Chimeric Antigen Receptor T-Cell Therapy

Clinical Guidelines
UN-CSTRANSPT001.E

Ohio Only

Effective Date: 09/01/2025

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Application

This clinical guideline applies only to the state of Ohio. Any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using Rule 5160-1-01 - Ohio Administrative Code | Ohio Laws

The Ohio Hematopoietic Transplant and Cellular Therapy Consortium is a consortium that ensures all Ohio residents have access to quality care for hematologic malignancies. The Consortium identifies patients for transplant based on patient selection criteria and clinical summaries. Reimbursement for cellular therapy is contingent upon review and the recommendation by the Ohio Hematopoietic Transplant and Cellular Therapy Consortium | Galena, OH | Cause IQ

Prior authorization activities must be conducted in accordance with the Ohio Department of Medicaid Managed Care Provider Agreements located at: Managed Care Agreements (ohio.gov)

Introduction

Chimeric antigen receptor (CAR) T-cell therapy is an adoptive T-cell therapy that uses engineered T cells from a patient's own immune system to attack cancer cells by targeting proteins expressed on the cellular membrane. The process involves obtaining T cells via a leukapheresis procedure. The cells are sent to a centralized manufacturing facility where they are genetically modified to produce specific chimeric antigen receptors and expanded in a cell culture. This process may take up to several weeks. The product is then returned to the treating facility and re-infused into the patient (Srivastava & Riddell, 2018).

The treatment is associated with the occurrence of several specific toxicities including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS is characterized by the rapid release of large amounts of cytokines into the blood after some types of immunotherapies. It is associated with fever, nausea, headache, rash, rapid heart rate, hypotension and dyspnea. It can range from a mild reaction to a severe life-threatening event. Treatment ranges from purely supportive to the use of an Il-6 antagonist such as tocilizumab. Neurologic toxicity is also observed and can range from mild to severe life-threatening events. Its pathophysiology is not adequately understood at the present time. Treatment is supportive in nature along with the use of steroids (Neelapu et al., 2018).

Optum expects facilities offering treatment with tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, idecabtagene vicleucel or ciltacabtagene autoleucel should be certified or in the process of obtaining certification in meeting Immune Effector Cell (IEC) standards by The Foundation for the Accreditation of Cellular Therapy (FACT).

The purpose of these guidelines is to identify the indications for and evidence supporting CAR T-cell therapy. Optum recognizes CAR T-cell therapy is a rapidly evolving field and makes every effort to apply the most recent clinical data and recommendations to this guideline. Requests for treatment are reviewed on an individual basis and, to the extent possible, consideration will be given to new peer-reviewed, published literature as they become available as well as updated FDA and National Comprehensive Cancer Network (NCCN) recommendations. Optum encourages providers to supply new, relevant information as indicated.

CAR T-cell therapy has shown impressive results in clinical trials in treating various hematologic malignancies (Wang et al., 2019). The trials have demonstrated impressive response rates with durable remissions in heavily pretreated individuals (Berdeja et al., 2017). This technology is being investigated to treat many other malignancies including but not limited to solid organ tumors (Schmidts & Maus, 2018). Recently, CD19-targeting-CAR T-cell therapy has been investigated as a treatment option in autoimmune diseases such as systemic lupus erythematosus (Mackensen et al., 2022; Muller et al., 2023) and antisynthetase syndrome (Pecher et al., 2023). Early results suggest efficacy in relieving symptoms in both autoimmune diseases, with minimal adverse events. As further results are evaluated and efficacy becomes more firmly established, indications other than those addressed within this guideline, including autoimmune diseases, are considered investigational. Optum routinely monitors the literature for evidence-based reports of outcomes from this rapidly evolving therapy.

FDA-approved Agents

Axicabtagene ciloleucel (Yescarta®) is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of 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, primary mediastinal large B-cell lymphoma, and high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma. In March 2021, the FDA granted approval for adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). FDA approval was received on April 1, 2022, for treatment of adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. It is not indicated for the treatment of patients with primary central nervous system lymphoma.

Brexucabtagene autoleucel (Tecartus®) is a CD19-directed genetically modified autologous T-cell immunotherapy agent indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) that received FDA approval July 24, 2020. This indication is approved under accelerated approval based on overall response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. Tecartus utilizes a patient's own T cells that are harvested and genetically modified ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single-chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains. On October 1, 2021, the FDA granted approval to add a new indication for adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Ciltacabtagene autoleucel (Carvykti™) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy that received FDA approval on February 28, 2022, for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. On April 5, 2024, the FDA approved the use of Carvykti earlier in the treatment algorithm for patients with relapsed or refractory multiple myeloma. Specifically, Carvykti may be used in patients who have received at least one prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

Idecabtagene vicleucel (Abecma®) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy that received FDA approval in March 2021 for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more lines of therapy including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. Abecma received FDA approval on April 4, 2024, for the treatment of adults with relapsed or refractory multiple myeloma following two or more lines of prior therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. This represents a shift earlier in the treatment algorithm.

Lisocabtagene maraleucel (Breyanzi®) is a CD19-directed genetically modified autologous T-cell immunotherapy that received initial FDA approval in February 2021 for the treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. In June 2022, Breyanzi received FDA approval for use in patients with refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy and for those with refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for HSCT due to comorbidities or age. Liso-cel is administered as a sequential infusion of 2 components (CD8 and CD4 CAR T cells) at equal target doses. In March 2024, the FDA granted accelerated approval of Breyanzi for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least two prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2)

inhibitor. The accelerated approval is 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 trials. On May 15, 2024, the FDA approved Breyanzi for the treatment of relapsed or refractory follicular lymphoma irrespective of grade in patients who have received 2 or more lines of systemic therapy. This approval represents an expansion of the previous FL indication which was specific to relapsed or refractory grade 3B. The expanded 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). On May 30, 2024, Breyanzi received FDA approval for a new indication, relapsed or refractory mantle cell lymphoma (MCL) in patients who have received at least 2 prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor.

Obecabtagene autoleucel (Aucatzyl®) is a CD 19-directed genetically modified autologous T- cell immunotherapy that received FDA approval in November 2024 for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Aucatzyl represents the first CAR T agent with leukemia burden-adjusted split dosing. Aucatzyl will be manufactured at Autolus Therapeutics' dedicated commercial manufacturing site, the Nucleus, in Stevenage, United Kingdom. Cardinal Health will serve as Autolus' commercial distribution partner in the United States.

Tisagenlecleucel (Kymriah®) 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. In May 2022, the FDA granted for treatment of adults with relapsed or refractory follicular lymphoma after 2 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).

On June 27, 2025, the FDA eliminated the Risk Evaluation and Mitigation Strategies (REMS) for currently approved BCMA- and CD 19-directed autologous CAR T cell immunotherapies. The elimination of REMS for CAR T removes the requirements that hospitals and their associated clinics that dispense products must be specially certified and have on-site, immediate access to tocilizumab. The information regarding the risks for these CAR T cell immunotherapies can be conveyed adequately via the current product labeling, which includes a boxed warning for the risks of cytokine release syndrome and neurological toxicities. These products will continue to be subject to safety monitoring through adverse event reporting requirements and does not change FDA requirements for manufacturers to conduct post-marketing observational studies to assess the risk of secondary malignancies and long-term safety with follow up of patients for 15 years after product administration (FDA, 2025).

Centers for Medicare and Medicaid Services

The Centers for Medicare & Medicaid Services (CMS) covers autologous treatment for cancer with T cells expressing at least one chimeric antigen receptor (CAR) when administered at health care facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and 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. Read the National Coverage Determination for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24) at the following: cms.gov/medicare-coverage-database/details/ncd-details.aspx?ncdid=374&bc=CAAAAAAAAAAA

Ohio Medical Necessity

Medical necessity for individuals covered by early and periodic screening, diagnosis and treatment (EPSDT) is criteria of coverage for procedures, items, or services that prevent, diagnose, evaluate, correct, ameliorate, or treat an adverse health condition such as an illness, injury, disease or it's symptoms, emotional or behavioral dysfunction, intellectual deficit, cognitive impairment, or developmental disability. [Ohio Administrative Code 5160-1-01 (A)].

Universal Minimum Eligibility Requirements

Along with disease indications, the patient's performance status and comorbidities are critical considerations for CAR T-cell therapy eligibility. In an expert panel opinion from the American Society for Transplantation and Cellular Therapy (ASTCT), Jain et al., (2019) recommend eligibility evaluation should consider the following:

- Renal function (GFR, Cr)
- Liver function (AST/ALT, bilirubin)
- Cardiac status (LVEF)
- Pulmonary status (dyspnea, pulse ox)
- Hematologic status (ANC< ALC, platelets)
- Baseline neurologic examination and evaluation
- Presence of autoimmune conditions and use of immunosuppressive agents
- Presence of active or uncontrolled infection

Universal Contraindications

The following are considered contraindications to CAR T-cell therapy regardless of the product:

- Pregnancy
- Members receiving immunosuppressive therapy for an autoimmune disorder
- Any active, uncontrolled infection
- Uncontrolled human immunodeficiency virus (HIV) infection. These patients should be under the management of an HIV specialist and their disease controlled prior to CAR T-cell therapy
- Active hepatitis B or hepatitis C infection for lymphomas
- Active hepatitis B or hepatitis C or CMV infection for multiple myeloma
- Hepatitis B or C infection
- Active graft vs. host disease in members with a history of allogeneic hematopoietic stem cell transplant
- Primary central nervous system lymphoma. The literature is evolving and Optum will continue to monitor outcomes for this potential indication.
- Solid tumors
- Members with relapsed or refractory disease who have received prior CAR T- cell therapy regardless of product or indication.

Indications

Acute Lymphoblastic Leukemia (ALL) in Adults

ALL is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs. The age-adjusted incidence rate of ALL in the United States is 1.8 per 100,000 individuals per year, with approximately 6550 new cases and 1330 deaths estimated in 2024. The median age at diagnosis for ALL is 17 years, with 53.5% of patients diagnosed at < 20 years of age. In contrast, 29.6% of patients are diagnosed at ≥ 45 years of age and approximately 13.7% of patients are diagnosed at ≥ 65 years of age. ALL represents 75% to 80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast, ALL represents approximately 20% of all leukemias among adults. Advances in the understanding of the molecular genetics and pathogenesis of ALL, the incorporation of minimal residual disease (MRD) testing, the refinement of risk-adapted treatment algorithms, the advent of new targeted agents, and the use of allogeneic hematopoietic cell transplantation (HCT) have dramatically improved cure rates and survival outcomes over the past several decades (Seigel et al., 2024).

NCCN guidelines (version 2.2024) for the treatment of ALL consider Tecartus as an option for AYA and adult patients with relapsed/refractory Ph-negative B-cell ALL as well as relapsed/refractory Ph-positive B-cell ALL following therapy that has included TKIs. The guidelines also state the role of allogeneic HSCT following treatment with Tecartus is unclear and further study will be required before conclusive recommendations can be made.

Treatment

Brexucabtagene autoleucel (Tecartus®)

Shah et al. (2021) reported the phase 2 results of ZUMA-3 (NCT02614066), an international multicenter, single arm, open-label study evaluating the safety and efficacy of the autologous anti-CD 19 chimeric antigen receptor (CAR) T-cell therapy KTE-X19 in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. Eligible patients were 18 years of age or older, with Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and morphological disease in the bone marrow (>5% blasts). Relapsed or refractory disease was defined as primary refractory, first relapse with remission of 12 months or less, relapsed or refractory after at least 2 previous lines of systemic therapy, or relapsed or refractory after allo-SCT. Patients could have received previous blinatumomab. Following leukapheresis and conditioning chemotherapy (intravenous fludarabine 25mg/m^2 on days -4, -3, and -2; and intravenous cyclophosphamide 900mg/m^2 on day -2) patients received a single KTE-X19 infusion ($1x10^6$ CAR T cells per kg body weight). Rate of overall complete remission or complete remission with incomplete hematological recovery by central assessment was the primary endpoint. Secondary endpoints included duration of remission and relapse-free survival, overall survival, centralized minimal residual disease (MRD) negativity rate, and rate of allo-SCT. Patients undergoing new anticancer therapies (including allo-SCT) were censored.

Between October 1, 2018, and October 9, 2019, 71 patients were enrolled and underwent leukapheresis. KTE-X19 was successfully manufactured for 65 (92%) patients and administered to 55 (77%). As of September 9, 2020, median follow-up was 16.4 months (IQR 13.8–19.6). The median age was 40 years (IQR 28–52), with 8 patients (15%) ages 65 years or older. Twenty-six (47%) patients had received 3 or more previous therapies; 25 (45%) previously received blinatumomab, 12 (22%) previously received inotuzumab ozogamicin, and 23 (42%) previously received allo-SCT. Eighteen (33%) patients had primary refractory disease, 24 (44%) had relapsed or refractory disease post allo-SCT, and 43 (78%) had relapsed or refractory disease to 2 or more lines of systemic therapy. Bridging chemotherapy was received by 51 (93%) of patients; 34 (62%) had confirmed M3 bone marrow involvement (> 25% bone marrow blasts) after bridging chemotherapy.

The primary endpoint was met, with 39 patients (71%; 95% CI 57–82, p<0.0001) reaching complete remission or complete remission with incomplete hematological recovery by central assessment, of whom 31 (56%) had complete remission. Among the 39 patients with complete remission or complete remission with incomplete hematological recovery, median time to first complete remission or complete remission with incomplete hematological recovery was 1.1 months (IQR 1.0–1.9).

The secondary endpoint of MRD negativity rate was met by 42 (76%) of all treated patients having MRD negativity (p<0.0001); among responders, 38 (97%) of 39 had MRD negativity, and samples were unavailable for one patient. Ten (18%) patients received allo-SCT after KTE-X19 infusion, at the discretion of the treating physician. Median time to transplant was 98 days (IQR 72–134) following infusion.

The median duration of remission both with and without censoring patients at subsequent allo-SCT was 12.8 months (95% CI 8.7 — not estimable with censoring, 9–4 — not estimable without censoring. At data cutoff, 12 (31%) of the 39 patients with complete remission or complete remission with hematological recovery were in ongoing remission; 9 (23%) proceeded to subsequent allo-SCT, 5 (13%) proceeded to other anticancer therapies, 12 (31%) relapse, and one (3%) died. Median relapse-free survival both with and without censoring at subsequent transplant was 11.6 months (2.7–15.5) in all treated patients and 14.2 months (11.6 — not estimable) in responders. The relapse-free survival rate at 6 months was 58% (95% CI 43–70) and the overall survival rate at 12 months was 71% (95% CI 57–82). Rates of relapse-free survival at 6 months and of overall survival at 12 months were largely consistent among subgroups, including patients with at least 25% bone marrow blasts, Philadelphia chromosome-positive disease, previous allo-SCT, or previous blinatumomab. Median overall survival was 18.2 months (15.9 — not estimable) in all treated patients and was not reached in responders.

Cytokine release syndrome occurred in 49 (89%) patients with grade 3 or 4 CRS occurring in 13 (24%); no grade 5 CRS events occurred. Median time to CRS onset was 5 days (IQR 3–7) and median duration was 7.5 days (IQR 5–18). Neurological events occurred in 33 (60%) patients, with events of grade 3 of higher occurring in 14 patients (25%), including one grade 5 event (brain herniation). Median time to onset was 9 days (IQR 7–11) and median duration was 7 days (IQR 4–19). Tocilizumab was administered to 44 (80%) patients, steroids were given to 41 (75%), and vasopressors to 22 (40%).

All patients with evaluable bone marrow samples (*n* = 53) had confirmed baseline CD19 expression. Median time to peak CAR T-cell levels in blood after product infusion (*n* = 50) was 15 days (IQR 11–16). CAR T-cells were no longer detectable by PCR in 22 (79%) of 28 patients with evaluable samples at 6 months. Twenty (36%) treated patients had died as of the data cutoff date, primarily from progressive disease.

Shah and colleagues concluded, in ZUMA-3 phase 2, KTE-X19 resulted in a high and durable response rate despite most patients having high disease burden and heavy pre-treatment, including novel agents, allo-SCT or both. Among the highest response rates were those observed in patients with one previous line of therapy (9 of 10 patients) and patients ages 65 and older (8 of 8 patients), suggesting that KTE-X19 might benefit certain subsets of patients, such as older patients who are often excluded form allo-SCT and tend to have poorer outcomes.

Brexucabtagene autoleucel (Tecartus®) is considered medically necessary for the treatment of adult patients (18 years and older) with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) when following criteria are met:
Member has Ph-negative (Ph-) disease and one of the following:

- The member has primary refractory disease
- The member is in first relapse with remission of 12 months or less
- The member's disease is relapsed or refractory:
  - After at least 2 previous lines of systemic chemotherapy **OR**
  - After allogeneic stem cell transplant

OR

Member has Ph-positive (Ph+) disease and has received prior TKI therapy consisting of one of the following:

- Second-line therapy with an alternative TKI (i.e., different from the TKI used as part of induction therapy) alone
- TKI combined with multiagent therapy
- TKI combined with corticosteroids

AND

- The member has received or will receive adequate standard lymphodepleting chemotherapy or a therapeutically equivalent regimen before infusion of TECARTUS. (The standard is a lymphodepleting chemotherapy regimen of fludarabine 25mg/m^2 intravenously on the preceding fourth, third and second days, and cyclophosphamide 90mg/m^2 on the second day prior to infusion).
- The member has not received prior treatment with CAR T-cell therapy
- If the member has had a prior allogeneic HSCT, the member does not currently have active GVHD

Obecabtagene autoleucel (Aucatzyl®)

Outcomes in the Phase Ib/II, multi-center, FELIX trial (NCT04404660) were recently reported by Roddie and colleagues (2024). Enrolled patients were adults (≥ 18 years of age) with relapsed or refractory B cell ALL. Patients with Philadelphia chromosome-positive (Ph+) ALL were eligible if intolerant to tyrosine kinase inhibitor (TKI) therapy, had failed two prior lines of any TKI, or failed one line of second-generation TKI, or if TKI therapy was contraindicated. Following lymphodepleting chemotherapy, patients received obecabtagene autoleucel (Aucatzyl®) as a bone marrow burden-adjusted split-dose infusion on days 1 and 10 (± 2 days) with a total dose of 410 x 10^6 CD19 CAR-positive viable cells. In total, 153 patients with relapsed or refractory B-cell ALL were enrolled. Phase Ib included two cohorts: cohort 1A, for patients with morphologic disease (≥5% bone marrow blasts), and cohort 1B, for those with MRD (<5% bone marrow blasts). The phase 2 component included a main pivotal cohort – cohort 2A, for patients with morphologic disease at enrollment – as well as two exploratory cohorts: cohort 2B, for patients with MRD, and cohort 2C, for those with isolated extramedullary disease.

Aucatzyl was successfully manufactured for 146 of 153 patients (95.4%) at a median of 21 days (range, 18-50) after leukapheresis. A total of 127 patients (83.0%) received at least one Aucatzyl infusion and were evaluable. Twenty-six patients did not receive an infusion due to physician choice (n=1), manufacturing failure (n=7) and death or uncontrolled disease (n=18). Among all the patients receiving at least one infusion, the median age was 47 years (range, 20-81), patients received a median of two previous lines of therapy (range, 2-6), and 52.0% were refractory to their last line of therapy. A total of 56 patients (44.1%) had previously undergone an allogeneic stem-cell transplantation. Patients had a median of 40.0% bone marrow blasts (range, 0-100) at enrollment. Twenty-nine patients (22.8%) had extramedullary disease, and 36 (28.3%) had Ph+ B-cell ALL. Bridging therapy between leukapheresis and lymphodepleting chemotherapy was administered to 118 of 127 patients (92.9%).

The primary endpoint was overall remission (complete remission [CR] or complete remission with incomplete hematologic recovery [CRi]) in cohort 2A (n=94; median follow-up, 20.3 months). Overall remission occurred in 77% (95% CI, 67-85), with CR in 55% (95% CI, 45-66) and CRi in 21% (95% CI, 14-31). In this same cohort, median response duration was 14.1 months (95% CI, 8.2 to not evaluable) and the median event-free survival was 9.0 months (95% CI, 6.1-15.0), both key secondary endpoints.

Cytokine release syndrome (CRS) developed in 87 of 127 patients (68.5%) infused, with events of grade 3 or higher in 3 patients (2.4%). The median time to onset of CRS was 8 days (range, 1-23) after infusion, and the median duration was 5 days (range, 1-21). Tocilizumab was administered to 66 patients (52.0%) and glucocorticoids were administered to 20 (15.7%). Immune effector cell-associated neurotoxicity syndrome (ICANS) developed in 29 of 127 patients (22.8%), with events of grade 3 or higher in 9 patients (7.1%). The median time to onset was 12 days (range, 1-31) after infusion, and the median duration was 8 days (range, 1-53). Of the 9 patients who experienced grade 3 or

higher ICANS, 5 (56%) had more than 75% bone marrow blasts prior to lymphodepletion and 4 (44%) had 5 to 75% bone marrow blasts. Grade 3 or higher ICANS developed in patients with < 5% bone marrow blasts before lymphodepletion. Of the 127 patients infused, 20 (15.7%) required admission to an intensive care unit (ICU) for a median of 5.5 days (range, 1-37). Management of ICANS (n=5) or CRS (n=2) was the primary reason for ICU admission.

NCCN guidelines (version 1.2025) for the treatment of ALL consider Aucatzyl among the preferred regimens for treatment of relapsed or refractory Ph-negative B-ALL and as an option for relapsed or refractory Ph-positive B-ALL following therapy that has included TKIs.

Obecabtagene autoleucel (Aucatzyl®) is considered medically necessary for the treatment of adult patients (18 years and older) with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) when the following criteria are met:
Member has Ph-negative (Ph-) disease and one of the following:

- Primary refractory disease
- Is in first relapse with remission of 12 months or less
- Disease is relapsed or refractory:
  - After at least 2 previous lines of systemic chemotherapy **OR**
  - After allogeneic stem cell transplant

OR

Member has Ph-positive (Ph+) disease and has received prior TKI therapy consisting of one of the following:

- Second-line therapy with an alternative TKI (i.e., different from the TKI used as part of induction therapy) alone
- TKI combined with multiagent therapy
- TKI combined with corticosteroids

AND

- Bone marrow blast count has been performed within 7 days prior to lymphodepletion
- Member has received or will receive a lymphodepleting chemotherapy regimen of fludarabine 30mg/m^2 /day intravenously for four days and cyclophosphamide 500mg/m^2 /day for two days starting with the first dose of fludarabine before infusion of Aucatzyl
- Member has not received prior treatment with CAR T-cell therapy
- If the member has had a prior allogeneic HSCT, the member does not currently have active GVHD

Acute Lymphoblastic Leukemia (ALL) in Children and Young Adults

ALL is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs. The age-adjusted incidence rate of ALL in the United States is 1.8 per 100,000 individuals per year, with approximately 6550 new cases and 1330 deaths estimated in 2024. The median age at diagnosis for ALL is 17 years, with 53.5% of patients diagnosed at < 20 years of age. In contrast, 29.6% of patients are diagnosed at ≥ 45 years of age and approximately 13.7% of patients are diagnosed at ≥ 65 years of age. ALL represents 75% to 80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast, ALL represents approximately 20% of all leukemias among adults. Advances in the understanding of the molecular genetics and pathogenesis of ALL, the incorporation of minimal residual disease (MRD) testing, the refinement of risk-adapted treatment algorithms, the advent of new targeted agents, and the use of allogeneic hematopoietic cell transplantation (HCT) have dramatically improved cure rates and survival outcomes over the past several decades (Seigel et al., 2024).

The NCCN Guideline for Pediatric Acute Lymphoblastic Leukemia (version 1.2025) recommends tisagenlecleucel (Kymriah®) as a single-agent therapy for Ph-positive B-cell ALL with less than complete response or MRD+ at end of consolidation and Ph-positive TKI intolerant/refractory B-ALL or relapse post-HSCT. Kymriah is also recommended for Ph-negative or Ph-like B-cell ALL that is MRD + after consolidation therapy, as well as relapsed/refractory Ph-negative B-cell ALL refractory or ≥ 2 relapses. The guidelines further states that the role of allogeneic HSCT following Kymriah is unclear.

Treatment

The efficacy of tisagenlecleucel (Kymriah®) in pediatric and young adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) was evaluated in an open-label, multicenter single-arm trial (ELIANA, NCT02228096). As reported by Maude and colleagues (2018), eligible patients were at least 3 years of age at screening and no older than 21 years of age at diagnosis and must have had at least 5% lymphoblasts in bone marrow screening. Any patients who had received anti-CD19 therapy were excluded. The primary endpoint was overall remission rate higher than 20%. Overall remission rate was defined as the rate of best overall response of either complete remission or complete remission with incomplete hematologic recovery within 3 months. Responses were required to be maintained for at least 28 days. Secondary endpoints included the rate of complete remission or complete remission with incomplete hematologic recovery with undetectable minimal residual disease (<0.01%) assessed by central multiparameter flow cytometry, the duration of remission, event-free survival, overall survival, cellular kinetics and safety.

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 a single infusion of tisagenlecleucel and were efficacy evaluable. The median duration of follow-up was 13.1 months. Median age of enrollees was 11 years (range, 2–23) and had received a median of 3 previous therapies (range, 1–8). The median marrow blast percentage was 74% (range, 5–99) and 46 patients (61%) had undergone previous allogeneic hematopoietic stem cell transplantation (HSCT). Prior to infusion, 72 of the 75 patients (96%) received lymphodepleting chemotherapy; the 3 remaining patients were leukopenic and chemotherapy was withheld at investigator discretion.

The overall remission rate within 3 months was 81%, with all patients who had a response found negative for residual disease. The rate of event-free-survival was 73% (95% CI, 60–82) and the overall survival rate was 90% (95% CI, 81–95) at 6 months and 50% (95% CI, 35–64) and 76% (95% CI, 63–86) at 12 months. Among the patients with complete remission with or without complete hematologic recovery, the median response duration was not reached. Among patients with complete remission, 17 had a relapse before receiving additional anticancer therapy. Relapse also occurred in 3 patients who received new cancer therapy for the emergence of minimal residual disease or loss of tisagenlecleucel persistence and

2 patients who had been classified as not having a response to treatment because remission was mot maintained for a minimum of 28 days. No patients were found to have relapses in the CNS during primary follow-up.

All patients had at least one adverse event. Grade 3 or 4 adverse events that were suspected to be related to infusion occurred in 73% of patients. Notably, CRS occurred in 77% of patients, 48% of whom received tocilizumab. Within 8 weeks following infusion, febrile neutropenia occurred in 35% of patients, and grade 3 or 4 neutropenia occurred in 46 of 75 patients (61%). Fever, neutropenia and CRS often occurred concurrently after lymphodepleting therapy and tisagenlecleucel infusion. Neurologic events occurred in 40% of patients and were managed with supportive care. The most common NEs of any grade were encephalopathy (11%), confusional state (9%), delirium (9%), tremor (8%), agitation (7%), and somnolence (7%). The majority of NEs occurred during CRS or shortly after its resolution.

Overall, high response rates were shown, and remissions were durable with a 6-month relapse-free survival rate of 80%. The durability of the clinical response was associated with persistence of tisagenlecleucel in peripheral blood and with persistent B-cell aplasia. The risks associated tisagenlecleucel are significant but were mitigated in most patients with supportive care and cytokine blockade.

Tisagenlecleucel (Kymriah®) is considered medically necessary for the treatment of refractory or second or later relapsed B-cell precursor acute lymphoblastic leukemia (ALL) when the following criteria are met:

- The member is 25 years of age or younger
- Philadelphia chromosome-negative (Ph-) disease that is refractory or has had 2 or more relapses
  OR
- Philadelphia chromosome-positive (Ph+) and one of the following:
  - Has refractory disease, including MRD (+) at conclusion of consolidation
  - Less than complete response
  - High-risk genetics
  - Tyrosine kinase inhibitor (TKI) intolerant or refractory (TKIs include dasatinib tablets, imatinib tablets, ponatinib tablets, nilotinib capsules, and bosutinib tablets)
  - Relapse following allogeneic hematopoietic stem cell transplantation
- Member has been treated with two cycles of standard chemotherapy without a complete response or achieved a complete response and experienced multiple relapses following at least two cycles of standard chemotherapy
- Member has received or will receive adequate standard lymphodepleting chemotherapy or a therapeutically equivalent regimen within two weeks preceding tisagenlecleucel infusion. (The standard is a lymphodepleting chemotherapy regimen of fludarabine 30mg/m^2 intravenously for four days and cyclophosphamide 500mg/m^2 intravenously daily for two days [starting with the first dose of fludarabine] within two weeks preceding infusion).
- Member does not have active, uncontrolled CNS ALL
- Member has not received prior treatment with CAR T-cell therapy
- If the member has had a prior allogeneic HSCT, member does not currently have active GVHD

Multiple Myeloma

Multiple myeloma (MM) is a malignant neoplasm of plasma cells in the bone marrow leading to bone destruction and marrow failure. According to the American Cancer Society, MM is most commonly diagnosed in people ages 65 to 74 years, and accounts for approximately 18% of hematologic malignancies in the United States. An estimated 34,920 new cases will be diagnosed in the U.S. in 2021, while approximately 12,410 deaths are expected (Siegel et al., 2021).

Newly diagnosed MM is usually sensitive to a variety of classes of drugs: immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies. Individuals presenting with active (symptomatic) myeloma are treated with primary therapy, followed by high-dose chemotherapy with autologous hematopoietic cell transplant (HCT) in those who are transplant-eligible (NCCN, Multiple Myeloma, version 3.2023). The NCCN Multiple Myeloma Panel prefers 3-drug regimens as standard for primary treatment of all patients who are transplant eligible based on improved response rates, depth of response, and rates of progression-free survival or overall survival seen with such regimens in clinical trials. Autologous HSCT is considered the standard of care after primary therapy, although relapses are common.

NCCN Guidelines for Multiple Myeloma (version 4.2024) gives Idecabtagene vicleucel (Abecma®) a category 1 recommendation for multiple myeloma in previously treated patients who have received at least 2 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor and an immunomodulatory agent. This same guideline includes ciltacabtagene autoleucel (Carvykti®) as a category 1 recommended agent for previously treated patients with relapsed or refractory disease who have received at least 1 prior therapy including an immunomodulatory agent and a proteasome inhibitor if lenalidomide-refractory.

Treatment

Idecabtagene vicleucel (Abecma®)

The KarMMa trial (NCT03361748), an open-label, single-arm, multicenter study, evaluated the efficacy and safety of the B-cell maturation antigen (BCMA)-directed CAR T-cell idecabtagene vicleucel (ide-cel) in patients with triple-class-exposed relapsed and refractory myeloma. All enrollees had Eastern Cooperative Oncology Group (ECOG) performance status 0–1, had received at least three prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody, and disease that was refractory to their last regimen (progression within 60 days after last dose) according to International Myeloma Working Group (IMWG) criteria. The median number of prior lines of therapy was 6 (range: 3–16), and 88% of the patients received 4 or more lines of therapy. A total of 112 patients (88%) received bridging therapy during the manufacturing period, with a median duration of 15 days. Responses to bridging were observed in 5 of the 112 patients.

Of the 140 patients enrolled, 128 received ide-cel at a target dose range of 150 x 10^6 to 450 x 10^6 CAR-positive T cells. At median follow-up (13.3 months), 94 of the 128 patients (73%; 95% CI, 66–81) had a response and 42 of 128 (33%) had a complete response. Minimal residual disease (MRD)-negative status was confirmed in 33 patients (26%). Median progression-free survival (PFS) was 8.8 months (95% CI, 5.6 to 11.6). The 450 x 10^6 dose appeared somewhat more effective than the other doses as evidenced by numerically longer PFS (11.3 months) and median response duration (12.1 months). Common toxic effects included neutropenia, anemia and thrombocytopenia. Cytokine release syndrome was reported in 107 (84%) enrollees, although most episodes were not severe at grade 3 or less, while neurotoxic effects were reported in 23 patients (18%). Fatal adverse reactions occurred in 6%. Patients with a history of CNS disease, including seizure or cerebrovascular ischemia, or requiring treatment with chronic immunosuppression were excluded from the trial (Munshi et al., 2021).

The KarMMa-3 trial (NCT03651128) evaluated efficacy of Abecma in adult patients with relapsed and refractory multiple myeloma who had received two to four prior lines of therapy including immunomodulatory agents, proteasome inhibitors, and daratumumab and who had disease refractory to the last regimen. A total of 386 patients were randomized 2:1 to receive either Abecma (n=254) or standard regimens (n-132). Standard regimens

represented available treatments in various countries and allowed investigators to select the most appropriate regimen based on the patient's previous exposure. Of the 254 patients randomized to receive Abecma, 249 (98%) patients underwent leukapheresis. Five (2%) patients did not undergo leukapheresis due to patient withdrawal (n=2), adverse event (n=1), or failure to meet lymphodepleting chemotherapy treatment criteria (n=2). Twenty-four (10%) patients did not receive Abecma either due to death (n=4), adverse event (n=4), physician decision (n=7), failure to meet lymphodepleting chemotherapy treatment criteria (n=6), or inability to manufacture product (n=3). Three (1.2%) patients received CAR-positive T cells that did not meet product release specifications (n=3). The median number of prior lines of therapy was 3 (range: 2-4) and 85% of patients had received prior autologous stem cell transplantation. Treatment with Abecma resulted in significantly longer progression-free survival than standard regimens, with a 51% lower risk of disease progression or death. Additionally, treatment with Abecma resulted in a significantly higher percentage of patients with a response and with deeper responses than were observed in the standard-regimen group (Rodriquez-Otero et al., 2023).

Most patients who received Abecma experienced grade 1 CRS that resolved within 5 days; events of grade 3 or higher were reported in 5% of the patients. The incidence of high-grade neurotoxic events (grade ≥ 3) was 3%; neurotoxic events of any grade mostly resolved within 5 days. Two patients had grade 5 CRS: one following a decline in organ function, and one from concomitant grade 5 candida-related sepsis. The safety profile of Abecma in KarMMa-3 was consistent with that of the prior KarMMa study (Rodriquez-Otero et al., 2023).

Idecabtagene vicleucel (Abecma®) is considered medically necessary for the treatment of active, measurable multiple myeloma, relapsed or refractory, and the following criteria are met:

- Member is 18 years of age or older
- Member has received 2 or more prior lines of therapy including, but not limited to, **ALL** of the following:
  - An immunomodulatory agent (e.g., lenalidomide, pomalidomide)
  - A proteasome inhibitor (e.g., bortezomib, carfilzomib, ixazomib)
  - An anti-CD38 monoclonal antibody (e.g., daratumumab, isatuximab)
- Disease was refractory to the last regimen (progression within 60 days after last dose) according to International Myeloma Working Group (IMWG) criteria
- Member has received or will receive adequate standard lymphodepleting chemotherapy or a therapeutically equivalent regimen before infusion of idecabtagene vicleucel. (The standard is a lymphodepleting chemotherapy regimen of Cyclophosphamide 300mg/m^2 intravenously and fludarabine 30mg/m^2 intravenously daily for three days prior to infusion).
- If member has had a prior allogeneic HSCT, the member does not currently have active GVHD
- Member does not have CNS involvement with myeloma

For a comprehensive list of drugs used to treat multiple myeloma, refer to the following link: Drugs Approved for Multiple Myeloma - National Cancer Institute

Ciltacabtagene autoleucel (Carvykti™)

The CARTITUDE-1 trial (NCT03548207) is a single-arm, open-label, phase 1b/2 study conducted at 16 centers in the United States to assess the safety and clinical activity of ciltacabtagene autoleucel (Carvykti) in patients with relapsed or refractory multiple myeloma. Enrollees were ages 18 years or older with a diagnosis of multiple myeloma, an ECOG performance status of 0–1, had received three or more prior lines of therapy or were double-refractory to a proteasome inhibitor and an immunomodulatory drug, and had received a proteasome inhibitor, immunomodulatory drug and anti-CD38 antibody. A single infusion (target dose 0.75 x 10^6 CAR-positive viable T cells per kg) was administered 5–7 days following the start of lymphodepletion. The primary endpoints were safety and confirmation of the recommended phase 2 dose (phase 1b), and the overall response rate (phase 2). Secondary endpoints included duration of response and progression-free survival.

CARTITUDE-1 enrolled 113 patients between July 16, 2018, and October 7, 2019. A total of 97 patients (29 in phase 1b and 68 in phase 20 received an infusion of cilta-cel at the recommended phase 2 dosage of 0.75 x 10^6 CAR-positive viable T cells/kg. As of the September 1, 2020, clinical cutoff, median follow-up was 12.4 months (IQR 10.6–15.2). Overall response rate was 97% (95% CI 91.2–99.4; 94 of 97 patients); 65 (67%) achieved stringent complete response; time to first response was one month (IQR 0.9–1.0). Median duration of response was not reached (95% CI 15.9 — not estimable), nor was progression-free survival (16.8 — not estimable). 12-month progression-free rate was 77% (95% CI 66.0–84.3) and overall survival was 89% (80.2–93.5). Cytokine release syndrome (CRS) occurred in 92 (95%) of 97 patients (4% were grade 3 or 4) with median time to onset of 7.0 days (IQR 5–8) and median duration of 4.0 days (IQR 3–6). CRS resolved in all but one patient. Based on the CRS characteristics observed in this study, CARTITUDE-2 and CARTITUDE-4 are exploring outpatient dosing of cilta-cel. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 16 (17%) patients: ten (10%) had grade 1, four (4%) had grade 2, one (1%) had grade 3, and one (1%) had grade 4. Median time to onset of ICANS was 8.0 days (IQR 6.0–8.0) and median duration was 4.0 days (IQR 3.0–6.5). All patients received supportive measures for ICANS, including corticosteroids, tocilizumab and anakinra. ICANS resolved in all 16 patients. Other neurotoxicities occurred in 12 (12%) of the 97 patients; all had previous CRS and ICANS. A partial response or better was observed in 97% of treated patients, with 79% achieving their first response within one month of infusion. Most patients (67%) achieved stringent complete response; median duration of response and median progression-free survival were not reached at data cutoff. Of those who achieved complete response or better, 62% did so within three months of infusion. Nearly all patients who were evaluable for minimal residual disease at the 10^{-5} threshold achieved negativity as early as a median of one-month post infusion (Berdeja et al., 2021).

In a matching-adjusted indirect treatment comparison, Martin and colleagues (2021), sought to estimate the comparative efficacy of ciltacabtagene autoleucel (cilta-cel) versus idecabtagene vicleucel (ide-cel) in patients with relapsed or refractory multiple myeloma who were previously treated with a proteasome inhibitor, an immunomodulatory drug, and an anti-CD 38 monoclonal antibody. Using individual patient level data from CARTITUDE-1 (cilta-cel) and published summary-level data from KarMMa (ide-cel), comparative efficacy was estimated for overall response rate (ORR), complete response or better (≥ CR) rate, duration of response (DoR), progression-free survival (PFS) and overall survival (OS). Prior to adjustment, observed baseline characteristics (with the exception of refractory status, cytogenetic profile, R-ISS stage and all plasmacytomas) were similar between the 97 treated patients in CARTITUDE-1 and the 124 patients who underwent infusion for the 300 x 10^6 and 450 x 10^6 CAR T cells dose cohorts in KarMMa. Of the two cohorts, CARTITUDE-1 had a greater proportion of patients who were penta-refractory (to at least two ImiDs, at least two PIs, and an anti-CD38 MoAB), while KarMMa had a greater proportion of patients with high-risk cytogenetics, R-ISS stage II or III, and all plasmacytomas. Cilta-cel was associated with statistically significantly improved ORR (odds ratio [OR]: 94:93 [95% CI 21.86, 412.25; $p < .0001$]; relative risk [RR]:1.34), ≥ CR rate (OR: 5.49 [95% CI 2.47, 12.21; $p < .0001$]; RR: 2.21), DoR (HR: 0.50 [95% CI: 0.20, 0.87; $p = .0137$]), and PFS (HR: 0.37 [95% CI: 0.22, 0.62; $p = .0002$]) when compared to ide-cel. For OS, the results were in favor of cilta-cel and clinically meaningful but with a CI overlapping one (HR: 0.55 [95% CI: 0.20, 1.05; $p = .0702$]). The authors concluded that their

analyses demonstrated clinically superior results for all outcomes studied (ORR, ≥ CR rate, DoR, PFS, and OS) and based on these findings, cilta-cel offers substantial clinical benefits for patients with triple-exposed relapsed or refractory multiple myeloma compared to ide-cel.

CARTITUDE-2 is an ongoing, phase 2, multicohort, open-label, multicenter study of cilta-cel. Cohen et al. (2023) recently reported on patients in Cohort C with heavily pretreated RRMM, who were previously exposed to BCMA-targeted therapy (excluding cellular immunotherapy). These patients progressed despite treatment with a proteasome inhibitor, immunomodulatory drug, anti-CD38 antibody, and noncellular anti-BCMA immunotherapy. A single cilta-cel infusion was given after lymphodepletion. The primary endpoint was MRD negativity at 10^{-5}. Overall, 20 patients were treated (13 ADC-exposed; 7 BsAb-exposed; 1 in the ADC group also had prior BsAb exposure. Sixteen (80%) were refractory to prior anti-BCMA therapy. At a median follow up of 11.3 months (range, 0.6-16.0), 7 of 20 (35%) patients were MRD negative (7 of 10 [70%] in the MRD-evaluable subset). Overall response rate was 60.0% (95% CI, 36.1 – 80.9). Median DoR was 11.5 months (95% CI, 7.9 – NE), and median PFS was 9.5 months (95% CI, 0.99 – NE). CRS occurred in 12 (60%) patients (all grade 1-2); 4 experienced ICANS (2 had grade 3-4); none had parkinsonism. Seven (35%) patients died (3 of progressive disease, 4 of adverse events [1 treatment related, 3 unrelated]). Cilta-cel induced favorable responses in patients with RRMM and prior exposure to anti-BCMA treatment who had exhausted other therapies.

The efficacy and safety results from an interim analysis of the phase 3 CARTITUDE-4 trial were reported by San-Miguel and colleagues (2023). CARTITUDE-4 compared a single infusion of cilta-cel with the physician's choice of pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd) in patients with lenalidomide-refractory multiple myeloma after one to three lines of therapy. Patients in the cilta-cel group received the physician's choice of PVd or DPd as bridging therapy. The primary outcome was PFS. Key secondary outcomes included CR or better, overall response, MRD negativity, OS, and patient-reported symptoms as assessed by the Multiple Myeloma Symptom and Impact Questionnaire. From July 10, 2020, through November 17, 2021, a total of 419 patients were randomly assigned to receive cilta-cel (2018 patients) or standard care (211 patients). Of the patients in the standard-care group, 183 received DPd and 28 received PVd. All patients in the cilta-cel group received bridging therapy (DPd in 182 or PVd in 26). Of the 208 patients assigned to receive cilta-cel, 176 (84.6%) actually received the treatment (as-treated population). The remaining 32 patients discontinued trial participation mainly because of disease progression during bridging therapy or lymphodepletion. Of the 211 patients assigned to receive standard care, 208 (98.6%) received it; of these patients, 131 (63.0%) discontinued treatment, primarily due to disease progression. A total of 21 deaths occurred in the cilta-cel group during follow-up after a progression event. By the data-cutoff date (November 1, 2022), the median follow up was 15.9 months (range, 0.1 to 27.3). Cilta-cel resulted in a significantly lower risk of disease progression or death than standard care (HR, 0.26; 95% CI, 0.18 to 0.38; P<0.001. The median duration of PFS was not reached in the cilta-cel group and was 11.8 months (95% CI, 9.7 to 13.8) in the standard care group. At 12 months in the intention-to-treat population, PFS was 75.9% (95% CI, 69.4 to 81.1) in the cilta-cel group and 48.6% (95% CI, 41.5 to 55.3) in the standard care group. MRD negativity at any time during the trial occurred in 60.6% of those in the cilta-cel group and in 15.6% of patients in the standard care group for a risk ratio of 2.2 (95% CI, 1.8 to 2.6; P<0.001) and an odds ratio of 8.7 (95% CI, 5.4 to 13.9). Among the patients who had evaluable samples (144 in the cilta-cel group and 101 in the standard care group), MRD negativity occurred in 126 (87.5%) and 33 (32.7%), respectively. Death from any cause was reported in 39 patients in the cilta-cel group and in 46 in the standard care group; 1 patient in the standard care group died before the initiation of treatment. Death from disease progression was reported in 14 patients in the cilta-cel group (8 of whom did not receive cilta-cel) and in 30 in the standard care group; 10 and 5 deaths, respectively, were caused by adverse events during treatment (associated with COVID-19 in 7 patients and 1 patient, respectively). Results of CARTITUDE-4 indicate cilta-cel is an effective treatment for patients with lenalidomide-refractory disease as early as the first relapse. The median duration of PFS in CARTITUDE-4 extended beyond the median duration of detectability in CAR-T cells, a result that was similar to observations in CARTITUDE-1. Overall, CAR-T-specific adverse events were manageable with appropriate supportive care. Lower rates

of cytopenias, CRS, and CAR-T-related neurotoxicity were seen in CARTITUDE-4 than in CARTITUDE-1, which suggests that cilta-cel may have a better side-effect profile when used earlier in treatment.

Ciltacabtagene autoleucel (Carvykti™) is considered medically necessary for the treatment of active, measurable multiple myeloma, relapsed or refractory, and the following criteria are met:

- Member is 18 years of age or older
- Member has received at least 1 prior line of therapy including a proteosome inhibitor and an immunomodulatory agent **AND** is refractory to lenalidomide.
- Disease was refractory to the last regimen (progression within 12 months or less after the last line of therapy) according to International Myeloma Working Group (IMWG) criteria
- Member has received or will receive adequate standard lymphodepleting chemotherapy or a therapeutically equivalent regimen before infusion of ciltacabtagene autoleucel. (The standard is a lymphodepleting chemotherapy regimen of cyclophosphamide 300mg/m^2 intravenously and fludarabine 30mg/m^2 intravenously daily for three days prior to infusion).
- Member has not had previous treatment with a CAR T-cell targeted therapy
- If member has had a prior allogeneic HSCT, the member does not currently have active GVHD
- Member does not have CNS involvement with myeloma

Non-Hodgkin Lymphomas

Non-Hodgkin lymphomas (NHLs) are a collection of neoplasms originating in lymphoid tissue and capable of spreading to other organs. Older adults are most often impacted in the sixth and seventh decades. Consequently, patients with NHL may also have significant comorbidities that can complicate treatment options. Prognosis is largely dependent on histologic type, stage and treatment. In 2021, an estimated 81,560 people will be diagnosed with NHL, and there will be approximately 20,720 deaths due to the disease (Siegel et al., 2021). NHLs range from indolent, with essentially a normal life span, to life-threatening, aggressive variants such as diffuse large B-cell lymphoma (DLBCL) which is the most common lymphoma, representing as much as 40% of NHL cases globally (Leick et al., 2021). Other major subtypes include chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 19%), follicular lymphoma (FL; 17%), marginal zone lymphoma (MZL; 8%), mantle cell lymphoma (MCL; 4%), and peripheral T-cell lymphoma not otherwise specified (PTCL-NOS; 2%) (Al-Hamadani et al., 2015). Diagnostic accuracy is critical in determining management. Basic pathologic assessment is the same for each subtype although additional evaluation is essential to clarify the diagnosis. Immunohistochemistry is essential for the differentiation of the various subtypes.

The NCCN guidelines include a series of algorithms to provide guidance for surgical pathologists as well as to assist clinicians in the interpretation of pathology reports (NCCN Guideline for B-cell Lymphoma, version 2.2024).

Standard treatment of NHL depends on the histologic type and stage. Options include a combination of radiation therapy, chemotherapy, monoclonal antibodies, watchful waiting in the case of indolent lymphomas, and hematopoietic stem cell transplant. Patients with aggressive subtypes who do not achieve a cure with initial treatment present unique challenges, often related to their age, comorbidities, or intolerance to high-dose chemotherapy.

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are characterized by progressive accumulation of leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues (National Cancer Institute, 2024). Morphologically, these leukemic cells appear as small, mature lymphocytes that can be found admixed with occasional larger or atypical cells, or prolymphocytes. CLL remains the most prevalent adult leukemia in Western countries. In 2024, an estimated 20,700 people will be diagnosed with CLL in the United States, and an estimated 4440 people will die from the disease (Siegel et al., 2023). Molecular and cytogenetic variables impact the selection of treatment regimens. Treatment options include chemotherapy with or without allogeneic hematopoietic stem cell transplantation, targeted therapy, and immunotherapy, however patients that experience relapse or become refractory have few treatment options. Recently, CAR T cell therapy has demonstrated promise and recently achieved FDA approval.

NCCN Guidelines for CLL/SLL (version 3.2024) names lisocabtagene maraleucel (Breyanzi®) as a treatment option for relapsed/refractory CLL/SLL after prior treatment with BTKi and venetoclax-based regimens.

Treatment

Lisocabtagene maraleucel (Breyanzi®)

TRANSCEND CLL 004 was a multicenter, open-label, single-arm, phase 1-2 study that enrolled adult patients ≥ 18 years of age with relapsed or refractory CLL or SLL and at least two previous lines of therapy, including a BTK inhibitor. Patients received an intravenous infusion of liso-cel at one of two target dose levels: 50 x 10^6 (dose level 1, DL1) or 100 x 10^6 (dose level 2, DL2) chimeric antigen receptor-positive T cells. The primary endpoint was complete response or remission (including with incomplete marrow recovery) in efficacy-evaluable patients with previous BYK inhibitor progression and venetoclax failure (the primary efficacy analysis set) at DL2.

Between January 2, 2018, and June 16, 2022, 137 enrolled patients underwent leukapheresis. Liso-cel was successfully manufactured for 131 (96%) patients and infused into 117 (full safety set), including 49 patients in the primary efficacy set at DL2. Six patients died before treatment due to disease progression (n=1), unspecified adverse event (n=1), septic shock (n=1), anaphylaxis from bridging therapy (n=1), and unknown cause (n=2). The median time from leukapheresis to liso-cel infusion was 36 days (IQR 33 – 48). Nine patients received DL1 at a median dose of 43.8 x 10^6 CAR T cells (IQR 41.9 – 45.1) and 108 received DL2 at a median dose of 100.0 x 10^6 CAR T cells (99.1 – 100.7). At data cutoff (September 29, 2022), median on-study follow-up for the full safety set was 21.1 months (IQR 7.3 – 28.2). Fourteen patients were treated in the outpatient setting.

In the full safety set (n=117), the median age was 65 years (IQR 59 – 70), 52 (44%) patients had bulky (≥ 5 cm) lymph nodes, and 97 (83%) had high-risk cytogenetics. Patients had a median of five lines of previous therapy (IQR 3 – 7), including BTK inhibitor (117, 100%), chemoimmunotherapy (101, 86%), and PI3K inhibitor (29, 25%); 103 (88%) were refractory to BTK inhibitor, 89 (76%) were refractory to venetoclax, and 70 (60%) had BTK inhibitor progression and venetoclax failure. Bridging therapy was received by 89 (76%) patients during liso-cel manufacturing, primarily venetoclax (39, 44%) and Obinutuzumab (25, 28%).

In the primary efficacy analysis set at DL2 (n=49), the rate of complete response or remission (including with incomplete marrow recovery) was statistically significant at 18% (n=9; 95% CI 9-32; p=0.0006). Grade 3 CRS was reported in 10 (9%) of 117, with no grade 4 or 5 events. Grade 3 neurological events were reported in 21 (18%; 1[1%] grade 4, no grade 5 events). Among 51 deaths on the study, 43 occurred after liso-cel infusion, of which 5 were due to treatment-emergent adverse events within 90 days of infusion. One death was related to liso-cel (macrophage activation syndrome-hemophagocytic

lymphohistiocytosis). Longer follow-up will provide further insight into the durability of response as well as longer term survival benefits (Siddiqi et al., 2023).

Lisocabtagene maraleucel (Breyanzi®) is considered medically necessary as a single infusion for the treatment of relapsed or refractory CLL or SLL when the following criteria are met:

- Member is 18 years of age or older
- Has received and had treatment failure on at least 2 prior lines of therapy including:
  - A Bruton tyrosine kinase (BTK) inhibitor (i.e., ibrutinib, acalabrutinib, zanubrutinib, or pirtobrutinib) **AND**
  - A B-cell lymphoma 2 (BCL-2) inhibitor (i.e., venetoclax)
- ECOG performance status ≤ 2
- Meets all minimum eligibility criteria described above
- Does not present with a universal contraindication described above
- Member will receive lymphodepleting chemotherapy regimen before infusion of lisocabtagene maraleucel: Fludarabine 30 mg/m^2/day IV and cyclophosphamide 300 mg/m^2/day IV for 3 days
- Member has not received prior treatment with CAR T-cell therapy

Diffuse Large B-Cell Lymphoma

The SCHOLAR-1 study, pooled data from 2 phase 3 clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials LY.12) and 2 observational cohorts (MD Anderson Cancer Center and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence). Among 861 patients, 636 were included on the basis of refractory disease inclusion criteria. For patients with refractory DLBCL, the objective response rate was 26% (complete response rate 7%) to the next line of therapy, and the median overall survival was 6.3 months. Twenty percent of patients were alive at two years. SCHOLAR-1 demonstrated poor outcomes in patients with refractory DLBCL, supporting the need for more effective therapies for these patients (Crump et al., 2017).

Adoptive cellular therapy via modulation of autologous T cells to express a chimeric antigen receptor (CAR) T cells has resulted in significant improvement in the outcomes for relapsed/refractory large B-cell lymphomas, including long-term durable responses and median overall survival of greater than two years (Locke et al., 2019).

Treatment

Axicabtagene ciloleucel (Yescarta®)

ZUMA-1 was a single-arm, multicenter, phase 1/2 trial at 22 sites in the United States and Israel and included 119 patients, of which 108 (91%) were administered the CAR T-cell product axicabtagene ciloleucel (Yescarta) between May 19, 2015, and September 15, 2016. Trial enrollees were 18 years of age or older, and had histologically confirmed large B-cell lymphoma, including diffuse large B-cell lymphoma, primary mediastinal B-cell lymphomas, and transformed follicular lymphoma; refractory disease or relapsed following autologous stem cell transplantation; an ECOG performance status of 0 or 1; and had previously received an anti-CD20 monoclonal antibody-containing regimen and an anthracycline-containing chemotherapy. Refractory disease was defined as progressive or stable disease as best response to the most recent chemotherapy regimen, or progression of disease or relapse within 12 months of autologous stem cell transplantation. Patients with transformed DLBCL must have received previous chemotherapy for follicular lymphoma and developed chemo refractory disease after transformation. No upper age limit was established. The study excluded those who had undergone autologous stem cell transplant within 6 weeks of informed consent for ZUMA-1, those with prior allogeneic stem cell transplantation, any history of central nervous system lymphoma, ECOG status ≥ 2 , absolute lymphocyte count < 100 µL, creatinine clearance < 60mL/min, hepatic transaminases > 2.5 times the upper limit of normal, cardiac ejection fraction < 50%, or active serious infection. Following conditioning chemotherapy with intravenous fludarabine (30 mg/m^2) and cyclophosphamide (500 mg/m^2) on days -5, -4, and -3, participants received one dose of axicabtagene ciloleucel on day 0 at a target dose of 2 x 10^6 CAR-positive viable T cells/kg. Bridging chemotherapy was not permitted. The primary endpoints were safety for phase 1 and the proportion of patients achieving an objective response for phase 2. Critical secondary endpoints were overall survival, progression-free survival and duration of response (Locke et al., 2019).

At a median follow-up of 15.4 months, 89 (82%) of 108 assessable patients with refractory LBCL had an objective response, 63 (58%) had a complete response, and 45 (42%) were in remission (Neelapu et al., 2017). These results led to approval of axicabtagene ciloleucel as third-line and higher treatment of relapsed or refractory large B-cell lymphomas including DLBCL, primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma, and transformed follicular lymphoma. All 108 treated patients experienced adverse events, and 106 (98%) had grade 3 or worse events. Grade 3 or worse CRS occurred in 12 (11%) patients and grade 3 or worse neurological events occurred in 35 (32%); all of the events were manageable and largely reversible. Since study initiation, 54 (50%) of 108 patients who received

treatment have died (4 in phase 1 and 50 in phase 2); 50 of the 54 patients died from progressive disease, with 6 of the deaths occurring after the 12-month analysis (Locke et al., 2019).

To contribute to the body of knowledge around optimal patient selection among those with baseline cardiovascular compromise, Alvi et al. (2019) conducted a retrospective cohort study evaluating the cardiac effects of CAR T-cell therapy. Across two institutions,137 patients received CAR T-cell therapy for relapsed DLBCL (61%), transformed follicular lymphoma (27%) and multiple myeloma (8%). Approximately 50% were treated with axicabtagene ciloleucel or tisagenlecleucel, while the remainder received noncommercial (investigational) products. Elevated troponin 29 of 53 (54%) and a decrease of LVEF 8 of 29 (28%) were common. Cardiac events occurred in 17 of 137 patients (12%), including 6 cardiovascular deaths, 6 decompensated heart failures and 5 arrythmias. All of the cardiac events occurred in the setting of grade 2 or greater CRS, and 95% of events occurred after an elevated troponin. Tocilizumab was administered to all patients with CRS at a median of 27 hours (IQR: 16 to 48 hours) after onset. The duration between CSR onset and tocilizumab administration was associated with CV events, where the risk increased 1.7-fold with each 12-hour delay to tocilizumab. Additional studies are warranted to better define the clinical utility of measuring troponin values, consider earlier intervention in less severe grades of CRS, and test the potential benefits of administering tocilizumab based on troponin values.

In the time since axicabtagene ciloleucel approval, many patients who would not have met the eligibility criteria for ZUMA-1, but who were otherwise eligible according to the FDA label, have received CAR T-cell therapy as a standard of care. In a large retrospective study of more than 150 patients treated with axicabtagene ciloleucel, Nastoupil and colleagues (2018) found short-term safety and activity similar to those in ZUMA-1 despite nearly half the patients not meeting ZUMA-1 criteria with respect to performance status, cytopenias, comorbidities or organ function. According to the authors, these results suggest that axicabtagene ciloleucel CAR T-cell therapy is a feasible treatment option for most patients with refractory/relapsed large B-cell lymphoma. The authors note that ZUMA-1 was not designed to assess quality of life and further studies are needed to understand mechanisms of resistance to CAR T-cell therapy.

ZUMA-7, a randomized, open-label, multicenter trial compared axicabtagene ciloleucel to second-line standard chemoimmunotherapy in adult patients with primary refractory LBCL or relapse within 12 months following completion of first-line therapy. Patients had not yet received treatment for relapsed or refractory lymphoma and were potential candidates for autologous HSCT. A total of 359 patients were randomized 1:1 to receive a single infusion of axicabtagene ciloleucel following fludarabine and cyclophosphamide lymphodepleting chemotherapy or to receive second-line standard therapy, consisting of 2 or 3 cycles of chemoimmunotherapy followed by high-dose therapy and autologous HSCT in those who attained CR or PR. In the axicabtagene ciloleucel arm, bridging therapy, administered between leukapheresis and lymphodepleting chemotherapy, was limited to corticosteroids and was permitted for patients with high disease burden (Locke et al., 2022).

Of the 180 patients randomized to receive axicabtagene ciloleucel, 178 underwent leukapheresis and 170 were treated, of whom 60 (33%) received bridging corticosteroid therapy. Eight patients (4%) were not treated following leukapheresis due to progressive disease, serious adverse events, or death. Of the 179 patients randomized to receive standard therapy, 168 received any study treatment, and 62 (35%) received high-dose therapy and on-protocol HSCT. Lack of response to salvage chemotherapy was the most common reason for not receiving HSCT.

The primary efficacy measure, event-free survival (EFS), was significantly longer in the axicabtagene ciloleucel arm (8.3 months; 95% CI, 4.5 to 15.8) than in the standard care arm (2.0 months; 95% CI, 1.6, 2.8). The estimated EFS at 24 months was 41% (95% CI, 33, 48) in the axicabtagene ciloleucel group, as compared with 16% (95% CI, 11, 22) in the standard care group. The percentage of patients with a response in the axicabtagene ciloleucel 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 axicabtagene ciloleucel patients and 32% of the standard care patients. The median overall survival, evaluated as an interim analysis, was not reached in the axicabtagene ciloleucel arm and was 35.1

months in the standard care arm (HR for death, 0.73; 95% CI, 0.53,1.01; P=0.054 [2-sided], statistical significance not reached). Overall, 72 patients (40%) in the axicabtagene ciloleucel arm and 81 (45%) in the standard care arm died from any cause; 52 patients (29%) in the axicabtagene ciloleucel group and 65 (36%) in the standard care group died from progressive disease.

Adverse events of grade 3 or higher were experienced by 155 of 170 patients (91%) who received axicabtagene ciloleucel and by 140 of 168 patients (83%) who received standard care. Neutropenia was the most commonly reported adverse event of grade 3 or higher occurring in 69% of patients receiving axicabtagene ciloleucel and 41% of those receiving standard care. Infections of any grade occurred in 41% of axicabtagene ciloleucel patients and 30% of standard care patients, with infections of grade 3 or higher occurring in 14% and 11%, respectively. Fatal adverse events occurred in seven patients (4%) in the axicabtagene ciloleucel group (of which only one event [hepatitis B virus reactivation] was considered by the investigators to be related to axicabtagene ciloleucel) and in two patients (1%) in the standard care group (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 patient (92%) of the axicabtagene ciloleucel group, with an event of grade 3 or higher occurring in 11 patients (6%). No deaths related to cytokine release syndrome occurred. Tocilizumab was administered to 65% of the patients, glucocorticoids to 24% and vasopressors to 6%. The median time to onset of cytokine release syndrome was three days (range 1–10) following infusion, and the median duration was seven days (range 2–43). All events resolved. Neurologic events occurred in 102 patients (60%) who received axicabtagene ciloleucel and 33 (20%) who received standard of care; events of grade 3 or higher occurred in 36 patients (21%) and 1 patient (1%), respectively. The median time to onset of neurologic events was 7 days in the axicabtagene ciloleucel group and 23 days in the standard care group, and the median duration was 9 days and 23 days, respectively. There were no deaths related to neurologic events.

Axicabtagene ciloleucel demonstrated superiority to standard of care, with a median event-free survival that was longer by a factor of more than 4, a 2-year EFS that was higher by a factor of 2.5, a significantly higher percentage of patients with a response, and double the percentage of patients with a complete response. The difference on overall survival 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; this occurred in 56% of patients. This may have confounded the analysis of overall survival (Locke et al., 2022).

The study authors concluded ZUMA-7 demonstrated a significant improvement in efficacy with axicabtagene ciloleucel as compared with second-line standard care in patients with relapsed or refractory LBCL. Axicabtagene ciloleucel appears to be a viable alternative to a regimen of chemoimmunotherapy, high-dose chemotherapy and autologous HSCT for second-line treatment of relapsed or refractory LBCL.

Recently, Westin and colleagues (2023) reported the results of the prespecified overall survival analysis of ZUMA-7 at five years after the first patient underwent randomization. A total of 359 patients underwent randomization to receive axicabtagene ciloleucel (axi-cel) (180 patients) or standard care (179 patients). At a median follow-up of 47.2 months, death had been reported in 82 patients in the axi-cel group and in 95 patients in the standard-care group. The median overall survival was not reached in the axi-cel group and was 31.1 months in the standard-care group; the estimated 4-year overall survival was 54.6& and 46.0%, respectively (HR for death, 0.73; 95% CI, 0.54 to 0.98; P=0.03 by stratified two-sided log-rank test). This increased survival with axi-cel was observed in the intention-to-treat population, which included 74% of patients with primary refractory disease and other high-risk features. The median investigator-assessed PFS was 14.7 months in the axi-cel and 3.7 months in the standard-care group, with estimated 4-year percentages of 41.8% and 24.4%, respectively (HR, 0.51; 95% CI, 0.38 to 0.67). These findings demonstrate the superiority of axi-cel over second-line platinum-based chemotherapy and autologous stem cell transplantation with a 27.4% reduction in the risk of death and an absolute improvement in survival of 8.6 percentage points at 4 years.

Axicabtagene ciloleucel (Yescarta®) is considered medically necessary for the treatment of relapsed or refractory B-cell lymphoma in members 18 years of age or older when the following criteria are met:

- Member has been diagnosed with relapsed/refractory B-cell lymphoma including any of the following:
  - Diffuse large B-cell lymphoma (DLBCL) not otherwise specified
  - Primary mediastinal large B-cell lymphoma
  - High-grade B-cell lymphoma
  - DLBCL arising from follicular lymphoma
  - AIDS-related B-cell lymphoma
  - Nongastric MALT lymphoma
  - Post-transplant lymphoproliferative disorders
  - Splenic marginal zone lymphoma
  - Histologic transformation of indolent lymphomas to DLBCL
  - Gastric MALT lymphoma
  - Extranodal marginal zone lymphoma of the stomach
  - Extranodal marginal zone lymphoma of nongastric sites (noncutaneous)
  - Nodal marginal zone lymphoma
- Member received prior treatment with two or more chemoimmunotherapy regimens that included at least one anthracycline or anthracenedione-based regimen, unless contraindicated and has experienced disease progression following the last treatment regimen or refractory/suboptimal response to the most recent therapy **OR**
- Member has disease that was refractory to or relapsed no more than 12 months following completion of first-line chemoimmunotherapy **AND**
- Member has received or will receive adequate standard lymphodepleting chemotherapy or a therapeutically equivalent regimen before infusion of axicabtagene ciloleucel. (The standard is a lymphodepleting chemotherapy regimen of cyclophosphamide 500mg/m^2 intravenously and fludarabine 30mg/m^2 intravenously on the fifth, fourth and third day before infusion).
- Member has not received prior treatment with CAR T-cell therapy
- If member has had a prior allogeneic HSCT, the member does not currently have active GVHD

Tisagenlecleucel (Kymriah®)

High rates of durable remission among patients with relapsed or refractory DLBCL were observed in a single-center case-series study (NCT02030834) by Schuster et al. (2017). A total of 28 adult patients with CD19+ DLBCL or follicular lymphoma with no curative treatment options, a limited prognosis (<2 years anticipated survival), and a partial response to or stable disease following most recent chemotherapy received tisagenlecleucel (previously known as CTL019) at a median total cell dose of $5.00x10^8$ (range$1.79x10^8$ to $5.00x10^8$). The median number of days from apheresis to infusion was 39 (range 27 to 145); 10 of the 28 patients received bridging therapy administered after apheresis and before lymphodepleting chemotherapy. Response rate was 50% at 3 months, with 43% of the patients having a complete response at 6 months. No patients with a complete response at 6 months had had a relapse by the median follow-up of 28.6 months. On the basis of Schuster, as well as a previous study (Maude et al., 2014; Maude et al., 2016) in children and young adults with relapsed or refractory acute lymphoblastic leukemia, a pivotal phase 2 study was conducted to evaluate safety and efficacy in adults with relapsed or refractory DLBCL.

The safety and efficacy of tisagenlecleucel (Kymriah®) was evaluated in the JULIET trial (NCT02445248), an open-label, multicenter, single-arm study enrolling 160 patients, ages 18 years and older with relapsed or refractory DLCBL who had received ≥ 2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous stem cell transplantation. Patients with active central nervous system malignancy, prior allogeneic stem cell transplantation, ECOG performance status of ≥ 2, a creatinine clearance < 60 mL/min, alanine aminotransferase > 5 times normal, cardiac ejection fraction < 45%, or

absolute lymphocyte concentration < 300/µL were excluded. Lymphodepleting chemotherapy consisting of either fludarabine (25 mg/m^2 IV daily for 3 days and cyclophosphamide 250 mg/m^2 IV daily for 3 days starting with the first dose of fludarabine or bendamustine 90mg/m^2, following which tisagenlecleucel was administered as a single intravenous infusion. Bridging chemotherapy between leukapheresis and chemotherapy was permitted to control disease burden. Objective response rate per Lugano criteria and duration of response were the major outcome measures. The most common adverse events were cytokine release syndrome (CRS) (58%) with a median time from infusion to the onset of symptoms three days and the median duration seven days. Patients responded to either tocilizumab or tocilizumab and glucocorticoids, with no patient receiving more than two doses of tocilizumab. Infections concurrent with CRS occurred in 6% of these patients. The study investigators concluded that a high rate and duration of response to tisagenlecleucel had been demonstrated among heavily pretreated adults with relapsed/refractory DLBCL. With rates of complete and partial response at 32% and 5%, respectively, and sustained through 6 months, suggests responses at 3 months are usually durable (Schuster et al., 2019).

A poster presentation at the 62nd ASH® Annual Meeting and Exposition, convened December 5–8, 2020, updated efficacy results with a 40-month median follow-up and associations with baseline Myc overexpression in tumor and tumor microenvironment characteristics (ASH, 2020). At median follow-up of 40.3 months (as of February 20, 2020), 115 patients had received tisagenlecleucel infusion. Relapse-free probability was 60.4% at 24 and 30 months and median duration of response was not reached (95% CI, 10 — not estimable [NE]) among the 61 patients with a response. Median OS among all infused patients was 11.1 months (95% CI, 6.6–23.9). Median OS of patients with CR (*n* = 37) or PR (*n* = 7) month 3 was not reached. 80% CR patients had an OS of 20 months or longer. Also reported were improved outcomes, including longer median DOR, PFS and OS in patients with baseline Myc status as compared with Myc + patients. The authors concluded that these updated data demonstrate sustained benefit in responding patients, particularly long-term OS for the majority of patients with CR and suggest that Myc overexpression, or an unfavorable immunosuppressive tumor microenvironment (TME) with restricted T-cell response, may impact CAR T efficacy on patients with DLBCL.

Tisagenlecleucel (Kymriah®) is considered medically necessary for the treatment of relapsed or refractory B-cell lymphoma when the following criteria are met:

- Member is 18 years of age or older
- Member has been diagnosed with relapsed/refractory B-cell lymphoma including any of the following:
  - AIDS-related B-cell lymphoma
  - Diffuse large B-cell lymphoma (DLBCL)
  - Follicular lymphoma
  - High-grade B-cell lymphoma
  - Histologic transformation of indolent lymphomas to DLBCL such as:
    - Diffuse large B-cell lymphoma arising from follicular lymphoma
    - Diffuse large B-cell lymphoma arising from nodal marginal zone lymphoma
  - Human herpes virus 8-positive diffuse large B-cell lymphoma
  - Large B-cell lymphoma
  - Post-transplant lymphoproliferative disorder
- Member has received two or more lines of systemic therapy
- For diffuse large B-cell lymphoma arising from follicular lymphoma or nodal marginal zone lymphoma:
  - Member received prior treatment with two or more chemoimmunotherapy regimens that included at least one anthracycline or anthracenedione-based regimen, unless contraindicated
- Member has received or will receive a lymphodepleting chemotherapy regimen within two weeks preceding tisagenlecleucel infusion. Standard lymphodepleting chemotherapy regimens, as directed on the FDA label include:

  - Fludarabine 25 mg/m^2 intravenously daily for three days and cyclophosphamide 250 mg/m^2 intravenously daily for three days starting with the first dose of fludarabine **OR**
  - Alternate therapy with bendamustine 90 mg/m^2 intravenously daily for two days for those unable to receive cyclophosphamide due to a previous Grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide containing regimen **OR**
  - Lymphodepleting chemotherapy may be omitted if WBC is ≤ 1 x 10^9/L within one week prior to tisagenlecleucel infusion
- Member has not received prior treatment with CAR T-cell therapy
- If member has had a prior allogeneic HSCT, the member does not currently have active GVHD

Lisocabtagene maraleucel (Breyanzi®)

TRANSCEND (NCT02631044), a multicenter, multicohort, seamless design study at 14 centers in the United States assessed the safety and activity of lisocabtagene maraleucel (Breyanzi) in patients with PET-positive relapsed or refractory DLBCL (de novo or transformed from any indolent lymphoma), high-grade B-cell lymphoma with rearrangements in *MYC* and either *BCL2, BCL6,* or both (double- or triple-hit lymphoma), primary mediastinal B-cell lymphoma, or follicular lymphoma grade 3B. Patients must have received 2 or more previous lines of systemic treatment, including anthracycline-based chemotherapy and an anti-CD20 antibody, with subsequent relapse and may have received a previous autologous or allogeneic hematopoietic stem cell transplant. Bridging chemotherapy, radiation therapy or both, after leukapheresis was allowed but required reconfirmation of PET-positive disease before lymphodepleting chemotherapy consisting of fludarabine (30mg.m^2) and cyclophosphamide (300mg/m^2) was administered daily for 3 days. A total of 159 (59%) patients received bridging therapy but it did not result in a lower tumor burden in most patients. Primary endpoints were the incidence of adverse events, the probability of dose-limiting toxicities, and the objective response rate. The proportion of patients achieving a complete response, duration of response, progression-free survival, and cellular kinetic variable were secondary endpoints. Of 344 patients with DLBCL who underwent leukapheresis between January 11, 2016, and July 5, 2019, 294 received CAR T cells a median of three days (IQR 3–4) after lymphodepleting chemotherapy. Lymphoma complications or death prior to infusion occurred in 48 patients and product could not be manufactured for two patients. Of the 294 who received CAR T cells, 269 received liso-cel, while 25 received a non-conforming CAR T product. The median dose was 91x10^6 CAR T cells (range 44–156x10^6). No maximum tolerated dose was identified, and no dose relationship was observed for overall safety and activity across all does levels. There were 25 patients across 5 treatment sites who received CAR T-cell infusions in the outpatient setting. Of those 25 patients, 18 (72%) were hospitalized for adverse events, including 10 with cytokine release syndrome (CRS), neurological events, or both. Median time from infusion to hospitalization was five days.

The most frequent treatment-emergent adverse events among the 269 patients treated with liso-cel were neutropenia in 169 (63%) patients, anemia in 129 (48%), fatigue in 119 (44%), CRS of any grade in 113 (42%) and nausea in 90 (33%). CRS grade 3 or worse occurred in six (2%) patients. No patients died from CRS although two patients died with ongoing CRS, one from septic shock and one from pulmonary hemorrhage. CRS was managed with tocilizumab, corticosteroids, or both, in 52 (20%) patients; 27 (10%) received tocilizumab alone. Other interventions included vasopressors, and both siltuximab and anakinra. Neurological events of any grade occurred in 80 (30%) patients with grade 3 or worse occurring in 27 (10%). The most common neurological events of any grade included encephalopathy in 57 patients; 21% of patients overall and 71% of patients with neurological events; tremor and aphasia in 26 patients; 10% of patients overall and 33% of patients with neurological events; delirium in 16 patients; 6% of patients overall and 20% of patients with neurological events. Higher tumor burden increased inflammatory markers and having received bridging therapy were associated with a higher incidence of CRS, neurological events, or both, of any grade.

The efficacy-evaluable set included 256 patients. An objective response rate was achieved by 186 (73%, 95% CI 66.8–78.0) patients and a complete response by 136 (53%, 95% CI 46.8–59.4) patients. Investigators reported the responses were durable with an estimated duration of response at one year of 55% among patients who had a complete or partial response, and 65% among those who achieved a complete response. Progression-free survival and overall survival at one year were 44% and 58%, respectively. TRANSCEND is notable for enrolling a large population of older patients (112 [42%] of 269 patients were ages ≥ 65 years) and including patients with understudied subtypes including follicular lymphoma grade 3B, DLBCL transformed from indolent lymphoma, and secondary CNS lymphoma. Additional studies of these subsets are warranted, owing to the small number of patients. TRANSCEND included 6 evaluable patients with secondary CNS lymphoma, while both ZUMA-1 and JULIET excluded such patients. Three of the six (50%) achieved a complete response, 2 (33%) patients experienced grade 3 neurological events, and none had severe CRS. Investigators call for additional studies on the management of these patients receiving CAR T-cell treatment, particularly with respect to neurological events. TRANSCEND investigators concluded their findings demonstrate that liso-cel can lead to rapid and durable remission, with low incidence of all-grade and severe CRS and neurological events in patients with high-risk aggressive relapsed or refractory large B-cell lymphomas (Abramson et al., 2020).

The efficacy of liso-cel (Breyanzi) in adult patients with relapsed or refractory LBCL following first-line chemoimmunotherapy was evaluated in the TRANSFORM trial (NCT03575351). A randomized, open-label, multicenter trial, TRANSFORM enrolled patients who had not yet received treatment for relapsed or refractory lymphoma, were potential candidates for autologous HSCT, and were required to have primary refractory disease or relapse within 12 months from CR to initial chemoimmunotherapy. A total of 184 patients were randomized in a 1:1 ratio to receive a single infusion of liso-cel (100 x 10^6 CAR-positive viable T cells) or to receive standard therapy consisting of 3 cycles of chemoimmunotherapy followed by high-dose therapy and autologous HSCT in patients who attained CR or PR. Standard of care consisted of 3 cycles of R-DHAP (rituximab, dexamethasone, cytarabine and cisplatin; R-ICE (rituximab, ifosfamide, etoposide, and carboplatin; or R-GDP (rituximab, dexamethasone, gemcitabine, and cisplatin), followed by high-dose chemotherapy and autologous HSCT in responders. Patients in the liso-cel group were allowed to receive once cycle of bridging therapy with one of the three salvage regimens allowed in the standard-of-care group at investigator discretion during manufacturing. 58 (63%) received bridging therapy, mostly due to high tumor burden or rapid disease progression. Of these 58 patients, 53 (91%) received one cycle of bridging therapy and five (9%) received more than one cycle (considered to be protocol deviations), four due to delay in the manufacturing process and one due to investigator decision. Liso-cel was administered in the outpatient setting to 19 (21%) patients. Of the 92 patients randomized to the standard-of-care group, 91 (99%) patients received salvage immunochemotherapy; 12 patients switched regimens. Of the 91 patients who received salvage immunochemotherapy, 43 (47%) were considered by the investigators to have a response and proceeded to high-dose chemotherapy, with 39 (43%) of those patients having an IRC-confirmed response (28 achieved a CR, 11 achieved a PR, while 4 had stable disease). At the time of data cutoff for this interim analysis, 42 (46%) patients had received autologous HSCT, and one patient had completed all high-dose chemotherapy drugs and was expected to go on to receive autologous HSCT after the data cutoff. 50 patients in the standard-of-care group were approved for crossover, with 40 (80%) patients crossing over during salvage immunochemotherapy and ten (20%) after high-dose chemotherapy or autologous HSCT. Reasons for crossover included disease progression (*n* = 36), suboptimal response or no response (*n* = 8), and relapse (*n* = 6). Of the 50 patients approved for crossover, 46 received liso-cel, and one received a non-conforming product. Three patients were not treated with liso-cel; two died of rapid disease progression prior to receiving the infusion, and one was still in the pretreatment evaluation period at data cutoff (Kamdar et al., 2022).

Primary endpoint was event-free survival. At interim analysis the median follow-up was 6.2 months (IQR 4.4–11.5). Median event-free survival was significantly improved in the liso-cel (10.1 months [95% CI 6.1 — not reached]) compared with the standard of care group (2.3 months [2.2–4.3]; stratified hazard ratio 0.35; 95% CI 0.23–0.53; stratified Cox proportional hazards model one-sided p<0.0001). Event-free survival rates at six months were 63% (95% CI 52%–75%) for the liso-cel group and 33% (95% CI 23%–44%) for the standard-of-care groups. Treatment with liso-cel also resulted in a higher CR rate (61 [66%]

of 92 patients; 95% CI 56–76) than standard-of-care (36 [39%] of 92 patients; 29–50; p<0.0001). Patients who achieved a CR in the liso-cel group had longer median duration of response than those in the standard-of-care group (median not reached [95% CI 6.8 — not reached] vs. 14.5 months [4.7 — not reached]). The ORR was 86% (79 patients; 95% CI 77% — 92%) in the liso-cel group and 48% (44 patients; 37%–59%) in the standard of care group (Kamdar et al., 2022).

The most common grade 3 or worse adverse events were neutropenia (74 [80%] of 92 patients in the liso-cel group vs. 46 [51%] of 91 patients in the standard-of-care group) anemia (45 [49%] vs. 45 [49%]), thrombocytopenia (45 [49%] vs. 58 [64%]), and prolonged cytopenia (40 [43%] vs. 3 [3%]). Grade 3 CRS and neurological events occurred in one (1%) and 4 (4%) of 92 patients in the liso-cel group, respectively. There were no grade 4 or 5 events. Serious treatment-emergent adverse events were reported in 44 (48%) patients in the liso-cel group and 44 (48%) in the standard of care group. There were no treatment-related deaths in the liso-cel group and one treatment-related death due to sepsis in the standard-of-care group. No new liso-cel safety concerns were identified in the second-line setting. The primary analysis will be conducted when 119 event-free survival events have occurred. These phase 3 results represent a clinically meaningful development in effective second-line treatment of relapsed or refractory LBCL. (Kamdar et al., 2022).

The PILOT study is an ongoing single-arm, open-label, multicenter, phase 2 study in the United States of liso-cel treatment in transplant-ineligible patients with relapsed or refractory LBCL following one line of chemoimmunotherapy. Organ function and age are the reasons patients were considered transplant-ineligible, while having adequate organ function for CAR T-cell therapy. Enrollment in PILOT required at least one of the following: age ≥ 70 years, adjusted diffusing capacity of the lung for carbon monoxide (DLCO) ≤ 60%; LVEF < 50%; creatinine clearance < 60mL/min; AST or ALT > 2 x ULN, or ECOG performance status of 2. The planned dose of liso-cel was 100 x 10^6 CAR-positive viable T cells. Bridging therapy was permitted between leukapheresis and the start of lymphodepleting chemotherapy. Of the 61 patients treated with liso-cel, 32 (53%) received bridging therapy. Of 74 patients who underwent leukapheresis, 61 (82%) received liso-cel and comprise the main efficacy population. One (1.4%) patient received CAR-positive T cells that did not meet the product specifications (manufacturing failure) and 12 (16%) did not receive CAR-positive T cells for other reasons. Diagnoses included de novo DLBCL NOS (51%), high-grade B-cell lymphoma (33%), and DLBCL arising from follicular lymphoma (15%). Of these patients, 53% had primary refractory disease, 23% had relapse within 12 months of completing first-line therapy, and 25% experienced relapse > 12 months following first-line therapy. In the primary analysis, with a median (range) on study follow-up of 12.3 months (1.2–26.5), objective response rate and CR were 80% and 54%, respectively; median (95% CI) DOR and PFS were 12.1 (6.2 — not reached) and 9.0 (4.2 — not reached) months, respectively, and median OS was not reached (Gordon et al., 2022).

Lisocabtagene maraleucel (Breyanzi®) is considered medically necessary for the treatment of relapsed or refractory B-cell lymphoma when the following criteria are met:

- Member is 18 years of age or older
- Member has been diagnosed with relapsed/refractory B-cell lymphoma including any of the following:
  - Diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma)
  - High-grade B-cell lymphoma
  - Primary mediastinal large B-cell lymphoma
  - AIDS-related B-cell lymphoma
  - Post-transplant lymphoproliferative disorders
- Member has refractory disease to first-line chemotherapy or relapse within 12 months of first-line chemoimmunotherapy **OR**
- Member has refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and is not eligible for HSCT due to comorbidities or age **OR**
- Member has disease progression following two or more lines of systemic therapy:

    - Previous chemoimmunotherapy included anthracycline-based chemotherapy (e.g., doxorubicin, epirubicin) and an anti-CD20 antibody (e.g., rituximab)
- Member will receive lymphodepleting chemotherapy regimen before infusion of lisocabtagene maraleucel: Fludarabine 30 mg/m^2/day IV and cyclophosphamide 300 mg/m^2/day IV for 3 days.
- Member has not received prior treatment with CAR T-cell therapy
- If member has had a prior allogeneic HSCT, the member does not currently have active GVHD

Follicular Lymphoma

Follicular lymphoma (FL) is the most common form of indolent lymphoma and accounts for approximately 22% of all lymphomas diagnosed (Al-Hamadani et al., 2015). According to National Institutes of Health Surveillance, Epidemiology, and End results Program (SEER) data, the rate of new cases of FL was 2.7 per 100,000 men and women per year and the death rate was 0.4 per 100,000 men and women per year based on analysis of 2014–2018 statistics. Clinical heterogeneity remains poorly understood. Some patients have an indolent disease trajectory over several decades, while others experience an aggressive clinical course, often accompanied by histologic transformation and poor prognosis. In a 2019 pooled cohort analysis of 1,654 newly diagnosed patients with follicular lymphoma grade 1–3A between 2001 and 2013, Sarkozy et al. (2019) examined 10-year overall survival to classify cause of death. In the overall cohort, lymphoma was the most common cause of death, with a cumulative incidence of 10.3% at 10 years, followed by treatment-related mortality (3.0%), other malignancy (2.9%), other causes (2.2%), and unknown (3.0%). Despite favorable (80%) 10-year overall survival, lymphoma remains the leading cause of death in the first decade after diagnosis, representing an unmet treatment need. CAR T cell therapies have shown efficacy in patients with relapsed/refractory FL in the third-line or later setting. However, there is no consensus on the optimal timing of CAR T cell therapy in the disease course of FL, especially in 2L treatment of patients with high-risk disease features such as progression of disease within 24 months (POD24) from diagnosis or disease that is refractory to both a CD20-targeting agent and an alkylator (Morschhauser et al., 2024).

The NCCN Guidelines for B-cell Lymphoma (version 3.2024) recommend axicabtagene ciloleucel (Yescarta®), lisocabtagene maraleucel (Breyanzi®), and tisagenlecleucel (Kymriah®) as preferred third-line and subsequent therapy (if not previously given) for partial response, no response, relapsed, or progressive disease. Each agent has an NCCN category 2A recommendation.

Treatment

Axicabtagene ciloleucel (Yescarta®)

Efficacy of axicabtagene ciloleucel as a treatment of FL is based on a single-arm, open-label multicenter trial (ZUMA-5; NCT03105336). ZUMA-5 evaluated a single infusion target dose of 2 x 10^6 anti-CD20 CAR T cells/kg following a lymphodepleting regimen of cyclophosphamide 500mg/m^2 intravenously and fludarabine 30mg/m^2 intravenously in adults with relapsed or refractory FL (grades 1–3A) or marginal zone lymphoma (MZL) (nodal or extranodal) following two or more lines of systemic therapy, including the combination of an alkylating agent and an anti-CD20 monoclonal antibody. The primary endpoint was objective response rate (ORR). Secondary endpoints included complete response (CR) rate, duration of response (DOR), progression-free survival (PFS), overall survival (OS), incidence of adverse events (AE), and levels of CAR T cells in blood and cytokines in serum.

Jacobson et al. (ASH 2020) reported that by March 12, 2020, 146 patients (124 FL; 22 MZL) had received an infusion; 84 patients with FL had ≥ 12 months' follow-up. The median age was 61 years (range, 34–79); 57% were male. Thirty-eight percent had ECOG 1, 86% had stage III/IV disease, 47% had ≥ 3 FLIPI, and 49% had high tumor bulk (GELF). Enrollees had a median three prior lines of therapy (range 1–10) and 64% had ≥ 3 prior lines. 55% of patients experienced disease progression < 2 years after initial chemoimmunotherapy and 68% were refractory to their last prior treatment.

At median follow-up of 17.5 months (range, 1.4–31.6), the ORR was 92% among 104 efficacy-evaluable patients, with a 76% CR rate. In patients with FL (*n* = 84), the ORR was 94% (80% CR rate) while in those with MZL (*n* = 20), the ORR was 85% (60% CR rate). The medians for DOR, PFS, and OS were not reached; the authors reported 12-month estimated rates were 72% (95% CI, 61–80), 74% (95% CI, 63082), and 93% (95% CI, 86–97), respectively.

AEs ≥ grade 3 occurred in 86% of patients (85% in FL; 95% in MZL). The most common AEs were neutropenia (33%), decreased neutrophil count (27%) and anemia (23%). Grade ≥ 3 cytokine release syndrome (CRS) occurred in 7% of patients (6% in FL; 9% in MZL), while grade ≥ 3 neurological events (NE) occurred in 19% of patients (15% in FL; 41% in MZL). Most CRS and NEs had resolved by data cutoff. Of note, grade 5 AEs occurred in 3 patients, including multisystem organ failure in the context of CRS (*n* = 1 FL), aortic dissection (*n* = 1 FL), and coccidioidomycosis infection (*n* = 1 MZL), the latter two AEs were considered unrelated to CAR T).

In ZUMA-5, patients were eligible for retreatment if they progressed after achieving a CR or PR at the 3-month post-infusion assessment, had no evidence of CD19 loss in progression biopsy, and had no grade 4 CRS or NEs with the first treatment. Chavez and colleagues reported (ASCO 2020) that 11 patients (9 FL; 2 MZL) had been retreated as of March 12, 2020. Prior to first treatment, 82% of patients had stage 3–4 disease, 91% had ≥ 3 FLIPI, and 91% had high tumor bulk (GELF). Median prior lines of therapy were four (range, 2–7); 60% of patients progressed < 2 years after initial anti-CD20 monoclonal antibody-containing therapy, and 82% had refractory disease. Those retreated had significantly higher tumor burden before first treatment than those who were not retreated. After first treatment, ten patients achieved a CR, and one patient achieved a PR. The first median DOR was 8.3 months (range, 1.9–11.8). CRS grade 4 occurred in one patient and 3 patients experienced grade 2. Grade 3 NEs occurred in one patient and 3 patients experienced grade 3. Among the FL patients, those who received retreatment (*n* = 9) had lower median peak CAR T-cell levels at first treatment, versus other FL patients (*n* = 115) who did not receive retreatment (13.2 vs. 41.9 cells/μL; *P* = 0.024); median peak CAR T-cell levels were also lower when normalized by tumor burden (0.003 vs. 0.023 cells/ μL x $mm^{2;}$ *P* = 0.006*).* Similar trends were observed in the patients with MZL. All 11 patients responded to retreatment, with 10 patients achieving a CR and one achieving a PR. With a median follow-up of 2.3 months, the median DOR to retreatment was not reached (range, < 1–8.4 months). Responses were ongoing for nine patients (82%) at data cutoff. Comparable instances of CRS and NE were observed with retreatment as with first treatment. Confirmatory analyses with more patients and longer follow-up are needed.

Axicabtagene ciloleucel (Yescarta®) is considered medically necessary for the treatment of relapsed or refractory follicular lymphoma when the following criteria are met:

- Member is 18 years of age or older
- Member demonstrates disease progression following two or more lines of systemic therapy **and**
  - Relapsed or refractory to last prior treatment
  - Has Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and adequate renal, hepatic, pulmonary and cardiac function
- Member does not have a primary central nervous system lymphoma
- Previous treatments must have included, but are not limited to, all of the following:
  - A combination of anti-CD20 monoclonal antibody (e.g., rituximab) **and**
  - An alkylating agent (e.g., bendamustine, cyclophosphamide)-containing regimen
- For members in whom disease progression occurred < 2 years after initial chemoimmunotherapy, additional documentation to describe follow-up prior to progression and this request may be required.
- Member has received or will receive adequate standard lymphodepleting chemotherapy or a therapeutically equivalent regimen before infusion of axicabtagene ciloleucel. (The standard is a lymphodepleting chemotherapy regimen of cyclophosphamide 500mg/m^2 intravenously and fludarabine 30mg/m^2 intravenously on the fifth, fourth and third day prior to infusion).
- Member has not received prior treatment with CAR T-cell therapy
- If member has had a prior allogeneic HSCT, the member does not currently have active GVHD

Lisocabtagene maraleucel (Breyanzi®)

The phase 2 TRANSCEND FL study evaluated lisocabtagene maraleucel (Breyanzi) in patients with relapsed/refractory FL, including those with high-risk disease features such as POD24 after treatment with an anti-CD20 antibody and alkylator administered ≤6 months of FL diagnosis and/or met modified GELF (mGELF) criteria. Morschhauser et al. (2024) reported on the primary analysis of patients in the relapsed/refractory cohort. The study population included patients with late-stage disease and high-risk disease features and with median age of 60 years; 86% had stage III/IV FL; 56% met mGELF criteria; 82% were intermediate or high risk per FLIPI; 65% had progressive disease (PD) during or ≤6 months of completing the last line of therapy; 56% had POD24 from initial immunochemotherapy; 62% were double refractory; and 38% received bridging therapy. The patient population in TRANSCEND FL was relatively young, which may have been mainly attributable to the willingness of physicians to provide cellular therapy to younger patients with high-risk disease who may have rapid progression after the last prior systemic therapy. Another contributing factor could have been the fairly short median time from initial treatment to first disease progression (1.5 years) and time from the most recent relapse to Breyanzi infusion (0.3 years). The median age of this study population was consistent with that reported for phase 2 studies of axicabtagene ciloleucel (Yescarta®), tisagenlecleucel (Kymriah®) and the CD20×CD3 bispecific antibody mosunetuzumab (Lunsumio™) in patients with 3L+ FL. The analysis found primary and key secondary endpoints were met and similar efficacy was observed across lines of therapy. In patients with 3L+ RR FL (*n*=101), ORR was 97% (95% CI 91.6, 99.4) and 94% (95% CI 87.5, 97.8) achieved CR. Median DOR was not reached (NR; 95% CI: 18.0-NR) at a median follow-up of 16.6 months, and 12-month DOR rate was 82% (95% CI 72.5-88.4). In patients with 2L FL (*n*=23) who were eligible only if they met POD24 from initial immunochemotherapy (65%) or mGELF criteria (70%), ORR was 96% (95% CI 78.1, 99.9) with all responders achieving CR. Median DOR was NR (95% CI 19.3-NR) at a median follow up of 16.8 months, and the DOR rate was 90% (95% CI 64.8-97.4). ORR, CR rate and 12-month DOR and PFS rates were consistently high across all subgroups, including patients with POD24 from initial immunochemotherapy, with double-refractory disease, patients with high tumor burden based on mGELF criteria, patients with high-risk FLIPI and patients who received bridging therapy. Reconfirmation of PET/ CT-positive measurable disease after the product manufacturing period was a requirement to proceed with lymphodepleting chemotherapy and Breyanzi infusion, including in patients who received optional bridging therapy during this period. For patients who received radiation therapy as bridging therapy, the presence of non-irradiated PET-positive lesions was required to continue to meet eligibility criteria. In this study, two patients reached CR after bridging therapy (one patient had PET-negative disease at the reassessment visit and was not treated, whereas the other patient relapsed, had measurable disease at the reassessment visit, received Breyanzi and was in ongoing CR as of data cutoff). In subgroup analyses, efficacy outcomes were similar regardless of bridging therapy status. Direct cross-trial comparisons of efficacy and safety cannot be made owing to differences in study design and definitions however Morschhauser points out the ORR and CR rate achieved by Breyanzi were consistent with those achieved by non-chemotherapy treatment strategies currently approved for 3L+ R/R FL. In phase 2, single-arm, registrational studies with other CAR T cell therapies axi-cel (ZUMA-5; efficacy evaluable [EE], n = 86) and tisagenlecleucel (ELARA; EE, n = 94) and Lunsumio (GO29781; EE, n = 90; treatment included 8–17 cycles), ORR ranged from 80% to 94%, and CR rates ranged from 60% to 79%. Median on-study follow-up after Breyanzi treatment in the primary analysis of TRANSCEND FL was 18.9 months. In primary publications, the median on-study follow-ups were in the same range (24.4 months for Yescarta (updated analysis), 16.9 months for Kymriah and 18.3 months for Lunsumio). CR rates with Breyanzi were the same for patients with versus without POD24 from initial immunochemotherapy (94% versus 94%). CR rates were numerically lower in patients with versus without POD24 from initial immunochemotherapy studies of Yescarta (72% versus 83%) and Kymriah (59% versus 88%).

Safety outcomes of Breyanzi in R/R FL were consistent with previous studies of Breyanzi in 2L and 3L+ R/R large B cell lymphoma (Abramson et al., 2023, 2020; Kamdar et al., 2022; and Sehgal et al., 2022). Among Breyanzi–treated patients with R/R FL, rates of severe CRS and NEs were low, with low tocilizumab/corticosteroid usage (25% for CRS; 7% for NEs), and no grade 4 or 5 events occurred. For

Breyanzi, rates of grade ≥3 CRS and NEs were 1% and 2%, respectively. For Yescarta (Jacobsen et al., 2022), Tecartus (Fowler et al., 2022), and Lunsumio (Budde et al., 2022), respectively, rates of grade ≥3 CRS were 6%, 0% and 2%, and rates of grade ≥3 NEs were 15%, 3% and 3%.

Lisocabtagene maraleucel (Breyanzi) is considered medically necessary for the treatment of relapsed or refractory follicular lymphoma when the following criteria are met:

- Member is 18 years of age or older
- Member has experienced disease progression following two or more lines of systemic therapy:
  - Previous chemoimmunotherapy included anthracycline-based chemotherapy (e.g., doxorubicin, epirubicin) and an anti-CD20 antibody (e.g., rituximab)
- Member has received or will receive adequate standard lymphodepleting chemotherapy or a therapeutically equivalent regimen prior to infusion of lisocabtagene maraleucel. (The standard is a lymphodepleting chemotherapy regimen of cyclophosphamide 300mg/m^2 intravenously and fludarabine 30mg/m^2 intravenously daily for three days before infusion).
- Member has not received prior treatment with CAR T-cell therapy
- If member has had a prior allogeneic HSCT, the member does not currently have active GVHD

Tisagenlecleucel (Kymriah®)

The ELARA trial (NCT03568461) enrolled 98 adult (≥ 18 years of age) patients with relapsed or refractory follicular lymphoma grade 1, 2 or 3A. Patients were excluded if they had evidence of histologic transformation, FL grade 3B, previous anti-CD19 therapy or allogeneic HSCT. As of the data cutoff date for interim analysis, 97 patients had received a tisagenlecleucel infusion; one patient was discontinued at investigator discretion based on CR to antineoplastic bridging therapy prior to infusion. At study entry, 63.9% of patients had bulky disease, 85.6% had stage III–V disease and 78.4% were refractory to the previous treatment. Tisagenlecleucel was administered in the outpatient setting in 18% of patients. Most (93/97, 95.9%) received the protocol-specified dose range of between 0.6 x 10^8 and 6.0 x 10^8 CAR-positive T cells; 4 patients received a lower dose of between 0.1 x 10^8 and 0.46 x 10^8 CAR T cells. Additionally, two patients received out-of-specification CAR T cells, one due to low cell viability and the other to high cell count; both were infused with doses within the protocol-specified dose range. The median CAR T-cell dose was 2.06 x 10^8 cells (IQR 1.40–2.67 x 10^8). The median time from enrollment to infusion was 46 days (IQR, 38–57) (Fowler et al., 2022).

The primary endpoint was CRR. Secondary endpoints included ORR, DOR, PFS, OS, pharmacokinetics and safety. As of the data cutoff date, 97/98 enrolled patients had received tisagenlecleucel (median follow-up, 16.59 months; IQR 13.8–20.21). The primary endpoint was met. In the efficacy set (*n* = 94), CRR was 69.1% (95% CI, 58.8–78.3) and ORR 86.2% (95% CI, 77.5–92.4). Within eight weeks of infusion, 96.9% of patients had at least one AE; 71% had grade 3 or 4 events. CRS occurred in 48.5% (grade ≥ 3, 1%), with median time to onset and resolution of CRS four days (IQR, 2–7 and 3–6 days, respectively) each. Among the 47 patients with CRS, 34% received tocilizumab and 6.4% received steroids. Any grade neurological events occurred in 37.1% (grade ≥ 3, 3%) and ICANS in 4.1% (grade ≥ 3, 1%). Any grade and grade 3 or higher hematological disorders, including cytopenias, were observed in 75.3% and 69.1% of patients, respectively, within eight weeks of infusion. Any-grade infections occurred in 18.6% of patients 8 weeks post infusion; 5.2% had grade ≥ 3 events. A total of seven patients died in the study: five due to progressive lymphoma, one due to CRS and another because of “general disorders and administration site conditions.” All deaths occurred > 30 days post infusion (Fowler et al., 2022).

Tisagenlecleucel (Kymriah®) is considered medically necessary for the treatment of relapsed or refractory follicular lymphoma following 2 or more lines of systemic therapy when the following criteria are met:

- Member is 18 years of age or older
- Member has been diagnosed with follicular lymphoma grade 1, 2 or 3A
- There is no evidence of histologic transformation
- Member has not received previous anti-CD19 therapy
- If member has had a prior allogeneic HSCT, the member does not currently have active GVHD
- Member has received or will receive a lymphodepleting chemotherapy regimen within two weeks preceding tisagenlecleucel infusion. Standard lymphodepleting chemotherapy regimens, as directed on the FDA label include:
  - Fludarabine 25 mg/m^2 intravenously daily for three days and cyclophosphamide 250 mg/m^2 intravenously daily for three days starting with the first dose of fludarabine **OR**
  - Alternate therapy with bendamustine 90 mg/m^2 intravenously daily for two days for those unable to receive cyclophosphamide due to a previous Grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide containing regimen **OR**
  - Lymphodepleting chemotherapy may be omitted if WBC is ≤ 1 x 10^9/L within one week prior to tisagenlecleucel infusion

Mantle Cell Lymphoma

Mantle cell lymphoma is a mature B-cell neoplasm typically composed of monomorphic small- to medium-sized lymphoid cells with irregular nuclear contours. There are several variants of mantle cell lymphoma, including blastoid, an aggressive variant where cells resemble lymphoblasts with dispersed chromatin and a high mitotic rate; pleomorphic, an aggressive variant where cells are pleomorphic, but many are large with oval to irregular nuclear contours, generally pale cytoplasm, and other prominent nucleoli in at least some of the cells; small-cell, distinguished by small round lymphocytes with more clumped chromatin, either admixed or predominant, mimicking a small lymphocytic lymphoma; and marginal zone-like in which there are prominent foci of cells with abundant pale cytoplasm resembling marginal zone or monocytoid B cells, mimicking a marginal zone lymphoma, sometime these paler foci also resemble proliferation centers of chronic lymphocytic leukemia/small lymphocytic lymphoma. Most patients present in stage III or IV. Spleen, bone marrow and liver are common metastatic sites. The median age of onset is 60 years and predominance is male. Mantle cell accounts for 3%–10% of all non-Hodgkin lymphomas. (NIH, National Cancer Institute, Surveillance, Epidemiology, and End Results Program, 2021).

Treatment

Brexucabtagene autoleucel (Tecartus®)

Wang et al. (2020) reported the results of ZUMA-2 (NCT02601212), a single-arm, open label, multicenter trial evaluating the safety and efficacy of a single infusion of brexucabtagene autoleucel (Tecartus) in adults with relapsed or refractory mantle cell lymphoma (MCL) who had previously received anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (BTKi; ibrutinib or acalabrutinib). Eligible patients also had disease progression after their last regimen or were refractory to their most recent treatment. BTKi therapy was not required to be the last line of therapy before trial entry and patients were not required to have disease that was refractory to BTKi therapy. ZUMA-2 excluded those with active or serious infections, prior allogeneic (HSCT), detectable cerebrospinal fluid malignant cells or brain metastasis, and any history of CNS lymphoma or CNS disorders. The primary endpoint was the percentage of patients with an objective response (complete or partial response). Secondary endpoints included DOR, PFS and OS.

A total of 74 patients were enrolled, and Tecartus was administered to 68. Of the 68 to receive a single infusion, 60 (88.23%) were considered efficacy-evaluable, having been followed for at least 6 months after their first objective response. Lymphodepleting therapy consisting of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously was administered to 53 (88%) of the 60 patients on the fifth, fourth and third days prior to Tecartus infusion. The remaining seven patients (12%) either received lymphodepletion over four or more days or received Tecartus four or more days after completing lymphodepletion. The primary efficacy analysis demonstrated 93% (95% CI, 84–98) of the 60 patients had an objective response; 67% (95% CI, 53–78) had a complete response. At a median follow-up of 12.3 months (range, 7.0–32.3), 57% of the 60 patients in the primary efficacy analysis were in remission. At 12 months, the estimated PFS was 61%, while OS was 83%. The most frequent adverse events of grade 3 or higher were cytopenias (in 94% of patients) and infections (32%). Grade 3 or higher CRS occurred in 15% and NEs occurred in 31%; none were fatal. Two patients experienced grade 5 infectious adverse events. Of the 60 evaluable patients, the median age was 65 years (range, 38–79) and 51 (85%) were male. 50 patients (83%) had stage IV disease. The median number of prior therapies was three (range, 2–5) and 26 (43%) of patients had relapsed following or were refractory to autologous HSCT. Twenty-one (35%) had relapsed after their last therapy for MCL, while 36 (60%) were refractory to their last therapy for MCL. Twenty-one (35%) received bridging therapy: 16 (27%) were treated with a BTKi, 9 (15%) with a corticosteroid, and 4 (7%) with both. Two patients who had disease progression following an objective response received a second infusion approximately one year and 1.3 years after the initial infusion. Analysis in these patients is ongoing.

NCCN Drugs and Biologics Compendium provides the following 2A recommendation concerning the use of Tecartus and Breyanzi as second-line and subsequent therapy for patients with relapsed/refractory mantle cell lymphoma after prior covalent BTKi if:

- No response or progressive disease following second-line therapy with covalent BTKi or other continuous treatment regimens i.e. lenalidomide and rituximab
- Partial response, no response, or progressive disease following second-line therapy with fixed-duration regimens
- Relapsed or progressive disease (relapse #2 or greater) if not previously given

Brexucabtagene autoleucel (Tecartus®) is considered medically necessary for second-line or subsequent treatment of relapsed or refractory mantle cell lymphoma when the following criteria are met:

- Member is 18 years of age or older
- Member has been treated with **ALL** of the following:
  - An anthracycline or bendamustine-containing chemotherapy
  - Anti-CD20 monoclonal antibody therapy (e.g., rituximab)
  - A Bruton tyrosine kinase (BTK) inhibitor indicated for mantle cell lymphoma (e.g., acalabrutinib, ibrutinib, zanubrutinib)
- Disease progression has occurred following the last regimen or disease is refractory to the most recent therapy
- Member has received or will receive adequate standard lymphodepleting chemotherapy or a therapeutically equivalent regimen before infusion of brexucabtagene autoleucel. (The traditional standard is a lymphodepleting chemotherapy regimen of cyclophosphamide 500mg/m^2 intravenously and fludarabine 30mg/m^2 intravenously on the fifth, fourth and third days prior to infusion).
- Member has not received prior treatment with CAR T-cell therapy
- If member has had a prior allogeneic HSCT, the member does not currently have active GVHD

Lisocabtagene maraleucel (Breyanzi®)

Wang et al. (2024) reported the primary analysis results from an open-label, multi-center, single-arm trial (TRANSCEND-MCL cohort; NCT02631044) in adult patients with relapsed or refractory MCL who had received at least two prior lines of therapy including a BTKi, an alkylating agent, and an anti-CD20 agent. Primary endpoints were AEs, dose-limiting toxicities, and ORR. Patients who had moderate renal and cardiac dysfunction, secondary CNS lymphoma, or received previous autologous or allogeneic HSCT were eligible. Of 104 leukapheresed patients, 88 were infused with Breyanzi. Median (range) number of previous lines of therapy were three (1-11) with 30% receiving ≥ 5 prior lines, 73% of patients were age 65 years and older, 69% had refractory disease, 57% had BTKi-refractory disease, 23% had *TP53* mutation, and 8% had secondary CNS lymphoma. In the efficacy set (n = 83), ORR was 83.1% (95% CI, 73.3 to 90.5) and CR rate was 72.3% (95% CI, 61.4 to 81.6). Median duration of response was 15.7 months (95% CI, 6.2 to 24.0) after a median follow-up of 22.8 months (95% CI, 16.7-23.0), median PFS was 15.3 months (95% CI, 6.6 to 24.9) after a median follow-up of 23.5 months (95% CI, 17.7-23.8) and median OS was 18.2 months (95% CI, 12.9-36.3) after a median follow up of 24.0 months (95% CI, 23.7-24.2). Seventy-six (86%) patients experienced grade ≥ 3 treatment-emergent AEs, most commonly neutropenia (56%), anemia (37%), and thrombocytopenia (25%). CRS was reported in 61% of patients, neurologic events in 31%, grade ≥ 3 infections in 15%, and prolonged cytopenia in 40%. Three (3%) patients had secondary primary malignancies of pancreatic cancer, basal cell carcinoma, and squamous cell carcinoma of the skin (n=1 each). A total of 46 deaths occurred in the Breyanzi-treated set. Most patients (n=29) died due to disease progression and seven died because of COVID-19. Four (5%) patients had grade 5 treatment-emergent AEs; three were considered related to Breyanzi (cryptococcal meningoencephalitis, lung infection [COVID-19 pneumonia], and tumor lysis syndrome), and one was considered unrelated to Breyanzi (cardiopulmonary arrest). Thirteen (15%) patients were treated in the outpatient setting; of those 12 were hospitalized for AEs after receiving Breyanzi. Median time from infusion to initial hospitalization was 4 days (range, 2-10) and median duration of initial hospitalization was 6.5 days (range, 2-43). One patient was admitted to

the ICU. For the 75 patients treated in the inpatient setting, median duration of hospitalization from infusion was 11 days (range, 2-31). Five patients were admitted to the ICU. TRANSCEND-MCL included seven patients with secondary CNS lymphoma. Among these patients, response rates (ORR, 85.7%; CR rate, 85.7%) were comparable with the overall population. While expanding knowledge about CAR T-cell therapy and the clinical landscape of R/R MCL, this study was limited by single-arm design and small sample size which precluded definitive conclusions in some subgroups, including patients with secondary CNS lymphoma. Additionally, efficacy results may have been influenced by the inclusion of patients with high-risk features including a wide range of previous therapies and those with *TP53* mutations.

Lisocabtagene maraleucel (Breyanzi®) is considered medically necessary for the treatment of relapsed or refractory mantle cell lymphoma when the following criteria are met:

- Member is 18 years of age or older
- Member has been treated with a BTKi indicated for mantle cell lymphoma (e.g., acalabrutinib, ibrutinib, zanubrutinib)
- Disease progression has occurred following the last regimen or disease is refractory to the most recent therapy
- Member has not received prior treatment with CAR T-cell therapy
- Member will receive lymphodepleting chemotherapy regimen before infusion of lisocabtagene maraleucel: fludarabine 30 mg/m^2/day IV and cyclophosphamide 300 mg/m^2/day IV for 3 days.
- If member has had a prior allogeneic HSCT, the member does not currently have active GVHD

Non-Covered Indications

In the absence of published evidence Optum considers second infusions of CAR T- cell therapy for relapsed and refractory disease unproven regardless of product or indication. At the current time there is a lack of adequate published evidence demonstrating efficacy.

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Appendix: NCCN Categories of Evidence and Consensus

- **Category 1**: The recommendation is based on high-level evidence (i.e., high-powered randomized clinical trials or meta-analyses), and the panel has reached uniform consensus that the recommendation is indicated. In this context, uniform means near unanimous positive support with some possible neutral positions.
- **Category 2A**: The recommendation is based on lower level evidence, but despite the absence of higher level studies, there is uniform consensus that the recommendation is appropriate. Lower level evidence is interpreted broadly and runs the gamut from phase II to large cohort studies to case series to individual practitioner experience. Importantly, in many instances, the retrospective studies are derived from clinical experience of treating large numbers of patients at a member institution, so panel members have first-hand knowledge of the data. Inevitably, some recommendations must address clinical situations for which limited or no data exist. In these instances the congruence of experience-based opinions provides an informed if not confirmed direction for optimizing patient care. These recommendations carry the implicit recognition that they may be superseded as higher level evidence becomes available or as outcomes-based information becomes more prevalent.
- **Category 2B**: The recommendation is based on lower level evidence, and there is nonuniform consensus that the recommendation should be made. In these instances, because the evidence is not conclusive, institutions take different approaches to the management of a particular clinical scenario. This nonuniform consensus does not represent a major disagreement, rather it recognizes that given imperfect information, institutions may adopt different approaches. A Category 2B designation should signal to the user that more than one approach can be inferred from the existing data.
- **Category 3**: The recommendation has engendered a major disagreement among the panel members. Several circumstances can cause major disagreements. For example, if substantial data exists about two interventions but they have never been directly compared in a randomized trial, adherents to one set of data may not accept the interpretation of the other side's results. Another situation resulting in a Category 3 designation is when experts disagree about how trial data can be generalized. A Category 3 designation alerts users to a major interpretation issue in the data and directs them to the manuscript for an explanation of the controversy.

Source: National Comprehensive Cancer Network (NCCN). Available at: Development and Update of Guidelines (nccn.org)

Review and Approval History

Version	Date and Description
1.0	**06/15/2020**: New guideline developed. Reviewed by Optum Hematopoietic Stem Cell Transplant Expert Panel. Effective date: 9/1/2020.
1.0	**08/06/2020**: Reviewed and approved by Medical Technology Assessment Committee.
1.0	**8/11/2020**: National Medical Care Management Committee advised of annual review.
1.0	**3/4/2021**: Update adding new product, lisocabtagene maraleucel (Breyanzi) to the guideline. Reviewed and approved by Medical Technology Advisory Committee.
2.0	**6/15/2021**: Annual review. Guideline reformatted and updated with literature review and the addition of idecabtagene vicleucel (Abecma) and the follicular lymphoma indication for axicabtagene ciloleucel (Yescarta). Reviewed by Optum Hematopoietic Stem Cell Transplant Expert Panel.
2.0	**7/8/2021**: Reviewed and approved by Medical Technology Assessment Committee.
2.0	**12/2/2021**: Interim update to add ALL in adults as a new indication for brexucabtagene autoleucel (Tecartus). New Non-covered Indications section added. Reviewed and approved by Medical Technology Assessment Committee.
2.0	**4/7/2022**: Interim update to add ciltacabtagene autoleucel as a new FDA-approved treatment for adults with relapsed/refractory multiple myeloma. Reviewed and approved by Medical Technology Assessment Committee.
2.0	**5/5/22**: Interim update to add second-line treatment of large B-cell lymphoma refractory to or relapsed within 12 months of first-line chemoimmunotherapy in adults as a new indication for axicabtagene ciloleucel (Yescarta). Reviewed and approved by Medical Technology Assessment Committee.
3.0	**6/29/2022**: Annual review with Optum Hematopoietic Stem Cell Transplant Expert Panel. Literature updated. New indications added: Tisagenlecleucel (Kymriah) as third-line or subsequent treatment for adults relapsed or refractory follicular lymphoma, and lisocabtagene maraleucel (Breyanzi) as second-line therapy for adults with relapsed or refractory LBCL within 12 months of first-line treatment and relapsed or refractory LBCL in adults not eligible for HSCT.
3.0	**8/4/2022:** Annual review. Approved by Medical Technology Assessment Committee
3.0	**8/8/2022**: National Medical Care Management Committee advised of annual update
3.0	**4/12/2023**: Interim updates to relapsed/refractory B-cell lymphoma indications, follicular lymphoma indications, acute lymphoblastic leukemia indications, and guideline reformatting for readability. Approved by Optum Clinical Guideline Advisory Committee.
3.0	**5/4/2023:** Interim updates approved by Medical Technology Assessment Committee
4.0	**7/12/2023:** Annual review with Optum Hematopoietic Stem Cell Transplant, CAR T-cell Therapy, and Gene Therapy Expert Panel
4.0	**7/31/2023:** Approved by Optum Clinical Guideline Advisory Committee
4.0	**8/19/2023:** Approved by P&T Committee
4.0	**9/7/2023:** Approved by Medical Technology Assessment Committee

4.0	**12/13/2023:** Interim update to include extranodal marginal zone lymphoma of the stomach, extranodal marginal zone lymphoma of nongastric sites (noncutaneous), and nodal marginal zone as indications for adults w/ relapsed/refractory B-cell lymphoma being treated with Yescarta; and. HIV-related B-cell lymphoma and post-transplant lymphoproliferative disorders in adults with B-cell lymphoma being treated with Breyanzi. Approved by Optum Clinical Guideline Advisory Committee.
4.0	**1/4/2024:** Interim update to include extranodal marginal zone lymphoma of the stomach, extranodal marginal zone lymphoma of nongastric sites (noncutaneous), and nodal marginal zone as indications for adults w/ relapsed/refractory B-cell lymphoma being treated with Yescarta; and. HIV-related B-cell lymphoma and post-transplant lymphoproliferative disorders in adults with B-cell lymphoma being treated with Breyanzi. Approved by Medical Technology Advisory Committee
4.0	**1/17/2024:** Interim update to include extranodal marginal zone lymphoma of the stomach, extranodal marginal zone lymphoma of nongastric sites (noncutaneous), and nodal marginal zone as indications for adults w/ relapsed/refractory B-cell lymphoma being treated with Yescarta; and. HIV-related B-cell lymphoma and post-transplant lymphoproliferative disorders in adults with B-cell lymphoma being treated with Breyanzi. Approved by Pharmacy and Therapeutics (P&T) Committee
4.0	**04/09/2024**: Interim update to add relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) as new indications for Breyanzi. Approved by Optum Clinical Guideline Advisory Committee.
4.0	**04/17/2024**: Interim update to add relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) as new indications for Breyanzi. Approval by Pharmacy & Therapeutics Committee.
4.0	**05/02/2024**: Interim update to add relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) as new indications for Breyanzi. Approval by Medical Technology Advisory Committee.
4.0	**05/08/2024:** Interim update to revise position of Abecma and Carvykti in the treatment algorithm for relapsed/refractory multiple myeloma. Approved by Optum Clinical Guideline Advisory Committee.
4.0	**05/15/2024:** Interim update to revise position of Abecma and Carvykti in the treatment algorithm for relapsed/refractory multiple myeloma. Approved by Pharmacy and Therapeutics Committee.
4.0	**06/06/2024:** Interim update to revise position of Abecma and Carvykti in the treatment algorithm for relapsed/refractory multiple myeloma. Approved by Medical Technology and Assessment Committee.
5.0	**8/28/2024:** Annual review by Optum Expert Panel. Guideline updated to add follicular lymphoma and mantle cell lymphoma as new indications for Breyanzi.
5.0	**9/9/2024:** Approved by Optum Clinical Guideline Advisory Committee.
5.0	**9/18/2024:** Approved by Pharmacy and Therapeutics Committee
5.0	**10/03/2024:** Approved by Medical Technology Assessment Committee
5.0	**12/11/2024:** Interim updates: • Added new FDA-approved obecabtagene autoleucel (Aucatzyl®) as a treatment for relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) in adults. • Updated medical necessity criteria for brexucabtagene autoleucel (Tecartus®) Approved by Optum Clinical Guideline Advisory Committee.
5.0	**12/18/2024:** Interim updates: • Added new FDA-approved obecabtagene autoleucel (Aucatzyl®) as a treatment for relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) in adults.

	• Updated medical necessity criteria for brexucabtagene autoleucel (Tecartus®) Approved by Pharmacy and Therapeutics Committee.
5.0	**01/09/2025:** Interim updates: • Added new FDA-approved obecabtagene autoleucel (Aucatzyl®) as a treatment for relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) in adults. • Updated medical necessity criteria for brexucabtagene autoleucel (Tecartus®) Approved by Medical Technology Assessment Committee.
6.0	**05/21/2025:** Annual review with Optum Expert Panel. No substantive changes.
6.0	**06/11/2025:** Annual review. No substantive changes. Approved by Optum Clinical Guideline Advisory Committee.
6.0	**07/10/2025:** Annual review. Removed requirement for participation in REMS from medical necessity criteria for all CAR T agents consistent with recent FDA determination. Approved by Medical Technology Assessment Committee.
6.0	**07/16/2025:** Annual review. Removed requirement for participation in REMS from medical necessity criteria for all CAR T agents consistent with recent FDA determination. Approved by Pharmacy and Therapeutics Committee.