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Subject: Chimeric Antigen Receptor (CAR) T-Cell Therapies

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Axicabtagene Ciloleucel (Yescarta)

Axicabtagene ciloleucel (Yescarta) is a CD19-directed, genetically-modified autologous T cell immunotherapy that was first approved by the U.S. Food and Drug Administration (FDA) in October 2017 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. In March 2021, the FDA approved a new indication for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This was an accelerated approval based on response rate, and continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). In April 2022, an additional large B-cell lymphoma indication was approved by the FDA. The new indication is for the treatment of adult patients with large B-cell lymphoma that is refractory to first line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. Axicabtagene ciloleucel was previously granted orphan designation by the FDA, as sponsored by the innovator drug company, for the treatment of DLBCL in March 2014, for the treatment of primary mediastinal B-cell lymphoma in April 2016, and for the treatment of follicular lymphoma in April 2016. Other orphan indications, as sponsored by the innovator drug company, include the treatment of nodal and extranodal marginal zone lymphoma (March 2020). Axicabtagene ciloleucel works by reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal B cells. Treatment involves removing, genetically modifying, and then re-infusing a patient's own T-cells. Axicabtagene ciloleucel was the second CAR T-cell therapy to be approved by the FDA. The first CAR T-cell therapy was tisagenlecleucel

(Kymriah) approved by the FDA in August 2017 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.

Diffuse large B-cell lymphomas are the most common lymphoid neoplasms in adults, and account for approximately 30% of non-Hodgkin's lymphomas (NHLs) cases diagnosed annually. The DLBCLs exhibits large heterogeneity in morphologic, genetic, and clinical aspects. Multiple clinicopathologic entities are defined by the 2022 World Health Organization (WHO) classification, which are sufficiently distinct to be considered separate diagnostic categories. Adequate immunophenotyping is essential to establish the diagnosis, and to determine germinal center B-cell like (GCB) vs. non-GBC origin. Combination chemoimmunotherapy in the first-line setting (e.g., rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) is associated with a 5-year survival rate ranging from 60% to 70%. Interim restaging should be performed to identify patients who disease has not responded to or has progressed on induction therapy. Based on a number of prognostic factors, 20% to 50% of DLBCL cases are refractory or relapse after first-line chemotherapy and the response rates to subsequent salvage chemotherapy and consolidation with autologous hematopoietic stem cell transplantation (HSCT) is suboptimal.

The National Comprehensive Cancer Network (NCCN) B-cell Lymphoma Guidelines list axicabtagene ciloleucel as a category 2A recommendation for the treatment of relapsed/refractory DLBLC, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma [with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma), or not otherwise specified (NOS)], HIV-related DLBCL, primary effusion lymphoma, HHV8-positive DLBCL, NOS, and monomorphic post-transplant lymphoproliferative disorders (PTLD) (B-cell type) for patients with two or more disease relapses (if not previously given), or for patients with a non-complete response (i.e., partial response or worse) to second-line therapy. Axicabtagene ciloleucel is a category 1 recommendation for these same large B-cell lymphomas when used as second-line therapy for patients with primary refractory disease (partial response, no response, or progression) or relapsed disease less than 12 months after completion of first-line therapy. Lisocabtagene maraleucel (Breyanzi) is also listed along with axicabtagene ciloleucel for this same use as a category 1recommendation. Axicabtagene ciloleucel is also a 2A recommendation for the treatment of follicular lymphoma with histological transformation to DLBCL and nodal marginal zone lymphoma with histological transformation to DLBCL in patients with 2 or more prior chemoimmunotherapy regimens (with at least one being an anthracycline or anthracenedione-based regimen, unless contraindicated). The guidelines also list axicabtagene ciloleucel as a category 2A recommendation for the third-line and subsequent therapy of classic follicular lymphoma. It is listed as a "Preferred regimen" under the subcategory of CAR T-cell therapy which also includes the other CAR-T cell therapies approved for FL of lisocabtagene maraleucel (Breyanzi) and tisagenlecleucel (Kymriah). The NCCN also includes axicabtagene ciloleucel as a category 2A recommendation for the third line and subsequent treatment of marginal zone lymphomas (i.e., extranodal marginal zone lymphoma of the stomach or non-gastric sites (noncutaneous), and nodal and splenic marginal zone lymphomas). The NCCN guidelines for Pediatric Aggressive Mature B-Cell Lymphomas include axicabtagene ciloleucel as a preferred category 2A recommendation for consolidation/additional therapy for pediatric primary mediastinal large B-cell lymphoma if partial response achieved after therapy for relapsed or refractory disease (after use of ≥ 2 prior chemoimmunotherapy regimens).

The safety and efficacy of axicabtagene ciloleucel leading to FDA approval for primary refractory large B-cell lymphoma or first relapse within 12 months was based on the results of a randomized, open-label,

multicenter trial called ZUMA-7 (NCT03391466). This trial enrolled adult patients with relapsed or refractory LBCL after first-line chemoimmunotherapy that included rituximab and anthracycline. Patients had not yet received treatment for relapsed or refractory lymphoma and were potential candidates for autologous HSCT. Patients were required to have primary refractory disease or relapse within 12 months following completion of first-line therapy. The study excluded patients with primary mediastinal B-cell lymphoma, any history of CNS lymphoma, need for urgent therapy due to tumor mass effect, active or serious infections, and ECOG performance status of 2 or greater. In total, 359 patients were randomized in a 1:1 ratio to receive a single infusion of axicabtagene ciloleucel or to receive second-line standard therapy, consisting of 2 or 3 cycles of chemoimmunotherapy followed by high-dose therapy and autologous HSCT in patients who attained CR or PR. Following lymphodepleting chemotherapy, axicabtagene ciloleucel was administered as a single IV infusion at a target dose of $2x10^6$ CAR-positive viable T cells/kg (maximum permitted dose: $2x10^8$ cells). The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m^2 IV and fludarabine 30 mg/m^2 IV, both given on the fifth, fourth, and third day before axicabtagene ciloleucel. All patients who received axicabtagene ciloleucel were monitored at a healthcare facility for a minimum of 7 days. Bridging therapy, administered between leukapheresis and lymphodepleting chemotherapy, was limited to corticosteroids and was permitted for patients with high disease burden. In the overall study population, the median age was 59 years (range: 21 to 81 years), 66% were male and 83% were white. The diagnoses included de novo DLBCL NOS (63%), HGBL with or without MYC and BCL-2 and/or BCL-6 rearrangements (19%), and large cell transformation of follicular lymphoma (13%). In total, 74% of patients had primary refractory LBCL, and 26% had relapsed disease within 12 months of first-line therapy. 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, primarily due to progressive disease, serious adverse events, or death. The median time from leukapheresis to product delivery was 18 days (range: 13 to 49 days), and from leukapheresis to axicabtagene ciloleucel infusion was 26 days (range: 16 to 52 days). The median dose was $2x10^6$ CAR-positive viable T cells/kg (range: 1 to $2.1x10^6$ cells/kg). Of the 179 patients randomized to receive standard therapy, 168 patients received any study treatment, and 62 (35%) received high-dose therapy and on-protocol HSCT. The most common reason for not receiving HSCT was lack of response to salvage chemotherapy. The primary efficacy measure was event-free survival (EFS) as determined by an independent review committee. Efficacy is summarized in Table 1. The primary efficacy measure was event-free survival (EFS) as determined by an independent review committee. EFS is defined as time from randomization to the earliest date of disease progression or relapse, best response of stable disease up to and including the Day 150 assessment, commencement of new lymphoma therapy, or death from any cause. The estimated EFS rate at 18 months was 41.5% [95% CI: 34.2, 48.6] in the axicabtagene ciloleucel arm and 17.0% [95% CI: 11.8, 23.0] in the standard therapy arm. In the axicabtagene ciloleucel arm, the estimated median DOR was 28.4 months (95% CI: 26.9, NE) in patients who achieved CR and 1.6 months (95% CI: 1.4, 1.9) in patients who achieved a best response of PR. An interim analysis of overall survival was conducted at the time of the primary EFS analysis. The interim analysis of overall survival has not met the criteria for statistical significance. Fifty-five percent of patients randomized to the standard therapy arm subsequently received CD19-directed CAR T therapy off protocol.

Table 1: Results of ZUMA-7 as Assessed by the Independent Review Committee

Outcome	Yescarta (n=180)	Standard Therapy (n = 179)
Event-Free Survival		
Number of events, n (%)	108 (60)	144 (80)
Median, months [95% CI]	8.3 [4.5, 15.8]	2.0 [1.6, 2.8]
Stratified hazard ratio [95% CI]	0.40 [0.31, 0.51]	
Stratified log-rank p-value	<0.0001	
Best Objective Response Rate, % [95% CI]	83 [77, 88]	50 [43, 58]
Difference in ORR, % [95% CI]	33 [23, 42]	
Stratified p-valued	<0.0001	
Complete remission rate, % [95% CI]	65 [58, 72]	32 [26, 40]
Partial remission rate, % [95% CI]	18 [13, 25]	18 [13, 24]
Progression-Free Survival		
Number of events, n (%)	93 (52)	81 (45)
Median, months [95% CI]	14.9 [7.2, NE]	5.0 [3.4, 8.5]
Stratified hazard ratio [95% CI]	0.56 [0.41, 0.76	
CI: confidence interval; NE: not estimable		

The safety and efficacy of axicabtagene ciloleucel leading to FDA approval for relapsed or refractory large B-cell lymphoma after at least two prior treatments was based on the results of a single-arm, open-label, multicenter phase 1/2 study called ZUMA-1, which reported complete remission (CR) rates and duration of response demonstrated in the phase 2 portion of the study. Adults (≥18 years of age) with aggressive B-cell NHL (which included DLBCL, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma according to the 2008 WHO classification system) that was primary refractory, refractory to a second or greater line of therapy, or relapsed within 1 year after autologous hematopoietic stem cell transplantation (HSCT) were enrolled in the study. The study excluded patients with prior allogeneic HSCT, any history of CNS lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/µL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection. Of the patients treated, the median age was 58 years (range: 23 to 76), 67% were male, and 89% were white. Most (76%) had DLBCL, 16% had transformed follicular lymphoma, and 8% had primary mediastinal large B-cell lymphoma. The median number of prior therapies was 3 (range: 1 to 10), 77% of the patients had refractory disease to a second or greater line of therapy, and 21% had relapsed within 1 year of autologous HSCT. Only two patients received axicabtagene ciloleucel after failure of one prior line of therapy. All patients received a lymphodepleting regimen of cyclophosphamide and fludarabine prior to infusion of axicabtagene ciloleucel. Of the 111 patients who underwent leukapheresis, 101 received the infusion (9 were not treated due to progressive disease or serious adverse reactions following leukapheresis and there was a manufacturing failure in 1 patient). Study protocol mandated hospitalization of patients for infusion and 7 days after infusion. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. The median time from leukapheresis to product delivery was 17 days (range, 14 to 51 days). The primary end point is objective response rate (ORR) as assessed by an independent review committee (IRC) according to the International Working Group (IWG) Response Criteria for Malignant Lymphoma (see “Other” section) based on a modified intention-to-treat population of all patients who has received axicabtagene ciloleucel. The main secondary endpoint is the duration of response (DOR) that was censored for HSCT

in remission. The median follow up for DOR was 7.9 months. Results are summarized in Table 2. The evaluation of DOR remains limited by the large amount of censoring before 6 months.

Table 2: Results of ZUMA-1 as Assessed by the Independent Review Committee

Outcome	Results, n (%) (95% Confidence Interval)
Primary end point (n=101)	
Objective response rate (CR + PR)	73 (72%) (62 to 81%)
CR	52 (51%) (41 to 62%)
PR	21 (21%) (13 to 30%)
SD	19 (19%)
PD	7 (7%)
Not evaluable	2 (2%)
Secondary end points	
Median duration of response (n=73)	
All patients	9.2 months (5.4 to NE)
CR only	NE (8.1 to NE)
PR only	2.1 months (1.3 to 5.3)
CR: complete response; NE: not estimable; PD: progressive disease; PR: partial response; SD: stable disease	

Safety data assessed 108 patients treated with axicabtagene ciloleucel. Adverse events of special interest are summarized in Table 3. All patients experienced at least one adverse event following infusion and 94% (n=102) experienced grade 3 or higher events. Serious adverse events were observed in 56 (52%) of patients, and serious adverse events that were grade 3 or higher occurred in 48 (44%) patients. Overall, 34 deaths were reported from the time of informed consent to the trial data cutoff (January 27, 2017). Thirty patients died of progressive disease and 4 deaths were attributed to axicabtagene ciloleucel as per FDA analysis, of which 3 occurred within 30 days of infusion. The median time to onset for cytokine release syndrome (CRS) was 2 days (range, 1 to 12 days), and the median time to resolution was 7 days (range for CRS duration, 2 to 58 days). Forty-five percent (49/108) of patients received tocilizumab for CRS management. The median time to onset of neurologic toxicity was 4 days (range, 1 to 43 days). The median duration was 17 days. The most common neurologic toxicities included encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, and anxiety. Ninety-eight percent (98%) of all neurologic toxicities occurred within first 8 weeks of axicabtagene ciloleucel infusion.

Table 3: Summary of Key Serious Adverse Events in ZUMA-1 (n=108)

Adverse Event	All Grades, n (%)	Grades ≥3, n (%)
Cytokine release syndrome	101 (94%)	14 (13%)
Encephalopathy	62 (57%)	31 (29%)
Serious infections	41 (38%)	25 (23%)
Febrile neutropenia	39 (36%)	35 (32%)
Prolonged cytopenia not resolved by day 30	--	30 (28%)
Hypogammaglobulinemia	16 (15%)	0

The safety and efficacy of axicabtagene ciloleucel leading to FDA approval for FL is based on a single-arm, open-label, multicenter trial (ZUMA-5; NCT03105336) that evaluated adult patients with relapsed or refractory FL after two of more lines of systemic therapy, including the combination of an anti-CD20

monoclonal antibody and an alkylating agent. The study excluded patients with active or serious infections, transformed lymphoma or other aggressive lymphomas, prior allogeneic HSCT, or any history of CNS lymphoma or CNS disorders. Following lymphodepleting chemotherapy with cyclophosphamide and fludarabine, axicabtagene ciloleucel was administered as a single IV infusion with a target of 2×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose of 2×10^8 cells). Of 123 patients who underwent leukapheresis, 120 received treatment. Of the remaining three patients (2%) who were not treated, one was ineligible due to thrombocytopenia, one went into remission prior to initiating lymphodepletion, and one died of cardiac arrest. There were no manufacturing failures. Of the 120 patients infused, the 81 consecutive patients included in the primary efficacy analysis had at least 9 months of potential follow-up from date of first response. Among these 81 patients, the median age was 62 years (range: 34 to 79), 46% were female, and 93% were white The he median number of prior systemic therapies was 3 (range: 2 to 9), with 32% having 2 prior lines, 22% having 3 prior lines, and 46% having ≥ 4 prior lines. Thirty-one percent had received a PI3K inhibitor, 72% had progression within 6 months of the most recent regimen, and 56% had progression within 24 months of initiating their first anti-CD20 combination therapy. One patient in the primary efficacy analysis received bridging therapy. The median time from leukapheresis to product delivery was 17 days (range: 13 to 33 days) and leukapheresis to product infusion was 27 days (range: 19 to 250 days). The median dose was 2.0×10^6 CAR T cells/kg (range 1.3 to 2.1×10^6 CAR T cells/kg). All treated patients were hospitalized until at least day 7 after infusion. Efficacy was established on the basis of objective response rate and DOR as determined by an independent review committee. The median time to response in the primary efficacy population was 1 month (range: 0.8 – 3.1 months). The median follow-up for time for DOR was 14.5 months.

Table 4: Results of ZUMA-5 as Assessed by the Independent Review Committee

Outcome	Results, n (%) (95% Confidence Interval)
Primary end point (n=81)	
Objective response rate (CR + PR)	74 (91%) (83 to 96%)
CR	49 (60%) (49 to 71%)
PR	25 (31%) (21 to 42%)
Secondary end points (n=74)	
Median duration of response	NE (20.8 months to NE)
Rate of Continued Remission At 12 months (95% CI)	76.2 (63.9 to 84.7%)
Rate of Continued Remission At 24 months (95% CI)	74.2% (61.5 to 83.2%)
CR: complete response; NE: not estimable; PR: partial response	

Safety data from ZUMA-5 included 146 patients with relapsed or refractory indolent NHL (124 patients with FL and 22 with marginal zone lymphoma). The most common non-laboratory adverse reactions (incidence ≥ 20%) included fever, CRS, hypotension, encephalopathy, fatigue, headache, infections with pathogen unspecified, tachycardia, febrile neutropenia, musculoskeletal pain, nausea, tremor, chills, diarrhea, constipation, decreased appetite, cough, vomiting, hypoxia, arrhythmia, and dizziness. Serious adverse reactions occurred in 48% of patients. Serious adverse reactions in >2% of patients included febrile neutropenia, encephalopathy, fever, CRS, infections with pathogen unspecified, pneumonia, hypoxia and hypotension. The most common (≥10%) Grade 3 or higher reactions included febrile neutropenia, encephalopathy, and infections with pathogen unspecified. Fatal adverse reactions occurred in 1% of patients and included CRS and fungal infection. Fifty-one percent (75/146) of patients received tocilizumab after infusion of axicabtagene ciloleucel infusion.

Table 5: Summary of Key Serious Adverse Events in ZUMA-5 (n=146)

Adverse Event	All Grades	Grades ≥3
Cytokine release syndrome	84%	8%
Encephalopathy	49%	16%
Infections with pathogen unspecified	45%	14%
Febrile neutropenia	41%	41%
Hypogammaglobulinemia	18%	0

Brexucabtagene Autoleucel (Tecartus)

Brexucabtagene autoleucel (Tecartus) is a CD19-directed, genetically modified, autologous T-cell immunotherapy that was first approved by the U.S. FDA in July 2020 for "the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL)". Brexucabtagene autoleucel is the third chimeric antigen receptor (CAR) T-cell therapy to be approved by the FDA, but it is the first CAR-T cell therapy to be approved for MCL. In October 2021, the FDA approved a new indication for "the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)". Tisagenlecleucel (Kymriah) is the only other CAR-T cell therapy approved for ALL; however, tisagenlecleucel is only approved for patients up to 25 years of age. Brexucabtagene autoleucel was previously granted orphan designation by the FDA, as sponsored by the innovator drug company, for the treatment of MCL in April 2016 and for the treatment of ALL in April 2016. Brexucabtagene autoleucel, and other CAR T-cell therapies, work by reprogramming a patient's own T cells with a transgene encoding a CAR to identify and eliminate CD19-expressing malignant and normal B cells. The CAR is comprised of a murine anti-CD19 single chain variable fragment linked to CD28 and CD3-zeta co-stimulatory domains. Upon binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the brexucabtagene autoleucel cells. Treatment involves removing, genetically modifying (for brexucabtagene autoleucel specifically, with a replication-incompetent retroviral vector), and then re-infusing the patient's own T-cells.

Mantle cell lymphoma is a subtype of non-Hodgkin lymphoma (NHL) that accounts for about 3 to 4% of all NHL cases. The incidence in the US and Europe is estimated to be 4 to 8 cases per million persons per year. MCL is thought to possess the worst characteristics of both indolent and aggressive NHL subtypes owing to the incurability of disease with conventional chemotherapies and a more aggressive disease course. Therapy for MCL is not curative, and, therefore, the disease will eventually relapse or stop responding to treatment. Treatment of MCL is dependent on the extent of disease (clinical stage), if the disease is more aggressive or indolent, and if the patient is a candidate for stem cell transplantation. Most patients with aggressive disease will require combination induction chemotherapy with rituximab followed by rituximab maintenance therapy (for patients that achieved a complete response). Aggressive therapy also involves consolidation with high-dose therapy followed by autologous stem cell rescue (i.e., autologous stem cell transplant) after induction therapy. Second-line agents are used when a complete response cannot be achieved with first-line induction or in patients with disease relapse. An allogeneic stem cell transplant can be considered as second-line consolidation therapy. The National Comprehensive Cancer Network (NCCN) Guidelines for B-cell Lymphomas state that the optimal approach for relapsed or refractory MCL remains to be defined and lists various second-line treatment options. In general, the NCCN guidelines state that the duration of response to prior chemoimmunotherapy is an important factor in the selection of second-line therapy. Treatment

regimens containing small-molecule inhibitors [i.e., Bruton Tyrosine Kinase inhibitors (BTKi) or venetoclax (Venclexta)] or lenalidomide (with or without rituximab) should be considered for patients with early relapse, whereas alternate non-cross-resistant chemoimmunotherapy regimens (not previously given) would be more appropriate for patients with late relapse. The NCCN Guidelines for B-cell lymphomas list brexucabtagene autoleucel (category 2A recommendation) as Second-Line and Subsequent Therapy under "Useful in Certain Circumstances" and under the subcategory of "Progressive disease after prior covalent BTKi". Lisocabtagene maraleucel (Breyanzi) and pirtobrutinib (Jayprica) are also listed in this same section.

Acute lymphoblastic leukemia (ALL) is heterogenous hematological disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. The median age of diagnosis is 17 years with 53.5% of patients diagnosed at younger than 20 years of age. In contrast, 29.6% of cases are diagnosed at 45 years or older and only 13.7% are diagnosed at 65 years or older. ALL represents about 20% of all leukemias among adults. ALL is broadly classified in 3 groups based on immunophenotype, which include precursor B-cell ALL, mature B-cell ALL (a.k.a., Burkitt leukemia/lymphoma), and T-cell ALL. In children, B-cell lineage ALL constitutes about 88% of cases and in adults B-cell lineage ALL is about 75% of cases (with mature B-cell only constituting 5%). Cure rates and survival outcomes have improved over the past several decades due to advances in understanding molecular genetics and pathogenesis of the disease, incorporation of risk-adapted therapy, and advent of new targeted agents. The 5-year overall survival (OS) rate for children and adolescent and young adults (AYA, 15 to 39 years of age) is 89% and 61% respectively; however, remains low at 20 to 40% in adults and is especially poor in older adults at 20%. The treatment of ALL represents one of the most complex and intensive programs in cancer therapy. Treatment varies depending on subtype, age, and treatment history. In general, the treatment phases can be largely grouped into induction, consolidation, and maintenance. The National Comprehensive Cancer Network (NCCN) guidelines for ALL list single-agent brexucabtagene autoleucel among the "Other Recommended Regimens" (as a category 2A recommendation) for relapsed/refractory BCR::ABL1-positive (Ph+) B-ALL (following therapy that has included TKIs) in AYA and adults, and among the "Preferred Regimens" (as a category 2A recommendation) for relapsed/refractory Ph- B-ALL in AYA and adults.

The safety and efficacy of brexucabtagene autoleucel leading to FDA-approval for MCL was assessed in a single-arm, open-label, multicenter trial (ZUMA-2; NCT02601313). A single infusion of brexucabtagene autoleucel was given to adult patients with relapsed or refractory MCL who had previously received anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTK inhibitor (BTKi; ibrutinib or acalabrutinib). Eligible patients also had disease progression after their last regimen or refractory disease to their most recent therapy. The study excluded patients with active or serious infections, prior allogeneic hematopoietic stem cell transplant (HSCT), detectable cerebrospinal fluid malignant cells or brain metastases, and any history of central nervous system (CNS) lymphoma or CNS disorders. A total of 74 patients were leukapheresed, five (7%) of whom did not begin conditioning chemotherapy or receive brexucabtagene autoleucel: three experienced manufacturing failure, one died of progressive disease, and one withdrew from the study. One patient received lymphodepleting chemotherapy but did not receive brexucabtagene autoleucel due to ongoing active atrial fibrillation. Sixty-eight of the patients who were leukapheresed received a single infusion of brexucabtagene autoleucel, and 60 of these patients were followed for at least six months after their first objective disease response, qualifying them as efficacy evaluable. Among the 60 efficacy-evaluable patients,

2×106 CAR-positive viable T cells/kg were administered to 54 (90%). The remaining six (10%) patients received doses of 1.0, 1.6, 1.8, 1.8, 1.9, and 1.9×10^6 CAR-positive viable T cells/kg. Of the 60 patients, the median age was 65 years (range: 38 to 79 years), 51 (85%) were male, and 56 (93%) were white. Most (50 patients; 83%) had stage IV disease. The median number of prior therapies among all 60 efficacy-evaluable patients was three (range: two to five). Twenty-six (43%) of the patients had relapsed after 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. Following leukapheresis and prior to administration of brexucabtagene autoleucel, 21 (35%) of the 60 patients received bridging therapy. Sixteen (27%) were treated with a BTKi, 9 (15%) with a corticosteroid, and 4 (7%) with both a BTKi and a corticosteroid.

Among the 60 patients, the median time from leukapheresis to product delivery was 15 days (range: 11 to 28 days), and the median time from leukapheresis to product infusion was 27 days (range: 19 to 63 days). The protocol-defined lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m2 intravenously and fludarabine 30 mg/m2 intravenously, both given on each of the fifth, fourth, and third days before brexucabtagene autoleucel infusion, was administered to 53 (88%) of the 60 patients. The remaining seven patients either received lymphodepletion over four or more days or received brexucabtagene autoleucel four or more days after completing lymphodepletion. All treated patients received brexucabtagene autoleucel infusion on Day 0 and were hospitalized until at least Day 7. The primary endpoint was objective response rate (ORR), the combined rate of complete responses and partial responses, per the Lugano Classification (2014) as determined by an independent review committee. The result, as reported in the product labeling, are provided in Table 6 below. The median time to response was 28 days (range: 24 to 92 days) with a median follow-up time for duration of response (DOR) of 8.6 months. Among patients evaluable for safety (n=82), 18% experienced Grade 3 or higher cytokine release syndrome (CRS), and 37% experienced Grade 3 or higher neurologic toxicities. The most common (≥10%) Grade 3 or higher adverse reactions were anemia, neutropenia, thrombocytopenia, hypotension, hypophosphatemia, encephalopathy, leukopenia, hypoxia, pyrexia, hyponatremia, hypertension, infection-pathogen unspecified, pneumonia, hypocalcemia and lymphopenia.

Table 6: ZUMA-2 Trial Results

	Efficacy-Evaluable Patients (n=60)	**All Leukapheresed Patients (ITT) (n=74)**
Response Rate		
Objective Response Rate, n (%) [95% CI]	52 (87%) [75, 94]	59 (80%) [69, 88]
Complete Remission Rate, n (%) [95% CI]	37 (62%) [48, 74]	41 (55%) [43, 67]
Partial Remission Rate, n (%) [95% CI]	15 (25%) [15, 38]	18 (24%) [15, 36]
Duration of Response (DOR)		
Median in months [95% CI] Range in months	NR [8.6, NE] 0.0+, 29.2+	NR [8.6, NE] 0.0+, 29.2+
DOR, if best response is CR, median in months [95% CI] Range in months	NR [13.6, NE] 1.9+, 29.2+	NR [13.6, NE] 0.0+, 29.2+
DOR, if best response is PR, median in months [95% CI] Range in months	2.2 [1.5, 5.1] 0.0+, 22.1+	2.2 [1.5, 5.1] 0.0+, 22.1+
Median Follow-up for DOR in months	8.6	8.1

The safety and efficacy of brexucabtagene autoleucel leading to FDA-approval for ALL was assessed in a single-arm, open-label, multicenter trial (ZUMA-3; NCT02614066). Eligible patients were adults with primary refractory ALL, first relapse following a remission lasting ≤12 months, relapsed or refractory ALL after second-line or higher therapy, or relapsed or refractory ALL at least 100 days after allogeneic stem cell transplantation (SCT). The study excluded patients with active or serious infections, active graft-vs-host disease or taking immunosuppressive medications within 4 weeks prior to enrollment, and any history of CNS disorders, including CNS-2 disease with neurologic changes and CNS-3 disease irrespective of neurological changes. Treatment consisted of lymphodepleting chemotherapy (fludarabine 25 mg/m^2 IV daily on Days -4, -3 and -2; cyclophosphamide 900 mg/m^2 IV on Day -2) followed by a single IV infusion of brexucabtagene autoleucel at a target dose of 1×10^6 anti-CD19 CAR T cells/kg (maximum 1×10^8 cells) on Day 0. All treated patients were hospitalized until at least Day 7. A total of 71 patients were enrolled and leukapheresed; six of these patients did not receive treatment due to manufacturing failure, eight patients were not treated primarily due to adverse events following leukapheresis, two patients underwent leukapheresis and received lymphodepleting chemotherapy but were not treated, and one patient treated was unevaluable for efficacy. Among the remaining 54 efficacy-evaluable patients, the median time from leukapheresis to product delivery was 16 days (range of 11 to 39 days) and the median time from leukapheresis to infusion was 29 days (range of 20 to 60 days). Of the 54 patients who were efficacy evaluable, the median age was 40 years (range of 19 to 84 years), 61% were male, and 67% were White. At enrollment, 46% had refractory relapse, 26% had primary refractory disease, 20% had untreated second or later relapse, and 7% had first untreated relapse. Among prior therapies, 43% of patients were previously treated with allogeneic SCT, 46% with blinatumomab (Blincyto), and 22% with inotuzumab ozogamicin (Besponsa). Twenty-six percent of patients were Philadelphia chromosome positive (Ph+). Fifty (93%) patients received bridging therapy between leukapheresis and lymphodepleting chemotherapy to control disease burden.

Efficacy was established on the basis of complete remission (CR) within 3 months after infusion and the duration of CR (DOCR). The results, as reported in the product labeling, are provided in Table 7 below. Twenty-eight (51.9%) of the 54 evaluable patients achieved CR, and with a median follow-up for responders of 7.1 months, the median DOCR was not reached. The median time to CR was 56 days (range: 25 to 86 days). All efficacy-evaluable patients had potential follow-up for ≥10 months with a median actual follow-up time of 12.3 months (range: 0.3 to 22.1 months).

Table 7: ZUMA-3 Trial Results

	Efficacy-Evaluable Patients (n=54)	**All Leukapheresed Patients (n=71)**
OCR rate (CR + CRi), n (%) [95% CI]	35 (64.8%) [51, 77]	36 (50.7%) [39, 63]
CR rate, n (%) [95% CI]	28 (51.9%) [37.8, 65.7]	29 (40.9%) [29.3, 53.2]
Duration of Remission, Median in months [95% CI] (Range in months)	13.6 [9.4, NE] (0.03+, 16.07+)	13.6 [8.7, NE] (0.03+, 16.07+)
DOR, if best response is CR, median in months [95% CI] (Range in months)	NR [9.6, NE] (0.03+, 16.07+)	13.6 [9.4, NE] (0.03+, 16.07+)
DOR, if best response is CRi, median in months [95% CI] (Range in months)	8.7 [1.0, NE] (0.03+, 10.15+)	8.7 [1.0, NE] (0.03+, 10.15+)
Median Follow-up for CR in months	7.1 (0.03+, 16.1+)	5.0 (0.03+, 16.1+)

CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete blood count recovery; DOR, duration of remission; NE, not estimable; NR, not reached, OCR, overall complete remission; NE, not estimable

Ciltacabtagene Autoleucel (Carvykti)

Ciltacabtagene autoleucel (cilta-cel) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy that was approved by the U.S. FDA in February 2022 for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) after 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Cilta-cel was previously granted orphan designation by the FDA, as sponsored by the innovator drug company, for the treatment of MM in February 2019. Carvykti is the second BCMA-directed CAR T-cell therapy approved for MM; the first being Abecma (idecabtagene vicleucel) approved in March 2021. In April 2024, the FDA approved a label expansion to allow for earlier treatment. The new indication is worded as "for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide". Relapsed or refractory MM is an incurable cancer of plasma cell in the bone marrow, and while numerous treatment options are available for relapsed or refractory (r//r) disease, including later-stage therapy, a preferred order for use has not been established. The choice of therapy is determined by prior therapies used, response and adverse effects to those treatments, duration of responses, patient comorbidities, risk stratification, and drugs costs. The National Comprehensive Cancer Network (NCCN) Multiple Myeloma Guidelines list ciltacabtagene autoleucel as a category 1 recommendation under "Preferred Regimens" for relapsed/refractory disease after 1-3 prior therapies under the sub-indication of "After one prior therapy including IMiD and a PI, and refractory to lenalidomide". It is also listed as a category 2A recommendation under "Preferred Regimens" for relapsed/refractory disease after 3 prior therapies under the sub-indication of "After at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent". Idecabtagene vicleucel (Abecma) and various bispecific antibodies are also listed in this same section.

The safety and efficacy of cilta-cel leading to the initial FDA approval was assessed in an open-label, single-arm, multicenter trial (CARTITUDE-1; NCT03548207) in adult patients with relapsed or refractory multiple myeloma, who previously received at least 3 prior lines of therapy including a proteasome inhibitor (PI), an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Patients with known active or prior history of significant CNS disease, including CNS MM, plasma cell leukemia, allogeneic stem cell transplant within 6 months before apheresis or ongoing treatment with immunosuppressants, creatinine clearance <40 mL/min, absolute lymphocyte concentration <300/µL, absolute neutrophil count <750 cells/mm^3, platelet count <50,000/mm^3, hepatic transaminases >3 times the upper limit of normal, cardiac ejection fraction <45%, or with active serious infection were excluded from the trial. Of the 113 patients who underwent leukapheresis, 16 patients did not receive cilta-cel due to progressive disease (n=2), death (n=9), or withdrawal from study (n=5). There were 97 patients in the efficacy evaluable population who received cilta-cel, including 17 patients (18%) with manufacturing failures either because they received cilta-cel that did not meet product release specifications for Carvykti or received cilta-cel for which there were insufficient data to confirm the product release specifications. Of the 97 efficacy-evaluable patients, the median age was 61 years (range: 43 to 78 years), 59% were male, 71% were white, and 18% were black. Most patients (86%) were International Staging System (ISS) Stage I or II. Of the 91 patients for whom baseline cytogenetic data were available, high-risk cytogenetics (presence of t(4:14), t(14:16), or 17p13 del) were present in 24% of patients. Thirteen percent of the patients had extramedullary disease. The median number of prior lines of

therapy was 6 (range 3 to 18), with 82% of patients receiving 4 or more prior lines of therapy, 90% of patients had received prior ASCT and 8% of patients received an allogeneic transplant. Ninety-nine percent of patients were refractory to their last line of prior therapy, and 88% were refractory to a PI, immunomodulatory agent, and anti-CD38 antibody. Most patients (75%) received bridging therapy for control of their MM during the manufacturing process. The median time from leukapheresis to product availability was 32 days (range 27 to 66 days). The most commonly used agents as bridging therapies (≥20% of patients) included dexamethasone: 62 patients (64%), bortezomib: 26 patients (27%), cyclophosphamide: 22 patients (23%), and pomalidomide: 21 patients (22%).

Efficacy was established on the basis of overall response rate (ORR), complete response rate (CR) and duration of response as assessed by the Independent Review Committee (IRC) using International Myeloma Working Group (IMWG) criteria. The median time to first response was 1 month (range 0.9 to 10.7 months). The IRC assessed overall response in the 113 patients that underwent leukapheresis was 84% (95%) (CI: 76, 90) with stringent CR rate of 67% (95% CI: 58, 76), very good partial response (VGPR) rate of 14% (95% CI: 8, 22) and PR rate of 3% (95% CI: 1, 8). The results of the cita-cel-treated population (n=97) is shown in Table 8 below.

Table 8: CARTITUDE-1 Trial Results

	Cita-Cel-Treated Population (n=97)
Response Rate	
Overall Response Rate (ORR); n (%) [95% CI]	95 (97.9%) [92.7, 99.7]
Stringent complete response (sCR); n (%) [95% CI]	76 (78.4%) [68.8, 86.1
Very good partial response (VGPR), n (%) [95% CI]	16 (16.5%) [(9.7, 25.4]
Partial response (PR); n (%) [95% CI]	3 (3.1%) [0.6, 8.8)
Duration of Response (DOR)	
Number of responders	95
DOR (Months):Median (95% CI)	21.8 (21.8, NE)
Number of responders with sCR	76
DOR if best response is sCR (Months):Median (95% CI)	NE (21.8, NE)
Number of responders with VGPR or better	92
DOR if best response is VGPR or better (Months):Median (95% CI)	21.8 (21.8, NE)

Based on a median duration of follow-up of 18 months. All complete responses were stringent CRs. CI, confidence interval; NE, not estimable.

The most common (greater or equal to 10%) Grade 3 or 4 non-laboratory adverse reactions were infections-pathogen unspecified (17%), pneumonia (11%), febrile neutropenia (10%), and hypotension (10%). The most common non-laboratory adverse reactions (incidence greater than or equal to 20%) included pyrexia, CRS, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections of unspecified pathogen, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting. Serious adverse reactions occurred in 55% of patients. The most common non-laboratory (greater than or equal to 5%) serious adverse reactions included CRS (21%), sepsis (7%), encephalopathy (10%), and pneumonia (7%). Fatal adverse reactions occurred in 9% of patients.

The safety and efficacy of cilta-cel leading to the expanded indication for MM was assessed in a randomized, open label, multicenter controlled study (CARTITUDE-4; NCT04181827) in adult patients with relapsed and lenalidomide-refractory MM who previously received at least 1 prior line of therapy including a proteasome inhibitor and an immunomodulatory agent. A total of 419 patients were

randomized 1:1 to receive either a sequence of apheresis, bridging therapy, lymphodepletion and cilta-cel (n=208) or standard therapy which included daratumumab, pomalidomide and dexamethasone (DPd) or bortezomib, pomalidomide and dexamethasone (PVd) selected by physician prior to randomization based on patient's prior antimyeloma therapy (n=211). Randomization was stratified by physician's choice of treatment (DPd vs. PVd), ISS (I vs. II vs. III) and number of prior lines of therapy (1 vs. 2 or 3). Patients with known active or prior history of CNS involvement, patients who exhibit clinical signs of meningeal involvement of MM and patients with a history of Parkinson's disease or other neurodegenerative disorder, were excluded from the trial. In the overall study population (n=419), the median age was 61 years (range: 27 to 80 years), 57% were male, and 75% were White. Most patients (94%) were International Staging System (ISS) Stage I or II. High-risk cytogenetics [presence of t(4:14), (14:16), and 17p13 del] were present in 34% of patients. Nineteen percent of patients had presence of soft tissue plasmacytoma. Patients had received a median of 2 (range: 1 to 3) prior lines of therapy and 85% of patients had received prior ASCT. Ninety-nine percent of patients were refractory to their last line of prior therapy. Forty-seven percent were refractory to a PI and 100% were refractory to an immunomodulatory agent.

All 208 patients randomized to the cilta-cel arm underwent apheresis, twelve (6%) were not treated with cilta-cel due to progressive disease (n=10) or death (n=2), and twenty (10%) progressed prior to infusion with cilta-cel but were able to receive cilta-cel as subsequent therapy. Eight (4%) patients received CAR-T positive T cells that did not meet product release specification for cilta-cel (non-conforming product). Patients randomized to cilta-cel were to receive lymphodepleting chemotherapy consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day concurrently for 3 days followed by cilta-cel infusion 5 to 7 days after completion of lymphodepleting chemotherapy. At least one cycle of DPd or PVd bridging therapy was received for disease control between leukapheresis and the start of the lymphodepleting chemotherapy. Cilta-cel was administered as a single IV infusion 5 to 7 days after the start of a lymphodepleting chemotherapy at a median dose of 0.71×10^6 CAR-positive viable T-cells/kg (range: 0.39 to 1.07×10^6 cells/kg). In the 176 patients that received cilta-cel as study treatment, the median time from the day after receipt of apheresis material at manufacturing facility to release of product for infusion was 44 days (range: 25 to 127 days) and the median time from first apheresis to cilta-cel infusion was 79 days (range: 45 days to 246 days).

The primary efficacy measure was PFS analyzed based on the Intent-To-Treat Analysis Set. The results are shown in Table 9 below. After a median follow-up of 15.9 months, median PFS was 12 months (95% CI: 9.8, 14) for standard therapy arm and NE (95% CI: 22.8, NE) for cilta-cel arm (HR: 0.41 [95% CI: 0.30, 0.56]). The estimated PFS rate at 12 months was 75.9% (95% CI: 69.4%, 81.1%) in the cilta-cel arm and 49.5% (95% CI: 42.3%, 56.3%) in the standard therapy arm. In the cilta-cel arm, the estimated median DOR has not been reached in patients who achieved PR or better or in patients who achieved CR or better. In the standard therapy arm, the estimated median DOR was 16.6 months (95% CI: 12.9, NE). A higher proportion of patients in the cilta-cel arm compared to the standard therapy arm died within the first 10 months of randomization.

Table 9: CARTITUDE-4 Trial Results

	Cita-Cel (n=208)	**Standard Therapy (n=211)**
Progression-Free Survival	-	-
Number of events, n (%)	65 (31.3)	119 (56.4)
Median, months [95% CI]	NE [22.8, NE]	12 [9.8, 14.0]

Hazard ratio [95% CI]	0.41 [0.30, 0.56]	-
p-value	<0.0001	-
Complete Response or Better Rate, % [95% CI]	74.0 [67.5, 79.9]	22.3 [16.8, 28.5]
p-value	<0.0001	-
Stringent Complete Response (sCR), n (%)	137 (65.9)	38 (18.0)
Complete Response (CR), n (%)	17 (8.2)	9 (4.3)
Overall Response Rate, ORR (sCR+CR+VGPR+PR), % [95% CI]	84.6 [79.0, 89.2]	67.8 [61.0, 74.0]
p-value	<0.0001	-
Very Good Partial Response (VGPR), n (%)	16 (7.7)	49 (23.2)
Partial Response (PR), n (%)	6 (2.9)	47 (22.3)

NE=not estimable; CI=confidence interval

Notes: Based on a median duration of follow up of 15.9 months

Idecabtagene Vicleucel (Abecma)

Idecabtagene vicleucel (ide-cel) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy that was approved by the U.S. FDA in March 2021 for treatment of adult patients with relapsed or refractory MM after 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Idecabtagene vicleucel was previously granted orphan designation by the FDA, as sponsored by the innovator drug company, for the treatment of MM in May 2016. In April 2024, the FDA approved a label expansion to allow for earlier treatment. The new indication is worded as "for the treatment of adult patients with relapsed or refractory multiple myeloma after two or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody." Relapsed or refractory MM is an incurable cancer of plasma cell in the bone marrow, and while numerous treatment options are available for relapsed or refractory (r//r) disease, including later-stage therapy, a preferred order for use has not been established. The choice of therapy fs determined by prior therapies used, response and adverse effects to those treatments, duration of responses, patient comorbidities, risk stratification, and drugs costs. The National Comprehensive Cancer Network (NCCN) Multiple Myeloma Guidelines list idecabtagene vicleucel as a category 1 recommendation under "Preferred Regimens" for relapsed/refractory disease after 1-3 prior therapies under the sub-indication of "After two prior therapies including an IMiD, an anti-CD38 monoclonal antibody and a PI". It is also listed as a category 2A recommendation under "Preferred Regimens" for relapsed/refractory disease after 3 prior therapies under the sub-indication of "After at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent". Ciltacabtagene autoleucel (Carvykti) and various bispecific antibodies are also listed in this same section.

The safety and efficacy of ide-cel leading to FDA approval was assessed in an open-label, single-arm, multicenter trial (KarMMa; NCT03361748). The study included adult patients with relapsed and refractory multiple myeloma who had received at least 3 prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody and had an ECOG performance status of 0 or 1. The study excluded patients with a creatinine clearance of ≤45 mL/min, alanine aminotransferase >2.5xULN, left ventricular ejection fraction <45%, ANC <1,000 cells/mm^3, and platelet count <50,000/mm3. Bridging therapy was permitted for disease control between apheresis and until 14 days before the start of lymphodepleting chemotherapy. Lymphodepleting chemotherapy consisted of cyclophosphamide and fludarabine starting 5 days prior to

the target infusion date. Patients were hospitalized for 14 days after ide-cel infusion to monitor for potential CRS, HLH/MAS, and neurotoxicity. Of the 135 patients who underwent leukapheresis for 300 x 10^6 and 450 x 10^6 CAR-positive T cell dose cohorts, 11 (8%) did not receive the CAR-positive T cells either due to death (n=2), adverse event (n=1), disease progression (n=1), consent withdrawal (n=3), physician decision (n=3), or inability to manufacture product [manufacturing failure (n=1)]. Two patients died after receiving lymphodepletion and prior to receiving ide-cel. Twenty-four (18%) either received ide-cel outside of the 300 to 460 x 10^6 CAR-positive T cells dose range (n=23) or received CAR-positive T cells that did not meet product release specifications (non-conforming product; n=1). The efficacy evaluable population consists of the 100 patients (74%) who received ide-cel in the dose range of 300 to 460 x 10^6 CAR-positive T cells. The overall manufacturing failure rate for patients who underwent leukapheresis was 1.5% (2 out of 135 patients). Of the 100 patients in the efficacy evaluable population, the median age was 62 years (range 33 to 78 years), 60% were male, 78% were white, most patients (78%) were International Staging System (ISS) Stage I or II, and high-risk cytogenetics were present in 37% of patients The median number of prior lines of therapy was 6 (range 3 to 16), and 88% of the patients received 4 or more prior lines of therapy. Ninety-five percent of the patients were refractory to an anti-CD38 monoclonal antibody. Eighty-five percent were triple class refractory (refractory to a proteasome inhibitor [PI], an immunomodulatory drug [IMiD] and an anti-CD38 monoclonal antibody), and 26% were penta-refractory (refractory to 2 PIs, 2 IMiD agents, and an anti-CD38 monoclonal antibody). Ninety-two percent had received prior autologous stem cell transplantation. Most patients (87%) treated with ide-cel received bridging therapy for control of their multiple myeloma during the manufacturing process.

The median time from leukapheresis to product availability was 33 days (range 26 to 49 days). Efficacy was established on the basis of overall response rate (ORR), complete response (CR) rate, and duration of response (DOR), as assessed by the Independent Response committee (IRC) based on the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. The result are shown in Table 10 below. The median time to first response was 30 days (range: 15 to 88 days).

Table 10: KarMMa Trial Results

	Abecma-Treated Population (300 to 460 x 10^6 CAR-Positive T Cells), n=100
Response Rate	
Overall Response Rate (ORR); n (%) [95% CI]	72 (72%) [62, 81]
Stringent complete response (sCR); n (%) [95% CI]	28 (28%) [19, 38]
Very good partial response (VGPR), n (%) [95% CI]	25 (25%) [17, 35]
Partial response (PR); n (%) [95% CI]	19 (19%) [12, 28]
MRD Negativity Rate	
All treated patients (n=100); n (%) [95% CI]	21 (21%) [13, 30]
Patients achieving CR or sCR status (n=28); n (%) [95% CI]	21 (75%) [55, 89]
Duration of Response (DOR)	
DOR for PR or better; median [95% CI]	n=72 11 months (10.3 to 11.4)
DOR for sCR; median [95% CI]	n=28 19 months (11.4 to not estimable)
Median Follow-up for DOR	10.7 months

MRD = Minimal Residual Disease

Within the recommended dose of 300 to 460 x 10^6 CAR-positive T cells, a dose-response relationship was observed with higher ORR and sCR rate in patients who received 440 to 460 x 10^6 compared to 300 to 340 x 10^6 CAR-positive T cells. Overall response rate of 79% (95% CI: 65%, 90%) and sCR rate of 31% (95% CI: 19%, 46%) was observed with 440 to 460 x 10^6 CAR-positive T cells. Overall response rate of 65% (95% CI: 51%, 78%) with sCR rate of 25% (95% CI: 14%, 39%) was observed in 300 to 340 x 10^6 CAR-positive T cells.

Any-grade cytokine release syndrome (CRS) was observed in 85% of patients, with Grade >3 CRS occurred in 9%, and Grade 5 CRS occurred in 0.8%. The median time to CRS onset was 1 day (range, 1 to 23 days), with a median duration of 7 days (range, 1 to 63 days). Cases of CRS most commonly manifested as pyrexia (98%), hypotension (41%), tachycardia (35%), chills (31%), hypoxia (20%), fatigue (12%), and headache (10%). There was also a 28% rate of neurotoxicity (NT) in the study. Grade 3 events of NT were seen in 4% of patients. The median time to onset of NT was 2 days (range, 1–42). Neurotoxicity did resolve in 92% of patients and median time to resolution was 5 days (range, 1–61). Hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) occurred in 4% of patients, including one patient who developed fatal multi-organ HLH/MAS with CRS and one patient with fatal bronchopulmonary aspergillosis. Three cases of Grade 2 HLH/MAS resolved. Forty-one percent and 49% of patients experienced prolonged Grade 3/4 neutropenia and thrombocytopenia, respectively.

The safety and efficacy of ide-cel leading to the expanded indication for MM was assessed in an open-label, multicenter, randomized, controlled study (KarMMa-3; NCT03651128) in adult patients with relapsed and refractory MM who had received two to four prior antimyeloma therapies including an immunomodulatory agent, a proteasome inhibitor and daratumumab, and were refractory to the most recent prior antimyeloma regimen. The study included patients who achieved a response (minimal response or better) to at least 1 prior treatment regimen and had ECOG performance status of 0 or 1. The study excluded patients with serum creatinine clearance <45 mL/min, serum AST or ALT >2.5 X ULN, and LVEF <45%. Patients were also excluded if absolute neutrophil count <1000/mcL and platelet count <75,000/mcL in patients in whom <50% of bone marrow nucleated cells are plasma cells and platelet count <50,000/mcL in patients in whom ≥50% of bone marrow nucleated cells are plasma cells. In total, 386 patients were randomized 2:1 to receive either ide-cel (n=254) or standard regimens (n=132). The standard regimens consisted of daratumumab, pomalidomide, dexamethasone [DPd], daratumumab, bortezomib, dexamethasone [DVd], ixazomib, lenalidomide, dexamethasone [IRd], carfilzomib, dexamethasone [Kd], or elotuzumab, pomalidomide, dexamethasone [Epd]), selected by Investigator prior to randomization contingent upon the patient's most recent antimyeloma treatment. Randomization was stratified by age, number of prior antimyeloma regimens, and presence of high-risk cytogenetics abnormalities. Patients randomized to ide-cel were to receive lymphodepleting chemotherapy consisting of cyclophosphamide (300 mg/m^2 IV infusion daily for 3 days) and fludarabine (30 mg/m^2 IV infusion daily for 3 days) starting 5 days prior to the target infusion date of ide-cel. Up to 1 cycle of DPd, DVd, Ird, Kd or Epd bridging therapy, dependent on the patient's most recent antimyeloma treatment regimen, was permitted for disease control between apheresis and until 14 days before the start of lymphodepleting chemotherapy.

Of the 254 patients randomized to receive ide-cel, 249 (98%) patients underwent leukapheresis: five (2%) patients did not receive 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 ide-cel 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); and three (1.2%) patients received CAR-positive T cells that did not meet product release specifications for ide-cel (non-conforming product; n=3). The overall manufacturing failure rate for patients who underwent leukapheresis was 2.4% (6 out of 249 patients). Of these 6 patients, 3 received CAR positive T cells that did not meet product release specifications for ide-cel, and in 3 patients there was an inability to manufacture ide-cel. Most patients (85%) treated with ide-cel received bridging therapy for control of their MM during the manufacturing process. The median time from leukapheresis to product availability was 35 days (range: 24 to 102 days). In overall study population, the median age was 63 years (range: 30 to 83 years), 61% were male, and 65% were white. Most patients (80%) were R-ISS Stage I or II. High-risk cytogenetics [presence of t(4:14), (14:16), and 17p13 del] were present in 42% of patients. Twenty-four percent of patients had presence of extramedullary disease. The median number of prior lines of therapy was 3 (range: 2 to 4). Thirty percent had received 2 prior lines, 37% had received 3 prior lines of therapy and 32% had received 4 prior lines of therapy. Ninety-five percent were refractory to an anti-CD38 monoclonal antibody. Sixty-six percent were triple class refractory (refractory to a PI, an ImiD and an anti-CD38 monoclonal antibody), and 5% were penta-drug-refractory (refractory to 2 Pis, 2 ImiD agents, and an anti-CD38 monoclonal antibody). Eighty-five percent of patients had received prior autologous stem cell transplantation.

The primary efficacy measure was PFS as determined by IRC based on the IMWG Uniform Response Criteria for MM. Other efficacy measures included ORR and OS. The results are shown in Table 11 below. The estimated median duration of follow-up at the primary PFS analysis was 15.9 months (95% CI: 14.1, 18.0). In the ide-cel arm, the median DOR was 14.8 months (95% CI: 12.0, 18.6) in patients with PR or better. In those patients with CR or better, the median DOR was 20 months (95% CI: 15.8, 24.3). A higher proportion of patients in the ide-cel arm compared to the standard regimen's arm died within the first 9 months of randomization.

Table 11: KarMMa-3 Trial Results

	Abecma Arm (n=254)	**Standard Regimens Arm (n=132)**
Progression Free Survival (PFS)		
Number of events, n (%)	149 (59)	93 (70)
Median, months [95% CI]	13.3 [11.8, 16.1]	4.4 [3.4, 5.9]
Hazard Ratio [95% CI]	0.49 [0.38, 0.64]	
One-sided p-value	< 0.0001	
Overall Response Rate (ORR), n (%)		
n (%)	181 (71)	55 (42)
95% CI (%)	66, 77)	(33, 50)
One-sided p-value	< 0.0001	
CR or better (sCR+CR)	98 (39)	7 (5)
sCR	90 (35)	6 (4.5)
CR	8 (3.1)	1 (0.8)
VGPR	55 (22)	13 (10)
PR	28 (11)	35 (27)

CI=confidence interval; CR=complete response; MRD=minimal residual disease; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

Lisocabtagene Maraleucel (Breyanzi)

Lisocabtagene maraleucel (Breyanzi) is a CD19-directed, genetically modified autologous T cell immunotherapy that was first approved by the U.S. FDA in February 2021 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including 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, the indication was expanded to earlier use, specifically, refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first line chemoimmunotherapy; or refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age. In March 2024, an additional indication was approved by the FDA for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor. 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). In May 2024, the FDA approved a new indication for adult patients with relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy. Similar to CLL/SLL, this indication was approved under accelerated approval based on response rate and duration of response. Also, in May 2024, the FDA-approved another indication for adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor. In December 2025, an additional indication was approved by the FDA for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least 2 prior lines of systemic therapy. Lisocabtagene maraleucel was previously granted orphan designation by the FDA for the treatment of DLBCL in April 2016, follicular lymphoma in September 2017, MCL in April 2020, and primary mediastinal large B-cell lymphoma in July 2018.

Lisocabtagene maraleucel is the fourth CD19-directed CAR T-cell therapy to be approved by the FDA, the third to be approved for treatment of r/r large B-cell lymphoma, third to be approved for treatment of r/r FL, first to be approved from the treatment of r/r MZL, and the first to be approved for the treatment of r/r CLL or SLL. The other FDA-approved, CD19-directed CAR-T cell therapies are tisagenlecleucel (Kymriah), axicabtagene ciloleucel (Yescarta), and (brexucabtagene autoleucel (Tecartus). Lisocabtagene maraleucel, and other CAR T-cell therapies, work by reprogramming a patient's own T cells with a transgene encoding a CAR to identify and eliminate CD19-expressing malignant and normal B cells. Treatment involves removing, genetically modifying, and then re-infusing a patient's own T-cells. One aspect in which lisocabtagene maraleucel differs from the other CAR T-cell therapies is that it is given as a sequential infusion of two components (CD8+ and CD4+ CAR+ T-cells) at equal doses.

Diffuse large B-cell lymphomas are the most common lymphoid neoplasms in adults, and account for approximately 30% of non-Hodgkin's lymphomas (NHLs) cases diagnosed annually. The DLBCLs exhibit large heterogeneity in morphologic, genetic, and clinical aspects. Multiple clinicopathologic entities are defined by the 2022 World Health Organization (WHO) classification, which are sufficiently distinct to be considered separate diagnostic categories. Adequate immunophenotyping is essential to establish the diagnosis, and to determine germinal center B-cell like (GCB) vs. non-GBC origin. Combination chemoimmunotherapy in the first-line setting (e.g., rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) is associated with a 5-year survival rate ranging from 60% to 70%.

Interim restaging should be performed to identify patients who disease has not responded to or has progressed on induction therapy. Based on a number of prognostic factors, 20% to 50% of DLBCL cases are refractory or relapse after first-line chemotherapy, and the response rates to subsequent salvage chemotherapy and consolidation with autologous hematopoietic stem cell transplantation (HSCT) is suboptimal.

The National Comprehensive Cancer Network (NCCN) B-cell Lymphomas Guideline includes lisocabtagene maraleucel, along with axicabtagene ciloleucel and tisagenlecleucel as category 2A recommendations for the treatment of r/r DLBLC, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma [with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma), or not otherwise specified (NOS)], HIV-related DLBCL, primary effusion lymphoma, HHV8-positive DLBCL, NOS, and monomorphic post-transplant lymphoproliferative disorders (PTLD) (B-cell type) for patients with two or more disease relapses (if anti-CD19 CAR T-cell therapy was not previously given), or for patients with a non-complete response (i.e., partial response or worse) to second-line therapy. All are also 2A recommendations for the treatment of indolent lymphomas with histological transformation to DLBCL in patients with 2 or more prior chemotherapy regimens (with at least one being an anthracycline or anthracenedione-based regimen, unless contraindicated). Lisocabtagene maraleucel is also a category 1 recommendation for these same large B-cell lymphomas when used as second-line therapy for patients with primary refractory disease (partial response, no response, or progression) or relapsed disease less than 12 months after completion of first-line therapy. In addition, lisocabtagene maraleucel is a category 2A recommendation for second-line therapy for patients with no intention to proceed to transplant. The NCCN guidelines for Pediatric Aggressive Mature B-Cell Lymphomas include lisocabtagene maraleucel as a preferred category 2A recommendation for consolidation/additional therapy for pediatric primary mediastinal large B-cell lymphoma if partial response achieved after therapy for relapsed or refractory disease (after use of ≥ 2 prior chemoimmunotherapy regimens).

The safety and efficacy of lisocabtagene maraleucel leading to FDA approval for its initial indication was based on the results of a single-arm, open-label, multicenter Phase 1 study called TRANSCEND NHL 001. The study enrolled a broad range of patients with r/r large B-cell lymphomas. Eligible histological subgroups included DLBCL, high-grade B-cell lymphoma with rearrangements of MYC and either BCL2, BCL6, or both (double-hit or triple-hit lymphoma), DLBCL transformed from any indolent lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma grade 3B. Mantle cell lymphoma is investigated in a separate cohort. Patients were assigned to one of three target dose levels of lisocabtagene maraleucel as they were sequentially tested in the trial (50×10^6 CAR+ T-cells one or two doses, 100×10^6 CAR+ T-cells, and 150×10^6 CAR+ T-cells), which were administered as a sequential infusion of two components (CD8+ and CD4+ CAR+ T-cells) at equal target doses. Primary endpoints of the study were adverse events, dose-limiting toxicities, and the objective response rate assessed per Lugano criteria. The endpoints were assessed by an independent review committee in the efficacy-evaluable set comprising all patients who had confirmed PET-positive disease and received at least one dose of lisocabtagene maraleucel.

A total of 344 patients were leukapheresed and 269 patients received lisocabtagene maraleucel at one of three dose levels (50×10^6 n=51; 100×10^6 n=177; and 150×10^6 n=41). There were 25 patients that received nonconforming product and there were two instances where product could not be manufactured. Patients had received a median of three previous lines of systemic treatment with 260

patients (97%) having had at least two lines. There were 112 patients (42%) who were aged 65 years or older, 181 patients (67%) had chemotherapy-refractory disease, and 7 patients (3%) had secondary CNS involvement. Bridging therapy was administered to 59% of patients. Overall safety and activity of lisocabtagene maraleucel did not differ by dose level. The recommended target dose was 100 x 10^6 CAR+ T-cells (50 x 10^6 CD8+ and 5 0x 10^6 CD4+ CAR+ T-cells). Of 256 patients included in the efficacy-evaluable set, the overall response rate (ORR) was 73% (187/256, 95% CI: 67 to 78%) with 53% of patients (136/256, 95% CI: 47 to 59%) achieving a complete response (CR). Responses were similar across all patient subgroups. The median duration of response (DOR) for all patients was not reached (95% CI: 8.6 months to NR) at a median follow-up of 12 months (95% CI: 11.2 to 16.7). Median progression-free survival (PFS) was 6.8 months (95% CI: 3.3 to 14.1) and median overall survival (OS) was 21.1 months (95% CI: 13.3 to NR). The median PFS and OS for patients who achieved a CR was not reached, with 65.1% of patients progression free and 85.5% of patients alive at 12 months, respectively.

Among all patients, 79% (213/269) had grade 3 or higher treatment-emergent adverse events (TEAE) including neutropenia (60%, 161/269), anemia (38%, 101/269) and thrombocytopenia (27%, 72/269). Instances of any grade cytokine release syndrome (CRS) occurred in 42% (113/269) of patients at a median onset of 5 days and grade 3 or higher CRS occurring in 2% (6/269) of patients. There were neurologic events (Nes) that occurred in 30% of patients (80/269) with grade 3 or higher Nes occurring in 10% (27/269) of patients at a median onset of 9 days. Nineteen and 21% of patients received tocilizumab and corticosteroids, respectively. There were four fatal TEAEs related to lisocabtagene maraleucel in the study from diffuse alveolar damage, pulmonary hemorrhage, multiple organ dysfunction syndrome or cardiomyopathy. There were three fatal TEAEs considered unrelated to lisocabtagene maraleucel from fludarabine leukoencephalopathy, septic shock and progressive multifocal leukoencephalopathy. Eight patients had ongoing CRS/NE at the time of death from other reasons. Prolonged grade 3 or higher cytopenias were reported in 37% (100/269) of patients.

The safety and efficacy of lisocabtagene maraleucel leading to FDA approval for CLL/SLL was based on the results of a single-arm, open-label, multicenter phase 1/2 study called TRANSCEND-CLL (NCT03331198). The study enrolled adult patients with R/R CLL or SLL who had received at least 2 prior lines of therapy including a BTK inhibitor and a BCL-2 inhibitor. Patients with del(17p), complex karyotype, and unmutated immunoglobulin heavy chain variable region (IGHV) were included in the study. The study enrolled patients with ECOG performance status of ≤1. The study excluded patients with a creatinine clearance of less than 30 mL/min, alanine aminotransferase >5 times the ULN (except for subjects with leukemic infiltration of the liver), or (LVEF <40%. There was no prespecified threshold for blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy. The planned dose was 100 × 10^6 CAR-positive viable T cells. Bridging therapy for disease control was permitted between apheresis and the start of lymphodepleting chemotherapy. Of the 89 patients, Breyanzi was administered 2 to 11 days following completion of lymphodepleting chemotherapy. The lymphodepleting chemotherapy regimen consisted of fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day concurrently for 3 days.

Breyanzi was administered in the inpatient (88%) and outpatient (12%) settings. Of 113 patients who underwent leukapheresis, 94 received Breyanzi. Of the 94, 84 received Breyanzi at 90 to 111 × 10^6 CAR-positive T cells and 10 received a cell-dose outside of this dose range; 3 received CAR-positive T cells that did not meet the product specifications (manufacturing failure); and 16 other patients did not

receive for other reasons. The median time from leukapheresis to product availability was 24 days (range: 19 to 84 days), and the median time from leukapheresis to product infusion was 36 days (range: 28 to 384 days). Of the 89 patients treated, 69 (78%) received bridging therapy. Patients had measurable disease present before administration based on IRC assessment. Nineteen of 84 patients were not evaluable for efficacy (13 patients did not have baseline disease assessments performed after completion of bridging therapy, 1 patient lacked measurable disease, and 5 had Richter's transformation). Of the 65 efficacy-evaluable patients, the median age was 66 years (range: 49 to 82 years), 68% were male, 80% were White. Eighty-three percent of patients had at least one high risk genetic attribute including 43% del(17p), 45% TP53 mutation, 45% unmutated IGHV, and 62% with complex karyotype. Fifty-one percent of the patients had bulky disease. The median number of prior therapies was 5 (range 2 to 12). All 65patients were exposed to a BTK inhibitor, of which 88% were refractory, 1.5% were relapsed, and 11% were intolerant. Of 65 patients who received a BCL-2 inhibitor, 92% were refractory, none relapsed, and 6% were intolerant. A total of 83% had disease refractory to last therapy. Efficacy was based on overall response rate (ORR) (including complete response [CR] and partial response [PR]) and duration of response (DOR) as determined by an independent review committee (IRC) using 2018 International Workshop CLL (iwCLL) criteria. The median time to first response (CR or PR) was 1.1 months (range: 0.8 to 17.4 months). The median time to first CR was 3 months (range 1.1 to 17.9 months). Among the 65 Breyanzi treated patients, the ORR was 45% (29/65, 95% CI: 32.3 to 57.5%) with 20% of patients (13/65, 95% CI: 14.8 to 36.9%) achieving a CR. The median DOR for all patients was 35.3 months (95% CI: 12.4 months to NR). If the best response was CR, median DOR was not reached (95% CI: 15 months to NR). For these same patients, the response rate at 12 and 18 months, was 100% and 87.5% respectively and the MRD-negativity rate was 100% (13/13) in peripheral blood and 92.3% (12/13) in the bone marrow.

The NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma include lisocabtagene maraleucel as a referred Category 2A recommendation for relapsed or refractory CLL/SLL after prior therapy with BTK inhibitor- and venetoclax-based regimens in patients with or without del(17p)/TP53 mutation, and as additional therapy for treatment of histologic (Richter) transformation to DLBCL (clonally related or unknown clonal status) in patients with del(17p)/TP53 mutation or who are chemotherapy refractory or unable to receive chemoimmunotherapy..

The safety and efficacy of lisocabtagene maraleucel leading to FDA approval for FL was based on the results of a Phase 2, open-label, multicenter, single-arm trial called TRANSCEND-FL (NCT04245839). The trial included adults with relapsed or refractory FL after two or more lines of systemic therapy (including an anti-CD20 antibody and an alkylating agent). Patients were eligible to enroll in the study if they had adequate bone marrow function to receive lymphodepleting chemotherapy and an ECOG performance status of 1 or less. Following apheresis and prior to lymphodepletion and subsequent administration of lisocabtagene maraleucel, patients could receive bridging therapy for disease control. Patients received a single dose of lisocabtagene maraleucel 2 to 7 days, following the completion of lymphodepleting chemotherapy (fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day concurrently for 3 days.) The primary efficacy population included 94 patients with PET-positive disease at baseline or after bridging therapy, received conforming product in the intended dose range, and had at least 9 months of follow up from first response.

The main efficacy outcome measures were overall response rate (ORR), defined as the percentage of patients with a best overall response (BOR) of complete response or partial response after lisocabtagene

maraleucel infusion, and duration of response (DOR) as determined by an independent review committee. The ORR was 95.7% (95% CI: 89.5, 98.8). After a median follow up of 16.8 months (95% CI: 16.3, 17.0), the median DOR was not reached (NR) (95% CI: 18.04, NR). The most common nonlaboratory adverse reactions (≥20%) were CRS, headache, musculoskeletal pain, fatigue, constipation, and fever.

The NCCN Guidelines for B-Cell Lymphomas include lisocabtagene maraleucel as a category 2A recommendation for the third-line and subsequent therapy of classic follicular lymphoma. It is listed as a "Preferred regimen" under the subcategory of CAR T-cell therapy which also includes the other CAR-T cell therapies approved for FL of tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta).

The safety and efficacy of lisocabtagene maraleucel leading to FDA approval for MCL was based on an open-label, multicenter, single-arm trial called TRANSCEND-MCL (NCT02631044). The trial included adult patients with relapsed or refractory MCL who had received at least two prior lines of therapy including a Bruton tyrosine kinase inhibitor, an alkylating agent, and an anti-CD20 agent. The trial included patients with an ECOG performance status of 1 or less, prior autologous and/or allogeneic hematopoietic stem cell transplantation, and secondary central nervous system lymphoma involvement. There was no prespecified threshold for blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy. Patients received a single dose of lisocabtagene maraleucel 2 to 7 days following the completion of lymphodepleting chemotherapy (fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day concurrently for 3 days). The primary efficacy analysis included a total of 68 patients with MCL who received at least 2 prior lines of therapy including a BTKi, had PET-positive disease at study baseline or after bridging therapy, received conforming product in the intended dose range, and had at least 6 months of follow-up from the date of first response.

The main efficacy outcome measure was overall response rate (ORR), defined as percentage of patients with best overall response (BOR) of either complete response (CR) or partial response (PR) after lisocabtagene maraleucel infusion, as determined by an independent review committee (IRC) using 2014 Lugano classification. Other efficacy measures included complete response rate (CRR) and duration of response (DOR), as determined by IRC. The ORR was 85.3% (95% CI: 74.6, 92.7) and the CRR was 67.6% (95% CI: 55.2, 78.5). After a median follow-up of 22.2 months (95% CI: 16.7, 22.8), the median DOR was 13.3 months (95% CI: 6.0, 23.3). The most common nonlaboratory adverse reactions (≥ 20%) were cytokine release syndrome (CRS), fatigue, musculoskeletal pain, encephalopathy, edema, headache, and decreased appetite. FDA approved lisocabtagene maraleucel with a Risk Evaluation and Mitigation Strategy due to the risk of fatal or life-threatening CRS and neurologic toxicities.

The NCCN Guidelines for B-Cell Lymphomas include lisocabtagene maraleucel (category 2A recommendation) as Second-Line and Subsequent Therapy under "Useful in Certain Circumstances" and under the subcategory of "Progressive disease after prior covalent BTKi". Brexucabtagene autoleucel (Tecartus) and pirtobrutinib (Jayprica) are also listed in this same section.

Obecabtagene Autoleucel (Aucatzyl)

Obecabtagene autoleucel (Aucatzyl) is a CD19-directed, genetically modified, autologous T-cell immunotherapy that was first approved by the U.S. FDA in November 2024 for "for "the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)". Obecabtagene

autoleucel is the seventh chimeric antigen receptor (CAR) T-cell therapy to be approved by the FDA, and the third CAR-T cell therapy to be approved for ALL. Brexucabtagene autoleucel (Tecartus) was approved for the treatment of adult patients with relapsed or refractory B-cell precursor ALL in October 2021. Tisagenlecleucel (Kymriah) is the only other CAR-T cell therapy approved for ALL; however, tisagenlecleucel is only approved for patients up to 25 years of age. Obecabtagene autoleucel was previously granted orphan designation by the FDA, as sponsored by the innovator drug company, for the treatment of ALL in November 2019. Obecabtagene autoleucel, and other CAR T-cell therapies, work by reprogramming a patient's own T cells with a transgene encoding a CAR to identify and eliminate CD19-expressing malignant and normal B cells. The CAR is composed of a murine anti-CD19 single chain variable fragment (scFv) linked to 4-1BB and CD3-zeta co-stimulatory domains. Upon binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the obecabtagene autoleucel cells. Treatment involves removing, genetically modifying (for obecabtagene autoleucel cells specifically, with a replication-incompetent lentiviral vector), and then re-infusing the patient's own T-cells. Obecabtagene autoleucel is unique compared to other CAR T-cell therapy as the treatment regimen consists of a split dose infusion to be administered on Day 1 and Day 10 (± 2 days). The dosage regimen is determined by tumor burden assessed by bone marrow blast percentage from a sample obtained within 7 days prior to the start of lymphodepletion. A lower first dose is used when the patient's bone marrow blast is >20%. This novel split dose regimen helps reduce the incidence of cytokine release syndrome (CRS) and neurologic toxicities.

Acute lymphoblastic leukemia (ALL) is heterogenous hematological disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. The median age of diagnosis is 17 years with 53.5% of patients diagnosed at younger than 20 years of age. In contrast, 29.6% of cases are diagnosed at 45 years or older and only 13.7% are diagnosed at 65 years or older. ALL represents about 20% of all leukemias among adults. ALL is broadly classified in 3 groups based on immunophenotype, which include precursor B-cell ALL, mature B-cell ALL (a.k.a., Burkitt leukemia/lymphoma), and T-cell ALL. In children, B-cell lineage ALL constitutes about 88% of cases and in adults B-cell lineage ALL is about 75% of cases (with mature B-cell only constituting 5%). Cure rates and survival outcomes have improved over the past several decades due to advances in understanding molecular genetics and pathogenesis of the disease, incorporation of risk-adapted therapy, and advent of new targeted agents. The 5-year overall survival (OS) rate for children and adolescent and young adults (AYA, 15 to 39 years of age) is 89% and 61% respectively; however, remains low at 20 to 40% in adults and is especially poor in older adults at 20%. The treatment of ALL represents one of the most complex and intensive programs in cancer therapy. Treatment varies depending on subtype, age, and treatment history. In general, the treatment phases can be largely grouped into induction, consolidation, and maintenance. The National Comprehensive Cancer Network (NCCN) guidelines for ALL list single-agent obecabtagene autoleucel and single-agent brexucabtagene autoleucel among the "Other Recommended Regimens" (as a category 2A recommendation) for relapsed/refractory BCR::ABL1-positive (Ph+) B-ALL (following therapy that has included TKIs) in AYA and adults, and among the "Preferred Regimens" (as a category 2A recommendation) for relapsed/refractory BCR::ABL1-negative (Ph-) B-ALL in AYA and adults. Tisagenlecleucel is also listed in these same respective sections, but use is limited to patients aged less than 26 years.

The safety and efficacy of obecabtagene autoleucel leading to FDA-approval for ALL was assessed in an open-label, multi-center, single-arm study (FELIX study; NCT04404660). The study enrolled patients with relapsed or refractory B-cell ALL. Eligible patients were adults with refractory ALL, first relapse following a remission lasting ≤ 12 months, relapsed or refractory ALL after two or more prior lines of systemic therapy, or relapsed or refractory ALL at least greater than 3 months after allogeneic STC and had disease burden of ≥ 5% blasts in bone marrow at screening. The study excluded patients with isolated extra medullary disease, active or serious infections requiring systemic antimicrobials, active GVHD, history or presence of CNS disorders. Treatment was administered in the in-patient setting and consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m^2 IV daily for 4 days; cyclophosphamide 500 mg/m^2 IV daily for 2 days starting with first dose of fludarabine) followed by obecabtagene autoleucel as a split dose infusion with a total recommended dose of 410 × 10^6 CD19 CAR-positive viable T cells.

A total of 112 patients were enrolled and underwent leukapheresis; 18 (16%) of whom discontinued without receiving an infusion due to the following: death (n=11), adverse event (n=1), physician decision (n=1), and manufacturing failure (n=5). Among the remaining 94 patients who received at least one infusion, 65 patients had ≥5% blasts in the bone marrow after screening and prior to the start of the lymphodepletion therapy, and received a conforming product, qualifying them as efficacy-evaluable patients. The population characteristics of efficacy-evaluable patients were as follows: median age was 51 years (range: 20 to 77 years) with 7 patients (11%) ≤ 25 years of age and 14 patients (22%) ≥ 65 years of age, 35 patients (54%) were female, and 47 patients (72%) were White. At enrollment, 35 patients (54%) were refractory to the last prior line of therapy, and 32 patients (49%) relapsed to first-line therapy within 12 months. The median number of prior lines of therapy was 2 (range of 1 to 6). Thirty-five patients (54%) received either blinatumomab or inotuzumab ozogamicin and 10 patients (15%) received both blinatumomab and inotuzumab ozogamicin, 22 (34%) patients received prior SCT therapy, 17 (26%) patients had Ph+ ALL and 13 (20%) patients had extramedullary disease. Fifty-nine patients (91%) received bridging therapy between leukapheresis and lymphodepleting chemotherapy. The median dose was 410 × 10^6 CD19 CAR-positive viable T cells (range: 10 to 418 × 10^6 CD19 CAR-positive viable T cells). Fifty-eight patients (89%) received the target dose of 410 × 10^6 CD19 CAR-positive viable T cells (+/- 25%). Five patients (8%) only received the first dose, primarily due to adverse events (5%). The median time from leukapheresis to product release was 20 days (range: 17 to 23 days) and the median time from leukapheresis to obecabtagene autoleucel infusion was 35 days (range: 26 to 74 days).

The major efficacy outcome measures were rate and duration of complete remission within 3 months after infusion. Additional outcome measures were rate and duration of overall complete remission which includes complete remission and complete remission with incomplete hematologic recovery, at any time. The efficacy results are summarized in Table 12 below.

Table 12: FELIX Trial Results

	Efficacy-Evaluable Patients (n=65)	**All Leukapheresed Patients (n=112)**
Complete Remission (within 3 months) Rate, n (%), 95% CI	27 (42%), (29%, 54%)	40 (36%), (27%, 45%)
Duration (months), median [95% CI]	14.1 (6.1, NR)	14.1 (6.2, NR)
(Range in months)	(0.5+, 21.2)	(0.5+, 21.2)
Overall Complete Remission (At Anytime) Rate*, n (%), 95% CI	41 (63%), (50%, 75%)	60 (54%), (44%, 63%)
Duration (months), median [95% CI]	14.1 (6.2, NR)	14.1 (8.1, NR)

(Range in months)	(0.03+, 21.2)	(0.03+, 21.2)

CI, confidence interval; NR, not reached

*Rate of Overall Complete Remission "At Anytime" includes Complete Remission and Complete Remission with incomplete hematologic recovery "At Anytime".

Among patients in the efficacy evaluable population who achieved a best response of complete remission "At Anytime" (n=33; 51%), the median duration for remission was 14.1 months (95% confidence interval [CI]: 6.1, not reached [NR]). Among patients in the efficacy evaluable population in whom best response was complete remission with incomplete hematologic recovery "At Anytime" (n=8; 12%), the median duration of remission was 10.5 months (95% CI: 1.8, NR)

Tisagenlecleucel (Kymriah)

Tisagenlecleucel (Kymriah) is a CD19-directed, genetically-modified autologous T cell immunotherapy that was first approved by the U.S. FDA in August 2017 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. The approval marked a historic moment being the first gene therapy and first chimeric antigen receptor (CAR) T-cell therapy approved by the FDA. In May 2018, the FDA-approved tisagenlecleucel for a second indication of “treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma”. Axicabtagene ciloleucel (Yescarta) was the first CAR T-cell therapy to be FDA-approved for r/r large B-cell lymphoma in October 2017. In May 2022, the FDA-approved tisagenlecleucel for a third indication of “treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy”. This approval makes tisagenlecleucel the second CAR T-cell therapy to be approved for FL, the first being axicabtagene ciloleucel (Yescarta) approved in March 2021. Tisagenlecleucel was previously granted orphan designation by the FDA, as sponsored by the innovator drug company, for the treatment of ALL in January 2014, for the treatment of DLBCL in February 2015, and for the treatment of follicular lymphoma in September 2020. Tisagenlecleucel works by reprogramming a patient’s own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal B cells. The CAR is comprised of a murine single-chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains. Upon binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the tisagenlecleucel cells. Treatment involves removing, genetically modifying, and then re-infusing a patient’s own T-cells. During the manufacturing process, a lentiviral vector encodes the CAR molecule via transduction; the vector enters the cell and becomes integrated into the chromosomes of T cells and directs transcription of the tisagenlecleucel CAR.

Acute lymphoblastic leukemia (ALL) is heterogenous hematological disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. The median age of diagnosis is 17 years with 53.5% of patients diagnosed at younger than 20 years of age. ALL represents 75 to 80% of acute leukemias among children, making it the most common form of childhood leukemia. ALL is broadly classified in 3 groups based on immunophenotype, which include precursor B-cell ALL, mature B-cell ALL (a.k.a., Burkitt leukemia/lymphoma), and T-cell ALL. In children, B-cell lineage ALL constitutes about 88% of cases. Cure rates and survival outcomes have improved dramatically over the past several decades due to advances in understanding molecular genetics and pathogenesis of the disease, incorporation of risk-adapted therapy, and advent of new targeted agents.

The 5-year overall survival (OS) rate for children is 89% and for adolescent and young adult (AYA) is 61%. However, despite major advances in the treatment of childhood ALL, about 20% of pediatric patients experience relapse after an initial complete response (CR) to frontline treatment. Among those who experience relapse, only 30% experience long-term remission with subsequent therapies. The treatment of ALL represents one of the most complex and intensive programs in cancer therapy. Treatment varies depending on subtype, age, and treatment history. In general, the treatment phases can be largely grouped into induction, consolidation, and maintenance. The National Comprehensive Cancer Network (NCCN) guidelines for ALL list single-agent tisagenlecleucel therapy as a Category 2A recommendation for: (1) relapsed/refractory BCR::ABL1-positive (Ph+) B-ALL in patients <26 years and with refractory disease or ≥2 relapses and following therapy that has included 2 tyrosine kinase inhibitors (TKIs) (listed under "Other Recommended Regimens"), and for (2) relapsed/refractory Ph- B-ALL in patients <26 years and with refractory disease or ≥2 relapses. The NCCN Guidelines for Pediatric ALL list single-agent tisagenlecleucel therapy as a Category 2A recommendation for relapsed/refractory Ph-negative B-ALL that is refractory or ≥2 relapses and relapsed/refractory Ph-positive TKI intolerant/refractory B-ALL or relapse post-HSCT (under "Preferred Regimens"). Single-agent tisagenlecleucel therapy is given a Category 2B recommendation for Ph-negative or Ph-like B-ALL that is minimal residual disease positive (MRD+) after consolidation therapy, and Ph-positive B-ALL with less than complete response or MRD+ at the end of consolidation.

Diffuse large B-cell lymphomas are the most common lymphoid neoplasms in adults, and account for approximately 30% of non-Hodgkin's lymphomas (NHLs) cases diagnosed annually. The DLBCLs exhibits large heterogeneity in morphologic, genetic, and clinical aspects. Multiple clinicopathologic entities are defined by the 2022 World Health Organization (WHO) classification, which are sufficiently distinct to be considered separate diagnostic categories. Adequate immunophenotyping is essential to establish the diagnosis, and to determine germinal center B-cell like (GCB) vs. non-GBC origin. Combination chemoimmunotherapy in the first-line setting (e.g., rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) is associated with a 5-year survival rate ranging from 60% to 70%. Interim restaging should be performed to identify patients who disease has not responded to or has progressed on induction therapy. Based on a number of prognostic factors, 20% to 50% of DLBCL cases are refractory or relapse after first-line chemotherapy and the response rates to subsequent salvage chemotherapy and consolidation with autologous hematopoietic stem cell transplantation (HSCT) is suboptimal. The National Comprehensive Cancer Network (NCCN) B-cell Lymphoma Guidelines list tisagenlecleucel as a category 2A recommendation for the treatment of relapsed/refractory DLBCL, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma [with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma), or not otherwise specified (NOS)], HIV-related DLBCL, primary effusion lymphoma, HHV8-positive DLBCL, NOS, and monomorphic post-transplant lymphoproliferative disorders (PTLD) (B-cell type) for patients with two or more disease relapses (if not previously given) or for patients with a non-complete response (i.e., partial response or worse) to second-line therapy. There is a footnote stating, "Tisagenlecleucel is not FDA-approved for relapsed/refractory primary mediastinal large B-cell lymphoma". Tisagenlecleucel ciloleucel is also a 2A recommendation for the treatment of follicular lymphoma with histological transformation to DLBCL and nodal marginal zone lymphoma with histological transformation to DLBCL in patients with 2 or more prior chemoimmunotherapy regimens (with at least one being an anthracycline or anthracenedione-based regimen, unless contraindicated). The guidelines also list tisagenlecleucel as a category 2A recommendation for the third-line and subsequent therapy of classic follicular lymphoma. It is listed as a

"Preferred regimen" under the subcategory of CAR T-cell therapy which also includes the other CAR-T cell therapies approved for FL of lisocabtagene maraleucel (Breyanzi) and axicabtagene ciloleucel (Yescarta). .

The safety and efficacy of tisagenlecleucel leading to FDA approval for ALL was evaluated in an open-label, multicenter, single-arm phase 2 trial (ELIANA) of pediatric and young adults with relapsed or refractory B-cell precursor ALL. A total of 107 patients were screened, 88 were enrolled, 68 were treated, and 63 were evaluable for efficacy. Eight subjects (9%) did not received treatment due to manufacturing failure. The 63 evaluable patients included 35 males and 28 females of median age 12 years (range, 3 to 23 years). Six (10%) had primary refractory disease, 30 (48%) had one prior stem cell transplantation, and 5 patients (8%) had two stem cell transplantations. The median number of prior lines of therapy was 3 (range 1 to 8). Treatment consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m^2 daily for 4 days and cyclophosphamide 500 mg/m^2 daily for 2 days) followed by a single dose of tisagenlecleucel. Of the 22 patients who had a WBC count less than 1,000/mcL, 20 received lymphodepleting chemotherapy prior to tisagenlecleucel while 2 received tisagenlecleucel infusion without lymphodepleting chemotherapy. Fifty-three patients received bridging chemotherapy between time of enrollment and lymphodepleting chemotherapy. Efficacy was established on the basis of complete remission (CR) or complete remission with incomplete blood count recovery (CRi) within 3 months after infusion, the duration of CR/CRi, and proportion of patients with CR/CRi and minimal residual disease (MRD)-negative (i.e., <0.01% by flow cytometry). Among the 63 infused patients, 52 (83%) achieved CR/CRi, all of which were MRD-negative. With a median follow-up of 4.8 months from response, the median duration of CR/CRi was not reached (range: 1.2 to 14.1+ months). Median time to onset of CR/CRi was 29 days with onset of CR/CRi between 26 and 31 days for 50/52 (96%) responders. The stem cell transplantation rate among those who achieved CR/CRi was 12% (6/52). Adverse events (AEs) were common. The incidence of serious AEs within 8 weeks of infusion was 69%. Cytokine release syndrome (CRS occurred in 78% of patients (21% grade 3; 27% grade 4); no CRS-associated deaths occurred. Tocilizumab for treatment of CRS was given to 38% of patients. The most common grade 3 or 4 non-hematologic adverse events (>15%), other than CRS, were hypotension (22%), hypoxia (18%), and increased aspartate aminotransferase (16%). Grade 3 neuropsychiatric AEs occurred in 15% of patients, with no grade 4 events and no cerebral edema reported. Grade 3 or 4 neutropenia with high (>38.3˚C) fever occurred in 60% of patients.

The safety and efficacy of tisagenlecleucel leading to FDA approval for r/r DLBCL was evaluated in an open-label, multicenter, single-arm phase 2 trial (JULIET). The study included adult patients with r/r DLBCL who received 2 or more lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous HSCT. The study excluded patients with active CNS malignancy, prior allogenic HSCT, and an ECOG performance status of 2 or more. Bridging chemotherapy was permitted at investigator discretion to support patients with progressive disease while awaiting product manufacture. Patients were treated with an IV infusion of 1-5 x 10^8 viable tisagenlecleucel cells after lymphodepletion with cyclophosphamide/fludarabine or bendamustine if their WBC was ≥ 1x10^6 cells/mcL. The primary endpoint was the objective response rate (ORR) per the Lugano criteria [2014] defined as the sum of the percent complete responses and partial responses (% CR + %PR) at the time of best overall response. The durability of response, a key secondary endpoint, was assessed from time of initial response to time of relapse or last observation. Of the 92 patients receiving tisagenlecleucel, 90% received physician's choice of bridging chemotherapy in the interval between start of screening and

tisagenlecleucel infusion. A retrospectively identified sub-group of 68 patients was evaluable for the major efficacy outcome measures. Among the efficacy evaluable population of 68 patients, the baseline characteristics were: median age 56 years (range: 22 to 74 years); 71% male; 78% had primary DLBCL not otherwise specified (NOS) and 22% had DLBCL following transformation from follicular lymphoma, of whom 17% were identified as high grade; and 44% had undergone prior autologous HSCT. The median number of prior therapies was three (range: 1 to 6), 56% had refractory disease and 44% relapsed after their last therapy. Seventy-three percent (73%) of patients received tisagenlecleucel in the inpatient setting. The ORR was 50% (n=34, 95% CI 37.6 to 62.4%). Complete response was seen in 22 patients (32%) and partial response in 12 patients (18%). The median time to first response (CR or PR) was 0.9 months (range: 0.7 to 3.3 months). The median duration of response was not reached. Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial response (PR). The most common adverse reactions were cytokine release syndrome (74%, Grade 3 or higher 23%), infections (42%, Grade 3 or higher 25%), diarrhea (31%), nausea (27%), pyrexia (34%), fatigue (26%), hypotension (26%, Grade 3 or higher 8%), edema (23%), headache (21%), febrile neutropenia (17%), encephalopathy (16%, Grade 3 or higher 11%), and hypogammaglobulinemia (14%).

POSITION STATEMENT:

NOTE: The FDA requires cell viability of 80% or greater to meet its specifications for the use of commercial CAR-T cell products. Therefore, a product that is less than 80% viability is not considered an FDA-approved medication and is not a covered benefit.

Axicabtagene Ciloleucel (Yescarta)

Administration of axicabtagene ciloleucel (Yescarta) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "9"):

1. Member will be 18 years of age or older at the time of the treatment infusion*

   **Does not apply to the indication of pediatric primary mediastinal large B-cell lymphoma*

2. Member has a diagnosis of **ANY** of the following ("a", "b", or "c"):
   a. Large B-cell lymphoma that includes any of the following subtypes ("i" to "xxiv") – documentation from the medical record confirming the diagnosis and specific subtype must be submitted:
      i. ALK-positive large B-cell lymphoma
      ii. Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) [includes germinal center and non-germinal center]
      iii. DLBCL arising from CLL/SLL [a.k.a., Richter transformation]
      iv. DLBCL arising from follicular lymphoma [a.k.a., follicular lymphoma with histological transformation to DLBCL or transformed follicular lymphoma (TFL)]
      v. DLBCL arising from nodal marginal zone lymphoma [a.k.a., nodal marginal zone lymphoma with histological transformation to DLBCL]
      vi. DLBCL associated with chronic inflammation

vii. DLBCL coexistent with follicular lymphoma of any grade, extranodal marginal zone lymphoma of non-gastric sites (noncutaneous), or extranodal marginal zone lymphoma of the stomach

viii. Double expressor DLBCL

ix. EBV (Epstein-Barr virus)-positive DLBCL, NOS

x. Fibrin-associated large B-cell lymphoma

xi. Follicular lymphoma grade 3B

xii. High-grade B-cell lymphoma (HGBL), NOS

xiii. High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* translocations [a.k.a., double-hit or triple-hit lymphomas]

xiv. HHV8 (human herpesvirus 8)-positive diffuse large B-cell lymphoma, NOS

xv. HIV-related diffuse large B-cell lymphoma

xvi. Intravascular large B-cell lymphoma

xvii. Large B-cell lymphoma with *IRF4/MUM1* rearrangement

xviii. Mediastinal grey zone lymphoma (MGZL)

xix. Monomorphic post-transplant lymphoproliferative disorders (PTLD) (B-cell type)

xx. Plasmablastic lymphoma (PBL)

xxi. Primary cutaneous DLBCL, leg type

xxii. Primary effusion lymphoma (PEL)

xxiii. Primary mediastinal large B-cell lymphoma (PMBCL or PMBL) [in adults]

xxiv. T-cell-/histiocyte-rich large B-cell lymphoma

b. Follicular lymphoma (grades 1, 2, or 3A) (i.e., classic follicular lymphoma) - documentation from the medical record confirming the diagnosis and grade must be submitted

c. Marginal zone lymphoma (MZL) that includes any of the following subtypes ("i" to "iv") – documentation from the medical record confirming the diagnosis and specific subtype must be submitted:

i. Extranodal marginal zone lymphoma of the stomach

ii. Extranodal marginal zone lymphoma of non-gastric sites (noncutaneous)

iii. Nodal marginal zone lymphoma

iv. Splenic marginal zone lymphoma

d. Pediatric (less than 18 years of age) primary mediastinal large B-cell lymphoma (PMBL) - documentation from the medical record confirming the diagnosis must be submitted

3. **ONE** of the following depending on the indication for use:

a. Adult (18 years of age and older) large B-cell lymphomas – **BOTH** of the following ("i" and ii"):

i. **ANY** of the following:

- Member has primary refractory disease [i.e., unable to achieve a complete response (CR) following first-line systemic chemotherapy] – treatment must include a minimum of 3 cycles of therapy
- Member had a disease relapse occurring less than 12 months after the completion of first-line systemic chemotherapy
- Member was unable to achieve a CR following their second line of systemic chemotherapy
- Member's disease is in second or greater relapse/recurrence

ii. **EITHER** of the following

- For primary refractory disease and disease relapse occurring less than 12 months after first-line systemic chemotherapy - member has received first-line systemic chemotherapy for their disease which must have included an anthracycline, unless contraindicated, and an anti-CD20 monoclonal antibody (e.g., rituximab) unless the tumor is CD20 negative or the member has an FDA-labeled contraindication to anti-CD20 therapy – medical record documentation of the member's first-line therapy for their lymphoma must be submitted
- For later relapses - member has received **TWO** or more unique lines of systemic chemotherapy for their disease (which may or may not include therapy supported by autologous stem cell transplant), **AND** prior therapy must have included an anti-CD20 monoclonal antibody (e.g., rituximab, obinutuzumab) unless the tumor is CD20 negative or the member has an FDA-labeled contraindication to anti-CD20 therapy – medical record documentation of the member's prior lines of therapy for their lymphoma must be submitted

b. Follicular lymphomas (i.e., classic follicular lymphoma) or marginal zone lymphomas - **BOTH** of the following ("i" and ii"):

i. Member has relapsed or refractory disease meeting **EITHER** of the following criteria:

- Member was unable to achieve a complete response (CR) following their second line of systemic chemotherapy
- Member's disease is in second or greater relapse/recurrence

ii. Member has received **TWO** or more unique lines of systemic chemotherapy for their disease (which may or may not include therapy supported by autologous stem cell transplant), **AND** prior therapy must have included an anti-CD20 monoclonal antibody (e.g., rituximab, obinutuzumab) unless the tumor is CD20 negative, or the member has an FDA-labeled contraindication to anti-CD20 therapy – medical record documentation of the member's prior lines of therapy for their lymphoma must be submitted

c. Pediatric (less than 18 years of age) primary mediastinal large B-cell lymphoma (PMBL) - **BOTH** of the following ("i" and ii"):

i. Member has achieved a partial response (PR) [does **NOT** include complete response (CR)] following second line or later systemic chemotherapy for relapsed or refractory disease

ii. Member has received **TWO** or more unique lines of systemic chemotherapy for their disease (which may or may not include therapy supported by autologous stem cell transplant), **AND** prior therapy must have included an anti-CD20 monoclonal antibody (e.g., rituximab,

obinutuzumab) unless the tumor is CD20 negative or the member has an FDA-labeled contraindication to anti-CD20 therapy – medical record documentation of the member's prior lines of therapy for their lymphoma must be submitted

4. Following the completion of lymphodepleting chemotherapy (as needed), axicabtagene ciloleucel will be used as single-agent therapy (i.e., not used in combination with maintenance chemotherapy)
5. Member has been assessed, and has stable and adequate organ function (kidney, liver, pulmonary and cardiac function) and bone marrow function with no significant deterioration expected within 4 weeks after apheresis as determined by the treating oncologist/hematologist
6. Axicabtagene ciloleucel will not be administered if the member has an uncontrolled systemic infection at the time of planned treatment initiation
7. Member has **NOT** previously received CD19-directed chimeric antigen receptor (CAR) T-cell therapy (including axicabtagene ciloleucel) in their lifetime for the treatment of lymphoma or leukemia
8. The healthcare facility administering axicabtagene ciloleucel is currently accredited by the Foundation for the Accreditation of Cellular Therapy (i.e., a FACT-accredited organization) specifically for the clinical service of "Immune Effector Cellular Therapy" - accreditation status must be verified at https://accredited.factglobal.org/
9. The administration of axicabtagene ciloleucel will not exceed one single dose as provided by the manufacturer.

Approval duration: 3 months to allow for a one-time infusion of therapy

Axicabtagene ciloleucel (Yescarta) is considered **experimental or investigational** for all other indications, including but not limited to the following, due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes:

- All non-lymphoma malignancies
- Burkitt lymphoma/leukemia (i.e., patients with mature B-cell ALL)
- Castleman's disease
- Lymphoblastic lymphoma
- Mantle cell lymphoma
- Non-B-cell lymphomas (e.g., T-cell lymphomas)
- Primary cutaneous B-cell lymphomas [other than primary cutaneous DLBCL, leg type]
- Primary DLBCL of the central nervous system (CNS)

Brexucabtagene Autoleucel (Tecartus)

Administration of brexucabtagene autoleucel (Tecartus) **meets the definition of medical necessity** for members diagnosed with **EITHER** of the following conditions ("1" or "2"), and **ALL** associated criteria are met:

1. Mantle cell lymphoma (MCL) - medical record documentation supporting the diagnosis must be submitted:

a. Member will be 18 years of age or older at the time of the treatment infusion

b. Member has relapsed or refractory disease

c. Member has been previously treated with **BOTH** of the following ("i" and "ii") - medical record documentation of the member's prior MCL treatment history must be submitted:

   i. A National Comprehensive Cancer Network (NCCN)-recommended chemoimmunotherapy induction regimen for MCL [for example: RDHA (rituximab, dexamethasone, cytarabine) + platinum agent, alternating RCHOP/RDHAP, NORDIC regimen alternating with rituximab + high-dose cytarabine, HyperCVAD + rituximab, bendamustine + rituximab, VR-CAP, RCHOP, lenalidomide + rituximab, RBAC500]

   ii. A Bruton Tyrosine Kinase (BTK) inhibitor [e.g., acalabrutinib (Calquence), ibrutinib (Imbruvica), zanubrutinib (Brukinsa)]

d. Following the completion of lymphodepleting chemotherapy, brexucabtagene autoleucel will be used as single-agent therapy (i.e., not used in combination with maintenance chemotherapy)

e. Member has been assessed, and has stable and adequate organ function (kidney, liver, pulmonary and cardiac function) and bone marrow function with no significant deterioration expected within 4 weeks after apheresis as determined by the treating oncologist/hematologist

f. Brexucabtagene autoleucel will not be administered if the member has an uncontrolled systemic infection at the time of planned treatment initiation

g. Member has **NOT** previously received CD19-directed chimeric antigen receptor (CAR) T-cell therapy (including brexucabtagene autoleucel) in their lifetime for the treatment of lymphoma

h. The healthcare facility administering brexucabtagene autoleucel is currently accredited by the Foundation for the Accreditation of Cellular Therapy (i.e., a FACT-accredited organization) specifically for the clinical service of "Immune Effector Cellular Therapy" - accreditation status must be verified at https://accredited.factglobal.org/

i. The administration of brexucabtagene autoleucel will not exceed one single dose as provided by the manufacturer

2. B-cell precursor acute lymphoblastic leukemia (ALL):

   a. The member will be 18 years of age or older at the time of the treatment infusion

   b. The member has relapsed, or refractory disease as defined by **ANY** of the following ("i" to "iv") – medical record documentation confirming the member's diagnosis, prior leukemia treatments, and treatment responses must be submitted:

      i. Member has primary refractory disease defined as the inability to achieve a complete remission (CR) at the end of initial induction chemotherapy

      ii. Member has had a first relapse occurring 12 months or less after their initial remission

      iii. Member has relapsed or refractory disease after an allogeneic stem cell transplant

      iv. Member has experienced **TWO** or more disease relapses (after achieving CR) following recommended systemic chemotherapies. For members with BCR::ABL1-positive ALL [aka, Philadelphia chromosome positive (Ph+) ALL], treatment must have included at least two different tyrosine kinase inhibitors (TKIs) unless TKI use is contraindicated or was not tolerated (the specific contraindication(s) and/or intolerance(s) must be provided).

c. The member will receive a lymphodepleting chemotherapy regimen (e.g., fludarabine and cyclophosphamide) to be completed 2 to 4 days prior to the administration of brexucabtagene autoleucel, **OR** the treating physician attests that a lymphodepleting regimen is not appropriate due to profound leukopenia

d. Following the completion of lymphodepleting chemotherapy (as needed), brexucabtagene autoleucel will be used as single-agent therapy (i.e., not used in combination with maintenance chemotherapy)

e. Member has been assessed, and has stable and adequate organ function (kidney, liver, pulmonary and cardiac function) and bone marrow function with no significant deterioration expected within 4 weeks after apheresis as determined by the treating oncologist/hematologist

f. Brexucabtagene autoleucel will not be administered if the member has an uncontrolled systemic infection at the time of planned treatment initiation

g. For members previously treated with blinatumomab (Blincyto) **ONLY** - the member is positive for CD19 tumor expression in bone marrow or peripheral blood

h. Member has **NOT** previously received CD19-directed chimeric antigen receptor (CAR) T-cell therapy (including brexucabtagene autoleucel and tisagenlecleucel) in their lifetime for the treatment of lymphoma or leukemia

i. The healthcare facility administering brexucabtagene autoleucel is currently accredited by the Foundation for the Accreditation of Cellular Therapy (i.e., a FACT-accredited organization) specifically for the clinical service of "Immune Effector Cellular Therapy" - accreditation status must be verified at https://accredited.factglobal.org/

j. The administration of brexucabtagene autoleucel will not exceed one single dose as provided by the manufacturer

Approval duration: 3 months to allow for a one-time infusion of therapy

Brexucabtagene autoleucel (Tecartus) is considered **experimental or investigational** for all other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes.

Ciltacabtagene Autoleucel (Carvykti)

Administration of ciltacabtagene autoleucel (Carvykti) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "8"):

1. Member will be 18 years of age or older at the time of the treatment infusion
2. Member has a diagnosis of relapsed or refractory multiple myeloma (MM), and **EITHER** of the following ("a" or "b") – medical record documentation confirming the patient's diagnosis and complete treatment history must be submitted:
    a. **ALL** of the following ("i", "ii", and "iii"):
        i. Member has received at least **ONE** appropriate prior line of therapy of adequate duration for the treatment of their MM

        NOTE: Primary therapy, with or without subsequent hematopoietic cell transplant, followed by maintenance therapy is considered a single line of therapy

ii. Member's prior MM treatment has included **BOTH** of the following ("1" and "2"):

1. A proteasome inhibitor [for example - bortezomib, carfilzomib (Kyprolis), or ixazomib (Ninlaro)]
2. An immunomodulatory agent [for example - lenalidomide (Revlimid), pomalidomide (Pomalyst), or thalidomide (Thalomid)]

iii. Member is refractory to lenalidomide (i.e., disease progression on treatment or progression within 60 days of the last dose of therapy; this includes disease progression during primary therapy or low-dose maintenance therapy)

b. **BOTH** of the following ("i" and "ii"):

i. Member has received **THREE** or more appropriate prior lines of therapy of adequate duration for the treatment of their MM

NOTE: Primary therapy, with or without subsequent hematopoietic cell transplant, followed by maintenance therapy is considered a single line of therapy

ii. Member's prior MM treatments have included **ALL** of the following (i.e., triple-class exposed):

- An anti-CD38 monoclonal antibody [for example - daratumumab (Darzalex), daratumumab-hyaluronidase (Darzalex Faspro), or isatuximab (Sarclisa)]
- A proteasome inhibitor [for example - bortezomib, carfilzomib (Kyprolis), or ixazomib (Ninlaro)]
- An immunomodulatory agent [for example - lenalidomide (Revlimid), pomalidomide (Pomalyst), or thalidomide (Thalomid)]

3. Following the completion of lymphodepleting chemotherapy, ciltacabtagene autoleucel will be used as single-agent therapy (i.e., not used in combination with maintenance chemotherapy)
4. Member has been assessed, and has stable and adequate organ function (kidney, liver, pulmonary and cardiac function) and bone marrow function with no significant deterioration expected within 4 weeks after apheresis as determined by the treating oncologist/hematologist
5. Ciltacabtagene autoleucel will not be administered if the member has an uncontrolled systemic infection at the time of planned treatment initiation
6. Member has **NOT** previously received BCMA-directed chimeric antigen receptor (CAR) T-cell therapy (including ciltacabtagene autoleucel and idecabtagene vicleucel) in their lifetime for the treatment of MM
7. The healthcare facility administering ciltacabtagene autoleucel is currently accredited by the Foundation for the Accreditation of Cellular Therapy (i.e., a FACT-accredited organization) specifically for the clinical service of "Immune Effector Cellular Therapy" - accreditation status must be verified at https://accredited.factglobal.org/
8. The administration of ciltacabtagene autoleucel will not exceed one single dose as provided by the manufacturer

Approval duration: 3 months to allow for a one-time infusion of therapy

Ciltacabtagene autoleucel (Carvykti) is considered **experimental or investigational** for all other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes.

Idecabtagene Vicleucel (Abecma)

Administration of idecabtagene vicleucel (Abecma) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "8"):

1. Member will be 18 years of age or older at the time of the treatment infusion
2. Member has a diagnosis of relapsed or refractory multiple myeloma (MM), and **BOTH** of the following ("a" and "b") – medical record documentation confirming the patient's diagnosis and complete treatment history must be submitted:
    a. Member has received **TWO or more** appropriate prior lines of therapy of adequate duration for the treatment of their MM

       NOTE: Primary therapy, with or without subsequent hematopoietic cell transplant, followed by maintenance therapy is considered a single line of therapy

    b. Member's prior MM treatments have included **ALL** of the following (i.e., triple-class exposed) ("i", "ii", and "iii"):
        i. An anti-CD38 monoclonal antibody [for example - daratumumab (Darzalex), daratumumab-hyaluronidase (Darzalex Faspro), or isatuximab (Sarclisa)]
        ii. A proteasome inhibitor [for example - bortezomib, carfilzomib (Kyprolis), or ixazomib (Ninlaro)]
        iii. An immunomodulatory agent [for example - lenalidomide (Revlimid), pomalidomide (Pomalyst), or thalidomide (Thalomid)]
3. Following the completion of lymphodepleting chemotherapy, idecabtagene vicleucel will be used as single-agent therapy (i.e., not used in combination with maintenance chemotherapy)
4. Member has been assessed, and has stable and adequate organ function (kidney, liver, pulmonary and cardiac function) and bone marrow function with no significant deterioration expected within 4 weeks after apheresis as determined by the treating oncologist/hematologist
5. Idecabtagene vicleucel will not be administered if the member has an uncontrolled systemic infection at the time of planned treatment initiation
6. Member has **NOT** previously received BCMA-directed chimeric antigen receptor (CAR) T-cell therapy (including idecabtagene vicleucel and ciltacabtagene autoleucel) in their lifetime for the treatment of MM
7. The healthcare facility administering idecabtagene vicleucel is currently accredited by the Foundation for the Accreditation of Cellular Therapy (i.e., a FACT-accredited organization) specifically for the clinical service of "Immune Effector Cellular Therapy" - accreditation status must be verified at https://accredited.factglobal.org/
8. The administration of idecabtagene vicleucel will not exceed one single dose as provided by the manufacturer

Approval duration: 3 months to allow for a one-time infusion of therapy

Idecabtagene vicleucel (Abecma) is considered **experimental or investigational** for all other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes.

Lisocabtagene Maraleucel (Breyanzi)

Administration of lisocabtagene maraleucel (Breyanzi) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "9"):

1. Member will be 18 years of age or older at the time of the treatment infusion*

   ** Does not apply to the indication of pediatric primary mediastinal large B-cell lymphoma*

2. Member has a diagnosis of **ANY** the following ("a" to "f"):
   a. Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) - documentation from the medical record confirming the diagnosis must be submitted
   b. Follicular lymphoma (grades 1, 2, or 3A) (i.e., classic follicular lymphoma) - documentation from the medical record confirming the diagnosis and grade must be submitted
   c. Large B-cell lymphoma that includes any of the following subtypes ("i" to "xxiv") - documentation from the medical record confirming the diagnosis and specific subtype must be submitted:
      i. ALK-positive large B-cell lymphoma
      ii. Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) [includes germinal center and non-germinal center]
      iii. DLBCL arising from CLL/SLL [a.k.a., Richter transformation]
      iv. DLBCL arising from follicular lymphoma [a.k.a., follicular lymphoma with histological transformation to DLBCL or transformed follicular lymphoma (TFL)]
      v. DLBCL arising from nodal marginal zone lymphoma [a.k.a., nodal marginal zone lymphoma with histological transformation to DLBCL]
      vi. DLBCL associated with chronic inflammation
      vii. DLBCL coexistent with follicular lymphoma of any grade, extranodal marginal zone lymphoma of non-gastric sites (noncutaneous), or extranodal marginal zone lymphoma of the stomach
      viii. Double expressor DLBCL
      ix. EBV (Epstein-Barr virus)-positive DLBCL, NOS
      x. Fibrin-associated large B-cell lymphoma
      xi. Follicular lymphoma grade 3B
      xii. High-grade B-cell lymphoma (HGBL), NOS
      xiii. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 translocations [a.k.a., double-hit or triple-hit lymphomas]

xiv. HHV8 (human herpesvirus 8)-positive diffuse large B-cell lymphoma, NOS

xv. HIV-related diffuse large B-cell lymphoma

xvi. Intravascular large B-cell lymphoma

xvii. Large B-cell lymphoma with *IRF4/MUM1* rearrangement

xviii. Mediastinal grey zone lymphoma (MGZL)

xix. Monomorphic post-transplant lymphoproliferative disorders (PTLD) (B-cell type)

xx. Plasmablastic lymphoma (PBL)

xxi. Primary cutaneous DLBCL, leg type

xxii. Primary effusion lymphoma (PEL)

xxiii. Primary mediastinal large B-cell lymphoma (PMBCL or PMBL) [in adults]

xxiv. T-cell-/histiocyte-rich large B-cell lymphoma

d. Mantle cell lymphoma (MCL) - documentation from the medical record confirming the diagnosis must be submitted

e. Marginal zone lymphoma (MZL) that includes any of the following subtypes ("i" to "iv") – documentation from the medical record confirming the diagnosis and specific subtype must be submitted:

   i. Extranodal marginal zone lymphoma of the stomach

   ii. Extranodal marginal zone lymphoma of non-gastric sites (noncutaneous)

   iii. Nodal marginal zone lymphoma

   iv. Splenic marginal zone lymphoma

f. Pediatric (less than 18 years of age) primary mediastinal large B-cell lymphoma (PMBL) - documentation from the medical record confirming the diagnosis must be submitted

3. **ONE** of the following depending on the indication for use:

   a. Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) - **BOTH** of the following ("i" and "ii"):

      i. Member has relapsed or refractory disease, **AND** has received **TWO** or more unique prior lines of systemic therapy for their disease

      ii. Prior therapy must have included **BOTH** a Bruton tyrosine kinase (BTK) inhibitor [e.g., acalabrutinib (Calquence), ibrutinib (Imbruvica), pirtobrutinib (Jaypirca), zanubrutinib (Brukinsa)] **AND** a B-cell lymphoma 2 (BCL-2) inhibitor [e.g., venetoclax (Venclexta)] - medical record documentation of the member's prior lines of therapy for their CLL or SLL must be submitted

   b. Follicular lymphoma (grades 1, 2, or 3A) (i.e., classic follicular lymphoma) or marginal zone lymphoma - **BOTH** of the following ("i" and "ii"):

      i. Member has relapsed or refractory disease meeting **EITHER** of the following criteria:

         - Member was unable to achieve a complete response (CR) following their second line of systemic chemotherapy

- Member's disease is in second or greater relapse/recurrence

ii. Member has received **TWO** or more unique lines of systemic chemotherapy for their disease (which may or may not include therapy supported by autologous stem cell transplant), **AND** prior therapy must have included an anti-CD20 monoclonal antibody (e.g., rituximab, obinutuzumab) unless the tumor is CD20 negative, or the member has an FDA-labeled contraindication to anti-CD20 therapy – medical record documentation of the member's prior lines of therapy for their lymphoma must be submitted

c. Adult (18 years of age and older) large B-cell lymphomas – **BOTH** of the following ("i" and "ii"):

i. **ANY** of the following criteria:

- Member has primary refractory disease [i.e., unable to achieve a complete response (CR) following first-line systemic chemotherapy] – treatment must include a minimum of 3 cycles of therapy
- Member had a disease relapse occurring less than 12 months after the completion of first-line systemic chemotherapy
- Member had a disease relapse occurring 12 or more months after the completion of first-line systemic chemotherapy, **AND** the member does **NOT** intend to proceed to hematopoietic stem cell transplantation – documentation of the member's lack of intent to proceed to transplant must be submitted
- Member was unable to achieve a complete response (CR) following their second line of systemic chemotherapy
- Member's disease is in second or greater relapse/recurrence

ii. **EITHER** of the following:

- For primary refractory disease and disease relapse after first-line systemic chemotherapy - member has received first-line systemic chemotherapy for their disease which must have included an anthracycline, unless contraindicated, and an anti-CD20 monoclonal antibody (e.g., rituximab) unless the tumor is CD20 negative, or the member has an FDA-labeled contraindication to anti-CD20 therapy – medical record documentation of the member's first-line therapy for their lymphoma must be submitted
- For later relapses - member has received **TWO** or more unique lines of systemic chemotherapy for their disease (which may or may not include therapy supported by autologous stem cell transplant), **AND** prior therapy must have included an anti-CD20 monoclonal antibody (e.g., rituximab, obinutuzumab) unless the tumor is CD20 negative or the member has an FDA-labeled contraindication to anti-CD20 therapy – medical record documentation of the member's prior lines of therapy for their lymphoma must be submitted

d. Mantle cell lymphoma (MCL) - **BOTH** of the following:

i. Member has relapsed or refractory disease

ii. Member has been previously treated with **BOTH** of the following ("1" and "2") - medical record documentation of the member's prior MCL treatment history must be submitted:

1. A National Comprehensive Cancer Network (NCCN)-recommended chemoimmunotherapy induction regimen for MCL [for example: RDHA (rituximab,

dexamethasone, cytarabine) + platinum agent, alternating RCHOP/RDHAP, NORDIC regimen alternating with rituximab + high-dose cytarabine, HyperCVAD + rituximab, bendamustine + rituximab, VR-CAP, RCHOP, lenalidomide + rituximab, RBAC500]

2. A Bruton Tyrosine Kinase (BTK) inhibitor [e.g., acalabrutinib (Calquence), ibrutinib (Imbruvica), zanubrutinib (Brukinsa)]

e. Pediatric (less than 18 years of age) primary mediastinal large B-cell lymphoma (PMBL) - **BOTH** of the following ("i" and ii"):

i. Member has achieved a partial response (PR) [does **NOT** include complete response (CR)] following second line or later systemic chemotherapy for relapsed or refractory disease

ii. Member has received **TWO** or more unique lines of systemic chemotherapy for their disease (which may or may not include therapy supported by autologous stem cell transplant), **AND** prior therapy must have included an anti-CD20 monoclonal antibody (e.g., rituximab, obinutuzumab) unless the tumor is CD20 negative or the member has an FDA-labeled contraindication to anti-CD20 therapy – medical record documentation of the member's prior lines of therapy for their lymphoma must be submitted

4. Following the completion of lymphodepleting chemotherapy (as needed), lisocabtagene maraleucel will be used as single-agent therapy (i.e., not used in combination with maintenance chemotherapy)*

**Exception allowed for treatment of CLL/SLL in which ibrutinib can be given as combination therapy*

5. Member has been assessed, and has stable and adequate organ function (kidney, liver, pulmonary and cardiac function) and bone marrow function with no significant deterioration expected within 4 weeks after apheresis as determined by the treating oncologist/hematologist

6. Lisocabtagene maraleucel will not be administered if the member has an uncontrolled systemic infection at the time of planned treatment initiation

7. Member has **NOT** previously received CD19-directed chimeric antigen receptor (CAR) T-cell therapy (including lisocabtagene maraleucel) in their lifetime for the treatment of lymphoma or leukemia

8. The healthcare facility administering lisocabtagene maraleucel is currently accredited by the Foundation for the Accreditation of Cellular Therapy (i.e., a FACT-accredited organization) specifically for the clinical service of "Immune Effector Cellular Therapy" - accreditation status must be verified at https://accredited.factglobal.org/

9. The administration of lisocabtagene maraleucel will not exceed one single dose (given as sequential infusions of the two separate $CD8^+$ and $CD4^+$ CAR T-cell components) as provided by the manufacturer

Approval duration: 3 months to allow for a one-time infusion of therapy

Lisocabtagene maraleucel (Breyanzi) is considered **experimental or investigational** for all other indications, including but not limited to the following, due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes:

- Burkitt lymphoma/leukemia (i.e., patients with mature B-cell ALL)
- Castleman's disease
- Lymphoblastic lymphoma

- Non-B-cell lymphomas (e.g., T-cell lymphomas)
- Primary cutaneous B-cell lymphomas [other than primary cutaneous DLBCL, leg type]
- Primary DLBCL of the central nervous system (CNS)

Obecabtagene Autoleucel (Aucatzyl)

Administration of obecabtagene autoleucel (Aucatzyl) meets the definition of medical necessity for members diagnosed with B-cell precursor acute lymphoblastic leukemia (ALL) when **ALL** of the following criteria are met ("1" to "10"):

1. The member will be 18 years of age or older at the time of the treatment infusion
2. The member has relapsed, or refractory disease as defined by **ANY** of the following ("a" to "d") – medical record documentation confirming the member's diagnosis, prior leukemia treatments, and treatment responses must be submitted:
    a. Member has primary refractory disease defined as the inability to achieve a complete remission (CR) at the end of initial induction chemotherapy
    b. Member has had a first relapse occurring 12 months or less after their initial remission
    c. Member has relapsed or refractory disease after an allogeneic stem cell transplant
    d. Member has experienced **TWO** or more disease relapses (after achieving CR) following recommended systemic chemotherapies. For members with BCR::ABL1-positive ALL [aka, Philadelphia chromosome positive (Ph+) ALL], treatment must have included at least two different tyrosine kinase inhibitors (TKIs) unless TKI use is contraindicated or was not tolerated (the specific contraindication(s) and/or intolerance(s) must be provided).
3. The member will receive a lymphodepleting chemotherapy regimen (e.g., fludarabine and cyclophosphamide) to be completed 2 to 4 days prior to the administration of obecabtagene autoleucel, **OR** the treating physician attests that a lymphodepleting regimen is not appropriate due to profound leukopenia
4. Following the completion of lymphodepleting chemotherapy (as needed), obecabtagene autoleucel will be used as single-agent therapy (i.e., not used in combination with maintenance chemotherapy)
5. Member has been assessed, and has stable and adequate organ function (kidney, liver, pulmonary and cardiac function) and bone marrow function with no significant deterioration expected within 4 weeks after apheresis as determined by the treating oncologist/hematologist
6. Obecabtagene autoleucel will not be administered if the member has an uncontrolled systemic infection at the time of planned treatment initiation
7. For members previously treated with blinatumomab (Blincyto) **ONLY** - the member is positive for CD19 tumor expression in bone marrow or peripheral blood
8. Member has **NOT** previously received CD19-directed chimeric antigen receptor (CAR) T-cell therapy (including obecabtagene autoleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, and tisagenlecleucel) in their lifetime for the treatment of lymphoma or leukemia
9. The healthcare facility administering obecabtagene autoleucel is currently accredited by the Foundation for the Accreditation of Cellular Therapy (i.e., a FACT-accredited organization) specifically

for the clinical service of “Immune Effector Cellular Therapy” - accreditation status must be verified at https://accredited.factglobal.org/

10. The administration of obecabtagene autoleucel will not exceed one split-dose treatment course [i.e., one partial-dose infusion given on day 1 and one partial-dose infusion on day 10 (± 2 days)]) as provided by the manufacturer [the manufacturer will send both required doses as a single shipment]

Approval duration: 3 months to allow for a one-time split-dose treatment course

Obecabtagene Autoleucel (Aucatzyl) is considered experimental or investigational for all other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes.

Tisagenlecleucel (Kymriah)

Initiation of tisagenlecleucel (Kymriah) **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions (“1”, “2”, or “3”), and **ALL** associated criteria are met:

1. B-cell precursor acute lymphoblastic leukemia (ALL):
    a. The member will be less than or equal to 25 years of age at the time of the of the treatment infusion
    b. The member is positive for CD19 tumor expression in bone marrow or peripheral blood – documentation from the medical record confirming the result must be submitted
    c. The member has relapsed, or refractory disease as defined by **ANY** of the following* (“i” to “iv”) – medical record documentation confirming the member’s diagnosis, prior leukemia treatments, and treatment responses must be submitted:
    d. Member has primary refractory disease defined as the inability to achieve a complete remission (CR) at the end of initial induction chemotherapy
    e. Member has had a first relapse occurring 12 months or less after their initial remission
    f. Member has relapsed or refractory disease after an allogeneic stem cell transplant
    g. Member has experienced **TWO or more** disease relapses (after achieving CR) following recommended systemic chemotherapies. For members with BCR::ABL1-positive ALL [aka, Philadelphia chromosome positive (Ph+) ALL], treatment must have included at least two different tyrosine kinase inhibitors (TKIs) unless TKI use is contraindicated or was not tolerated (the specific contraindication(s) and/or intolerance(s) must be provided).
    h. The member will receive a lymphodepleting chemotherapy regimen (e.g., fludarabine and cyclophosphamide) to be completed 2 to 14 days prior to the administration of tisagenlecleucel, **OR** the treating physician attests that a lymphodepleting regimen is not appropriate due to profound leukopenia
    i. Following the completion of lymphodepleting chemotherapy (as needed), tisagenlecleucel will be used as single-agent therapy (i.e., not used in combination with maintenance chemotherapy)
    j. Member has been assessed, and has stable and adequate organ function (kidney, liver, pulmonary and cardiac function) and bone marrow function with no significant deterioration expected within 4 weeks after apheresis as determined by the treating oncologist/hematologist

k. Tisagenlecleucel will not be administered if the member has an uncontrolled systemic infection at the time of planned treatment initiation

l. Member has **NOT** previously received CD19-directed chimeric antigen receptor (CAR) T-cell therapy (including tisagenlecleucel) in their lifetime for the treatment of lymphoma or leukemia

m. The healthcare facility administering tisagenlecleucel is currently accredited by the Foundation for the Accreditation of Cellular Therapy (i.e., a FACT-accredited organization) specifically for the clinical service of "Immune Effector Cellular Therapy" - accreditation status must be verified at https://accredited.factglobal.org/

n. The dose of tisagenlecleucel will not exceed the following based on the member's body weight at the time of leukapheresis:

- 50 kg or less: 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg
- Greater than 50 kg: administer 0.1 to 2.5 x 10^8 CAR-positive viable T cells (non-weight based)

2. Follicular lymphoma

a. Member is 18 years of age or older at the time of the of the treatment infusion

b. The member has follicular lymphoma grade 1, 2, or 3A (i.e., classic follicular lymphoma) - documentation from the medical record confirming the diagnosis and grade must be submitted

c. Member has relapsed or refractory disease meeting **EITHER** of the following criteria ("i" or ii"):

i. Member was unable to achieve a complete response (CR) following their second line of systemic chemotherapy

ii. Member's disease is in second or greater relapse/recurrence

d. Member has received **TWO** or more unique lines of systemic chemotherapy for their disease (which may or may not include therapy supported by autologous stem cell transplant), **AND** prior therapy must have included an anti-CD20 monoclonal antibody (e.g., rituximab, obinutuzumab) unless the tumor is CD20 negative, or the member has an FDA-labeled contraindication to anti-CD20 therapy – medical record documentation of the member's prior lines of therapy for their lymphoma must be submitted

e. Following the completion of lymphodepleting chemotherapy (as needed), tisagenlecleucel will be used as single-agent therapy (i.e., not used in combination with maintenance chemotherapy)

f. Member has been assessed, and has stable and adequate organ function (kidney, liver, pulmonary and cardiac function) and bone marrow function with no significant deterioration expected within 4 weeks after apheresis as determined by the treating oncologist/hematologist

g. Tisagenlecleucel will not be administered if the member has an uncontrolled systemic infection at the time of planned treatment initiation

h. Member has **NOT** previously received CD19-directed chimeric antigen receptor (CAR) T-cell therapy (including tisagenlecleucel) in their lifetime for the treatment of lymphoma or leukemia

i. The healthcare facility administering tisagenlecleucel is currently accredited by the Foundation for the Accreditation of Cellular Therapy (i.e., a FACT-accredited organization) specifically for the clinical service of "Immune Effector Cellular Therapy" - accreditation status must be verified at https://accredited.factglobal.org/

j. The administration of tisagenlecleucel will not exceed one single dose as provided by the manufacturer

3. Large B-cell lymphoma:
    a. Member is 18 years of age or older at the time of the of the treatment infusion
    b. The members large B-cell lymphoma includes any of the following subtypes (“i” to “xxiv”) - documentation from the medical record confirming the diagnosis and specific subtype must be submitted:
        i. ALK-positive large B-cell lymphoma
        ii. Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) [includes germinal center and non-germinal center]
        iii. DLBCL arising from CLL/SLL [a.k.a., Richter transformation]
        iv. DLBCL arising from follicular lymphoma [a.k.a., follicular lymphoma with histological transformation to DLBCL or transformed follicular lymphoma (TFL)]
        v. DLBCL arising from nodal marginal zone lymphoma [a.k.a., nodal marginal zone lymphoma with histological transformation to DLBCL]
        vi. DLBCL associated with chronic inflammation
        vii. DLBCL coexistent with follicular lymphoma of any grade, extranodal marginal zone lymphoma of non-gastric sites (noncutaneous), or extranodal marginal zone lymphoma of the stomach
        viii. Double expressor DLBCL
        ix. EBV (Epstein-Barr virus)-positive DLBCL, NOS
        x. Fibrin-associated large B-cell lymphoma
        xi. Follicular lymphoma grade 3B
        xii. High-grade B-cell lymphoma (HGBL), NOS
        xiii. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 translocations [a.k.a., double-hit or triple-hit lymphomas]
        xiv. HHV8 (human herpesvirus 8)-positive diffuse large B-cell lymphoma, NOS
        xv. HIV-related diffuse large B-cell lymphoma
        xvi. Intravascular large B-cell lymphoma
        xvii. Large B-cell lymphoma with *IRF4/MUM1* rearrangement
        xviii. Mediastinal grey zone lymphoma (MGZL)
        xix. Monomorphic post-transplant lymphoproliferative disorders (PTLD) (B-cell type)
        xx. Plasmablastic lymphoma (PBL)
        xxi. Primary cutaneous DLBCL, leg type
        xxii. Primary effusion lymphoma (PEL)
        xxiii. Primary mediastinal large B-cell lymphoma (PMBCL or PMBL)
        xxiv. T-cell-/histiocyte-rich large B-cell lymphoma
    c. Member has relapsed or refractory disease meeting **EITHER** of the following criteria (“i” or ii”):

i. Member was unable to achieve a complete response (CR) following their second line of systemic chemotherapy

ii. Member's disease is in second or greater relapse/recurrence

d. Member has received **TWO** or more unique lines of systemic chemotherapy for their disease (which may or may not include therapy supported by autologous stem cell transplant), **AND** prior therapy must have included an anti-CD20 monoclonal antibody (e.g., rituximab, obinutuzumab) unless the tumor is CD20 negative, or the member has an FDA-labeled contraindication to anti-CD20 therapy – medical record documentation of the member's prior lines of therapy for their lymphoma must be submitted

e. Following the completion of lymphodepleting chemotherapy (as needed), tisagenlecleucel will be used as single-agent therapy (i.e., not used in combination with maintenance chemotherapy)

f. Member has been assessed, and has stable and adequate organ function (kidney, liver, pulmonary and cardiac function) and bone marrow function with no significant deterioration expected within 4 weeks after apheresis as determined by the treating oncologist/hematologist

g. Tisagenlecleucel will not be administered if the member has an uncontrolled systemic infection at the time of planned treatment initiation

h. Member has **NOT** previously received CD19-directed chimeric antigen receptor (CAR) T-cell therapy (including tisagenlecleucel) in their lifetime for the treatment of lymphoma or leukemia

i. The healthcare facility administering tisagenlecleucel is currently accredited by the Foundation for the Accreditation of Cellular Therapy (i.e., a FACT-accredited organization) specifically for the clinical service of "Immune Effector Cellular Therapy" - accreditation status must be verified at https://accredited.factglobal.org/

j. The administration of tisagenlecleucel will not exceed one single dose as provided by the manufacturer

Approval duration: 3 months to allow for a one-time infusion of therapy

Tisagenlecleucel (Kymriah) is considered **experimental or investigational** for all other indications including but not limited to the following, due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes:

- Burkitt lymphoma/leukemia (i.e., patients with mature B-cell ALL)
- Castleman's disease
- Lymphoblastic lymphoma
- Mantle cell lymphoma
- Marginal zone lymphomas
- Non-B-cell lymphomas (e.g., T-cell lymphomas)
- Primary cutaneous B-cell lymphomas [other than primary cutaneous DLBCL, leg type]
- Primary DLBCL of the central nervous system (CNS)
- T-cell ALL

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Axicabtagene Ciloleucel (Yescarta)

- Indicated for the treatment of (1) adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy, (2) adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma, and (3) adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.
    - Limitation of Use: axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.
    - The follicular lymphoma 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).
- Each single infusion bag contains a suspension of chimeric antigen receptor (CAR)-positive T cells in approximately 68 mL. The target dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells, to be infused within 30 minutes. Do NOT use a leuko-depleting filter, and premedicate with acetaminophen and an H1-antihistamine. Consider the use of prophylactic corticosteroid in patients after weighing the potential benefits and risks.
- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously on the fifth, fourth, and third day before infusion of axicabtagene ciloleucel.
- Tocilizumab and emergency equipment should be available prior to infusion and during the recovery period.
- Monitor patients at least daily for 7 days following infusion for signs and symptoms of CRS and neurologic toxicities. The product labeling gives specific treatment recommendations for the different grades of CRS and neurologic toxicity. Instruct patients to remain within proximity of the healthcare facility for at least 2 weeks following infusion. Advise patients to avoid driving for at least 2 weeks following infusion.
- For further information on the preparation, administration, and monitoring of axicabtagene ciloleucel can be found in the product labeling.

Brexucabtagene Autoleucel (Tecartus)

- Indicated for: (1) the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) [this indication is approved under accelerated approval based on overall response rate and durability of response, and continued approval may be contingent upon verification and description of

clinical benefit in a confirmatory trial], and (2) the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

- Each single infusion bag contains a suspension of chimeric antigen receptor (CAR)-positive T cells in approximately 68 mL.
    - MCL - the target dose is $2x10^6$ CAR-positive viable T cells per kg body weight, with a maximum of $2x10^8$ CAR-positive viable T cells.
    - ALL - the target dose is $1x10^6$ CAR-positive viable T cells per kg body weight, with a maximum of $1x10^8$ CAR-positive viable T cells.
- Administer a lymphodepleting chemotherapy regimen of the following based in indication for use:
    - MCL - cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously on each of the fifth, fourth, and third day before infusion of brexucabtagene autoleucel
    - ALL - fludarabine 25 mg/m^2 intravenously on each of the fourth, third and second day and cyclophosphamide 900 mg/m^2 over 60 minutes on the second day before infusion of brexucabtagene autoleucel
- Premedicate with acetaminophen and diphenhydramine or another H1-antihistamine approximately 30 to 60 minutes prior to brexucabtagene autoleucel infusion. Avoid prophylactic use of systemic corticosteroids as it may interfere with the activity of brexucabtagene autoleucel.
- Infuse the entire contents of the brexucabtagene autoleucel bag within 30 minutes by either gravity or a peristaltic pump. Brexucabtagene autoleucel is stable at room temperature for up to three hours after thaw.
- Monitor patients daily for at least seven days following infusion for signs and symptoms of Cytokine Release Syndrome (CRS) and neurologic events. Instruct patients to remain within proximity of the certified healthcare facility for at least 2 weeks following infusion. Advise patients to avoid driving for at least 2 weeks following infusion.

Ciltacabtagene Autoleucel (Carvykti)

- Indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.
- Product is supplied as a single dose for infusion containing a suspension of CAR-positive T cells in one infusion bags. The recommended dose range is 0.5 to 1 x 10^6 CAR-positive viable T cells per kg of body weight, with a maximum dose of 1 x 10^8 CAR-positive viable T cells per single infusion.
- Administer the lymphodepleting chemotherapy regimen: cyclophosphamide 300 mg/m^2 IV and fludarabine 30 mg/m^2 IV daily for 3 days. Administer Carvykti 2 to 4 days after completion of lymphodepleting chemotherapy. Delay the infusion if a patient has clinically significant active infection or inflammatory disorders or Grade ≥3 non-hematologic toxicities of cyclophosphamide and fludarabine conditioning, except for Grade 3 nausea, vomiting, diarrhea, or constipation. The infusion should be delayed until resolution of these events to Grade ≤1.
- Administer an antipyretic (acetaminophen 650 mg to 1000 mg orally or IV) and an antihistamine (diphenhydramine 25 to 50 mg orally or 50 mg, or equivalent) approximately 30 to 60 minutes before infusion of Carvykti. Avoid prophylactic use of systemic corticosteroids because their use may interfere with the activity of Carvykti. Ensure that a minimum of 2 doses of tocilizumab and emergency equipment are available prior to infusion and during the recovery period.

- Monitor patients at least daily for 7 days following infusion for signs and symptoms of CRS and neurologic toxicities. Instruct patients to remain within proximity of a healthcare facility for at least 2 weeks following infusion. Advise patients to avoid driving for at least 2 weeks following infusion.

Idecabtagene Vicleucel (Abecma)

- Indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after two or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an antiCD38 monoclonal antibody.
- Product is supplied as a single dose for infusion containing a suspension of CAR-positive T cells in one or more infusion bags. The recommended dose range is 300 to 510 x 10^6 CAR-positive T cells.
- Administer the lymphodepleting chemotherapy regimen: cyclophosphamide 300 mg/m^2 IV and fludarabine 30 mg/m^2 IV for 3 days. Administer Abecma 2 days after completion of lymphodepleting chemotherapy. Delay the infusion up to 7 days if a patient has unresolved serious adverse events (especially pulmonary events, cardiac events, or hypotension), including those after preceding chemotherapies, active infections, or inflammatory disorders.
- Administer acetaminophen (650 mg orally) and diphenhydramine (12.5 mg IV or 25 to 50 mg orally, or another H1-antihistamine) approximately 30 to 60 minutes before infusion of Abecma. Avoid prophylactic use of dexamethasone or other systemic corticosteroids, as the use may interfere with the activity. Ensure that a minimum of 2 doses of tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- Monitor patients at least daily for 7 days following infusion for signs and symptoms of CRS and neurologic toxicities. Instruct patients to remain within proximity of a healthcare facility for at least two weeks following infusion. Advise patients to avoid driving for at least 2 weeks following infusion.

Lisocabtagene Maraleucel (Breyanzi)

- Indicated for the treatment of the following:
    - Adult patients with large B-cell lymphoma, including 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, and follicular lymphoma grade 3B who have:
        - refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first line chemoimmunotherapy; or
        - refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
        - relapsed or refractory disease after two or more lines of systemic therapy

      Limitations of Use: Not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma.
    - Adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor. 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).

- Adult patients with relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior 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)
- Adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor
- Adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least 2 prior lines of systemic therapy.

- For relapsed or refractory LBCL after one line of therapy, FL, MCL, MZL, and CLL/SLL, a single dose of lisocabtagene maraleucel contains 90 to 110 x 10^6 CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components), with each component supplied separately in one to four single-dose vials. For relapsed or refractory LBCL after two or more lines of therapy, a single dose of lisocabtagene maraleucel contains 50 to 110 x 10^6 CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components), with each component supplied separately in one to four single-dose vials. The CD8 component is given first immediately followed by administer the CD4 component second.
- Administer the lymphodepleting chemotherapy regimen before the infusion of lisocabtagene maraleucel: fludarabine 30 mg/m^2/day IV and cyclophosphamide 300 mg/m^2/day IV for 3 days. Infuse lisocabtagene maraleucel 2 to 7 days after completion of lymphodepleting chemotherapy. To minimize the risk of infusion reactions, premedicate the patient with acetaminophen (650 mg orally) and diphenhydramine (25-50 mg, IV or orally), or another H1-antihistamine, 30 to 60 minutes prior to treatment. Avoid prophylactic use of systemic corticosteroids, as they may interfere with the activity of lisocabtagene maraleucel.
- Refer to the product label (package insert) for detailed instructions on dose preparation, administration, monitoring, and management of adverse reactions. Do NOT use a leuko-depleting filter. Ensure tocilizumab and emergency equipment are available prior to infusion and during the recovery period. Monitor patients daily for at least 7 days following infusion for signs and symptoms of CRS and neurologic toxicities. Instruct patients to remain within proximity of a healthcare facility for at least 2 weeks following infusion. Advise patients to avoid driving for at least 2 weeks following infusion.

Obecabtagene Autoleucel (Aucatzyl)

- For the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
  - The total recommended dose is 410 × 10^6 CD19 chimeric antigen receptor (CAR)-positive viable T cells supplied in three to five infusion bags. Bags are supplied in three color-coded bag configurations for split dose administration.

CAR+ T Cell Dose(Bag Configuration	Color Code	Volume	Fully Infused
10 x 106	Blue	10 mL	No
100 x 106	Orange	Variable	Yes

300 x 106	Red	Variable	Yes

  - The treatment regimen consists of a split dose infusion to be administered on Day 1 and Day 10 (± 2 days). Refer to the product labeling for additional information.
  - The dosage regimen will be determined by the tumor burden assessed by bone marrow blast percentage from a sample obtained within 7 days prior to the start of lymphodepletion.
  - See the Release for Infusion Certificate and Dose Schedule Planner for the actual cell counts and volumes to be infused and to select the appropriate dosage regimen.

- Pretreatment
  - Confirm availability of Aucatzyl prior to starting the lymphodepleting chemotherapy treatment.
  - Administer the lymphodepleting chemotherapy regimen before infusion of Aucatzyl: fludarabine (FLU) 30 mg/m^2/day intravenously (IV) for four days and cyclophosphamide (CY) 500 mg/m^2/day IV for two days starting with the first dose of fludarabineb (total dose: FLU 120 mg/m^2; CY 1000 mg/m2). Infuse Aucatzyl 3 days (± 1 days) after completion of lymphodepleting chemotherapy treatment (Day 1), allowing a minimum 48-hour washout.
  - Delay Aucatzyl treatment if the patient is experiencing severe intercurrent infection. If the patient requires supplementary oxygen Aucatzyl should only be infused if considered appropriate based on the treating physician's benefit/risk assessment.
  - A delay to the second split dose may be required to manage toxicities
- Premedication
  - To minimize the risk of an infusion reaction, premedicate with acetaminophen approximately 30 minutes prior to Aucatzyl infusion.
  - Avoid prophylactic use of systemic corticosteroids as they may interfere with the activity of Aucatzyl.
- Monitor patients for signs and symptoms of CRS, neurologic toxicities/ICANS and other acute toxicities daily for at least 14 days at the healthcare facility following the first infusion. Continue to monitor patients for at least 4 weeks following each infusion. Instruct patients to remain within proximity of a healthcare facility for at least 4 weeks following the first infusion. Instruct patients to refrain from driving or hazardous activities for at least 8 weeks following infusion.

Tisagenlecleucel (Kymriah)

- 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.
  - One treatment course consists of fludarabine and cyclophosphamide lymphodepleting chemotherapy followed by infusion of tisagenlecleucel.
    - For patients 50 kg or less: administer 0.2 to 5 x 10^6 CAR-positive viable T cells per kg body weight reported at the time of leukapheresis
    - For patients above 50 kg: administer 0.1 to 2.5 x 10^8 CAR-positive viable T cells (non-weight based)
  - Lymphodepleting chemotherapy consists of fludarabine (30 mg/m^2 intravenous daily for 4 days) and cyclophosphamide (500 mg/m^2 intravenous daily for 2 days starting with the first dose of

fludarabine). Infuse tisagenlecleucel 2 to 14 days after completion of the lymphodepleting chemotherapy.

- For the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two 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. Per the package labeling, "Limitation of Use: Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma".
    - One treatment course consists of fludarabine and cyclophosphamide lymphodepleting chemotherapy (or bendamustine as an alternative regimen) followed by infusion of tisagenlecleucel.
        - Administer 0.6 to 6 x 10^8 CAR-positive viable T cells (non-weight based)
    - Lymphodepleting chemotherapy consists of fludarabine (25 mg/m^2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m^2 intravenous daily for 3 days starting with the first dose of fludarabine). An alternate lymphodepleting chemotherapy of bendamustine 90 mg/m^2 IV daily for 2 days can be used if a patient experienced a previous Grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide containing regimen. Lymphodepleting chemotherapy may be omitted if a patient's WBC count is less than or equal to 1 x 10^9/L within 1 week prior to the planned tisagenlecleucel infusion. Infuse tisagenlecleucel 2 to 11 days after completion of the lymphodepleting chemotherapy.
- For the treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
    - One treatment course consists of fludarabine and cyclophosphamide lymphodepleting chemotherapy (or bendamustine as an alternative regimen) followed by infusion of tisagenlecleucel.
        - Administer 0.6 to 6 x 10^8 CAR-positive viable T cells (non-weight based)
    - Lymphodepleting chemotherapy consists of fludarabine (25 mg/m^2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m^2 intravenous daily for 3 days starting with the first dose of fludarabine). An alternate lymphodepleting chemotherapy of bendamustine 90 mg/m^2 IV daily for 2 days can be used if a patient experienced a previous Grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide containing regimen. Lymphodepleting chemotherapy may be omitted if a patient's WBC count is less than or equal to 1 x 10^9/L within 1 week prior to the planned tisagenlecleucel infusion. Infuse tisagenlecleucel 2 to 6 days after completion of the lymphodepleting chemotherapy.
- Premedicate patients with acetaminophen and an H1-antihistamine. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of tisagenlecleucel. Tocilizumab (Actemra) and emergency equipment should be available prior to infusion and during the recovery period. Consult the package labeling for specific directions on the preparation and administration of tisagenlecleucel.
- Monitor patients daily during the first week following infusion for signs and symptoms of CRS and neurologic toxicities. Instruct patients to remain within proximity of a healthcare facility for at least 2 weeks following infusion. Advise patients to avoid driving for at least 2 weeks following infusion.

Dose Adjustments

All CAR T-Cell Therapies

- Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.
- Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Drug Availability

Axicabtagene Ciloleucel (Yescarta)

- Supplied in an infusion bag containing approximately 68 mL of frozen suspension of genetically modified autologous T cells in 5% DMSO and 2.5% albumin (human). Each infusion bag is individually packed in a metal cassette. Axicabtagene ciloleucel is stored in the vapor phase of liquid nitrogen and supplied in a liquid nitrogen dry shipper.

Brexucabtagene Autoleucel (Tecartus)

- Supplied in an infusion bag containing approximately 68 mL of frozen suspension of genetically modified autologous T cells in 5% DMSO and human serum albumin. Each infusion bag is individually packed in a metal cassette. The NDC is different depending on the indication for use:
  - MCL: Infusion Bag: 71287-219-01, Metal Cassette: 71287-219-02
  - ALL: Infusion Bag: 71287-220-01, Metal Cassette: 71287-220-02
- Brexucabtagene autoleucel is stored in the vapor phase of liquid nitrogen and supplied in a liquid nitrogen dry shipper.

Ciltacabtagene Autoleucel (Carvykti)

- Supplied in one infusion bag (see below) containing a frozen suspension of genetically modified autologous T cells in 5% DMSO. The infusion bag is individually packed in an aluminum cryo-cassette. Store and transport below -120°C, e.g., in a container for cryogenic storage in the vapor phase of liquid nitrogen.
  - 70 mL suspension in an infusion bag and metal cassette (NDC 57894-111-01)
  - 30 mL suspension in an infusion bag and metal cassette (NDC 57894-111-02)

Idecabtagene Vicleucel (Abecma)

- Supplied in one or more infusion bag(s) (see below) containing a frozen suspension of genetically modified autologous T cells in 5% DMSO. Each infusion bag is individually packed in a metal cassette. Abecma is stored in the vapor phase of liquid nitrogen and supplied in a liquid nitrogen dry vapor shipper.
  - 50 mL infusion bag and metal cassette (NDC 59572-515-01)
  - 250 mL infusion bag and metal cassette (NDC 59572-515-02)
  - 500 mL infusion bag and metal cassette (NDC 59572-515-03)

Lisocabtagene Maraleucel (Breyanzi)

- Lisocabtagene maraleucel consists of genetically modified autologous T cells, supplied in vials as separate frozen suspensions of each CD8 component (NDC 73153-901-08) and CD4 component (NDC 73153-902-04). Each CD8 or CD4 component is packed in a carton containing up to 4 vials, depending upon the concentration of the cryopreserved drug product CAR-positive viable T cells. The cartons for each CD8 component and CD4 component are in an outer carton (NDC 73153-900-01).
- Lisocabtagene maraleucel is shipped directly to the cell lab or clinical pharmacy associated with the infusion center in the vapor phase of a liquid nitrogen shipper. A Release for Infusion (RFI) Certificate for each component and patient-specific syringe labels are affixed inside the shipper. Store vials in the vapor phase of liquid nitrogen (less than or equal to minus 130°C) in a temperature-monitored system.

Obecabtagene Autoleucel (Aucatzyl)

- Supplied in three to five infusion bags (see below) containing a frozen suspension of genetically modified autologous T cells in PBS, HSA, EDTA and 7.5% DMSO.
- Each infusion bag of is individually packed within an overwrap and then enclosed within a metal cassette. Aucatzyl is shipped from the manufacturing facility to the cellular therapy laboratory associated with the infusion center in a cryogenic shipper charged with liquid nitrogen. A Release for Infusion certificate is provided to the infusion site in the shipper and via the Autolus Scheduling Portal with the product.
    - 10×10^6 CD19 CAR-positive viable T cells in one 50 mL infusion bag, 10 mL (NDC 83047-0010-10)
    - 100×10^6 CD19 CAR-positive viable T cells in one or more 50 mL infusion bags, 10 to 20 mL (NDC 83047-0100-10)
    - 100×10^6 CD19 CAR-positive viable T cells in one 250 mL infusion bag, 30 to 70 mL (NCD 83047-0100-30)
    - 300×10^6 CD19 CAR-positive viable T cells in one or more 250 mL infusion bags, 30 to 70 mL (NDC 83047-0300-30)

Tisagenlecleucel (Kymriah)

- Supplied as a frozen suspension of genetically modified autologous T cells in one or more infusion bags labeled for the specific recipient. Product is shipped directly to the cell lab associated with the infusion center in a liquid nitrogen Dewar. Product and patient-specific labels are located inside the Dewar. The product will have a difference NDC depending on the indication for use - Ped ALL: NDC 0078-0846-19 or DLBCL: NDC 0078-0958-19.
- Based on the patient's indication and weight reported at the time of leukapheresis, different dosages will be prepared for the patient:
    - DLBCL: 0.6 to 6.0 x 10^8 CAR-positive viable T cells
    - ALL (for patients 50 kg or less): 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight
    - ALL (for patients above 50 kg): 0.1 to 2.5 x 10^8 CAR-positive viable T cells

- The actual number of CAR-positive T cells in the product is reported on the Certificate of Analysis (CoA) that is shipped with the product. The volume of CAR-positive viable T cells in an infusion bag ranges from 10 mL to 50 mL.

PRECAUTIONS:

Boxed Warning

Axicabtagene Ciloleucel (Yescarta)

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving axicabtagene ciloleucel. Do not administer axicabtagene ciloleucel to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving axicabtagene ciloleucel, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with axicabtagene ciloleucel. Provide supportive care and/or corticosteroids as needed.
- T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including axicabtagene ciloleucel.

Brexucabtagene Autoleucel (Tecartus)

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- Cytokine Release Syndrome (CRS), including life-threatening reactions, occurred in patients receiving Tecartus. Do not administer Tecartus to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurologic toxicities, including life-threatening reactions, occurred in patients receiving Tecartus, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with Tecartus. Provide supportive care and/or corticosteroids as needed.
- T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies.

Ciltacabtagene Autoleucel (Carvykti)

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS, PROLONGED and RECURRENT CYTOPENIA, and SECONDAY HEMATOLOGICAL MALIGNANCIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with Carvykti. Do not administer Carvykti to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which may be fatal or life-threatening, occurred following treatment with Carvykti, including before CRS onset, concurrently

with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with Carvykti. Provide supportive care and/or corticosteroids as needed.

- Parkinsonism and Guillain-Barré syndrome and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with Carvykti.
- Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with Carvykti. HLH/MAS can occur with CRS or neurologic toxicities.
- Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with Carvykti.
- Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred in patients following treatment with Carvykti. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA and CD19-directed genetically modified autologous T-cell immunotherapies, including Carvykti.

Idecabtagene Vicleucel (Abecma)

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS, PROLONGED CYTOPENIA, AND SECONDARY HEMATOLOGICAL MALIGNANCIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with Abecma. Do not administer Abecma to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurologic toxicities, which may be severe or life-threatening, occurred following treatment with Abecma, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with Abecma. Provide supportive care and/or corticosteroids as needed.
- Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS) including fatal and life-threatening reactions, occurred in patients following treatment with Abecma. HLH/MAS can occur with CRS or neurologic toxicities.
- Prolonged Cytopenia with bleeding and infection, including fatal outcomes following stem cell transplantation for hematopoietic recovery, occurred following treatment with Abecma.
- T cell malignancies have occurred following treatment of hematologic malignancies with BCMA and CD19-directed genetically modified autologous T cell immunotherapies, including Abecma.

Lisocabtagene Maraleucel (Breyanzi)

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, AND SECONDARY HEMATOLOGICAL MALIGNANCIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving Breyanzi. Do not administer Breyanzi to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids.

- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving Breyanzi, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with Breyanzi. Provide supportive care and/or corticosteroids as needed.
- T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including Breyanzi.

Obecabtagene Autoleucel (Aucatzyl)

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

- Cytokine Release Syndrome (CRS), occurred in patients receiving Aucatzyl. Do not administer Aucatzyl to patients with active infection or inflammatory disorders. Prior to administering Aucatzyl, ensure that healthcare providers have immediate access to medications and resuscitative equipment to manage CRS.
- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), including fatal or life-threatening reactions, occurred in patients receiving Aucatzyl, including concurrently with CRS or after CRS resolution. Monitor for neurologic signs and symptoms after treatment with Aucatzyl. Prior to administering Aucatzyl, ensure that healthcare providers have immediate access to medications and resuscitative equipment to manage neurologic toxicities. Provide supportive care and/or corticosteroids, as needed.
- T cell malignancies have occurred following treatment of hematologic malignancies with BCMA-and CD19-directed genetically modified autologous T cell immunotherapies.

Tisagenlecleucel (Kymriah)

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving tisagenlecleucel. Do not administer tisagenlecleucel to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurological toxicities, which may be severe or life-threatening, can occur following treatment with tisagenlecleucel, including concurrently with CRS. Monitor for neurological events after treatment with tisagenlecleucel. Provide supportive care as needed.
- T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19- directed genetically modified autologous T cell immunotherapies, including tisagenlecleucel.

Contraindications:

All CAR-T Cell Therapies

- None

Precautions/Warnings

Axicabtagene Ciloleucel (Yescarta)

- **Cytokine Release Syndrome (CRS):** CRS, including fatal or life-threatening reactions, occurred following treatment. CRS occurred in 93% (256/276) of patients with large B-cell lymphoma,

including ≥Grade 3 CRS in 9%. Among patients who died after receiving axicabtagene ciloleucel, four had ongoing CRS events at the time of death. Key manifestations of CRS (>10%) include fever (85%), hypotension (40%), tachycardia (32%), hypoxia (20%), chills (22%), headache (15%), and fatigue (12%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). Ensure that 2 doses of tocilizumab are available prior to infusion. Monitor patients at least daily for 7 days following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 2 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids as indicated.

- **Neurologic Toxicities**: Neurologic toxicities, that were fatal or life-threatening, occurred following treatment. Neurologic toxicities occurred in 78% (330/422) of patients with NHL receiving Yescarta, including ≥Grade 3 cases in 25%. Monitor patients at least daily for 7 days following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 2 weeks after infusion and treat promptly. Advise patients to avoid driving for at least 2 weeks following infusion.
- **Hypersensitivity Reactions**: Allergic reactions may occur with the infusion of axicabtagene ciloleucel. Serious hypersensitivity reactions including anaphylaxis may be due to dimethyl sulfoxide (DMSO) or residual gentamicin. Monitor for hypersensitivity reactions during infusion.
- **Serious Infections**: Severe or life-threatening infections occurred in patients after infusion. Monitor patients for signs and symptoms of infection before and after infusion and treat appropriately. Administer prophylactic antimicrobials according to local guidelines. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated.
- **Prolonged Cytopenias**: Patients may exhibit Grade 3 or higher cytopenias for several weeks following infusion. Monitor complete blood counts.
- **Hypogammaglobulinemia**: B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment. Monitor immunoglobulin levels after treatment and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement as needed.
- **Secondary Malignancies**: T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including Yescarta. In the event that a secondary malignancy occurs after treatment, contact Kite at 1-844-454-KITE (5483).

Brexucabtagene Autoleucel (Tecartus)

- **Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS):** HLH/MAS occurred in 4% (3/78) of patients with ALL. All three patients with HLH/MAS had concurrent CRS symptoms and neurologic events. Administer treatment per institutional standards.
- **Hypersensitivity Reactions**: Monitor for hypersensitivity reactions during infusion.
- **Severe Infections**: Monitor patients for signs and symptoms of infection; treat appropriately.
- **Prolonged Cytopenias**: Patients may exhibit Grade 3 or higher cytopenias for several weeks following brexucabtagene autoleucel infusion. Monitor complete blood counts.

- **Hypogammaglobulinemia**: Monitor and provide replacement therapy.
- **Secondary Malignancies**: In the event that a secondary malignancy occurs after treatment with brexucabtagene autoleucel, contact Kite at 1-844-454-KITE (5483).

Ciltacabtagene Autoleucel (Carvykti)

- **Increased Early Mortality**: In CARTITUDE-4, there was a numerically higher percentage of early deaths in patients randomized to the Carvykti treatment arm compared to the control arm. Among patients with deaths occurring within the first 10 months from randomization, a greater proportion (29/208; 14%) occurred in the Carvykti arm compared to (25/211; 12%) in the control arm. Of the 29 deaths that occurred in the Carvykti arm within the first 10 months of randomization, 10 deaths occurred prior to Carvykti infusion, and 19 deaths occurred after Carvykti infusion. Of the 10 deaths that occurred prior to Carvykti infusion, all occurred due to disease progression, and none occurred due to adverse events. Of the 19 deaths that occurred after Carvykti infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The most common adverse events were due to infection (n=12).
- **Cytokine Release Syndrome**: See Boxed Warning. Among patients receiving Carvykti for relapsed or refractory MM in the CARTITUDE-1 and CARTITUDE-4 studies (n=285), CRS occurred in 84% (238/285), including ≥ Grade 3 CRS in 4% (11/285) of patients. The median time to onset of CRS, any grade, was 7 days (range: 1 to 23 days). Cytokine release syndrome resolved in 82% with a median duration of 4 days (range: 1 to 97 days). The most common manifestations of CRS in all patients combined (≥ 10%) included fever (84%), hypotension (29%) and aspartate aminotransferase increased (11%). Serious events that may be associated with CRS include pyrexia, hemophagocytic lymphohistiocytosis, respiratory failure, disseminated intravascular coagulation, capillary leak syndrome, and supraventricular and ventricular tachycardia. Cytokine release syndrome occurred in 78% of patients in CARTITUDE-4 (3% Grade 3 to 4) and in 95% of patients in CARTITUDE-1 (4% Grade 3 to 4).
- **Neurologic Toxicities**: See Boxed Warning. Neurologic toxicities included ICANS, neurologic toxicity with signs and symptoms of parkinsonism, Guillain-Barré Syndrome, immune mediated myelitis, peripheral neuropathies and cranial nerve palsies. Among patients receiving Carvykti in the CARTITUDE-1 and CARTITUDE-4 studies, one or more neurologic toxicities occurred in 24% (69/285), including ≥ Grade 3 cases in 7% (19/285) of patients. The median time to onset was 10 days (range: 1 to 101) with 63/69 (91%) of cases developing by 30 days. Neurologic toxicities resolved in 72% (50/69) of patients with a median duration to resolution of 23 days (range: 1 to 544). Of patients developing neurotoxicity, 96% (66/69) also developed CRS. Subtypes of neurologic toxicities included ICANS in 13%, peripheral neuropathy in 7%, cranial nerve palsy in 7%, parkinsonism in 3%, and immune mediated myelitis in 0.4% of the patients.
- **Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS):** See Boxed Warning. Among patients receiving Carvykti in the CARTITUDE-1 and CARTITUDE-4 studies, HLH/MAS occurred in 1% (3/285) of patients. All events of HLH/MAS had onset within 99 days of receiving Carvykti, with a median onset of 10 days (range: 8 to 99 days) and all occurred in the setting of ongoing or worsening CRS. The manifestations of HLH/MAS include hypotension, hypoxia with diffuse alveolar damage, coagulopathy, cytopenia and multi-organ dysfunction, including renal dysfunction. HLH is a life-threatening condition with a high mortality rate if not recognized and treated early. Treatment of HLH/MAS should be administered per institutional standards.

- **Prolonged and Recurrent Cytopenias:** Patients may exhibit ≥Grade 3 cytopenias following Carvykti infusion. One or more recurrences of Grade 3 or higher cytopenias may occur after partial or complete recovery of cytopenias. Monitor blood counts prior to and after Carvykti infusion. Prolonged neutropenia has been associated with increased risk of infection.
- **Infections:** Monitor patients for signs and symptoms of infection; treat appropriately.
- **Hypogammaglobulinemia:** Monitor and consider immunoglobulin replacement therapy
- **Hypersensitivity Reactions:** Hypersensitivity reactions have occurred. Monitor for hypersensitivity reactions during infusion.
- **Secondary Malignancies:** Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including Carvykti. In the event that a secondary malignancy occurs after treatment with Carvykti, contact Janssen Biotech, Inc. at 1-800-526-7736.

Idecabtagene Vicleucel (Abecma)

- **Early Death:** In KarMMa-3, a higher proportion of patients experienced death within 9 months after randomization in the Abecma arm (45/254; 18%) compared to the standard regimens arm (15/132; 11%). Early deaths occurred in 8% (20/254) and 0% prior to Abecma infusion and standard regimen administration, respectively, and 10% (25/254) and 11% (15/132) after Abecma infusion and standard regimen administration, respectively. Out of the 20 deaths that occurred prior to Abecma infusion, 15 occurred from disease progression, 3 occurred from adverse events and 2 occurred from unknown causes. Out of the 25 deaths that occurred after Abecma infusion, 10 occurred from disease progression, 11 occurred from adverse events, and 4 occurred from unknown causes.
- **Cytokine Release Syndrome:** See Boxed Warning. Among patients receiving Abecma for relapsed or refractory MM in the KarMMa and KarMMa-3 studies (n=349), CRS occurred in 89% (310/349), including ≥ Grade 3 CRS in 7% (23/349) of patients and Grade 5 CRS in 0.9% (3/349) of patients. The median time-to-onset of CRS, any grade, was 1 day (range: 1 to 27 days), and the median duration of CRS was 5 days (range: 1 to 63 days). In the pooled studies, the rate of ≥ Grade 3 CRS was 10% (7/71) for patients treated in dose range of 460 to 510 x 10^6 CAR-positive T cells and 5.4% (13/241) for patients treated in dose range of 300 to 460 x 10^6 CAR-positive T cells. The most common manifestations of CRS (greater than or equal to 10%) included pyrexia (87%), hypotension (30%), tachycardia (26%), chills (19%), and hypoxia (16%).
- **Neurologic Toxicities:** See Boxed Warning. In patients receiving Abecma in the KarMMa and KarMMa-3 studies, CAR T cell-associated neurotoxicity occurred in 40% (139/349), including Grade 3 in 4% (14/349) and Grade 4 in 0.6% (2/349) of patients. The median time to onset of neurotoxicity was 2 days (range: 1 to 148 days). The median duration of CAR T cell-associated neurotoxicity was 8 days (range: 1 to 720 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. CAR T cell-associated neurotoxicity resolved in 123 of 139 (88%) patients and median time to resolution was 5 days (range: 1 to 245 days). One-hundred and thirty four out of 349 (38%) patients with neurotoxicity had CRS. The onset of neurotoxicity during CRS was observed in 93 patients, before the onset of CRS in 12 patients, and after the CRS event in 29 patients. The rate of Grade 3 or 4 CAR T cell-associated neurotoxicity was 5.6% (4/71) and 3.7% (9/241) for patients treated in dose range of 460 to 510 x 10^6 CAR-positive T cells and 300 to 460 x 10^6 CAR-positive T cells, respectively. The most frequent (greater than or equal to 5%) manifestations of CAR

T cell-associated neurotoxicity include encephalopathy (21%), headache (15%), dizziness (8%), delirium (6%), and tremor (6%).

- **Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS):** See Boxed Warning. In patients receiving Abecma in the KarMMa and KarMMa-3 studies, HLH/MAS occurred in 2.9% (10/349) of patients. All events of HLH/MAS had onset within 10 days of receiving Abecma, with a median onset of 6.5 days (range: 4 to 10 days) and occurred in the setting of ongoing or worsening CRS. Five patients with HLH/MAS had overlapping neurotoxicity. The manifestations of HLH/MAS include hypotension, hypoxia, multiple organ dysfunction, renal dysfunction, and cytopenia. HLH/MAS is a potentially life-threatening condition with a high mortality rate if not recognized early and treated. Treatment of HLH/MAS should be administered per institutional standards.
- **Hypersensitivity Reactions**: Monitor for hypersensitivity reactions during infusion.
- **Infections**: Monitor patients for signs and symptoms of infection; treat appropriately.
- **Prolonged Cytopenias**: Patients may exhibit prolonged Grade 3 or higher cytopenias following Abecma infusion. Monitor blood counts prior to and after Abecma infusion.
- **Hypogammaglobulinemia**: Monitor and consider immunoglobulin replacement therapy.
- **Secondary Malignancies**: T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including Abecma. In the event that a secondary malignancy occurs after treatment with Abecma, contact Bristol-Myers Squibb at 1-888-805-4555.

Lisocabtagene Maraleucel (Breyanzi)

- **Cytokine Release Syndrome**: See Boxed Warning
- **Neurologic Toxicities**: See Boxed Warning
- **Hypersensitivity Reactions**: Monitor for hypersensitivity reactions during infusion.
- **Serious Infections**: Monitor patients for signs and symptoms of infection; treat appropriately.
- **Prolonged Cytopenias**: Patients may exhibit Grade 3 or higher cytopenias for several weeks following Breyanzi infusion. Monitor complete blood counts.
- **Hypogammaglobulinemia**: Monitor and consider immunoglobulin replacement therapy.
- **Secondary Malignancies**: T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including Breyanzi. In the event that a secondary malignancy occurs after treatment with Breyanzi, contact Bristol-Myers Squibb at 1-888-805-4555.
- **Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IEC-HS):** IEC-HS is a life-threatening condition with a high mortality rate if not recognized and treated early. Treatment of IEC-HS should be administered per current practice guideline

Obecabtagene Autoleucel (Aucatzyl)

- **Cytokine Release Syndrome**: See Boxed Warning
- **Neurologic Toxicities**: See Boxed Warning

- **Prolonged Cytopenias**: Patients may exhibit Grade 3 or higher cytopenias for several weeks following Aucatzyl infusion. Monitor complete blood counts.
- **Infections**: Monitor patients for signs and symptoms of infection; treat appropriately
- **Hypogammaglobulinemia**: Monitor and consider immunoglobulin replacement therapy
- **Hemophagocytic Lymphohistiocytosis/ Macrophage Activation Syndrome**: Administer treatment per institutional standards
- **Hypersensitivity Reactions**: Monitor for hypersensitivity reactions during infusion
- **Secondary Malignancies**: T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies. In the event that a secondary malignancy occurs after treatment with Aucatzyl, contact Autolus Inc at 1-855-288-5227
- **Effects on Ability to Drive and Use Machines**: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving Aucatzyl

Tisagenlecleucel (Kymriah)

- **Cytokine Release Syndrome (CRS)**: CRS, including fatal or life-threatening reactions, occurred following treatment with tisagenlecleucel. CRS occurred in 61 (77%) of the 79 pediatric and young adult patients with r/r ALL and 85 (74%) of the 115 adult patients with r/r DLBCL, including ≥ Grade 3 (Penn grading system1) in 48% of patients with r/r ALL and in 23% of patients with r/r DLBCL. The median times to onset and resolution of CRS for patients with r/r ALL were 3 days (range: 1 to 22; 1 patient with onset after Day 10) and 8 days (range: 1 to 36), respectively. The median times to onset and resolution of CRS for patients with r/r DLBCL were 3 days (range: 1 to 51; 1 patient with onset after Day 10) and 7 days (range: 2 to 30), respectively. Of the 61 patients with r/r ALL who had CRS, 31 (51%) received tocilizumab. Ten (16%) patients received two doses of tocilizumab and 3 (5%) patients received three doses of tocilizumab; 17 (28%) patients received addition of corticosteroids (e.g., methylprednisolone). Of the 85 patients with r/r DLBCL who had CRS, 19 (22%) received systemic tocilizumab or corticosteroids. Seven (8%) patients received a single dose of tocilizumab and 11 (13%) patients received two doses of tocilizumab; 11 (13%) patients received corticosteroids in addition to tocilizumab. One patient with r/r DLBCL received corticosteroids for CRS without concomitant tocilizumab, and two patients received corticosteroids for persistent neurotoxicity after resolution of CRS. CRS occurred in 51 (53%) of the 97 adult patients with r/r FL receiving tisagenlecleucel; all were Grade 1 or 2 CRS. The median times to onset and resolution of CRS were 4 days (range: 1-14) and 4 days (range: 1-13), respectively Among patients with CRS, key manifestations include fever (93% in r/r ALL; 85% in r/r DLBCL; 92% in r/r FL), hypotension (69% in r/r ALL; 45% in r/r DLBCL; 40% in r/r FL), hypoxia (57% in r/r ALL; 35% in r/r DLBCL; 19% in r/r FL), and tachycardia (26% in r/r ALL; 13% in r/r DLBCL 2% in r/r FL). CRS may be associated with hepatic, renal, and cardiac dysfunction, and coagulopathy.). Risk factors for severe CRS are high pre-infusion tumor burden (greater than 50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infections, and/or inflammatory processes. Ensure that tocilizumab is available on site prior to infusion. Monitor patients daily during the first week following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 2 weeks after treatment. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, immediately evaluate patient for

hospitalization and institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated. Refer to the package labeling for detailed recommendation on the management of CRS.

- **Neurological Toxicities**: Neurological toxicities including severe or life-threatening reactions, occurred in 56 (71%) of the 79 patients with r/r ALL and 69 (60%) of the 115 patients with r/r DLBCL, including ≥ Grade 3 in 22% of patients with r/r ALL and 19% of patients with r/r DLBCL. Among patients who had a neurological toxicity, 83% occurred within 8 weeks following infusion. The median time to the first event was 6 days from infusion (range: 1 to 301) for patients with r/r ALL and 5 days (range: 1 to 368) for patients with r/r DLBCL. The median duration was 7 days for patients with r/r ALL and 17 days for patients with r/r DLBCL. Resolution occurred within 3 weeks in 71% of patients with r/r ALL and 50% of patients with r/r DLBCL. Encephalopathy lasting up to 50 days was noted. The onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS. Neurologic toxicities occurred in 42 (43%) of the 97 patients with r/r FL, including ≥ Grade 3 in 6%. The median times to the first event and duration were 8 days (range: 1-345) and 5 days, respectively. The most common neurological toxicities observed include headache (35% in r/r ALL; 21% in r/r DLBCL; 25% in r/r FL), encephalopathy 30% in r/r ALL; 16% in r/r DLBCL; 3% in r/r FL), delirium (19% in r/r ALL; 5% in r/r DLBCL; 1% in r/r FL), anxiety (16% in r/r ALL; 10% in r/r DLBCL; 2% in r/r F), sleep disorders (11% in r/r ALL; 10% in r/r DLBCL; 6% in r/r FL), dizziness (5% in r/r ALL; 12% in r/r DLBCL; 8% of r/r FL), tremor (8% in r/r ALL; 6% r/r DLBCL; 3% of r/r FL), and peripheral neuropathy (4% in r/r ALL; 12% in r/r DLBCL; 7% of r/r FL). Other manifestations included seizures and aphasia. Monitor patients daily during the first week following infusion for signs and symptoms of neurologic toxicities. Rule out other causes of neurological symptoms. Monitor patients for signs or symptoms of neurologic toxicities for at least 2 weeks after infusion and treat promptly. Neurologic toxicity should be managed with supportive care and/or corticosteroids as needed. Advise patients to avoid driving for at least 2 weeks following infusion.
- **Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS):** HLH/ MAS, which can be life-threatening or fatal, has occurred following treatment. HLH was reported in 6% (5/79) of patients with r/r ALL (time to onset ranged from 3 to 18 days) and 2% (2/115) of patients with r/r DLBCL (times to onset were Day 7 and Day 10); all HLH events occurred during ongoing CRS and resolved. One patient (1%) with r/r FL developed HLH > 1 year after receiving tisagenlecleucel with a fatal outcome. The patient did not have CRS during or immediately preceding HLH. Treatment of HLH should be administered as per institutional standards.
- **Hypersensitivity Reactions**: Monitor for hypersensitivity reactions during infusion. Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) or dextran 40.
- **Serious Infections**: Infections, including life-threatening or fatal infections, occurred in 125 (64%) of 194 patients with r/r ALL or r/r DLBCL. Seventy-seven patients (40%) experienced Grade ≥ 3 infections, including fatal infections in 2 patients (3%) with r/r ALL and 1 patient (1%) with r/r DLBCL. Prior to infusion, infection prophylaxis should follow local guidelines. Patients with active uncontrolled infection should not start treatment until the infection is resolved. Monitor patients for signs and symptoms of infection after treatment and treat appropriately. Febrile neutropenia (≥ Grade 3) was also observed in 34% of patients with r/r ALL, 17% of patients with r/r DLBC, and 13% of patients with r/r FL; and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated.
- **Prolonged Cytopenias**: Patients may exhibit cytopenias for several weeks following tisagenlecleucel infusion. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved.

- **Hypogammaglobulinemia**: Hypogammaglobulinemia and agammaglobulinemia (IgG) related to B-cell aplasia can occur in patients with a complete remission (CR) after infusion. Hypogammaglobulinemia was reported in 53% of patients treated with tisagenlecleucel for r/r ALL, 17% of patients with r/r DLBCL, and 18% of patients with r/r FL. Monitor and provide replacement therapy until resolution. Assess immunoglobulin levels in newborns of mothers treated with tisagenlecleucel.
- **Secondary Malignancies**: T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including Kymriah. In the event that a secondary malignancy occurs after treatment with tisagenlecleucel, contact Novartis Pharmaceuticals Corporation at 1-844-4KYMRIAH.
- **HIV Testing**: HIV and the lentivirus used to make tisagenlecleucel have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid test (NAT) tests may yield false-positive results in patients who have received tisagenlecleucel.
- **Pregnancy**: There are no available data with use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted and it is not known if tisagenlecleucel has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, tisagenlecleucel is not recommended for women who are pregnant.

BILLING/CODING INFORMATION:

The collection of leukapheresis provides the starting material for the manufacturing of these CAR T-cell therapies and should **NOT** be billed separately.

HCPCS Coding

Q2041	Axicabtagene ciloleucel, up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2042	Tisagenlecleucel, up to 600 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2053	Brexucabtagene autoleucel, up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2054	Lisocabtagene maraleucel, up to 110 million autologous anti-cd19 car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2055	Idecabtagene vicleucel, up to 510 million autologous b-cell maturation antigen (bcma) directed car-positive t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2056	Ciltacabtagene autoleucel, up to 100 million autologous b-cell maturation antigen (bcma) directed car-positive t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2058	Obecabtagene autoleucel, up to 400 million cd19 car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose

ICD-10 Diagnosis Codes That Support Medical Necessity

Q2058 - Obecabtagene autoleucel (Aucatzyl)

C83.50 – C83.59	Lymphoblastic (diffuse) lymphoma
C91.00 – C91.02	Acute lymphoblastic leukemia

Q2055 - Idecabtagene Vicleucel (Abecma)

C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.32	Solitary plasmacytoma in relapse

Q2054 - Lisocabtagene Maraleucel (Breyanzi)

B20	Human immunodeficiency virus [HIV] disease [for HIV-related B-cell lymphomas only and only used in combination with C83.30-C83.39, C83.80-C83.89, or C85.80-C85.89]
C82.00 – C82.09	Follicular lymphoma grade I
C82.10 – C82.19	Follicular lymphoma grade II
C82.20 – C82.29	Follicular lymphoma grade III, unspecified
C82.30 – C82.39	Follicular lymphoma grade IIIa
C82.40 – C82.49	Follicular lymphoma grade IIIb
C82.50 – C82.59	Diffuse follicle center lymphoma
C82.60 – C82.69	Cutaneous follicle center lymphoma
C82.80 – C82.89	Other types of follicular lymphoma
C82.90 – C82.99	Follicular lymphoma, unspecified
C83.00 – C83.09	Small cell B-cell lymphoma
C83.10 – C83.19	Mantle cell lymphoma
C83.30 – C83.38	Diffuse large B-cell lymphoma
C83.398	Diffuse large B-cell lymphoma of other extranodal and solid organ sites
C83.80 – C83.89	Other non-follicular lymphoma
C83.90 – C83.99	Non-follicular (diffuse) lymphoma, unspecified
C85.10 – C85.19	Unspecified B-cell lymphoma
C85.20 – C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80 – C85.89	Other specified types of non-Hodgkin lymphoma
C88.40	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma] not having achieved remission
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)

Q2056 - Ciltacabtagene Autoleucel (Carvykti)

C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.32	Solitary plasmacytoma in relapse

Q2041 – Axicabtagene Ciloleucel (Yescarta)

B20	Human immunodeficiency virus [HIV] disease [for HIV-related B-cell lymphomas only and only used in combination with C83.30-C83.39, C83.80-C83.89, or C85.80-C85.89]
C82.00 – C82.09	Follicular lymphoma grade I
C82.10 – C82.19	Follicular lymphoma grade II
C82.20 – C82.29	Follicular lymphoma grade III, unspecified
C82.30 – C82.39	Follicular lymphoma grade IIIa
C82.40 – C82.49	Follicular lymphoma grade IIIb
C82.50 – C82.59	Diffuse follicle center lymphoma
C82.60 – C82.69	Cutaneous follicle center lymphoma
C82.80 – C82.89	Other types of follicular lymphoma
C82.90 – C82.99	Follicular lymphoma, unspecified
C83.00	Small cell B-cell lymphoma, unspecified site
C83.07	Small cell B-cell lymphoma, spleen
C83.08	Small cell B-cell lymphoma, lymph nodes of multiple sites
C83.30 – C83.38	Diffuse large B-cell lymphoma
C83.398	Diffuse large B-cell lymphoma of other extranodal and solid organ sites
C83.80 – C83.89	Other non-follicular lymphoma
C83.90 – C83.99	Non-follicular (diffuse) lymphoma, unspecified
C85.10 – C85.19	Unspecified B-cell lymphoma
C85.20 – C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80 – C85.89	Other specified types of non-Hodgkin lymphoma
C88.40	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma] not having achieved remission
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)

Q2042 - Tisagenlecleucel (Kymriah)

B20	Human immunodeficiency virus [HIV] disease [for HIV-related B-cell lymphomas only and only used in combination with C83.30-C83.39, C83.80-C83.89, or C85.80-C85.89]
C82.00 – C82.09	Follicular lymphoma grade I
C82.10 – C82.19	Follicular lymphoma grade II

C82.20 – C82.29	Follicular lymphoma grade III, unspecified
C82.30 – C82.39	Follicular lymphoma grade IIIa
C82.40 – C82.49	Follicular lymphoma grade IIIb
C82.50 – C82.59	Diffuse follicle center lymphoma
C82.60 – C82.69	Cutaneous follicle center lymphoma
C82.80 – C82.89	Other types of follicular lymphoma
C82.90 – C82.99	Follicular lymphoma, unspecified
C83.30 – C83.38	Diffuse large B-cell lymphoma
C83.398	Diffuse large B-cell lymphoma of other extranodal and solid organ sites
C83.50 – C83.59	Lymphoblastic (diffuse) lymphoma
C83.80 – C83.89	Other non-follicular lymphoma
C83.90 – C83.99	Non-follicular (diffuse) lymphoma, unspecified
C85.10 – C85.19	Unspecified B-cell lymphoma
C85.20 – C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80 – C85.89	Other specified types of non-Hodgkin lymphoma
C91.00 – C91.02	Acute lymphoblastic leukemia
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)

Q2053 - Brexucabtagene Autoleucel (Tecartus)

C83.10 – C83.19	Mantle cell lymphoma
C83.50 – C83.59	Lymphoblastic (diffuse) lymphoma
C91.00 – C91.02	Acute lymphoblastic leukemia

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: The following National Coverage Determination (NCD), located at cms.gov, was reviewed on the last guideline review date: Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24).

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Autologous: Cells or tissues obtained from the same individual (as opposed to from a different person).

CD19: Cluster of Differentiation 19 is a protein found on the surface of B-cells in humans. Fully differentiated plasma cells no longer express CD19.

Chimeric antigen receptor (CAR) T-cell therapy: A type of treatment in which a patient's T cells are changed in the laboratory so they will attack cancer cells. T cells are taken from a patient's blood. Then the gene for a special receptor that binds to a certain protein on the patient's cancer cells is added in the laboratory. The special receptor is called a chimeric antigen receptor (CAR). Large numbers of the CAR T cells are grown in the laboratory and given to the patient by infusion.

Complete response (CR) (in ALL): (1) no circulating blast or extramedullary disease including no lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, or CNS involvement (2) trilineage hematopoiesis (TLH) and <5% blasts, (3) absolute neutrophil count (ANC) >1,000/mcL, (4) platelets >100,000/mcL, and (5) no recurrence for 4 weeks.

Complete response with incomplete blood count recovery (CRi) (in ALL): Same criteria for CR except platelet count and/or ANC.

Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS): The 2008 WHO classification of mature B-cell lymphomas included DLBCL, NOS as a new category to include germinal center B-cell (GCB) subtype, activated B-cell (ABC) subtype as well as other DLBCL cases that do not belong to any of the four specific subtypes (T-cell/histiocyte rich large B-cell lymphoma, primary CNS DLBCL, primary cutaneous DLBCL ("leg type"), or EBV+ DLBCL of the elderly). The updated 2016 WHO classification system created additional categories that fall outside of the definition of DLBCL, NOS.

Gene therapy: Gene therapies treat diseases by modifying or manipulating the expression of a gene or altering the properties of living cells for therapeutic use including: (1) replacing a disease-causing gene with a healthy copy of the gene, (2) inactivating a disease-causing gene that is not functioning properly, or (3) introducing a new or modified gene into the body to help treat a disease.

Heavy chain – the larger component of an immunoglobulin. There are five types: IgG, IgA, IgM, IgD, and IgE.

Immunoglobulins (a.k.a., antibodies) – proteins made by normal plasma cells that have an important role in fighting infection as part of the humoral immune response. Antibodies are composed of two heavy chains and two light chains that form a larger complex. Each plasma cell produces only one type of heavy chain and one type of light chain.

Leukapheresis: A laboratory procedure in which white blood cells (WBC) are separated from a sample of blood. It is a specific type of apheresis, the more general term for separating out one particular constituent of blood and returning the remainder to the circulation. It is the first step in CAR T-cell therapy.

Light chain – the smaller component of an immunoglobulin. There are two types: kappa and lambda.

Minimal Residual Disease (MRD): The presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieved a CR by morphologic assessment alone can

potentially harbor a large number of leukemic cells in the bone morrow. There is a strong correlation between MRD and risk for relapse. Current methods for MDR assessment include multicolor flow cytometry assays specifically designed to detect abnormal MRD immunophenotypes, real-time quantitative PCR assays, and next-generation sequencing-based assays. Current multicolor flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-4}$ (<0.01%) bone marrow mononuclear cells.

Myeloma Protein (M-Protein) – a nonfunctional immunoglobulin protein or protein fragment produced by malignant plasma cells (or myeloma cells). Since myeloma cells are monoclonal, the M-proteins for a given patient are structurally identical. Both portions of an immunoglobulin (the heavy chain and light chain) can be found in the serum, while only light chains can be found in the urine.

Plasma cell - a fully differentiated B lymphocyte (a type of white blood cell) that is specialized for immunoglobulin production and is found primarily in bone marrow.

Primary mediastinal large B-cell lymphoma (PMBL): A distinct subtype of NHL presenting with primary site of disease in the mediastinum with or without other site and has histology of DLBCL. It tends to occur in young adults with a median age of 35 years with a slight female predominance.

Primary refractory MM - patients who never achieve at least a MR to initial induction therapy and progress while on therapy

Progressive ALL: Increase of at least 25% in the absolute number of circulating or bone marrow blasts or the development of extramedullary disease.

Progressive MM - at least a 25% increase from nadir in the serum M-protein (absolute increase must be ≥0.5 g/dL) or urine M-protein (absolute increase must be ≥200mg/24 hours), or in the difference between involved and uninvolved serum-free light-chain (FLC) levels (with an abnormal FLC ratio and FLC difference >100 mg/L).

Refractory ALL: Failure to achieve a CR at the end of induction therapy.

Relapsed ALL: Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR.

Relapsed and refractory MM - patients who never achieve at least a MR or who progress within 60 days of their last therapy

RELATED GUIDELINES:

Adoptive Immunotherapy, 01-96400-01

OTHER:

Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

International Working Group (IWG) Response Criteria for Malignant Lymphoma

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
Complete remission (CR)	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immuno-histochemistry should be negative
Partial remission (PR)	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	
Stable disease (SD)	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or progressive disease (PD)	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
FDG - [^{18}F]fluorodeoxyglucose; PET - positron emission tomography; CT - computed tomography; SPD - sum of the product of the diameters				

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/14/26.

GUIDELINE UPDATE INFORMATION:

05/15/21	New Medical Coverage Guideline.
07/01/21	Added HCPCS code C9076.
07/15/21	Revision to guideline consisting of updating the position statement.
10/01/21	Revision: Added HCPCS codes C9081 and Q2054 and deleted code C9076.
11/01/21	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, and reference based on the approval of a new indication for Tecartus.
01/01/22	Revision: Added HCPCS code Q2055 and deleted codes C9081 and J9999.
02/15/22	Review and revision to guideline consisting of updating the description section, position statement, warning/precautions, and references.
04/01/22	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, and references based on the approval of Carvykti.
05/01/22	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, and reference.
07/01/22	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, and references based on the new FDA-approved indication of r/r FL for Kymriah and updated NCCN guidelines. Added HCPCS code C9098.
08/01/22	Revision to guideline consisting of updating the description, position statement, dosage/administration, and references based on the updated FDA-approved indication for large B-cell lymphoma for Breyanzi and updated NCCN guidelines.
10/01/22	Revision: Added HCPCS code Q2056 and deleted codes C9098 and J9999.
02/15/23	Review and revision to guideline consisting of updating the description section, position statement, billing/coding, and references. Yescarta and Breyanzi added as treatment options for pediatric primary mediastinal large B-cell lymphoma in certain circumstances.
02/15/24	Review and revision to guideline consisting of updating the description section (NCCN info), position statement, and references.
05/01/24	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, and reference based on a new FDA-approved indication for Breyanzi for relapsed or refractory CLL or SLL and expanded FDA-approved MM indications for Abecma and Carvykti.
07/01/24	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, and references based on new FDA-approved indications for Breyanzi for relapsed or refractory FL and MCL. Updated description for HCPCS code Q2055.
10/01/24	Revision: ICD-10 code updates.
01/01/25	Review and revision to guideline consisting of updating the description section (NCCN info), position statement, dosage/administration, precautions, billing/coding, and references. Addition of obecabtagene autoleucel (Aucatzyl approved in November 2024 for “for “the treatment of adults with relapsed or refractory B-cell precursor acute

	lymphoblastic leukemia (ALL)". Added boxed warning of "T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies" to all CAR T-cell therapies as this is now a class-wide warning in the labeling.
04/01/25	Revision: Added HCPCS code C9301.
07/01/25	Revision: Added HCPCS code Q2058 and removed codes C9301 and J9999.
09/15/25	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, and references based on the removal of the REMS requirements from the package labeling of all CAR T-cell therapies. Revision to Carvykti criteria to allow use despite not being lenalidomide refractory when at least three prior lines of therapy for the member's MM have been tried.
01/15/26	Review and revision to guideline consisting of updating the description section, position statement, dosage/administration, billing/coding, and references. New indication added for Breyanzi of relapsed or refractory marginal zone lymphoma (MZL) who have received at least 2 prior lines of systemic therapy. For Breyanzi for CLL/SLL treatment, added an exception allowing ibrutinib to be given as combination therapy. Plasmablastic lymphoma (PBL) and DLBCL arising from CLL/SLL [a.k.a., Richter transformation] added as additional subtypes of large B-cell lymphoma that are appropriate for CAR-T cell treatment.
02/15/26	Review and revision to guideline consisting of updating the position statement and references. New requirement that the healthcare facility where the CAR T-cell therapy is being administered must be FACT-accredited for the clinical service of "Immune Effector Cellular Therapy".