Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCONC104.0425	**ANTINEOPLASTIC AGENTS** **T-CELL THERAPY** See Appendix A for medications covered by policy
Effective Date: 6/1/2025	**Review/Revised Date**: 12/17, 01/18, 07/18, 08/18, 01/19, 03/19, 12/19, 09/20, 12/20, 03/21, 06/21, 12/21, 05/22, 02/23, 12/23, 01/24, 06/24, 10/24, 12/24, 01/25, 03/25 (SAB)
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Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For all requests, the following criteria must be met:

1. Use must be for an indication supported by National Comprehensive Cancer Network (NCCN) guidelines with recommendation 2A or higher
2. Documentation of adequate bone marrow, cardiac, pulmonary and organ function (such as kidney, liver)
3. One of the following regarding functional status must be met:
    a. For Kymriah® for B-cell precursor acute lymphoblastic leukemia (ALL) only: Karnofsky or Lansky Scale greater than or equal to 50%
    b. Provider attestation/documentation that the patient’s functional status is sufficient to undergo treatment. This may include but is not limited to a documented Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, Karnofsky or Lansky Scale greater than or equal to 50%, or a written statement acknowledging that the patient is fit to tolerate therapy.
4. No evidence of active infection or inflammatory disorder (including hepatitis B or C, active graft vs. host disease)
5. For B-cell lymphomas, patient does not have primary central nervous system lymphoma

For patients established on therapy with Elrexfio, Epkinly, Imdelltra, Kimmtrak Lunsumio, Talvey, Tecvayli, or Blincyto (for relapsed or refractory ALL) continuing authorization will be approved if the member is responding positively to therapy **AND** there is no unacceptable toxicity from the drug.

a. Note: Examples of unacceptable toxicity include: neurologic toxicity including Immune Cell-Associated Neurotoxicity Syndrome (ICANS), severe administration-related/local injection-site reactions, cytokine release syndrome (CRS), hepatotoxicity, neutropenia/febrile neutropenia, severe infections, etc.
b. Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy

EXCLUSION CRITERIA:
Combination use of T-cell therapies included in this policy.

Note: Bi-specific T-Cell Engager (BiTE) antibody use may be considered in accordance with NCCN guideline recommendations following CAR-T therapy with evidence of disease progression after CAR-T therapy administration. Consideration of CAR-T therapy following progression or intolerance to BiTE therapy will be considered based on NCCN guideline recommendations.

For CAR T-cell therapy, Amtagvi, and Tecelra: Repeat administration of the same or similar T-Cell therapy (e.g., administration of a different CAR-T for the same indication) is not considered medically necessary as the effectiveness of this approach has not been established.

For Tecelra: Heterogenous or homozygous for HLA-A*02:05P

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, an oncologist

COVERAGE DURATION:
For Blincyto: Initial authorization will be approved for six months. Reauthorization for relapsed or refractory acute lymphoblastic leukemia (ALL) will be approved for one year. No reauthorization beyond 18 months.

For Columvi: Initial authorization will be approved for one year. No reauthorization.

For Elrexfio, Epkinly, Imdelltra, Kimmtrak, Lunsumio, Talvey, and Tecvayli: Initial authorization and reauthorization will be approved for one year and with up to four doses of tocilizumab at up to 800 mg per dose.

For chimeric antigen receptor (CAR) T-cell therapy, Amtagvi, and Tecelra: Two months (limited to one treatment course per lifetime, with four doses of tocilizumab at up to 800 mg per dose).

For off-label use criteria please see the Chemotherapy Treatment Utilization Criteria; Coverage for Non-FDA Approved Indications ORPTCOPS105.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, obecabtagene autoleucel, and tisagenlecleucel are chimeric antigen receptor T-cell (CAR-T) targeted therapies that are directed against CD19 and idecabtagene vicleucel and ciltacabtagene autoleucel are a BCMA-directed CAR-T therapy. CAR-T therapy is a type of immunotherapy that utilizes a patient's own immune system to attack cancer cells with engineered T cells. CAR-T therapy is intended as a one-time treatment of a single infusion of the patient's own engineered T cells. The process begins with harvesting the patient's white blood cells via leukapheresis. The T cells are then isolated and activated and engineered with chimeric antigen components (CARs) which allow the T cells to recognize an antigen on target cancer cells. Once the CAR-T cells are constructed, they are stimulated to proliferate, and once a sufficient number of cells are available, they are infused into the patient.

Bi-specific T-Cell engager (BiTE) antibodies are a class of therapeutic monoclonal antibodies that include two binding domains, one targeting a cancer antigen or

receptor and the other binding to the surface of T-cells. These therapies bring cancer cells and T-cells into close proximity and cause T-cells to release inflammatory cytokines and cytolytic proteins, resulting in recruitment of other immune cells and lysis of cancer cells. These antibodies are available "off-the-shelf" and do not require patient specific manufacturing, unlike chimeric antigen receptor T-cell therapies which may take four weeks or longer to produce and administer. BiTEs have been developed to target different malignancies (Table 1).

Table 1 – BiTE Therapies

Bi-specific T-Cell Engager (BiTE) antibodies		
Drug name	**Indication**	**Cancer receptor targeted**
talquetamab-tgys (Talvey)	Multiple Myeloma	GPRC5D
teclistamab-cqyv (Tecvayli)	Multiple Myeloma	BCMA
elranatamab-bcmm (Elrexfio)	Multiple Myeloma	BCMA
blinatumomab (Blincyto)	ALL	CD19
glofitamab-gxbm (Columbi)	DLBCL	CD20
epcoritamab-bysp (Epkinly)	DLBCL, FL	CD20
mosunetuzumab-axgb (Lunsumio)	FL	CD20
tebendafusp-tebn (Imdelltra)	SCLC	DLL3
tarlatamab-dlle (Kimmtrak)	Uveal melanoma	gp100

Abbreviations: ALL – acute lymphocytic leukemia, DLBCL – diffuse large B-cell lymphoma, FL – follicular lymphoma, SCLC – small cell lung cancer

Lifileucel (Amtagvi) is an unmodified tumor-derived autologous T cell immunotherapy [also known as tumor-infiltrating lymphocyte (TIL) therapy] for treatment of adult patients with unresectable or metastatic melanoma. The specific mechanism of action is unknown. It is composed primarily of CD4+T and CD8+T cells. Tumor-infiltrating lymphocytes are isolated from a patient's resected tumor tissue, expanded ex-vivo into the billions and then infused back to the patient. The patient will receive lymphodepleting chemotherapy prior to lifileucel infusion followed by in vivo T cell expansion with high-dose aldesleukin (IL-2) after lifileucel infusion.

Afamitresgene autoleucel (Tecelra) is a melanoma-associated antigen A4-(MAGE-A4)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen. Tecelra is a type of immunotherapy that leverages the patient's own immune system to attack cancer cells using engineered T cells. It is administered as a one-time infusion of the patient's own engineered T cells. The treatment process begins with leukapheresis to harvest the patient's white blood cells. The T cells are then isolated and genetically modified with T cell receptors (TCRs) that enable them to recognize

MAGE-A4-specific antigens. Once the engineered T cells are expanded to sufficient numbers, they are infused back into the patient.

Acute lymphoblastic leukemia
ALL is a heterogeneous hematologic malignancy characterized by abnormal proliferation of immature lymphoid cells (plasma cells) in the bone marrow, peripheral blood, or other organs. ALL occurs predominantly in children with a median age at diagnosis of 17 years and 53.5% of cases diagnosed at age <20 years old. This contrasts with the adult and geriatric populations where 29.6% of patients are diagnosed at ≥45 years and only 13.7% of patients ≥65 years old. Overall, ALL represents only 20% of leukemias among adults. There is an estimated incidence of ALL in 1.8 per 100,000 individuals per year, with approximately 6,550 new cases per year in the U.S. and 1,330 deaths estimated in 2024. B-ALL represents more than two-thirds of all new cases of ALL. Survival rates have increased modestly over the past several decades; however, survival rates for adults are poor at approximately 20-40% and only about 20% of older adults.

Currently available therapy in r/r ALL may include blinatumomab (Blincyto®), inotuzumab ozogamicin (Besponsa®), CAR-T therapies brexucabtagene autoleucel (Tecartus™), obecabtagene autoleucel (Aucatyzl®), and tisagenlecleucel (Kymriah®), as well as allogenic hematopoietic stem cell transplant. Stem cell transplant allows for use of higher doses of chemotherapy; however, not all patients may be eligible based on factors such as age, organ function (renal/hepatic/pulmonary function), disease progression.

Large B-cell lymphoma
Outcomes for refractory aggressive Non-Hodgkin's Lymphoma (NHL) are poor. NHL accounts for about 4% of all cancers in the United States, DLBCL being the most common form of this disease (33% of all NHL cases). If adults with DLBCL do not respond to initial chemotherapy, they often receive second-line therapy. If patients respond to second-line chemotherapy, they are then considered candidates for autologous stem cell transplant (SCT). However, even after SCT, five-year disease-free survival is only about 10-20%. Patients who do not respond to second-line therapy or progress after transplant only have palliative options available. According to SCHOLAR-1 study, the median survival rate for refractory large B cell lymphoma is 6.3 months.

CAR-T and BiTE therapies are NCCN supported or FDA indicated for use in the second or later line of therapy for relapsed or refractory NHL.

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is a type of B-cell non-Hodgkin lymphoma (NHL) in which tumor cells originate from the "mantle zone" of the lymph node. MCL makes up about 7% of adult NHL with the median age at diagnosis of 68 years. Despite advances in therapy, most patients will experience refractory or recurrent disease. Potential treatment options for r/r MCL include R-CHOP, lenalidomide, ibrutinib. National Comprehensive Cancer Network (NCCN) recommends brexucabtagene autoleucel or lisocabtagene maraleucel only after chemoimmunotherapy and a Bruton's tyrosine kinase inhibitor.

Follicular Lymphoma
Follicular lymphoma (FL) is another type of B-cell non-Hodgkin Lymphoma (NHL) and is the most common subtype of indolent NHL (accounts for about 22% of all newly diagnosed NHLs)[6]. Follicular lymphoma is usually treated with regimens containing chemotherapy and an anti-CD20 monoclonal antibody (such as rituximab or obinutuzumab). CAR-T and BiTE therapy may be used in third or subsequent lines of therapy for FL.

Multiple Myeloma
Multiple myeloma is a type of cancer that begins in the plasma cells. Abnormal plasma cells build up in the bone marrow, often causing skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic features. Multiple myeloma is often suspected when one or more of the following are present: bone pain with lytic lesions, increased total serum protein and/or presence of a monoclonal protein in urine/serum, signs, or symptoms suggestive of malignancy such as unexplained anemia, hypercalcemia, or acute renal failure. According to the National Cancer Institute, 34,920 new cases of multiple myeloma will be diagnosed, and 12,410 deaths will occur in 2021.

Relapses of multiple myeloma are common, and outcomes are poor for those who do not experience complete responses, with a median progression-free survival of three to four months, and a median overall survival of eight to nine months. The main three classes of therapy for multiple myeloma are the immunomodulatory agents, proteasome inhibitors, and anti-CD38 monoclonal antibodies.

CAR-T and BiTE therapy is NCCN recommended or FDA approved for use in the second-line or later for relapsed or refractory disease after failure of conventional treatments.

Melanoma
Melanoma is the most serious form of skin cancer and accounts for 5% of all cancers in the United States. Approximately 98,000 new cases of melanoma (excluding in situ) and nearly 8000 deaths from melanoma were estimated in the

U.S. in 2023[46]. One year and five year survival rates for metastatic melanoma (stage IV) are approximately 50% and 35%, respectively. Preferred regimens for metastatic or unresectable disease recommended by the National Comprehensive Cancer Network (NCCN) is a combination checkpoint blockade, either with nivolumab/ipilimumab or nivolumab and relatlimab. If a combination checkpoint blockade is not used, anti-PD-1 monotherapy, i.e., pembrolizumab or nivolumab, is preferred. Progression within a year or non-response to first-line agents is common and there are limited subsequent treatment options. Guideline recommendations for second-line or subsequent therapy include using a first-line regimen not previously used or either re-induction of the same agent if disease progression/relapse occurred greater than three months after treatment.[43,45,46]

Synovial Sarcoma

Synovial sarcoma (SyS) is a rare mesenchymal malignancy that can occur in various parts of the body, although it most commonly develops in the extremities, particularly near joint capsules and tendon sheaths (e.g., foot, knee, or ankle). Patients with SyS typically present with nonspecific symptoms, such as swelling or pain, often caused by the compression of adjacent tissues. In the United States, an estimated 800 to 1,000 cases of SyS are diagnosed annually, with the majority of patients being adult males, who have a mean age at diagnosis of 39 years. Approximately 70% of patients with SyS express MAGE-A4, and roughly 40% are HLA-eligible to receive afamitresgene autoleucel.[50,51]

Afamitresgene autoleucel is the first FDA-approved T-cell receptor (TCR) gene therapy and the second cell therapy for treating solid tumor cancers. Prior to its approval, chemotherapy was the only available treatment option for patients with SyS following surgery and first-line chemotherapy.[51]

FDA APPROVED INDICATIONS:

CAR T-cell therapies:

Abecma®:

1. Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

Aucatzyl®:

1. Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Breyanzi®:

1. Adult patients with large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from

indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B who have:
   a. refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
   b. 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
   c. relapsed or refractory disease after two or more lines of systemic therapy
2. Adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor.
3. Adult patients with relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy.
4. Adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor.

Carvykti®:
1. Adult patients with relapsed or refractory multiple myeloma, after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Kymriah®:
1. B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse for patients up to 25 years of age.
2. Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
3. Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Tecartus™:
1. Adult patients with relapsed or refractory mantle cell lymphoma (MCL).
2. Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Yescarta®:
1. Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.

2. Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
3. Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Limitation: Breyanzi®, Kymriah® and Yescarta® are NOT indicated for treatment of patients with primary central nervous system lymphoma.

Bispecific T-Cell engager antibodies (BiTEs):
Blincyto®
1. Adult and pediatric patients one month and older with CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.
2. Adult and pediatric patients one month and older with relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL).
3. Adult and pediatric patients one month and older with CD19-positive Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia (ALL) in the consolidation phase of multiphase chemotherapy.

Columvi™
1. Adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) who are not candidates for autologous stem cell transplant (ASCT) in combination with gemcitabine and oxaliplatin.
2. Adult patients with relapsed or refractory DLBCL, NOS or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapy.

Elrexfio™, Talvey®, Tecvayli®:
1. Adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

Epkinly™:
1. Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy.

Imdelltra™:
1. Adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

Kimmtrak®:
1. Adult patients with HLA-A*02:01-positive unresectable or metastatic uveal melanoma.

Lunsumio™:
1. Adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

Tumor-derived autologous T-cell immunotherapy (TIL therapy):

Amtagvi™:
1. Adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

MAGE-A4-directed T-cell receptor (TCR) immunotherapy:

Tecelra®:
1. Adult patients with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices.

POSITION STATEMENT:
Acute lymphoblastic leukemia (ALL)[4]: Aucatzyl®, Blincyto®, Kymriah®, Tecartus™
According to the National Comprehensive Cancer Network (NCCN), blood and bone marrow response is considered complete (CR) when there are no circulating blasts or extramedullary disease (no lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/ central nervous system involvement); trilineage hematopoiesis (TLH) and less than 5% blasts; absolute neutrophil count (ANC) greater than 1000/ microliter; platelets greater than 100,000 per microliter; no recurrence for four weeks. Complete response with incomplete hematologic recovery (CRi) is defined when the conditions of CR above are met except recovery of platelet count above 100,000/microL is not reached or ANC recovery to greater than 1000/microL is not reached. Disease is considered refractory if there is a failure to achieve CR at end of induction. Relapsed disease is characterized by the reappearance of blasts in the blood or bone marrow greater than 5% or in any extramedullary site after CR.

Aucatzyl® (obecabtagene autoleucel)

- The approval of obecabtagene autoleucel (obe-cel) was based on the FELIX pivotal trial which was a moderate quality, single-arm, open-label study. Obe-cel showed a complete remission rate of 78% (95% CI, 70-85) and a median overall survival of 15.6 months (95% CI, 12.9 to NE).[52]
- FELIX enrolled 127 patients between the phase 1b portion of the trial (n=16) and the phase 2 portion of the trial (n=111).
    - Key Inclusion Criteria: Age ≥ 18, ECOG PS of 0 or 1, relapsed/refractory CD19 positive B-ALL, adequate renal/hepatic/pulmonary/cardiac function
    - Key Exclusion Criteria: History of any clinically relevant CNS pathology within 3 months, relevant clinical infections (fungal, bacterial, viral, hepatitis B/C, or HIV)
- The primary endpoint was Overall response rate defined as the rate of complete remission (CR) or complete remission with incomplete cell recovery (CRi) without initiation of any non-protocol anticancer therapies.
    - Primary Endpoint: CR or CR: 78% (95% CI 70-85). CR reached in 57% of patients and CRi in 20%
- Key Secondary endpoint included overall survival (OS)
    - Overall survival (OS): Median OS 15.6 months (95% CI, 12.9 to NE), 6 month OS = 80.3% and 12 month OS = 61.1%.
        - In subgroup analysis, OS was best in patients with <5% bone marrow blasts prior to infusion (median not reached) and worst in patients with >75% bone marrow blasts (median OS 13.2 months (95% CI, 7.9-15.6))
- Safety
    - In the FELIX trial, all patients (100%) experienced treatment emergent adverse events (AEs).
        - 81% had grade 3 or higher AEs
    - Rates of CRS and ICANS were specified separately
        - 69% of patients experienced any grade of CRS and 2% experienced grade 3 or higher CRS.
        - 23% of patients experienced any grade of ICANS and 7% experienced grade 3 or higher ICANS.
    - Obe-cel demonstrated a safety advantage regarding grade 3 or higher CRS or ICANS compared to brexu-cel (Tecartus™), CRS = 24% and ICANS = 24%, and tisa-cel (Kymriah®), CRS = 46% and ICANS = 13%. This is thought to be due to the novel dosing schema used in obe-cel therapy.

Blincyto® (blinatumomab)

- The approval of blinatumomab (as a single-agent therapy) was based on a pivotal, phase 2, open-label, single-arm study in 189 adult patients with Ph(-) R/R B-precursor ALL.
    - Inclusion criteria: R/R disease with 1) first remission duration ≤ 12 months in first salvage, or 2) after first salvage, or 3) ≤ 12 months of allogeneic HSCT.
    - The primary endpoint was the rate of complete remission with full (CR) or partial (CRh) hematological recovery within the first two cycles of treatment. The achievement of CR in acute leukemia is clinically meaningful and has been established as a surrogate for clinical benefit in predicting longer life. The combined CR/CRh rate within the first 2 cycles of blinatumomab was 43% (33% CR/ 10% CRh; 95% CI: 36-50).
    - Current dosing recommendations for blinatumomab limit treatment to a total of 4 cycles for MRD+ B-ALL, Ph+ B-ALL in consolidation phase, and up to 9 cycles for relapsed/refractory B-ALL.

Kymriah® (tisagenlecleucel)

- FDA approval of tisagenlecleucel (Kymriah®) was based on a single arm, open-label, multi-center, phase II study to determine the efficacy and safety of a single infusion of tisagenlecleucel in young patients with relapsed/refractory B-cell ALL (ELIANA; NCT02435849).
    - Inclusion criteria: Patients aged three to 21 years with relapsed or refractory B-cell ALL, positive for CD19 tumor expression, Karnofsky (participants age greater than or equal to 16 years) or Lansky (participants age less than 16 years) performance status of greater than or equal to 50 at screening.
    - Exclusion criteria: Patients with isolated extra-medullary relapse, concomitant genetic syndrome (except Down Syndrome), Burkitt's lymphoma/leukemia, uncontrolled infection, grade 2-4 graft versus host disease, active central nervous system disease, treatment with a prior gene therapy product or anti-CD19/anti-CD3 therapy, active or latent hepatitis B or active hepatitis C within eight weeks of screening, or any uncontrolled infection at screening, positive HIV test within eight weeks of screening.
    - The primary endpoint was overall remission rate (complete remission + complete remission with incomplete recovery) at three months' post infusion. ORR =83% with a 95% confidence interval 71-91.
    - Tisagenlecleucel (Kymriah®) is associated with cytokine release syndrome (CRS), including fatal or life-threatening reactions. Of all patients in the ELIANA study, 78% experienced CRS and 43% (N=32)

experienced grade 3-4 CRS. CRS may result in hypotension, altered mental status, and seizures. It is not recommended to administer tisagenecleucel to patients with active infection or inflammatory disorders. CRS may be treated with tocilizumab (Actemra®, Tyenne®, Tofidence®).

The NCCN guidelines for Pediatric Acute Lymphoblastic Leukemia (patients aged 18 years and younger) also give a category 2B recommendation for Kymriah® (tisagenlecleucel) as single-agent therapy for Ph-negative or Ph-like B-ALL that is minimal residual disease (MRD) positive after consolidation therapy and for Ph-positive B-ALL with less than complete response, MRD+ at end of consolidation, or high-risk genetics, noting "the use of tisagenlecleucel in this setting is strongly recommended in the context of a clinical trial."

Tecartus™ (brexucabtagene autoleucel)

- For adults with relapsed or refractory B-cell ALL, brexucabtagene autoleucel (Tecartus™) was studied in the ZUMA-3 trial (NCT02614066) which was an open-label, single arm, phase 1/2 study.
    - Inclusion criteria included: Adults with primary refractory ALL, first relapse following a remission lasting ≤ 12 months, relapsed or refractory ALL after second-line or higher therapy, or relapsed or refractory ALL at least 100 days after allogeneic stem cell transplantation (HSCT); EOCG 0 to 1; adequate renal, hepatic, cardiac function; Philadelphia chromosome positive (Ph+) disease are eligible if they are intolerant to tyrosine kinase inhibitor (TKI) therapy, or if they have relapsed/refractory disease despite treatment with at least two different TKIs.
    - Exclusion criteria: Patients with active or serious infections, active graft-vs-host disease or taking immunosuppressive medications within four 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.
    - The primary endpoint was completed remission (CR) within three 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 (Table 8). The median time to CR was 56 days (range: 25 to 86 days). All efficacy evaluable patients had potential follow-up for ≥ 10 months with a median actual follow-up time of 12.3 months (range: 0.3 to 22.1 months).

Large B-cell lymphoma: Breyanzi®, Kymriah®, Yescarta®, Columvi™

The Lugano response criteria is used to define response to treatment (complete response, partial response, no response or stable disease, progressive disease),

taking into consideration history, physical examination, laboratory studies, and imaging studies.

- For adult relapsed or refractory diffused large B-cell lymphoma, tisagenlecleucel (Kymriah®) was studied in the JULIET trial (NCT02445248) which was an international, open-label, single arm, phase 2 study
    - Eligible patients were greater than or equal to 18 years of age with relapsed or refractory DLBCL, who received greater than or equal to two lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT).
    - The study excluded patients with active central nervous system malignancy, prior allogenic HSCT, an ECOG performance status greater than or equal to two, a creatinine clearance less than 60, alanine aminotransferase more than times normal, cardiac ejection fraction less than 45%, or absolute lymphocyte concentration less than 300/µL.
    - The primary endpoint was the best overall response rate (i.e., the combined percentage of patients who achieved complete or partial response rate), as determined by an independent review committee.
    - The best overall response rate was 52% (95% CI 41 to 62) with 40% of all patients achieving complete response and 12% had partial response.
- The FDA approval of axicabtagene ciloleucel (Yescarta®) for large B-cell lymphoma was based on efficacy data from the ZUMA-1 trial (NCT02348216).
    - This phase 1 & 2 (phase 2 expansion) study was single-arm, open-label and included patients with refractory or relapsed disease to two or more lines of therapy.
    - Inclusion criteria – adults with aggressive B-cell non-Hodgkin's lymphoma (NHL), including diffuse large B-cell lymphoma (DLBCL), T-cell rich large B-cell lymphoma, primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (FL), that is primary refractory, refractory to second or greater line of therapy, or relapsed ≤ 1 year after autologous stem cell transplant (SCT), received prior anthracycline and anti-CD20 therapies, eastern cooperative oncology group (ECOG) performance status <2.
    - Exclusion criteria - prior allogeneic hematopoietic stem cell transplant (HSCT), prior CD19-directed therapy, any history of central nervous system lymphoma, ECOG performance status of two or greater, absolute lymphocyte count < 1000/µL, creatinine clearance <60 mL/min, hepatic transaminases > 2.5 times the upper limit of normal, cardiac ejection fraction <50%, or active serious infection.
    - At a minimum of 12 months follow up, the ORR was 82% (95% CI 72-89), including a CR of 58%.
    - At a median of 15.4 months' post-infusion, 42% of patients remained in response, including 40% in complete remission.

  - The progression-free survival rates was 41% (95 CI, 31-50) with an overall survival rate of 52% (95% CI, 41-62) at 18 months. However, CR may be skewed as it does not include patients who enrolled into the trial but did not receive the study medication.
  - 95% of all patients had grade 3 or higher adverse events; the most common of these being neutropenia (78%), anemia (43%), and thrombocytopenia (38%). CRS occurred in 93% of all patients, 13% of whom experienced grade 3 or higher CRS.
- The FDA approval of axicabtagene ciloleucel (Yescarta®) for relapsed or refractory follicular lymphoma was based on efficacy data from the ZUMA-5 trial (NCT02348216).
  - This phase 2 study was single-arm, open-label and included patients with refractory or relapsed disease to two or more lines of therapy.
  - Inclusion criteria: Adults 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, eastern cooperative oncology group (ECOG) performance status 0-1.
  - Exclusion criteria: Active or serious infections, transformed lymphoma or other aggressive lymphomas, prior allogeneic HSCT, or any history of CNS lymphoma or CNS disorders.
  - Efficacy was established on the basis of ORR and DOR
    - ORR was 91% (95% CI: 83-96), including a CR of 60%.
    - The median DOR was not reached, and the 1-year rate of continued remission was 76.2% (95% CI: 63.9, 84.7).
- The FDA approval of lisocabtagene maraleucel (Breyanzi®) for large B-cell lymphoma was based on efficacy data from the TRANSCEND NHL 001 trial (NCT03105336).
  - This phase 1 study was single-arm, open-label and included patients who received two or more previous lines of systemic treatment .
  - Inclusion criteria - received two or more previous lines of systemic treatment (including previous chemoimmunotherapy containing anti-CD20 and anthracycline) with subsequent relapse; ECOG performance status < 2; could have received prior autologous and/or allogenic hematopoietic stem cell transplant.
  - Exclusion criteria- central nervous system only involvement; active hepatitis B, hepatitis C, or human immunodeficiency virus infection at time of screening; uncontrolled systemic fungal, bacterial, viral, or other infection despite appropriate treatment ; presence of acute or chronic graft-versus-host disease; prior CAR-T or other genetically modified T-cell therapy.
  - ORR was 73% (95% CI 67-80).

- Median duration of response (DOR) was 16.7 months (95% CI: 5.3, not reached).
- Among the complete responders, 68 (65%) had remission lasting at least six months and 64 (62%) had remission lasting at least nine months.
- Serious adverse reactions occurred in 46% of patients. The most common non-laboratory, serious adverse reactions (>2%) were CRS, encephalopathy, sepsis, febrile neutropenia, aphasia, pneumonia, fever, hypotension, dizziness, and delirium.

Mantle cell lymphoma: Tecartus™

Accelerated approval of (brexucabtagene autoleucel) Tecartus™ was based on the ZUMA-2 trial (NCT02601313), a single-arm, open-label, phase 2 trial

- The ZUMA-2 trial included patients with relapsed or refractory disease who had previously received therapy with all of the following: anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (BTKi; ibrutinib or acalabrutinib); and had an Eastern Cooperative Oncology Group performance status of 0 or 1.
  - Patients were excluded if they had prior CART-T therapy, history of allogenic stem cell transplantation, presence of uncontrolled infection, history of human immunodeficiency virus infection or acute or chronic active hepatitis B or C infection, detectable cerebrospinal fluid malignant cells or brain metastases, history or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement.
  - 87% of the 60 evaluable patients had an objective response, and 62% had a complete response.
  - Tecartus™ is a 2A recommendation by the National Comprehensive Cancer Network (NCCN) for patients with relapsed or refractory disease (only given after chemoimmunotherapy and Bruton's tyrosine kinase inhibitor).

Multiple Myeloma: Abecma®, Carvykti®, Tecvayli®, Elrexfio™, Talvey™

NCCN guidelines Version 2.2024 for multiple myeloma[7] lists the following as preferred regimens, after at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent, (all NCCN category 2A):

- CAR T-cell therapy:
  - Ciltacabtagene autoleucel (Carvykti®)
  - Idecabtagene vicleucel (Abecma®)
- Bispecific antibodies
  - Talquetamab (Talvey™)

- Teclistamab (Tecvayli®)
- Elranatamab (Elrexfio™)

NCCN guidelines note that patients can receive more than one B-cell maturation antigen (BCMA) targeted therapy, but optimal order is unclear.[7]

- Limited data for selecting which 5th line agent is used first. Choice will depend on patient specific characteristics and availability of therapies.
- Optimal sequencing and time from one therapy to the next is not yet known. This is an area of active study. There is some published evidence from small cohorts of individuals with previous T cell therapy. Other current active areas of investigation include CAR T in earlier lines of therapy and combination use of bispecific antibodies.

Idecabtagene vicleucel (Abecma®)

Idecabtagene vicleucel was the first CAR-T therapy approved for multiple myeloma and the first CAR-T therapy that targets the BCMA protein. The FDA approval of idecabtagene vicleucel (Abecma®) for multiple myeloma was based on efficacy data from the KarMMa trial (NCT03361748).

- This phase 2 study was open-label, single arm and included patients who received at least three prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
- Inclusion criteria- age 18 years or older, ECOG performance status of 0 or 1, had disease that was refractory to their last regimen (progression within 60 days after the last dose) according to International Myeloma Working Group (IMWG) criteria, had measurable disease.
- Exclusion criteria - Known central nervous system involvement with myeloma, creatinine clearance of less than or equal to 45 mL/minute, alanine aminotransferase >2.5 times upper limit of normal and left ventricular ejection fraction <45% , absolute neutrophil count <1000 cells/mm3 and platelet count <50,000/mm3, previous history of an allogeneic hematopoietic stem cell transplantation or treatment with any gene therapy-based therapeutic for cancer or investigational cellular therapy for cancer or BCMA targeted therapy, evidence of human immunodeficiency virus (HIV) infection, seropositive for and with evidence of active viral infection with hepatitis B virus (HBV), seropositive for and with active viral infection with hepatitis C virus (HCV), subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study. This includes systemic fungal, bacterial, viral, or other infection that is uncontrolled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antimicrobial treatment) or requiring IV antimicrobials for management

- 72% of evaluable patients had an overall response and 28% had a complete response.
- Median overall survival = 19.4 months; 95% CI: 18.2, NE, with an overall survival of 78% at 12 months (OS data immature).
- Abecma® has a 2A recommendation by the National Comprehensive Cancer Network (NCCN) for patients with relapsed or progressive disease who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Ciltacabtagene autoleucel (Carvykti®)

The FDA approval of ciltacabtagene autoleucel (Carvykti®) for multiple myeloma was based on efficacy data from the CARTITUDE-1 trial (NCT03548207).

- This phase 1b/2 study was open-label, single arm and included patients who received at least three prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
- Inclusion criteria- age 18 years or older, ECOG performance status of 0 or 1
- Exclusion criteria - Known central nervous system involvement with myeloma, previous history of treatment with any CAR-T therapy directed at any target or BCMA targeted therapy, seropositive for human immunodeficiency virus (HIV), seropositive for and with evidence of active viral infection with hepatitis B virus (HBV), seropositive for and with active viral infection with hepatitis C virus (HCV), serious underlying medical condition, such as: evidence of uncontrolled systemic fungal, bacterial, or viral infection, creatinine clearance <40 mL/min, absolute lymphocyte concentration <300/µL, absolute neutrophil count <750 cells/mm3, platelet count <50,000/mm3, hepatic transaminases >3 times the upper limit of normal, cardiac ejection fraction <45%
- 97% of evaluable patients had an overall response
- Carvykti® has a 2A recommendation by the National Comprehensive Cancer Network (NCCN) for patients with relapsed or progressive disease who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Teclistamab (Tecvayli®)

Teclistamab (Tecvayli®) is a bispecific T-cell engager (BiTE) approved for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) through the Phase 1-2 study MajesTEC-1 (NCT03145181 and NCT04557098):

- This was a single-arm, multicohort, open label Phase ½ study (MajesTEC-1) with n = 110 patients who previously received three or more prior therapies
- Inclusion criteria: Age >18 years old; documented diagnosis of relapsed or refractory MM; receipt of >3 lines of therapy including an IMiD, a PI, and an anti-CD38 antibody; Eastern Cooperative Oncology Group (ECOG) score of 0 or 1.

- Exclusion criteria: Previous treatment with a BCMA-directed therapy.
- With median duration of treatment of about 10 months, results of the study include an overall response rate of 61.8%, complete response rate of 28.2%, and estimated duration of response rate among responders of 90.6% at six months and 66.5% at nine months.
- Potentially life-threatening adverse events include cytokine release syndrome (CRS) (72%, grade 3, 0.6%; no grade 4), all grade neurotoxicity (57%), and immune effector cell–associated neurotoxicity syndrome (ICANS) (6%). Boxed warnings for fatal CRS and ICANs were included in package labeling.
- Drug labeling and REMS guidance do not recommend specific supportive agents for CRS. In clinical trial, tocilizumab was used for 60 patients (36.4%) and glucocorticoids for 14 patients. Five patients used more than one dose of tocilizumab at any time during the study and four patients used more than one dose for a single CRS event.
- The recommended dosage of teclistamab is step-up doses of 0.06 mg/kg and 0.3 mg/kg followed by 1.5 mg/kg once weekly until disease progression or unacceptable toxicity. Nearly 96% of CRS events occurred during step-up dosing.

Elranatamab (Elrexfio™)

Elranatamab (Elrexfio™) was studied in a phase II, single-arm, open-label trial (MagnetisMM-3), for patients with relapsed/refractory MM who had previously received at least four prior systemic therapies. Patients received subcutaneous elranatamab once weekly.

- The primary study population were patients (n= 123) without prior BCMA-directed therapy.
- Efficacy:
    - Overall response rate (ORR) was 61% (95% CI, 51.8-69.6)
    - 39 patients (31.7%) experienced complete response (CR) or stringent CR, 29 (23.6%) achieved very good partial response and 7 (5.7%) achieved partial response
    - Median DOR had not been reached; probability of maintaining response at 12 months was 74.1% (95% CI, 60.5-83.6).
    - 48 responders, after 24 weeks, switched to biweekly dosing, and 45 of those (93.8%) improved or maintained their response for greater than 12 weeks.
- Safety:
    - Most common adverse effects (>20%): pyrexia, CRS, injection site reaction, musculoskeletal pain, fatigue, upper respiratory infection, pneumonia, cough, rash, diarrhea, nausea, decrease appetite. With biweekly dosing, grade 3–4 adverse events decreased from 58.6% to 46.6%

  - Most common Grade 3 or 4 laboratory abnormalities (≥30%): decrease count of white blood cells, lymphocytes, neutrophils, platelets and hemoglobin
  - Serious infections, including opportunistic infections, occurred in 42% of patients receiving elranatamab, including Grade 3 or 4 infections in 31% of patients and fatal infections in 7% of patients. The most common infections were pneumonia and sepsis.
  - Fatal adverse reactions occurred in 10% of patients
- In MagnetisMM-3 trial a cohort of 64 patients with a history of BCMA-targeted therapy (33% exposed to CAR T-cell therapy and 72% exposed to an antibody-drug conjugate e.g., belantamab, teclistamab) had an ORR of 33%, (95% CI: 22.0%, 46.3%) with an estimated 84% of responders maintaining response for at least 9 months. The median duration of response was not reached.

Talquetamab (Talvey™)

Talquetamab (Talvey™) was evaluated in a single-arm, open-label, multicenter trial, (MonumenTAL-1). Patients (n=187) with relapsed/refractory MM had previously received at least four prior systemic therapies received either talquetamab subcutaneously weekly or talquetamab biweekly until disease progression or unacceptable toxicity.

- Efficacy:
  - Overall response rate (ORR) in 0.4 mg/kg weekly cohort (N=100) was 73% (95% CI: 63.2%, 81.4%) and median duration of response (DOR) was 9.5 months (95% CI: 6.5, not estimable)
  - ORR in 0.8 mg/kg biweekly cohort (N=87) was 73.6% (95% CI: 63%, 82.4%) and median DOR was not estimable
  - About 85% of responders maintained response for at least 9 months
- Safety:
  - Most common adverse effects (>20%): pyrexia, CRS, dysgeusia, nail disorders, musculoskeletal pain, skin disorders, rash, fatigue, decreased weight, dry mouth, xerosis, dysphagia, upper respiratory infection, diarrhea, hypotension, headache
  - Most common Grade 3 or 4 laboratory abnormalities (≥30%): decrease count of white blood cells, lymphocytes, neutrophils, and hemoglobin
  - Serious adverse reactions reported in >2% of patients included CRS (13%), bacterial infections including sepsis (8%), pyrexia (4.7%), ICANS (3.8%), COVID-19 (2.7%), neutropenia (2.1%), and upper respiratory tract infection (2.1%)
  - Fatal adverse reactions occurred in 3.2% of patients
- In the Monumental-1 trial there was a cohort of 32 people who had a history of T-cell redirecting therapy (81% exposed to CAR T-cell therapy and 25% exposed to a bispecific antibody). The over-all response rate (ORR) was 72% (95% CI: 53%,

86%) and the median duration of response was not reached. The median duration of follow-up was 10.3 months (95%CI: 6.5, 11.4).

Unresectable or metastatic melanoma: Amtagvi™

Lifileucel (Amtagvi™) is recommended in the NCCN Guidelines for Cutaneous Melanoma (Version 2.2024) as an option for second-line or subsequent therapy in metastatic or unresectable disease[46]. For progression during or shortly after first-line therapy, the NCCN guidelines recommend use of another agent with a different mechanism of action. For those who experience disease control with no residual toxicity but have progression or relapse >3 months after treatment , the guidelines state reinitiation of the same agent or same class of agent can be considered[46].

Lifileucel was evaluated in a Phase 2, global, multicenter, multicohort, open-label, single-arm clinical trial. The primary efficacy endpoint was objective response rate (ORR) in adult patients with unresectable or metastatic melanoma who had progressed following ≥ 1 prior systemic therapy, including a PD-1 blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.[44]

- Efficacy:
  - Cohorts 2 & 4 (n=153): ORR 31.4% (95% CI: 24.1%-39.4%)
  - The median duration of response (DOR) was not reached at 21.5 months (NR, 95% CI: 8.3, NR).
    - Durable response at 6, 9, and 12 months was 62.5%, 56.3%, and 54.2%, respectively

FDA only included 82 participants in their analysis of Cohort 4 citing product comparability issues between manufacturing facilities. Their primary efficacy analysis supporting accelerated approval is below.[45]

  - Cohort 4 (n=82): ORR 28.0% (95% CI: 18.7% to 39.1%); complete response (CR) in 3 (3.7%) subjects and partial response (PR) in 20 (24.4%). The median duration of response (DOR) was not reached at 18 months (NR, 95% CI: 4.1, NR). Among the 23 responders, durable response at 6, 9, and 12 months was 56.5%, 47.8%, and 43.5%, respectively.

- Safety:
  - Boxed warning: treatment related mortality, prolonged cytopenia, severe infection, cardiopulmonary and renal impairment
  - Warning and precautions: monitor for hypersensitivity reactions during infusion
  - Deaths: 12 deaths (7.5%) – 2 during lymphodepleting period, 6 within 30 days following lifileucel and 4 during days 38-150 after lifileucel. Adverse

reactions associated with these deaths include severe infection (sepsis, pneumonia and encephalitis), internal organ hemorrhage (abdominal and intracranial), acute renal failure, acute respiratory failure, cardiac arrythmia, extensive ascites, live injury and bone marrow failure
- Most common (≥20%) non-laboratory adverse reactions in order of decreasing frequency were chills, pyrexia, fatigue, tachycardia, diarrhea, febrile neutropenia, edema, rash, hypotension, alopecia, infection, hypoxia, and dyspnea

Approximately 34 days is needed from tumor harvest to lifileucel infusion. Pretreatment with a lymphodepleting chemotherapy regimen of cyclophosphamide intravenously with mesna daily for two days followed by fludarabine intravenously daily for five days is required. Lifileucel is administered 24 hours to four days after fludarabine. It is given as a one-time single dose infusion (1-4 bags of 7.5×10^9 to 72×10^9 viable cells). IL-2 (aldesleukin) is given three to 24 hours after lifileucel infusion, for up to 6 doses to support cell expansion in vivo.

Soft Tissue Sarcoma - Synovial Sarcoma: Tecelra®
Afamitresgene autoleucel (Tecelra®) is recommended in the NCCN Guidelines for Soft Tissue Sarcoma (Version 4.2024) as subsequent lines of therapy for advanced/metastatic disease with disseminated metastases (synovial sarcomas only) and HLA-A*02:01P, HLA-A*02:02P, HLA-A*02:03P or HLA-A*02:06P positive and whose tumor expresses the MAGE-A4 antigen (NCCN category 2A). Prior to the approval of afamitresgene autoleucel, no FDA-approved therapies existed for synovial sarcoma in any treatment setting, and chemotherapy was the only subsequent treatment option after surgery and first-line chemotherapy.[51]

Afamitresgene autoleucel (Tecelra®) is the first FDA-approved T-cell receptor (TCR) gene therapy for synovial sarcoma. The accelerated approval of afamitresgene autoleucel was based on efficacy data from the SPEARHEAD-1 trial (NCT04044768).[48-50]

- This phase 2 study was single-arm, open-label, and included the following patient population:
  - Advanced (metastatic or unresectable) synovial sarcoma confirmed by cytogenetics
  - Received prior chemotherapy with either an anthracycline and/or ifosfamide
  - Positive for HLA-A*02:01, HLA-A*02:02, HLA-A*02:03, or HLA-A*02:06 allele
  - Tumor sample showing MAGE-A4 staining intensity of ≥2 in ≥30% of tumor cells by an analytically validated immunohistochemistry

- Measurable disease as per RECIST version 1.1
- ECOG performance status of 0 or 1, and had adequate organ function defined as GFR ≥60 mL/min (Cohort 1)
- The trial excluded patients with HLA-A*02:05P in either allele, patients taking systemic corticosteroids for ≥14 days prior to leukapheresis and lymphodepletion, and recipients of allogeneic hematopoietic stem cell transplants
- Efficacy was established on the basis of ORR and DOR
  - ORR was 43.2% (95% CI: 28.4, 59.0)
  - The median DOR was 6 months (95% CI: 4.6, not reached)
- Safety:
  - Boxed Warning: Cytokine Release Syndrome (CRS)
  - Contraindications: Adults who are heterozygous or homozygous for HLA-A*02:05P
  - Warnings/Precautions: CRS, ICANS, prolonged severe cytopenia's, infections, secondary malignancies, hypersensitivity reactions, and potential for HIV nucleic acid test false-positive results
  - The most common Grade 3 or 4 laboratory abnormalities (incidence ≥20%) are lymphocyte count decreased (98%), neutrophil count decreased (91%), white blood cell decreased (86%), red blood cell decreased (32%), and platelet count decreased (21%)

Pretreatment with a lymphodepleting chemotherapy regimen consisting of intravenous cyclophosphamide for three days and fludarabine for four days, both starting on the seventh day before afamitresgene autoleucel infusion. It is given as a one-time single dose infusion contains 2.68×10^9 to 10×10^9 MAGE-A4 TCR positive T cells in one or more infusion bag(s).[48,49]

Safety of T-cell therapies
Infections are common with T-cell therapies. Bispecific antibodies may have more persistent infection risk as well as higher incidence of severe infections compared to CAR-T.

The CAR-T agents and T-cell engaging bispecific antibodies are only available through the respective REMS programs which mitigates risks of cytokine release syndrome (CRS) and neurological toxicities of these agents. Neurological toxicities of CAR-T therapy include encephalopathy, headache, delirium, aphasia, anxiety, and tremors. CRS may be treated with tocilizumab (Actemra®, Tyenne®, Tofidence®). Due to the rigor of therapy, as well as the lag time between evaluation

and receipt of therapy, therapy may not be appropriate for clinically fragile patients. The Eastern cooperative oncology group (ECOG) performance status scale and the Karnofsky performance status scale are two commonly used methods to assess a patient's functional status in clinical trials. These as well as other performance status scales can be utilized to help assess whether an individual is fit to tolerate CAR-T therapy.

Sequencing of T-Cell therapies

The appropriate sequencing of different T-Cell therapies differs based on the indication being treated. Given the rapidly changing body of evidence in oncology, NCCN guideline recommendations and, in some cases, high-quality medical evidence will be used to consider requests for sequenced T-Cell therapies. A summary of current guidelines follows:

In adults, for Philadelphia chromosome positive B-cell acute lymphoblastic leukemia (Ph+ B-ALL), the NCCN recommends blinatumomab as treatment induction in combination with a tyrosine kinase inhibitor (TKI) (category 2A).[4] Upon disease relapse or in the case of disease that is refractory to induction therapy, brexucabtagene autoleucel, tisagenlecleucel, and obecabtagene autoleucel are recommended as second line therapy (category 2A). Blinatumomab may also be used in the second-line setting (category 1). For Ph- B-ALL both blinatumomab (category 1) and CAR-T therapy (category 2A) are recommended in the second-line of treatment. For B-ALL, there does not appear to be an optimal sequence of T-Cell therapies as there is no recommendation in the NCCN guidelines or FDA label that would preclude the use of a CAR-T therapy prior to BiTE therapy or vice versa in this disease state.

For B-Cell lymphomas, recommendations of T-Cell therapy sequence vary. In mantle cell lymphoma, brexucabtagene autoleucel and lisocabtagene maraleucel are recommended in the second or subsequent lines of therapy (category 2A) and glofitamab is recommended after CAR-T therapy only in certain circumstances (category 2B).[6] Additionally, glofitamab is recommended only in non-candidates for CAR-T for the treatment of diffuse large B-cell lymphoma (DLBCL) when early relapse occurs (less than 12 months). For disease relapsed after >12 months, CAR-T therapies and glofitamab are recommended equally in non-transplant eligible patients in the second-line of therapy. For third-line therapy, sequencing of therapy for DLBCL is recommended to be CAR-T therapy or transplant prior to consideration of BiTE therapy. For follicular lymphoma, epcoritamab and glofitamab are also recommended behind CAR-T or transplant in the third or subsequent lines of therapy.

For multiple myeloma, the NCCN states that "Patients can receive more than one B-cell maturation antigen (BCMA) targeted therapy. Optimal sequencing of sequential BCMA targeted therapies is not known; however accumulated data suggests immediate follow on with second BCMA directed therapy after relapse may be associated with lower response rates."[7] Bi-specific antibodies elranatamab and teclistamab and CAR-T therapies idecabtagene vicleucel and ciltacabtagene autoleucel are all BCMA targeted therapy and therefore the optimal sequence of BiTE and CAR-T therapy for multiple myeloma is not known.

Other considerations
Centers for Medicare and Medicaid Services (CMS) National Coverage Determination (NCD): 110.24

- Effective for services performed on or after August 7, 2019, CMS covers autologous treatment for cancer with T-cells expressing at least one CHIMERIC antigen receptor (CAR) when administered at healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and used for a medically accepted indication as defined at Social Security Act section 1861(t)(2) -i.e., is used for either an FDA-approved indication (according to the FDA-approved label for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia.

Repeat administration of Amtagvi and Tecelra, and administration of CAR T-cell therapies in patients who have previously received CAR T-cell therapy or use in primary CNS lymphomas is not considered medically necessary. There is insufficient evidence to establish safety and efficacy. The NCCN Central Nervous System Cancers guideline does not include use of CAR T-cell therapy in primary CNS lymphoma.

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APPENDIX A. BILLING GUIDELINES AND CODING:

HCPCS Code	Code Description	Brand Name
CAR T-cell therapies		
Q2055	Idecabtagene vicleucel, up to 460 million autologous b-cell maturation antigen (bcma) directed car-positive t cells, including leukapheresis and dose preparation procedures, per therapeutic dose	Abecma™
C9301	obecabtagene autoleucel, up to 400 million cd19 car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose	Aucatzyl®
J9999	Unclassified drugs or biologicals, not otherwise classified, antineoplastic drugs	
Q2054	Lisocabtagene maraleucel, up to 110 million autologous anti-cd19 car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose	Breyanzi®
Q2056	Ciltacabtagene autoleucel, up to 100 million autologous b-cell maturation antigen (bcma) directed car-positive t cells, including leukapheresis and dose preparation procedures, per therapeutic dose	Carvykti®
Q2042	Tisagenlecleucel, up to 250 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per infusion	Kymriah®
Q2053	Brexucabtagene autoleucel, up to 200 million autologous anti-cd19 car positive viable t cells,	Tecartus™

	including leukapheresis and dose preparation procedures, per therapeutic dose	
Q2041	Axicabtagene Ciloleucel, up to 200 million autologous Anti- CD19 CAR T Cells, Including leukapheresis and dose preparation procedures, per infusion	Yescarta®
Bi-specific T-Cell Engager (BiTE) antibodies		
J3055	talquetamab-tgvs, 0.25 mg	Talvey®
J9380	teclistamab-cqyv, 0.5 mg	Tecvayli®
J1323	elranatamab-bcmm, 1 mg	Elrexfio™
J9039	blinatumomab, 1 mcg	Blincyto®
J9286	glofitamab-gxbm, 2.5 mg	Columvi™
J9321	epcoritamab-bysp, 0.16 mg	Epkinly™
J9274	tebentafusp-tebn, 1 mcg	Kimmtrak®
J9026	tarlatamab-dlle, 1 mg	Imdelltra™
J9350	mosunetuzumab-axgb, 1 mg	Lunsumio™
Tumor-infiltrating lymphocyte (TIL) therapy		
C9399	Unclassified drugs or biologicals	Amtagvi™
J9999	Not otherwise classified, antineoplastic drugs	
T-cell receptor (TCR) immunotherapy		
Q2057	Afamitresgene autoleucel, including leukapheresis and dose preparation procedures, per therapeutic dose	Tecelra®