primary end point was the best overall response rate (i.e., the combined percentage of patients who had a complete or partial response), as determined by an independent review committee using the Lugano classification. Secondary end points included response duration, overall survival, safety, and cellular kinetics data for all patients who received an infusion.

The full analysis set and safety set were made up of all the patients who received an infusion, including those treated with tisagenlecleucel manufactured in the United States (main cohort) and those treated with tisagenlecleucel manufactured in the European Union (cohort A). The efficacy analysis set consisted of all the patients in the main cohort who had 3 months or more of follow-up before the data cutoff date. All the patients in the main cohort, regardless of their geographic location and participating site, received an infusion of U.S.-manufactured, cryopreserved tisagenlecleucel. Cohort A was evaluated separately from the main cohort to determine the effect of the manufacturing site on clinical outcomes (analysis in progress).

Between July 2015 and the data cutoff date, December 8, 2017, a total of 238 patients were

screened and 165 were enrolled. Of the enrolled patients, 111 (67%) received an infusion: 95 in the main cohort and 16 in cohort A, 4 patients (2%) were awaiting infusion at the time of analysis.

Patients received infusions in either inpatient or outpatient settings. The median time from enrollment to infusion was 54 days (90% of patients received infusions between 30 days and 92 days after enrollment). The median time from infusion to data cutoff was 14 months (range, 0.1 to 26). The baseline characteristics of the enrolled patients and the patients who received an infusion were similar; however, the patients who did not receive an infusion tended to have a lower performance status than those who did receive an infusion, and a greater proportion of the patients who did not receive an infusion had DLBCL that was refractory to the last therapy they received before enrollment.

Before infusion, 92% of the patients received bridging therapy, including combinations of rituximab (54%), gemcitabine (40%), etoposide (26%), dexamethasone (25%), cisplatin (19%), and cytarabine (19%), as well as newer agents such as ibrutinib (9%) and lenalidomide (7%). A total of 103 patients (93%) received lymphodepleting chemotherapy (73% received combination fludarabine–cyclophosphamide, and 20% received bendamustine). All 111 patients received a single infusion of tisagenlecleucel (median dose, 3.0×10^8 CAR-positive viable T cells; range, 0.1×10^8 to 6.0×10^8).

Among the 93 patients in the efficacy analysis set who had 3 months or more of follow-up or had discontinued participation in the study before 3 months, the best overall response rate was 52% (95% confidence interval [CI], 41 to 62): 40% of patients had a complete response, and 12% of patients had a partial response. The rates of overall and complete response were 38% and 32%, respectively, at month 3 and were 33% and 29% at month 6. A high concordance (85%) was found between local and central assessments of response. Response rates did not differ substantially according to the type of lymphodepleting therapy received, and univariate analyses showed a homogeneous and consistent treatment effect across major demographic and prognostic subgroups, including the subgroup based on disease response to previous therapy.

Of the 37 patients who had a complete response, 16 had either stable disease (4 patients) or a partial response (12 patients) 1 month after infusion that improved to a complete response in a median of 2 months (range, 1 to 17). A conversion from a partial to a complete response occurred in 54% of the patients (13 of 24), including in 2 patients who were confirmed to have a complete response by positron-emission–tomography scanning performed 15 to 17 months after their initial response. Among the 35 patients who were in remission at month 3, the estimated probability of remaining in remission at month 12 was 81% (95% CI, 63 to 91). In an intention-to-treat analysis that included all 165 enrolled patients, including patients who discontinued participation before tisagenlecleucel infusion (mostly as a result of disease progression and death), the overall response rate was 34% (95% CI, 27 to 42). The median response duration has not been reached (95% CI, 10 months to not reached); however, 79% (95% CI, 60 to 89) of patients who had a complete response and 65% (95% CI, 49 to 78) of all patients who had a response are projected to remain relapse-free at 12 months after having a response.

Durable responses were observed for up to 18.4 months after infusion. No patient proceeded to undergo transplantation while having a response. Six patients who did not have a response proceeded to undergo hematopoietic stem-cell transplantation (five underwent allogeneic transplantation, and one underwent autologous transplantation followed by allogeneic transplantation).

The median progression-free survival has not been reached for patients who had a complete response; the estimated rate of progression-free survival at 12 months was 83% among patients who had a complete or partial response at 3 months. The median overall survival among patients who received an infusion was 12 months (95% CI, 7 months to not reached). The estimated probability of survival at month 12 was 49% (95% CI, 39 to 59) among all

patients and 90% (95% CI, 74 to 96) among patients with a complete response. In an intention-to-treat analysis that included all 165 enrolled patients, the median overall survival from the time of enrollment was 8.3 months (95% CI, 5.8 to 11.7) and the estimated probability of survival at month 12 was 40% (95% CI, 32 to 49).

The most common adverse events of any grade were cytokine release syndrome (58%), anemia (48%), pyrexia (35%), decreased neutrophil count (34%), decreased platelet count (33%), decreased white-cell count (33%), and diarrhea (32%).

The median time from infusion to the onset of symptoms of cytokine release syndrome was 3 days (all patients except one had onset within 9 days), and the median duration was 7 days (range, 2 to 30). The median time to the onset of grade 3 or 4 cytokine release syndrome was 4 days (range, 2 to 8); 97% of cases had resolved by data cutoff. Overall, 14% of the patients received tocilizumab, and 10% received both tocilizumab and glucocorticoids. No patient received more than two doses of tocilizumab (5% received one dose and 9% received two doses). Patients with cytokine release syndrome received supportive care, including oxygen supplementation (24%), endotracheal intubation (7%), high-dose vasopressors (6%), and dialysis (5%); 24% were admitted to the intensive care unit. Infections concurrent with cytokine release syndrome occurred in 6% of the patients.

Neurologic events of any grade occurred in 21% of the patients within 8 weeks after infusion; the median time to onset was 6 days (range, 1 to 17), and the median duration was 14 days. Headaches (not classified as a nervous system disorder) occurred in 20% of the patients 8 weeks or less after infusion. A total of 13 patients (12%) had grade 3 or 4 events, the majority of which had resolved by data cutoff with supportive treatment in accordance with local guidelines (e.g., glucocorticoids). Nine patients with grade 3 or 4 neurologic events had concurrent cytokine release syndrome. No fatal cerebral edema was observed.

Only one patient had normal CD19+ B-cell counts in peripheral blood before tisagenlecleucel infusion (normal range, 80 to 616 per cubic millimeter); the majority had CD19+ B-cell counts below the lower limit of quantitation (0.2 per cubic millimeter). After infusion, six patients with ongoing complete response had CD19+ B-cell counts return to the normal range (five patients at >6 months after infusion and one patient at month 3).

Three patients died within 30 days after infusion, all from lymphoma progression. No deaths after infusion were attributed to tisagenlecleucel by the investigators.

Adult Relapsed or Refractory Follicular Lymphoma
From Food and Drug Administration (FDA) Kymriah, Novartis Pharmaceuticals. Package Insert (Revised: 04/2024)
The efficacy of Kymriah was evaluated in a multicenter, single-arm, open-label trial (ELARA, Study 3; NCT03568461) that included patients who were refractory to or relapsed within 6 months after completion of two or more lines of systemic therapy (including an anti-CD20 antibody and an alkylating agent), relapsed during or within six months after completion of an anti-CD20 antibody maintenance therapy following at least two lines of therapy, or relapsed after autologous hematopoietic stem cell transplant (HSCT). The trial excluded patients with active or serious infections, transformed lymphoma, or other aggressive lymphomas, prior allogeneic HSCT, or disease with active CNS involvement.

Following lymphodepleting (LD) chemotherapy, Kymriah was administered as a single dose intravenous infusion with a target dose of 0.6 to 6.0 × 10^8 CAR-positive viable T cells. The median dose administered was 2.06 × 10^8 CAR-positive viable T-cells (range, 0.1 to 6.0 × 10^8 CAR-positive viable T cells). The LD chemotherapy regimen consisted of either fludarabine (25 mg/m^2 intravenously daily for 3 days) and cyclophosphamide (250 mg/m2 intravenously daily for 3 days starting with the first dose of fludarabine) or bendamustine (90 mg/m^2 IV daily for 2 days); bridging chemotherapy between leukapheresis and LD chemotherapy was permitted as needed.

Of the 90 patients included in the primary efficacy analysis, 40 patients (45%) were treated with bridging therapies. The most commonly used agents (in ≥ 5% of patients) were rituximab (22%), dexamethasone (13%), gemcitabine (12%), prednisone (11%), oxaliplatin (8%), etoposide (8%), and vincristine (6%).

Of 98 patients who were enrolled and underwent leukapheresis, 97 patients received infusion with Kymriah and one patient without measurable disease did not receive Kymriah. There were no manufacturing failures for the 98 enrolled patients. Of the 97 patients infused with Kymriah, the efficacy evaluable population, as specified in the protocol, included the first 90 patients with measurable disease who received Kymriah consecutively and had at least 9 months follow-up from first objective response or discontinued earlier.

Among the 90 patients with FL included in the efficacy analysis, the median age was 58 years (range, 29 to 73 years), 31% were female, 78% were White, 10% were Asian, and 1% were Black or African American. The median number of prior therapies was 4 (range, 2 to 13), with 24% receiving 2 prior lines, 21% receiving 3 prior lines, and 54% receiving ≥4 prior lines. Eighty-seven percent had Stage III-IV disease at study entry, 64% had bulky disease, 36% had a prior autologous HSCT, 79% were refractory to the most recent regimen, and 66% had progression within 24 months of initiating their first anti-CD20 combination therapy (POD24).

Efficacy was established on the basis of objective response rate and duration of response (DOR) as determined by an independent review committee. The first disease assessment was scheduled to be performed at Month 3 post-infusion; the median time to first response was 2.9 months (range, 0.6 to 6.0 months). All responders achieved their response (complete response [CR] or partial response [PR]) at the first performed post-infusion disease assessment.

Response Rates in Patients with Relapsed or Refractory FL		
Response	**Primary efficacy population N = 90**	**All leukapheresed patients N = 98**
Overall response rate (ORR), n (%) (95% CI)	77 (86%) (76.6, 92.1)	84 (86%) (77.2, 92.0)
Complete response rate (CRR)[a,b] n (%) (95% CI)	61 (68%) (57.1, 77.2)	66 (67%) (57.1, 76.5)

[a] Two patients, included in the Primary Efficacy Population, with best overall response of CR, had their disease relapsed more than 6 months after the last line of therapy.
[b] Of the 30 patients who initially achieved a PR, 14 patients (47%) converted to a CR, including 10 patients at the next subsequent visit and within 6 months post-infusion.

Duration of Response in Patients with Relapsed or Refractory FL	
	From N = 90
Overall DOR, months	N = 77
Median (95% CI)[a,b]	NE (15.6, NE)
Range[c]	(0.03+, 21.1+)
Median Follow-up	9.1*
% event-free probability	
At 9 months (95% CI)	75.2 (63.5, 83.6)
At 12 months (95% CI)	70.8 (58.0, 80.3)
DOR if best response is CR, months	N = 61
Median (95% CI)[a, b]	NE (15.6, NE)
Range[c]	(2.7, 21.1+)
% event-free probability	
At 9 months (95% CI)	87.7 (75.8, 93.9)
At 12 months (95% CI)	85.2 (72.2, 92.4)

Abbreviations: CR, complete response; DOR, duration of response; NE, not estimable.
*The first disease assessment was scheduled to be performed at Month 3 post-infusion. The median follow up is the time from first objective response to last disease assessment.
[a] Among responders. DOR measured from date of first objective response to date of progression or death from relapse.
[b] Kaplan-Meier estimate in months.
[c] A + sign indicates a censored value.

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.

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. In the phase III BELINDA trial, tisagenlecleucel failed to improve event-free survival vs standard-of-care treatment strategies in patients with aggressive, relapsed or refractory non-Hodgkin lymphoma (Bishop et al., 2022).

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 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	Q2042	Tisagenlecleucel, up to 600 million CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose

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.

Kymriah (tisagenlecleucel) 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 Kymriah (tisagenlecleucel) 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

Origination date:	07/01/2024
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.