LOUISIANA BLUE

Chimeric Antigen Receptor T-cell (CAR-T) Therapy

Policy # 00605
Original Effective Date: 02/21/2018
Current Effective Date: 08/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

Note: Other forms of adoptive immunotherapy such as using adoptive cellular therapy for the administration of cytotoxic T lymphocytes, cytokine-induced killer cells, tumor-infiltrating lymphocytes, or antigen-loaded autologous dendritic cells are addressed separately in medical policy 00248.

tisagenlecleucel (Kymriah®)

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Acute Lymphoblastic Leukemia

Based on review of available data, the Company may consider the use of tisagenlecleucel (Kymriah®)‡ for the treatment of relapsed or refractory B cell acute lymphoblastic leukemia (ALL) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of tisagenlecleucel (Kymriah) will be considered when ALL of the following criteria are met:

- Patient has a confirmed diagnosis of CD19-positive B-cell ALL with morphologic bone marrow tumor involvement (greater than or equal to 5% lymphoblasts); AND
- Patient is 25 years old or younger at time of infusion; AND
- Disease is refractory to initial therapy or in second or later relapse
    - Refractory is defined as failure to obtain complete response with induction therapy, i.e., failure to eradicate all detectable leukemia cells (less than 5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (greater than 25% marrow cellularity and normal peripheral blood counts);
    - Relapsed is defined as the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission (CR) with chemotherapy and/or allogeneic stem cell transplant; AND

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- Patient has NOT received prior CD19-directed chimeric antigen receptor T-cell therapy (CAR-T) or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient does NOT have ANY of the following:
  - Burkitt lymphoma; OR
  - Active hepatitis B virus, hepatitis C virus, or other uncontrolled fungal, bacterial, or viral infection requiring intravenous antimicrobials; OR
  - Grade 2-4 graft-vs-host disease; OR
  - Concomitant genetic syndrome with the exception of Down syndrome; OR
  - Received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to tisagenlecleucel infusion; OR
  - Active central nervous system (CNS) disease defined by the National Comprehensive Cancer Network (NCCN) guidelines to be a presence of greater than or equal to 5 white blood cells (WBC) per microliter (μL) in the cerebrospinal fluid (CSF) in addition to the presence of lymphoblasts
    *(Note: These specific patient selection criteria [except the criterion regarding active infections] are additional company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*

B-cell Lymphoma

Based on review of available data, the Company may consider the use of tisagenlecleucel (Kymriah™)‡ for the treatment of relapsed or refractory B-cell lymphoma to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of tisagenlecleucel (Kymriah) will be considered when ALL of the following criteria are met:

- Patient has a diagnosis of ONE of the following:
  - Diffuse large B-cell lymphoma (DLBCL), not otherwise specified; OR
  - High grade B-cell lymphoma; OR
  - DLBCL arising from follicular lymphoma; OR
  - Follicular lymphoma AND:
- Patient is greater than or equal to 18 years old at the time of infusion; AND
- Disease is relapsed or refractory, defined as progression after 2 or more lines of systemic therapy (which may or may not include therapy supported by autologous cell transplant); AND
- Patient has failed two or more lines of systemic therapy including:
  - Anti-CD20 monoclonal antibody (such as rituximab) unless tumor is CD20-negative; AND

  - An anthracycline-containing chemotherapy regimen (e.g., regimens containing doxorubicin, daunorubicin, or epirubicin); AND

*(Note: The patient selection criteria requiring specific systemic agents are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met. If patient has not failed two or more lines of any systemic therapy, request will be denied as investigational*.)*

- Patient has NOT received prior CD19-directed chimeric antigen receptor T-cell therapy (CAR-T) or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); AND
  *(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient does NOT have ANY of the following:
  - Primary CNS lymphoma; OR
  - Active hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or other uncontrolled fungal, bacterial, or other viral infection requiring intravenous antimicrobials.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of tisagenlecleucel (Kymriah) when ANY of the following criteria for their respective disease listed below (and denoted in the patient selection criteria above) are not met to be **not medically necessary:****

- For acute lymphoblastic leukemia
  - Patient has NOT received prior CD19-directed CAR-T or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); OR
  - Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; OR
  - Patient does NOT have ANY of the following:
    - Burkitt lymphoma; OR
    - Grade 2-4 graft vs host disease; OR
    - Concomitant genetic syndrome (except Down syndrome) ; OR
    - Received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to Kymriah infusion; OR
    - Active CNS disease; OR
- For B-cell lymphoma
  - Patient has failed two or more lines of systemic therapy including:
    - An anti-CD20 monoclonal antibody unless tumor is CD20-negative; OR
    - An anthracycline-containing chemotherapy regimen; OR
  - Patient has NOT received prior CD19-directed CAR-T therapy or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); OR
  - Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of tisagenlecleucel (Kymriah) when patient selection criteria are not met (except those listed as **not medically necessary****) to be **investigational.***

axicabtagene ciloleucel (Yescarta™)

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of axicabtagene ciloleucel (Yescarta™)‡ for the treatment of relapsed or refractory B-cell lymphoma or follicular lymphoma to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of axicabtagene ciloleucel (Yescarta) will be considered when ALL of the following criteria are met:

- Patient has a documented diagnosis of ONE of the following:
  - Diffuse large B-cell lymphoma (DLBCL), not otherwise specified; OR
  - Primary mediastinal large B-cell lymphoma; OR
  - High grade B-cell lymphoma; OR
  - DLBCL arising from follicular lymphoma; OR
  - Follicular lymphoma; AND
- Patient is greater than or equal to 18 years old at the time of infusion; AND
- If patient has a diagnosis of follicular lymphoma, disease is relapsed or refractory, defined as progression after 2 or more lines of systemic therapy (which may or may not include therapy supported by autologous cell transplant); AND
- Patient has failed at least one line of systemic therapy including:
  - An anti-CD20 monoclonal antibody (such as rituximab) unless tumor is CD20-negative; AND
  - An anthracycline containing chemotherapy regimen (e.g., regimens containing doxorubicin, daunorubicin, or epirubicin); AND

  *(Note: The patient selection criteria requiring specific systemic agents are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met. If patient has not failed two or more lines of any systemic therapy, request will be denied as investigational*.)*
- Patient has NOT received prior CD19-directed chimeric antigen receptor T-cell therapy (CAR-T) or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); AND

*(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  *(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient does NOT have active hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or other uncontrolled fungal, bacterial, or other viral infection requiring intravenous antimicrobials.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of axicabtagene ciloleucel (Yescarta) when ANY of the following criteria listed below (and denoted in the patient selection criteria above) are not met to be **not medically necessary:****

- Patient has failed at least one line of systemic therapy including:
  - An anti-CD20 monoclonal antibody unless tumor is CD20-negative; AND
  - An anthracycline containing chemotherapy regimen; OR
- Patient has NOT received prior CD19-directed CAR-T or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); OR
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of axicabtagene ciloleucel (Yescarta) when patient selection criteria are not met (except those listed as **not medically necessary****) to be **investigational.***

brexucabtagene autoleucel (Tecartus™)

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Mantle Cell Lymphoma

Based on review of available data, the Company may consider the use of brexucabtagene autoleucel (Tecartus™)‡ for the treatment of mantle cell lymphoma to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of brexucabtagene autoleucel (Tecartus) will be considered when ALL of the following criteria are met:

- Patient has a diagnosis of mantle cell lymphoma; AND
- Disease is relapsed or refractory, defined as disease progression after last regimen or failure to achieve a partial response or complete response to the last regimen; AND
- Patient is greater than or equal to 18 years of age at the time of infusion; AND
- Patient has tried and failed all of the following treatments unless there is clinical evidence or patient history suggesting the treatment option will be ineffective or cause an adverse reaction to the patient:
    - An anthracycline or bendamustine-containing chemotherapy regimen (e.g., regimens containing doxorubicin, daunorubicin, or epirubicin); AND
    - An anti-CD20 monoclonal antibody (such as rituximab); AND
    - A Bruton's tyrosine kinase (BTK) inhibitor (such as ibrutinib [Imbruvica®]‡, acalabrutinib [Calquence®]‡, or zanubrutinib [Brukinsa™]‡); AND

  *(Note: The patient selection criteria requiring specific systemic agents are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient has at least one measurable lesion; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Platelet count is greater than or equal to 75,000/µL; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient has NOT received prior CD19-directed chimeric antigen receptor T-cell therapy (CAR-T) or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient does NOT have:
    - Active hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or other uncontrolled fungal, bacterial, or other viral infection requiring intravenous antimicrobials.

Acute Lymphoblastic Leukemia

Based on review of available data, the Company may consider the use of brexucabtagene autoleucel (Tecartus) for the treatment of relapsed or refractory B cell acute lymphoblastic leukemia (ALL) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of brexucabtagene autoleucel (Tecartus) will be considered when ALL of the following criteria are met:

- Patient has a diagnosis of B cell precursor acute lymphoblastic leukemia (ALL); AND
- Patient is greater than or equal to 18 years of age at the time of infusion; AND
- Disease is refractory to initial therapy or in second or later relapse
    - Refractory is defined as failure to obtain complete response with induction therapy, i.e., failure to eradicate all detectable leukemia cells (less than 5% blasts) from the bone marrow and the blood with subsequent restoration of normal hematopoiesis (greater than 35% marrow cellularity and normal peripheral blood counts);
    - Relapsed is defined as the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission (CR) with chemotherapy and/or allogeneic stem cell transplant; AND
- Patient has NOT received prior CD19-directed chimeric antigen receptor T-cell therapy (CAR-T) or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient does NOT have ANY of the following:
    - Active Graft Versus Host Disease (GVHD); OR
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
    - Treatment with immunosuppressive medications in the past 4 weeks; OR
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
    - Treatment with hematopoietic stem cell transplant in the past 100 days; OR
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
    - Active hepatitis B virus, hepatitis C virus, or other uncontrolled fungal, bacterial, or viral infection requiring intravenous antimicrobials.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of brexucabtagene autoleucel (Tecartus) when ANY of the following criteria listed below (and denoted in the patient selection criteria above) are not met to be **not medically necessary:****

- For mantle cell lymphoma:
    - Patient has tried and failed all of the following treatments:
        - An anthracycline or bendamustine-containing chemotherapy regimen; AND
        - An anti-CD20 monoclonal antibody; AND
        - A BTK inhibitor; AND

  - Patient has at least one measurable lesion; AND
  - Platelet count is greater than or equal to 75,000/ μL; AND
  - Patient has NOT received prior CD19-directed CAR-T or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); AND
  - Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis.
- For acute lymphoblastic leukemia:
  - Patient has NOT received prior CD19-directed CAR-T or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); AND
  - Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  - Patient does NOT have active GVHD; AND
  - Patient has NOT been treated with immunosuppressive medications in the past 4 weeks; AND
  - Patient has not been treated with a hematopoietic stem cell transplant in the past 100 days.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of brexucabtagene autoleucel (Tecartus) when patient selection criteria are not met (except those listed as **not medically necessary****) to be **investigational.***

lisocabtagene maraleucel (Breyanzi®)

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of lisocabtagene maraleucel (Breyanzi®)‡ for the treatment of relapsed or refractory B-cell lymphoma to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of lisocabtagene maraleucel (Breyanzi) will be considered when ALL of the following criteria are met:

- Patient meets one of the following:
  - Diagnosis of diffuse large B-cell lymphoma (DLBCL), not otherwise specified; High grade B-cell lymphoma; Primary mediastinal large B-cell lymphoma; DLBCL arising from follicular lymphoma; OR Follicular lymphoma grade 3B; AND

- Disease is relapsed or refractory, defined by one of the following:
  - ❖ 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; AND
- Patient has failed all of the following:
  - ❖ An anti-CD20 monoclonal antibody (such as rituximab) unless tumor is CD20-negative; AND
  - ❖ An anthracycline-containing chemotherapy regimen (e.g., regimens containing doxorubicin, daunorubicin, or epirubicin); OR
    *(Note: The patient selection criteria requiring specific systemic agents are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*

- o Diagnosis of follicular lymphoma grade 1-3A; AND
  - Disease is relapsed or refractory after at least 2 lines of systemic therapy (may include prior autologous or allogeneic HSCT); AND
  - Patient has failed all of the following therapies:
    - ❖ An anti-CD20 monoclonal antibody (such as rituximab) unless tumor is CD20 negative; AND
    - ❖ An alkylating agent-containing chemotherapy regimen (e.g., regimens containing cisplatin, oxaliplatin, carboplatin, chlorambucil, cyclophosphamide, mechlorethamine, or melphalan); OR
      *(Note: The patient selection criteria requiring specific systemic agents are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*
- o Diagnosis of mantle cell lymphoma; AND
  - Disease is relapsed or refractory after at least 2 lines of systemic therapy (may include prior autologous or allogeneic HSCT); AND
  - Patient has failed treatment with a Bruton's Tyrosine Kinase inhibitor (BTKi) such as acalabrutinib (Calquence), ibrutinib (Ibrance), or zanubrutinib (Brukinsa); OR
- o Diagnosis of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL); AND
  - Disease is relapsed or refractory after at least 2 lines of systemic therapy (may include prior autologous or allogeneic HSCT); AND
  - Patient has failed all of the following therapies:
    - ❖ A BTKi such as Calquence, Imbruvica, or Brukinsa; AND
    - ❖ A B-cell lymphoma 2 inhibitor (BCL2i) such as venetoclax (Venclexta®)‡; OR
- o Diagnosis of marginal zone lymphoma (MZL); AND
  - Disease is relapsed or refractory after at least 2 lines of systemic therapy (may include prior autologous or allogeneic HSCT); AND

- Patient is greater than or equal to 18 years of age at the time of infusion; AND
- Patient has NOT received prior CD19-directed chimeric antigen receptor T-cell therapy (CAR-T) or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient does NOT have ANY of the following:
  - Primary CNS lymphoma; OR
  - Active hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or other uncontrolled fungal, bacterial, or other viral infection requiring intravenous antimicrobials.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of lisocabtagene maraleucel (Breyanzi) when ANY of the following criteria listed below (and denoted in the patient selection criteria above) are not met to be **not medically necessary.****

- Patient has a diagnosis of DLBCL not otherwise specified, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, DLBCL arising from follicular lymphoma or follicular lymphoma and has tried and failed first-line chemoimmunotherapy including:
  - An anthracycline-containing chemotherapy regimen; AND
  - An anti-CD20 monoclonal antibody.
- Patient has NOT received prior CD19-directed CAR-T or any other genetically modified T-cell therapy (including experimental CAR-NK therapy).
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis.
- Patient has a diagnosis of follicular lymphoma grade 1-3A and has tried and failed an alkylating agent-containing chemotherapy regimen.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of lisocabtagene maraleucel (Breyanzi) when patient selection criteria are not met (except those listed as **not medically necessary****) to be **investigational.***

idecabtagene vicleucel (Abecma®), ciltacabtagene autoleucel (Carvykti™)

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of idecabtagene vicleucel (Abecma®)‡ or ciltacabtagene autoleucel (Carvykti™)‡ for the treatment of multiple myeloma to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of idecabtagene vicleucel (Abecma) or ciltacabtagene autoleucel (Carvykti) will be considered when all of the following criteria are met:

- Patient has a diagnosis of relapsed or refractory multiple myeloma; AND
- Patient is greater than or equal to 18 years of age at the time of infusion; AND
- For Abecma requests only, patient has received at least two prior treatment regimens for multiple myeloma. Note that induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered a single regimen; AND
- Patient has received at least one agent from each of the following classes:
    - Immunomodulatory agents (e.g., thalidomide [Thalomid®]‡, lenalidomide [Revlimid®]‡, pomalidomide [Pomalyst®]‡); AND
    - Proteasome inhibitors (e.g., bortezomib [Velcade®]‡, carfilzomib [Kyprolis®]‡, ixazomib [Ninlaro®]‡); AND
    - Anti-CD38 monoclonal antibody (e.g., daratumumab [Darzalex®]‡, daratumumab and hyaluronidase-fihj [Darzalex Faspro®]‡, isatuximab [Sarclisa®]‡); AND
- Patient has NOT received prior B-cell maturation antigen (BCMA)-directed CAR-T therapy or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

- Patient does NOT have ANY of the following:
  - Active or history of plasma cell leukemia; OR
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
  - Active hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or other uncontrolled fungal, bacterial, or other viral infection requiring intravenous antimicrobials.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of idecabtagene vicleucel (Abecma) or ciltacabtagene autoleucel (Carvykti) when ANY of the following criteria listed below (and denoted in the patient selection criteria above) are not met to be **not medically necessary.****

- Patient has NOT received prior BCMA-directed CAR-T or any other genetically modified T-cell therapy (including experimental CAR-NK therapy)
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis
- Patient has an ECOG performance status of 0 or 1
- Patient does NOT have a history of plasma cell leukemia.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of idecabtagene vicleucel (Abecma) or ciltacabtagene autoleucel (Carvykti) when patient selection criteria are not met (except those listed as **not medically necessary****) to be **investigational.***

obecabtagene autoleucel (Aucatzyl®)

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of obecabtagene autoleucel (Aucatzyl®)‡ for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of obecabtagene autoleucel (Aucatzyl) will be considered when all of the following criteria are met:

- Patient has a diagnosis of B cell precursor acute lymphoblastic leukemia (ALL); AND

- Patient is greater than or equal to 18 years of age at the time of infusion; AND
- Patient has relapsed or refractory disease defined by one of the following:
    - First relapse following a remission lasting less than or equal to 12 months; OR
    - Relapsed or refractory ALL after greater than or equal to 2 prior lines of systemic therapy; OR
    - Relapsed or refractory ALL greater than or equal to 3 months after allogeneic stem cell transplant (SCT) and disease burden of greater than or equal to 5% blasts in the bone marrow at screening; AND
- Patient has NOT received prior CD19-directed chimeric antigen receptor T-cell therapy (CAR-T) or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient does not have ANY of the following:
    - Acute Graft Versus Host Disease; OR
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
    - Treatment with immunosuppressive medications in the past 4 weeks; OR
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
    - Treatment with hematopoietic stem cell transplant in the past 100 days; OR
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
    - Active hepatitis B virus, hepatitis C virus, or other uncontrolled fungal, bacterial, or viral infection requiring intravenous antimicrobials.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of obecabtagene autoleucel (Aucatzyl) when ANY of the following criteria listed below (and denoted in the patient selection criteria above) are not met to be **not medically necessary.****

- Patient has NOT received prior CD19-directed chimeric antigen receptor T-cell therapy (CAR-T) or any other genetically modified T-cell therapy (including experimental CAR-NK therapy); AND
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
- Patient does not have ANY of the following:
    - Acute Graft Versus Host Disease; OR
    - Treatment with immunosuppressive medications in the past 4 weeks; OR
    - Treatment with hematopoietic stem cell transplant in the past 100 days.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of obecabtagene autoleucel (Aucatzyl) when the patient selection criteria are not met (except those noted above as **not medically necessary****) to be **investigational.***

Policy Guidelines

Although adequate organ function can have varying definitions, the following was used in clinical trials of Kymriah in pediatric patients.

- Serum Creatinine within normal limits for patient age

Age (years)	Serum Creatinine (mg/dL)
1 - < 2	≤ 0.6
2 - < 6	≤ 0.8
6 - < 10	≤ 1
10 - < 13	≤ 1.2
13 - < 16	≤ 1.5 (Male) ≤ 1.4 (Female)
≥ 16	≤ 1.7 (Male) ≤ 1.4 (Female)

- ALT < 5 times the upper limit of normal (ULN) for age
- Bilirubin < 2.0 mg/dL
- Minimum level of pulmonary reserve < Grade 1 dyspnea and pulse oxygenation > 91% on room air
- Left Ventricular Shortening Fraction > 28% confirmed by echocardiogram or Left Ventricular Ejection Fraction > 45% confirmed by echocardiogram or Multiple Uptake Gated Acquisition

The definitions of adequate organ function in the initial adult pivotal trials with each agent are described in the table below.

Drug (trial)	CrCl	ALT	LVEF	Hematologic
Kymriah (JULIET)	≥60 mL/min	≤5 x ULN	≥45%	Absolute lymphocyte concentration ≥300/µL
Yescarta (ZUMA-1)	≥60 mL/min	≤2.5 x ULN	≥50%	Absolute lymphocyte concentration ≥100/µL
Yescarta (ZUMA-5)	≥60 mL/min	≤2.5 x ULN	≥50%	---
Tecartus (ZUMA-2)	≥60 mL/min	---	≥60%	Platelet count ≥75,000/µL
Breyanzi (TRANSCEND)	>30 mL/min	---	≥40%	----
Abecma (KarMMa)	>45/mL/min	>2.5 x ULN	>45%	ANC≥1000 cells/m^3 Platelet count ≥50,000/µL
Carvykti (CARTITUDE-1)	≥40 mL/min	≤3.0 x ULN	≥45%	ANC≥0.75 x 10^9/L Platelets ≥50 x 10^9/L

Background/Overview

CAR-T is a form of cellular immunotherapy in which a patient's own T-cells are removed and programmed to destroy cells marked with a certain protein. In the case of Kymriah, Yescarta, Tecartus, Breyanzi, and Aucatzyl, that protein is CD19 which is expressed on most B-cells. These drugs are therefore indicated for certain cancers involving proliferation of B-cells. Abecma and Carvykti target B-cell maturation antigen (BCMA) which is present in normal and malignant plasma cells. They are therefore used to treat multiple myeloma, a cancer caused by malignant plasma cells.

Kymriah is a CAR-T therapy approved for the treatment of relapsed or refractory ALL in patients younger than 25 years of age, adults with relapsed or refractory large B-cell lymphoma, and adults with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy. Treatment involves reprogramming a patient's own T-cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing cells. The patient's T-cells are removed and reprogrammed *in vitro* then re-infused at a rate of 10-20 mL/min. The recommended dosage of Kymriah for patients with B-cell ALL who are 50 kg or less is 0.2 to 5.0×10^6 CAR-positive viable T-cells per kilogram of body weight intravenously; for patients above 50 kg, the recommended dose is 0.1 to 2.5×10^8 total CAR-positive viable T-cells (non-weight-based) intravenously. The recommended dose of Kymriah for patients with large B-cell lymphoma or follicular lymphoma is 0.6 to 6.0 $x10^8$ CAR-positive viable T-cells intravenously. Prior to infusion, the patient must be pre-treated with fludarabine and cyclophosphamide to deplete the patient's lymphocytes and reduce the risk of severe cytokine release syndrome (CRS). CRS is one of the most common adverse effects and occurred in 79% of patients in the ALL pivotal trial. Severe CRS may be life-threatening and should be treated with tocilizumab.

Yescarta is a CAR-T therapy currently approved for the treatment of adults with relapsed or refractory large B-cell lymphoma after at least one line of systemic therapy and for the treatment of adults with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy. Similar to Kymriah, Yescarta is a cellular immunotherapy in which the T-cells of a patient are modified genetically to selectively target and bind to CD19 antigen expressed on the surface of normal and malignant B cells. Prior to infusion of Yescarta, the patient must be pre-treated with a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine. The recommended dosage of Yescarta is 2 x 10^6 CAR-positive viable T-cells per kilogram body weight with a maximum of 2 x 10^8 CAR-positive viable T-cells. After infusion of Yescarta, patients must be monitored at least daily for 7 days at a certified healthcare facility for signs and symptoms of CRS and neurologic toxicities and then remain within proximity of the certified healthcare facility for at least 4 weeks following infusion. In February 2026, The FDA removed the exclusion of patients with primary CNS lymphoma from the Yescarta label based on phase 1 data demonstrating a manageable safety profile and no new safety signals in this population. Earlier exclusions were driven by theoretical concerns regarding increased neurotoxicity and lack of clinical data; however, prospective evidence showed toxicity rates comparable to the established CAR-T safety profile.

Tecartus is an anti-CD19 CAR-T therapy approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma as well as adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). It is very similar to Yescarta but is manufactured using a different process that includes T-cell selection and lymphocyte enrichment. Additionally, the dosing, administration, and monitoring requirements vary slightly between the two indications of Tecartus.

For the treatment of mantle cell lymphoma, the patient must be pre-treated with a lymphodepleting regimen of cyclophosphamide and fludarabine prior to treatment (administered on the 5^{th}, 4^{th}, and 3^{rd} days prior to infusion of Tecartus). The recommended dosage of Tecartus is 2 x 10^6 CAR-positive viable T-cells per kilogram body weight with a maximum of 2 x 10^8 CAR-positive viable T-cells. After infusion of Tecartus, patients must be monitored at least daily for 7 days at a certified healthcare facility for signs and symptoms of CRS and neurologic toxicities and then remain within proximity of the certified facility for at least 4 weeks following infusion. For the treatment of ALL, the patient must be pre-treated with a lymphodepleting regimen of fludarabine on the 4^{th}, 3^{rd}, and 2^{nd} day prior to treatment with cyclophosphamide administered only on the second day prior to treatment. The recommended dosage of Tecartus for ALL is 1 x10^6 CAR-positive viable T cells per kg with a maximum of 1 x 10^8 CAR-positive viable T cells. After infusion of Tecartus, patients must be monitored at least daily for 14 days at a certified healthcare facility and then remain within proximity of the certified facility for at least 4 weeks following infusion.

Breyanzi is an anti-CD19 CAR-T therapy approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy or who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy or who have refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for HSCT due to comorbidities or age. It is also approved for the treatment of adults 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; for adult patients with relapsed or refractory mantle cell lymphoma who have received at least 2 prior lines of systemic therapy, including a BTK inhibitor for adult patients with relapsed or refractory follicular lymphoma who have received 2 or more prior lines of systemic therapy; and for adult patients with relapsed or refractory marginal zone lymphoma who have received 2 or more prior lines of systemic therapy. It should be dosed at 50 to 110 x 10^6 CAR-positive viable T cells. As with the other CAR-T agents, patients must be pretreated with lymphodepleting chemotherapy for 3 days and then receive Breyanzi 2-7 days later. Patients must be monitored daily at a certified healthcare facility for the first week following infusion and must remain within proximity of the facility for at least 4 weeks following infusion.

Abecma is an anti-BCMA CAR-T therapy indicated for the treatment of adults 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. The recommended dose is 300 to 460 x 10^6 CAR positive T-cells administered as a single IV infusion 2 days after completion of lymphodepleting chemotherapy with cyclophosphamide and fludarabine. As with the other CAR-T agents, Abecma must be administered at a qualified treatment center experienced in CAR-T therapy and management of associated toxicities and patients must be monitored at the facility daily for 7 days following infusion. Patients must remain within proximity of the certified facility for at least 24 weeks following infusion.

Carvykti is an anti-BCMA CAR-T therapy indicated for the treatment of adults with relapsed or refractory multiple myeloma after one or more prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent and are refractory to lenalidomide. The recommended dose is 0.5 to 1.0 x 10^6 CAR-positive T cells per kg of body weight administered as a single IV infusion 2-4

days after completion of lymphodepleting chemotherapy with cyclophosphamide and fludarabine. Carvykti must be administered at a qualified treatment center experienced in CAR-T therapy and management of associated toxicities, and patients must be monitored at least daily at the facility for 7 days following the infusion. Additionally, patients must remain within proximity of the certified facility for at least 24 weeks following infusion.

Aucatzyl is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Unlike the other CAR-T therapies, Aucatzyl is administered as a split dose on days 1 and 10 for a total dose of 410 x 10^6 CD19 CAR-positive viable T cells. A bone marrow assessment should be done within 7 days prior to infusion to determine the percentage of the dose that should be given on each dosing day. Additionally, patients should be pre-treated with fludarabine and cyclophosphamide 3 days (± 1 day) prior to the first dose of Aucatzyl. As with the other CAR-T agents, Aucatzyl must be administered at an authorized treatment center. Patients must be monitored for signs and symptoms of CRS, neurologic toxicities/ ICANS, and other acute toxicities daily for at least 7 days following each infusion and then monitored for at least 24 weeks following each infusion. Patients should refrain from driving or hazardous activities for at least 2 weeks following each infusion.

Acute lymphoblastic leukemia (ALL)
ALL is one of the most common childhood malignancies. Despite having a relatively high 5-year overall survival rate of 85%, prognosis is poor for those who do not respond to initial treatment. Relapse following ALL treatment is the second most common cause of cancer-related death in children. Initial treatment is approached in three stages: induction, consolidation, and maintenance. The goal of induction therapy, which usually lasts 3-4 weeks, is to achieve an initial CR. If CR is not reached during this stage, the disease is considered refractory. Consolidation treatment is designed to prevent leukemic regrowth, reduce residual tumor burden, and prevent emergence of drug resistance in the remaining leukemic cells. This phase typically lasts 4-8 months and includes drugs tailored to the patient based on risk of re-occurrence. The final phase of treatment, the maintenance phase, is a less intensive continuation regimen of daily therapy that is continued for a total treatment duration of 30-42 months. Re-occurrence after completion of the maintenance phase is considered relapse and requires aggressive reinduction therapy and intensification, which is often ineffective. Patients who achieve a second remission are candidates for allogeneic hematopoietic stem cell transplantation (HSCT). Relapse of ALL can occur in many extramedullary sites, but most often occurs in the bone marrow, CNS, or testicles. Bone marrow relapse is the most common site of relapse and usually presents with persistent peripheral blood cytopenias. When the relapse occurs in the CNS, the NCCN guidelines classify the disease into the following categories:

- CNS 1: No lymphoblasts in CSF regardless of the WBC count;
- CNS 2: WBC < 5/µL in CSF with presence of lymphoblasts;
- CNS 3: WBC ≥ 5/µL in CSF with presence of lymphoblasts.

Current NCCN guidelines for ALL recommend (category 2A) Kymriah as a treatment option for:

- Philadelphia chromosome-positive patients 26 years or less in age with refractory disease or 2 or more relapses and failure of 2 tyrosine kinase inhibitors.
- Philadelphia chromosome-negative patients 26 years or less in age with refractory disease or 2 or more relapses.

Diffuse large B-cell lymphoma (DLBCL)
DLBCL is the most common histologic subtype of non-Hodgkin lymphoma and accounts for approximately 25% of non-Hodgkin lymphoma cases. DLBCL exhibits large heterogeneity in morphologic, genetic, and clinical aspects and multiple clinicopathologic entities are defined by the 2016 World Health Organization classification, which are sufficiently distinct to be considered separate diagnostic categories.

It has been estimated that 27,650 new cases of DLBCL were diagnosed in the United States in 2016. Treatment in the first-line setting (particularly rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) is associated with a 5-year survival rate ranging from 60-70%. However, based on a number of prognostic factors, 20-50% of DLBCL cases are refractory or relapse after first-line chemotherapy. The response to subsequent salvage chemotherapy and consolidation with autologous cell transplantation is suboptimal with one study finding only 7% of patients with refractory DLBCL achieving a complete response to the next line of therapy.

Current NCCN guidelines for B-cell lymphomas recommend (category 2A) Yescarta or Kymriah as a treatment option:

- For histological transformation to DLBCL after multiple lines of prior therapies which includes $\geq$ 2 chemo-immunotherapy regimens for indolent or transformed disease.
- For relapse or refractory disease DLBCL after multiple lines of prior therapies which includes $\geq$ 2 chemo-immunotherapy regimens for indolent or transformed disease.

Mantle Cell Lymphoma (MCL)
MCL is a rare B-cell malignancy classified as an aggressive form of non-Hodgkin lymphoma that arises from cells originating in the “mantle zone” of the lymph node and accounts for approximately 3 to 6% of lymphomas in the United States. MCL typically affects men over the age of 60 with the median age at the time diagnosis of 68 years. As an aggressive disease, MCL is not curable and over 70% of patients present with stage IV disease. There is no standard frontline therapy for MCL although several rituximab-based regimens are initially used and can prolong response durations. Regimens are chosen based on several factors such as the patient age and fitness. However, no therapy is curative as disease relapse inevitably occurs. Patients with disease progression following BTK inhibitor therapy have a low response rate and a median overall survival of 6 to 10 months.

The NCCN guidelines for B-cell lymphomas (version 2.2024) recommend CAR T-cell therapy as a treatment option in certain circumstances, without regard to the duration of response to previous treatment, in patients with relapsed or refractory disease and progressive disease after treatment with a covalent BTK inhibitor.

Follicular Lymphoma (FL)
FL is the second most common subtype of non-Hodgkin lymphomas and is associated with an excellent prognosis for most patients with a median overall survival greater than 20 years. Approximately 40-80% of patients treated respond to initial chemoimmunotherapy while 10% do not respond. However, conventional therapy for FL is not curative and most of these patients ultimately develop progressive disease. The prevalence of follicular lymphoma in the United States is approximately 2.7 per 100,000 individuals per year. The 5-year survival rate may be as high as

89.7% and the median age at diagnosis is 63 years old. Patients with advanced-stage FL after ≥ 2 lines of therapy reported complete response rate with approved therapies is < 14% and median duration of response is ≤ 13 months.

There is no standard therapy for patients with relapsed or refractory FL and practice varies widely. Patients with late relapse are treated with an anti-CD20 monoclonal antibody either alone or in combination with chemotherapy or lenalidomide. The choice between immunotherapy alone versus combination therapy in late relapse depends largely on patient performance status. Novel FDA approved agents for treatment in the multiple relapse/refractory setting include phosphoinositide 3-kinase (PI3K) inhibitors (copanlisib [Aliqopa®]‡, duvelisib [Copiktra®]‡, idelalisib [Zydelig®]‡, umbralisib [Ukoniq™]‡), lenalidomide (Revlimid), tazemetostat (Tazverik®)‡ and radioimmunotherapy. The choice is primarily made based on the patient's prior treatment, the expected toxicity profile of the selected regimen, route of administration, and clinician experience with the regimens.

Multiple Myeloma
Multiple Myeloma is a hematologic malignancy characterized by the abnormal growth of plasma cells with production of abnormal proteins instead of typical antibodies. Plasma cell proliferation in the marrow causes bone pain and fractures due to lytic lesions and displaces other marrow cellular elements. The majority of patients with myeloma present with symptoms related to organ involvement, including hypercalcemia, renal insufficiency, anemia, and bone lesions. This is a relatively rare cancer with an annual incidence of approximately 7 in 100,000 Americans. Multiple myeloma is primarily a disease of older adults, with a median age at diagnosis of 69 years.

Relapsed or refractory multiple myeloma is commonly identified through routine monitoring with laboratory studies using the standard 2016 International Myeloma Working Group response criteria for categorizing progression and relapse. Progression is usually identified by an increase in monoclonal (M) protein in the serum or urine or in the serum free light chain ratio. Not all patients with progression on laboratory testing need immediate treatment. Therapy is indicated if there is a clinical relapse, extramedullary disease, or a rapid increase in paraproteins.

The majority of patients with multiple myeloma respond to initial therapies that consist of combination treatment and autologous stem cell transplant. However, conventional therapy is not curative and most of these patients will ultimately progress. A small proportion of patients do not respond (i.e., refractory disease).

There is no single standard treatment for patients with relapsed/refractory multiple myeloma and multiple treatment options are used. Most patients experience serial relapse and are treated with the majority of available agents at some point during their disease course. The main pharmacological treatments used are monoclonal antibodies (daratumumab [Darzalex], daratumumab and hyaluronidase-fihj [Darzalex Faspro], isatuximab [Sarclisa]), proteasome inhibitors (bortezomib [Velcade], carfilzomib [Kyprolis], ixazomib [Ninlaro]), immunomodulatory drugs (thalidomide [Thalomid], lenalidomide [Revlimid], pomalidomide [Pomalyst]), alkylators, anthracyclines, panobinostat [Farydak®]‡, selinexor [Xpovio®]‡, and corticosteroids. A preferred order for their use has not been established. The choice of therapy at each relapse is informed by prior therapies used, response to these treatments, comorbidities, risk stratification, and the location of disease (e.g.,

extramedullary disease). Three-drug regimens are preferred over two-drug regimens. However, two-drug regimens are acceptable alternatives for frail patients who may not be able to tolerate three-drug regimens. According to the most recent NCCN clinical practice guideline, the triplet regimen including dexamethasone combined with a proteasome inhibitor, an immunomodulatory agent, or an anti-CD38 monoclonal antibody should be used as a primary standard therapy for multiple myeloma (category 2A recommendation).

Patients with myeloma who have been treated with the three main backbones of interventional therapy (proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies) have poor outcomes to subsequent treatment. Patients with heavily pretreated multiple myeloma that are daratumumab refractory have an expected median overall survival ranging from 6.6. to 9.3 months. Reported median progression-free survival for this population is 2.3 to 3.4 months. Other than CAR-T therapy, belantamab mafodotin (Blenrep®)‡, an anti-BCMA antibody conjugated to an antineoplastic agent, is the only FDA-approved single agent treatment for patients who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Kymriah

Kymriah was approved for ALL based on an open-label, multicenter single-arm trial including 63 patients treated with lymphodepleting chemotherapy followed by a single dose of Kymriah. Efficacy endpoints included achievement of CR within 3 months after infusion, duration of CR, and proportion of patients with CR and minimal residual disease (MRD) < 0.01% by flow cytometry. CR designation required remission status to be maintained for at least 28 days without clinical evidence of relapse. 83% of patients achieved a CR or CR with incomplete blood count recovery (CRi), and all patients were negative for MRD. Median duration of remission was not reached at the time that the study data was submitted (median follow-up of 4.8 months from response).

Patients were only included in the study if they had adequate organ function defined based on measures of serum creatinine, alanine aminotransferase (ALT), bilirubin, pulse oxygenation, and left ventricular ejection fraction. In addition, Kymriah was not studied in patients with extra-medullary disease relapse, Burkitt lymphoma, or concomitant genetic syndromes that pre-dispose patients to leukemia, such as Fanconi anemia or Kostmann syndrome. Patients with Down syndrome were not excluded.

Kymriah was approved for the treatment of relapsed or refractory B-cell lymphoma based on the open-label, multicenter, single-arm, JULIET trial. Studied patients were ≥ 18 years of age with relapsed or refractory DLBCL, who received ≥ 2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous HSCT. The study excluded patients with active CNS malignancy, prior allogenic HSCT, an ECOG performance status ≥ 2, a creatinine clearance < 60,

ALT > 5 times normal, cardiac ejection fraction < 45%, or absolute lymphocyte concentration less than 300/µL. Following 2 to 11 days after completion of lymphodepleting chemotherapy, Kymriah was administered as a single intravenous infusion. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was permitted to control disease burden. Lymphodepleting chemotherapy could be omitted if the white blood cell count was < 1000 cells/µL. The major efficacy outcomes were objective response rate per Lugano criteria as assessed by an independent review committee and duration of response. Of the 160 patients enrolled, 106 patients received Kymriah, including 92 patients who received product manufactured in the U.S. and were followed for at least 3 months or discontinued earlier. Eleven out of the 160 patients enrolled did not receive the drug due to manufacturing failure. 38 other patients did not receive Kymriah, primarily due to death (n = 16), physician decision (n = 16), and adverse events (n = 3). A retrospectively identified sub-group of 68 patients was evaluable for the major efficacy outcome measures. Patients included in this sub-group had either had no bridging chemotherapy or had imaging that showed measurable disease after completion of bridging chemotherapy prior to Kymriah infusion. Of the 24 patients not included, 8 had no evidence of disease at baseline prior to Kymriah infusion, 15 did not have baseline imaging following bridging chemotherapy, and 1 was excluded because of initial misclassification of a neuroendocrine tumor as DLBCL.

Among the efficacy evaluable population of 68 patients, the median time to first response was 0.9 months. The median duration of response was not reached. Response durations were longer in patients who achieved complete response, as compared to patients with a best response of partial response. Of the 22 patients who experienced a complete response, 9 achieved this status by 1 month, 12 more by month 3, and the last by month 6 after Kymriah infusion. The overall response rate which includes complete and partial responses was 50% with a complete response rate of 32% and partial response rate of 18%.

Kymriah was approved in relapsed or refractory follicular lymphoma (FL) based on a multicenter, single-arm, open-label trial (ELARA) that included patients who were refractory to or relapsed within 6 months after completion of 2 or more lines of systemic therapy (including an anti-CD20 antibody and an alkylating agent), relapsed during or within 6 months after completion of an anti-CD20 antibody maintenance therapy following at least 2 lines of therapy, or relapsed after autologous HSCT. The trial excluded patients with active or serious infections, transformed lymphoma, or other aggressive lymphomas, prior allogeneic HSCT, or disease with active CNS involvement. Following lymphodepleting chemotherapy, Kymriah was administered as a single dose IV infusion with a target dose of 0.6 to 6.0 $x10^8$ CAR-positive viable T-cells. The efficacy analysis included 90 patients with FL who were treated with Kymriah. Efficacy was established on the basis of overall response rate (ORR) and duration of response (DOR) as determined by an independent review committee. The ORR was 86% (achieved by 88 patients) and included 61 patients (68%) who achieved a complete response. At a median follow up of 9.1 months, the overall DOR was not estimable.

Yescarta
Yescarta was approved for DLBCL based on the results of an open-label, multicenter phase 1/2 study, which reported CR rates and duration of response demonstrated in the phase 2 portion of the study. Adults with aggressive B-cell non-Hodgkin lymphoma that was primary refractory, refractory to a second or greater line of therapy, or relapsed within 1 year after autologous hematopoietic cell

transplantation were enrolled in the study. Patients with prior allogeneic hematopoietic cell transplantation, any history of CNS lymphoma, Eastern Cooperative Oncology Group Performance Status score 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 ULN, cardiac ejection fraction less than 50%, or active serious infection were excluded. Most patients (74%) had de novo DLBCL and 32% had double- or triple-hit lymphoma. The median age was 58, with 24% being aged 65 years or older; the median number of prior therapies was 3; 77% had refractory disease to a second or greater line of therapy; and 21% had relapsed within 1 year after autologous hematopoietic cell transplantation (HCT).

All patients received a lymphodepleting regimen consisting of cyclophosphamide and fludarabine prior to infusion of Yescarta. 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. The primary end point was objective response rate based on a modified intention-to-treat population, which was defined as all patients treated with at least 1.0 x 10^6 CAR-T cells per kilogram. Objective response was seen in 72% of patients with 51% achieving a complete response and 21% achieving a partial response.

Yescarta was approved for relapsed or refractory follicular lymphoma based on the results of an ongoing open-label, phase 2 study called ZUMA-5. This trial enrolled 146 patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. Patients received a single infusion of Yescarta at 2 x 10^6 CAR-T cells/kg after leukapheresis and lymphodepleting therapy. The median time from leukapheresis to product delivery was 17 days (range: 13-33 days) and leukapheresis to product infusion was 27 days (range: 19-250 days). All treated patients received infusion on day 0 and were hospitalized until at least day 7. The primary endpoint was the objective response rate (ORR) by central review. Of the 120 patients dosed, data of 81 consecutive patients who had at least 9 months of follow-up from the date of first response were included in the primary efficacy analysis. The ORR in these patients was found to be 91% (95% CI: 83, 96).

Yescarta was approved for relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy in a randomized, open-label, multicenter trial called ZUMA-7. All patients had previously received a regimen 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. In total, 359 patients were randomized in a 1:1 ratio to receive a single infusion of Yescarta 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. Randomization was stratified by response to first-line therapy and second-line age-adjusted International Prognostic Index. Patients received a single IV infusion of Yescarta at 2 x 10^6 CAR-positive viable T cells/kg following a lymphodepletion regimen given the fifth, fourth, and third day before Yescarta. Bridging therapy, administered between leukapheresis and lymphodepleting chemotherapy, was limited to corticosteroids and was permitted for patients with

high disease burden. In the Yescarta group, 170 patients were ultimately treated. The median time from leukapheresis to product delivery was 18 days (range: 13 to 49 days), and from leukapheresis to Yescarta infusion was 26 days (range: 16 to 52 days). In the standard therapy group, 168 patients received any study treatment, and 62 (35%) received high-dose therapy and on-protocol HSCT. The primary efficacy measure was event-free survival (EFS) as determined by an independent review committee. The estimated EFS rate at 18 months was 41.5% [95% CI: 34.2, 48.6] in the Yescarta arm and 17.0% [95% CI: 11.8, 23.0] in the standard therapy arm.

Tecartus
Tecartus was approved based on a phase II single-arm study (the ZUMA-2 study). This study enrolled adult patients with relapsed or refractory MCL who were heavily pretreated. Of 74 patients enrolled, therapy was successfully manufactured for 71 (96%) and administered to 68 (92%). The primary efficacy analysis demonstrated an objective response rate (ORR) of 93% with a 67% rate of complete response. The median duration of response, progression-free survival (PFS), and median overall survival (OS) were not reached. At data cutoff, 57% of patients remained in remission, and the estimated 12-month PFS and OS were 61% and 83%, respectively. In subgroup analyses, the ORR and PFS at 6 months were consistent across groups, including those with high-risk features. The efficacy of Tecartus in adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) was evaluated in ZUMA-3, an open-label, single-arm, multicenter trial. Eligible patients were adults with primary refractory ALL, first relapse following a remission lasting $\leq$ 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. 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 followed by a single IV infusion of Tecartus at a target dose of 1 x 10^6 anti-CD19 CAR-T cells (maximum 1 x 10^8 cells). All treated patients were hospitalized until at least Day 7. Among the 54 patients treated with Tecartus, the median time from leukapheresis to product delivery was 16 days (range: 11 to 39 days) and the median time from leukapheresis to infusion was 29 days (range: 20 to 60 days). The efficacy of Tecartus was established on the basis of complete remission (CR) within 3 months after infusion and the duration of CR (DOCR). 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.

Breyanzi
The approval of Breyanzi in patients who had relapsed or refractory disease after two or more lines of therapy was based on the results of 1 single arm, open-label trial (TRANSCEND). Trial participants were required to have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have relapsed or refractory disease after at least 2 lines of systemic therapy or autologous stem cell transplant. Of the 299 patients who received leukapheresis, 15% (n = 44) did not receive CAR-positive T-cells either due to manufacturing failures (n = 2), death (n = 29), disease complications (n = 6), or other reasons (n = 7). Of the 255 patients who received treatment, 192 were evaluable for efficacy (including 25 manufacturing failures who received CAR T-cells that did not meet product specifications). The primary endpoint was the percentage of patients with treatment-emergent adverse events and the ORR, defined as the proportion of patients who achieved a best overall response of CR or PR based on assessment by the independent review committee according

to the Lugano classification. The primary efficacy analysis demonstrated at ORR of 73% with a 55% rate of complete response (CR) among 192 patients evaluable for efficacy. Cytokine release syndrome occurred in 36% of patients with ≥ Grade 3 CRS in 4% of patients. One patient had fatal CRS and 2 had ongoing CRS at the time of death. CRS resolved in 119 of 122 patients with a median duration of 5 days (range: 1-17 days).

The approval of Breyanzi in adult patients with relapsed or refractory LBCL after first-line chemoimmunotherapy was evaluated in a randomized, open-label, multicenter trial (TRANSFORM). Included patients had not yet received treatment for relapsed or refractory lymphoma, were potential candidates for autologous HSCT, and were required to have primary refractory disease or relapse within 12 months from complete response to initial chemoimmunotherapy. Patients were randomized in a 1:1 ratio to receive a single infusion of Breyanzi or standard therapy consisting of 3 cycles of chemoimmunotherapy followed by high-dose therapy and autologous HSCT in those who responded. In total, 89 patients received Breyanzi. The median time from leukapheresis to product availability was 26 days (range: 19 to 84 days), and the median time from leukapheresis to product infusion was 36 days (range: 25 to 91 days). In the standard of care group, 91 patients began treatment and 43 (47%) received high-dose therapy and HSCT. The most common reason for not receiving HSCT was lack of efficacy of the salvage chemotherapy. The primary efficacy measure was event-free survival (EFS) as determined by an independent review committee. The estimated 1-year EFS was 45% [95% CI: 29, 59] in the Breyanzi arm and 24% [95% CI: 14, 35] in the standard therapy arm.

The approval of Breyanzi in adult transplant-ineligible patients with relapsed or refractory LBCL after one line of chemoimmunotherapy was evaluated in a single-arm, open-label, multicenter trial (PILOT). The study enrolled patients who were not eligible for high-dose therapy and autologous HSCT due to organ function or age, while also having adequate organ function for CAR-T cell therapy. The study required at least one of the following criteria: age ≥ 70 years, adjusted diffusing capacity of the lunch for carbon monoxide (DLCO) ≤ 60%, LVEF < 50%, creatinine clearance <60 mL/min, AST or ALT > 2 x ULN, or ECOG performance status of 2. The planned dose of Breyanzi was 100 x 10^6 CAR positive viable T cells. Bridging therapy for disease control was permitted between leukapheresis and the start of lymphodepleting chemotherapy. Breyanzi was administered 2 to 7 days following completion of lymphodepleting chemotherapy and was administered in both the inpatient (67%) and outpatient (33%) setting. The main efficacy population included 61 patients who received Breyanzi. Efficacy was based on complete response (CR) rate and duration of response (DOR), as determined by an independent review committee. The median time to CR was 1 month (range 0.8 to 6.9 months) and 33 patients (54%) experienced a CR.

The efficacy of Breyanzi in relapsed or refractory CLL or SLL was evaluated in a phase 1/2, open-label, multicenter, single-arm trial (TRANSCEND-CLL) in adult patients who had received at least 2 prior lines of therapy including a BTKi and a BCL-2i. Patients were given Breyanzi within 2 to 11 days after completion of lymphodepleting chemotherapy. In this trial, Breyanzi was administered in the inpatient (88%) and outpatient (12%) settings. The median time from leukapheresis to product availability was 24 days (range: 19-84 days), and the median time from leukapheresis to product infusion was 36 days (range: 28-384 days). Of the 89 patients treated with Breyanzi, 69 received bridging therapy. Patients had measurable disease present before Breyanzi administration based on IRC assessment. Nineteen of the 84 patients were not evaluable for efficacy (13 did not have baseline

disease assessments performed after completion of bridging therapy, 1 lacked measurable disease, and 5 had Richter's transformation). Of the 65 efficacy-evaluable patients, the median age was 66 years and median number of prior therapies was 5.

Efficacy was based on ORR (including CR and PR) and DOR. The median time to first response was 1.1 months (range: 0.8 to 17.4 months). The median time to first CR was 3.0 months (range: 1.1 to 17.9 months). The ORR was 45% with 29 patients achieving a CR or PR. Median DOR was 35.3 months.

The efficacy of Breyanzi in relapsed or refractory follicular lymphoma was evaluated in a Phase 2, open-label, multicenter, single-arm trial (TRANSCEND-FL) in adult patients with relapsed or refractory FL after 2 or more lines of systemic therapy (including an anti-CD20 antibody and an alkylating agent). A single dose of Breyanzi was administered 2 to 7 days following completion of lymphodepleting chemotherapy. Six percent of patients were treated with Breyanzi in an outpatient setting. Of the 114 patients who underwent leukapheresis, 107 received Breyanzi. The primary efficacy analysis included 94 patients who had PET-positive disease at study baseline or confirmation of PET-positive disease after bridging therapy, received conforming product in intended dose range and had at least 9 months of follow up from the date of first response. The median time from leukapheresis to product availability was 29 days (range: 20 to 55 days) and the median time from leukapheresis to product infusion was 50 days (range: 31 to 313 days). Of the 107 patients treated with Breyanzi, 40 received bridging therapy.

Efficacy was based on ORR, defined as the percentage of patients with a best overall response of CR or PR after Breyanzi infusion and duration of response as determined by an IRC. The median time to first response was 1.0 month (range: 0.6 to 3.3 months). The median time to first CR was 3.0 months (range 0.6 to 18 months). The ORR was found to be 95.7% with 73.4% of patients achieving a CR and 22.3% achieving a PR. Median duration of response was not reached.

The efficacy of Breyanzi in relapsed or refractory mantle cell lymphoma was evaluated in an open-label, multicenter, single-arm trial (TRANSCEND-MCL) in adult patients with relapsed or refractory MCL who had received at least two prior lines of therapy including a BTK inhibitor, an alkylating agent, and an anti-CD20 agent. Breyanzi was administered 2 to 7 days following completion of lymphodepleting chemotherapy. Of 89 patients who underwent leukapheresis. The primary efficacy analysis included a total of 68 patients with MCL who received at least 2 prior lines of therapy including a BTK inhibitor, 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 median time from leukapheresis to product availability was 24 days (range: 17 to 80 days), and the median time from leukapheresis to product infusion was 36 days (range: 28 to 489 days). Of the 68 patients in the main efficacy population, 44 (65%) received bridging therapy.

Efficacy was based on ORR defined as the percentage of patients with the best overall response of CR or PR after Breyanzi infusion. Both the median time to first response and the median time to first CR were 1 month (range: 0.7 to 3 months). The ORR was 85.3% with 67.6% being complete responses and 17.6% being partial responses.

The efficacy of Breyanzi in relapsed or refractory marginal zone lymphoma (MZL) was evaluated in an open-label, multicenter, single-arm study (JCAR017-FOL-001; MZL cohort). Eligible patients were adults with relapsed or refractory MZL who had received at least two prior lines of systemic therapy, including an anti-CD20 antibody and an alkylating agent, or had relapsed after hematopoietic stem cell transplantation (HSCT). The study included patients with an ECOG performance status of 0 or 1 and excluded those with significant organ dysfunction, including creatinine clearance ≤ 30 mL/min, ALT > 5 times the upper limit of normal, or left ventricular ejection fraction < 40%, as well as those with transformed lymphoma, active or serious infections, active autoimmune disease requiring immunosuppressive therapy, or a history of central nervous system disorders.

Patients received a single infusion of Breyanzi at a target dose of 100×10^6 CAR-positive viable T cells 2 to 7 days following completion of lymphodepleting chemotherapy consisting of fludarabine and cyclophosphamide administered for 3 days. Bridging therapy was permitted between leukapheresis and initiation of lymphodepleting chemotherapy. Of the 77 patients who underwent leukapheresis, 67 received Breyanzi, and the primary efficacy analysis included 66 patients who had measurable disease at baseline or after bridging therapy and received conforming product within the intended dose range.

The median time from leukapheresis to product availability was 29 days, and the median time from leukapheresis to infusion was 50 days. The primary efficacy endpoint was overall response rate (ORR), defined as the proportion of patients achieving a complete or partial response as assessed by an independent review committee. The median time to first response was 0.95 months, and the median time to first complete response was 5.55 months. The overall response rate was 95.5% in the Breyanzi-treated patients (95% CI: 87.3, 99.1) and the complete response rate was 62.1% (95% CI 49.3, 73.8).

Abecma
Abecma was approved for multiple myeloma based on the single arm, open-label, phase 2 KarMMa trial. This trial enrolled adult patients with relapsed or refractory multiple myeloma who received at least 3 different prior lines of therapy including proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies. The primary endpoint was an overall response (partial response or better). A total of 149 patients were enrolled in the trial. FDA analysis included data from 100 patients who received Abecma in the dose range of 300×10^6 and 450×10^6. The overall manufacturing failure rate was 1.5% (2 out of 135 patients). All patients were hospitalized for 14 days after infusion of Abecma to monitor for potential CRS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, and neurotoxicity. After a median follow-up of 10.7 months, the primary efficacy analysis demonstrated an overall response of 72% (95% CI: 62, 81) with a 28% (95% CI: 19, 38) rate of stringent complete response.

The KarMMa-3 trial was an open-label, multicenter, randomized, controlled study in adults with relapsed and refractory multiple myeloma 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 386 patients who were randomized 2:1 to receive either Abecma (n = 254) or standard regimens (n = 132). The primary efficacy endpoint was the ORR. In the Abecma arm, 181 patients (71%) responded compared to 55 patients (42%) in the standard regimen arm.

Carvykti
The efficacy of Carvykti in multiple myeloma was evaluated in CARTITUDE-1, an open-label, single-arm, multicenter trial in adult patients with relapsed or refractory multiple myeloma, who previously received at least 3 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Patients with known active or prior history of significant CNS disease including CNS multiple myeloma, 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, ANC < 750 cells/mm^3, platelet count < 50,000/mm^3, hepatic transaminases > 3 x ULN, cardiac ejection fraction < 45%, or with active serious infection were excluded from the trial. There were 97 patients in the efficacy evaluable population who received Carvykti, including 17 patients (18%) with manufacturing failures either because they received product that did not meet product release specifications or received ciltacabtagene autoleucel for which there were insufficient data to confirm product release specifications for Carvykti. Most patients (75%) treated with Carvykti received bridging therapy for control of their multiple myeloma during the manufacturing process. The median time from leukapheresis to product availability was 32 days (range: 27 to 66 days).

Efficacy was established on the basis of overall response rate (ORR), complete response rate (CR), and duration of response (DOR) as assessed by the independent review committee using International Myeloma Working Group criteria. The median time to first response was 1 month. The ORR was 97.9% with 95 patients experiencing a stringent complete response (78.4%), very good partial response (16.5%), or partial response (3.1%). In all responders, the DOR was 21.8 months, but it should be noted that the median DOR was not estimable in the patients with a stringent complete response.

The CARTITUDE-4 trial was a randomized, open-label multicenter trial in adult patients with relapsed and lenalidomide-refractory multiple myeloma, 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 Carvykti (n = 208) or standard therapy selected by physician prior to randomization based on the patient's prior antimyeloma therapy (n = 211). Patients had received a median of 2 prior lines of therapy and 85% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-nine percent of patients were refractory to their last line of prior therapy. Carvykti was ultimately administered to 176 patients as a single IV infusion 5 to 7 days after the start of a lymphodepleting chemotherapy. 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 Carvykti infusion was 79 days (range: 45 days to 246 days).

The primary efficacy measure was progression-free survival (PFS) analyzed based on the Intent-To-Treat Analysis Set. After a median follow-up of 15.9 months, median PFS was 12 months for standard therapy arm and NE (95% CI: 22.8, NE) for Carvykti arm (Hazard ratio: 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 Carvykti arm and 49.5% (95% CI: 42.3%, 56.3%) in the standard therapy arm.

Aucatzyl
The efficacy of Aucatzyl was evaluated in an open-label, multi-center, single-arm study (FELIX study). The study enrolled patients with relapsed or refractory B-cell acute lymphoblastic leukemia (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 stem cell transplantation (SCT) 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 graft versus host disease, history or presence of CNS disorders. Treatment was administered in the inpatient 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 Aucatzyl 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 Aucatzyl 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 of Aucatzyl, 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.

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: 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 HCT 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 Aucatzyl 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. Of the 65 efficacy evaluable patients, 27 (42%) achieved a complete remission (95% CI 29%, 54%) with a median duration of response of 14.1 months (95% CI 6.1, NR).

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Policy History

Original Effective Date: 02/21/2018
Current Effective Date: 08/01/2026

02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. New policy
04/01/2018	Coding update
05/22/2018	Coding update
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. Updated criteria for Kymriah to include coverage for new B-cell lymphoma indication. Updated background information and references to reflect the most current literature.
01/01/2019	Coding update
09/05/2019	Medical Policy Committee review
09/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Title changed from "Chimeric Antigen Receptor T-cell Therapy (CAR-T)" to "Chimeric Antigen Receptor T-cell (CAR-T) Therapy". Reformatted criteria to be listed by drug instead of indication. Added new drug, Tecartus, to policy with criteria and relevant background information. Updated criterion regarding prior anti-CD19 cellular immunotherapy to be more clinically relevant.
12/11/2020	Coding update

Policy # 00605
Original Effective Date: 02/21/2018
Current Effective Date: 08/01/2026

08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. Updated Yescarta criteria to include new indication of Follicular Lymphoma. Removed exclusion for patients with active CNS disease from all drugs. Added new drugs Breyanzi and Abecma with criteria and relevant background information. Added policy guidelines section to include description of adequate organ function.
09/30/2021	Coding update
12/20/2021	Coding update
06/08/2022	Coding update
08/04/2022	Medical Policy Committee review
08/10/2022	Medical Policy Implementation Committee approval. Added new product, Carvykti, with relevant criteria and background information. Updated criteria and background information for Yescarta, Tecartus, Kymriah, and Breyanzi to reflect updated FDA approvals.
09/20/2022	Coding update
10/18/2022	Coding update
08/03/2023	Medical Policy Committee review
08/09/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/01/2024	Medical Policy Committee review
08/14/2024	Medical Policy Implementation Committee approval. Updated criteria and background information for Breyanzi to reflect new FDA approvals for relapsed or refractory mantle cell lymphoma, chronic lymphocytic leukemia, and small lymphocytic leukemia. Updated criteria and background information for Abecma and Carvykti to reflect FDA approval in 3rd line therapy.
12/10/2024	Coding update
03/25/2025	Coding update
06/05/2025	Medical Policy Committee review
06/11/2025	Medical Policy Implementation Committee approval. Added new product, Aucatzyl, with relevant criteria and background information.
07/21/2026	Pre-Pharmacy and Therapeutics Committee approval.
07/22/2026	Pharmacy and Therapeutics Committee approval. Updated criteria and background information for Breyanzi to reflect new approval in marginal zone lymphoma. Removed primary CNS lymphoma limitation for Yescarta. Removed REMS requirements from background information and adjusted monitoring requirements due to FDA labeling updates.

Next Scheduled Review Date: 07/2027

Coding

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Policy # 00605
Original Effective Date: 02/21/2018
Current Effective Date: 08/01/2026

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Code Type	Code
CPT	38225, 38226, 38227, 38228
HCPCS	Q2041, Q2042, Q2053, Q2054, Q2055, Q2056, Q2058 Delete code effective 07/01/2025: C9301
ICD-10 Diagnosis	All Related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.