

Advanced Cellular Therapy

Cigna LifeSOURCE Transplant Network®

Understanding Advanced Cellular Therapy

Historically, the three main forms of cancer treatment have been surgery (to physically remove the cancer), chemotherapy (to kill cancer cells with medications), and radiation therapy (to burn cancer cells with radiation). Over time, advances in surgical and radiation techniques, along with the development of better chemotherapeutic agents, have improved the outcomes for many patients. Unfortunately, a large number of patients still develop progressive disease, demonstrating the need for continued research to develop new treatment options. There has been significant progress with immunotherapy, which harnesses the body's own immune system to combat diseases, particularly cancer, by stimulating or modifying its ability to recognize and target cancer cells. CAR T-cell therapies have shown promising outcomes in the treatment of certain blood cancers such as leukemia, lymphoma, and multiple myeloma. Tumor infiltrating lymphocyte therapy is utilized to treat melanoma that has spread and does not respond to other treatments. The first T-cell receptor therapy was approved in 2024 for the treatment of synovial sarcoma, a solid tumor cancer. Collectively, these immunotherapies are known as advanced cellular therapy (ACT).

The Cigna Healthcare ACT Program

The Cigna Healthcare® Advanced Cellular Therapy (ACT) Program is a comprehensive program designed to deliver access to and ease the burden and stress of treatment with advanced cellular therapies. Services begin when the prior-authorization request is submitted by the customer's oncologist. The program is composed of a highly specialized network of providers, orchestrated by a care management team, and includes a travel benefit, all designed to ensure our customers receive the right treatment, at the right place, at the right time.

Advanced Cellular Therapy basics

Advanced Cellular Therapies fight cancer using the patient's own immune system. T-cells or T-lymphocytes, are a type of

white blood cell that play a crucial role in the immune system. They are normally able to identify abnormal cells, such as cancer cells, and destroy them before they multiply and cause disease. Sometimes, however, T-cells have trouble detecting cancer cells. Advanced Cellular Therapies are customized for each patient. They are made by collecting T-cells from a patient's blood or tumor and reengineering them in a manufacturing site to produce proteins or receptors on their surface. In certain ACTs, these are called chimeric antigen receptors, or CARs. The CARs recognize and bind to specific proteins, or antigens, on the surface of specific cancer cells. Millions of these new CAR T-cells are manufactured in the laboratory and then reinfused back into the patient. CAR T-cells will continue to multiply in the patient's body and recognize, bind to and kill cancer cells that have the target antigen on their surfaces.

In some cases, CAR T-cell therapy is used as a "bridge" to other treatments, such as a stem cell transplant, to reduce the amount of disease.

What are the steps to receive CAR T-cell therapy?

There are several steps to develop and deliver CAR T-Cell therapy.

- Collecting the patient's T-cells through leukapheresis, a procedure that separates and removes T-lymphocytes and returns all the other blood cells and plasma back into the bloodstream. This is typically performed in an outpatient clinic over four to six hours.
- Sending the collected cells to the manufacturing site where the cells are genetically modified.
- Expanding or growing cells in the laboratory until there are hundreds of millions of them. The time from leukapheresis to therapy delivery can range from 16 days to more than

33 days. During that time, patients undergo a series of tests to confirm they are healthy enough to receive the therapy infusion.

- Administering conditioning chemotherapy to prepare the body for the CAR T-cell therapy. This process is called lymphodepletion. Some patients are hospitalized for this treatment, while others may receive it in an outpatient clinic.
- Intravenously infusing the CAR T-cell therapy into the body in either an outpatient or inpatient setting, under the supervision of a health care professional. The infusion typically takes 30 to 60 minutes. Depending on which therapy is received and whether complications develop after the infusion, it may be necessary for the patient to be hospitalized for several days or weeks, or to return to the hospital following the infusion.
- Monitoring for complications after treatment; the time between the collection of T-lymphocyte cells and follow-up care after therapy administration is typically four to eight weeks.

Does Advanced Cellular Therapy cure cancer?

Although Advanced Cellular Therapies don't work for everyone, in some individuals it may lead to:

- Complete remission (no evidence of disease) for many months or years
- Remission for a period of time before the disease comes back
- A partial remission (there is still evidence of disease, but the amount is less)
- No remission at all

Advanced Cellular Therapy clinical trials have shown remission rates as high as 90%¹ in some severe forms of blood cancer. This is particularly impressive considering most Advanced Cellular Therapy clinical trials enroll patients with cancer that has been treated with many prior treatments but has not responded to many or all of them.²

What is our approach to Advanced Cellular Therapy?

Cigna Healthcare includes Advanced Cellular Therapy under the strong national Cigna LifeSOURCE Transplant Network[®]. The LifeSOURCE network currently includes 53 facilities to treat adult or pediatric patients.

What Advanced Cellular Therapies are FDA approved?

There are currently seven CAR T-cell therapies, one tumor infiltrating lymphocyte therapy, and one T-cell receptor therapy that have been approved by the U.S. Food and Drug

Administration (FDA) for treatment of patients with certain cancers. Advanced cellular therapies are being researched for treating a variety of cancers, including additional subtypes of leukemia and lymphoma, and solid tumors cancers such as breast cancer, lung cancer, pancreatic cancer and prostate cancer.

New Advanced Cellular Therapies emerge

On February 16, 2024, Amtagvi[®] became the first FDA-approved T-cell therapy for a solid tumor cancer and is the first treatment option for advanced melanoma after anti-PD-1 and targeted therapy. Amtagvi is manufactured from patient-specific immune cells isolated from a surgically removed tumor that recognize and fight cancer.

What is Amtagvi and how does it work?

Amtagvi is an individualized T-cell therapy that is indicated for the treatment of advanced melanoma in patients who have failed initial therapies. T-cells are one of the two main types of lymphocytes (white blood cells that work to kill virus-infected cells and cancer cells). In many patients with melanoma, tumor-infiltrating lymphocytes (TILs) can be found naturally invading and attacking melanoma tumors. However, in some patients, for reasons that are not fully understood, they are not able to fully destroy the melanoma cells by themselves.

With Amtagvi, a portion of the patient's tumor is removed and sent to a specialized lab that collects the patient's naturally occurring TILs. The TILs are grown in a lab and sent back to be infused into the patient. With the infusion of reinvigorated, personalized TILs, along with a course of medications that promote T-cell activity, the body is better able to recognize specific markers of melanoma tumor cells and kill the cancer.

What is Tecelra[®] and how does it work?

On August 1, 2024, Tecelra became the first T-cell receptor (TCR) therapy engineered from of a patient's own T-cells approved to treat a solid tumor cancer called synovial sarcoma.

Like CAR T-cell therapy, T-cell receptor therapies begin with the patient's own T cells collected from the blood and engineered in a lab to target specific proteins. Different from CAR T-cell therapies that target markers on the surface of cancer cells, Tecelra is engineered with an extra tool that allows it to target a specific protein inside synovial sarcoma cancer cells in adults with a specific immune system subtype.

As new Advanced Cellular Therapies are approved by the FDA, we expect to add them to the Cigna Healthcare Advanced Cellular Therapy Program. The chart on the next page includes the therapies currently included in the program.

Chimeric Antigen Receptor (CAR) T-cell Therapies

Name	Wholesale Acquisition Cost (WAC) ³	Manufacturer	Indication [FDA Approval Date]
Abecma [®] (idecabtagene vicleucel)	\$528,312	Bristol Myers Squibb and Bluebird Bio, Inc.	Adults with relapsed or refractory multiple myeloma (MM) after 4 or more prior lines of therapy [Mar. 2021]
Aucatzyl [®] (obecabtagene autoleucel)	\$525,000	Autolus Therapeutics	Adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) [Nov. 2024]
Breyanzi [®] (lisocabtagene maraleucel)	\$531,350	Bristol Myers Squibb	Adults with large B-cell lymphoma (LBCL) including diffuse large B-cell lymphoma (DLBCL), DLBCL arising from indolent lymphoma, high grade B-Cell lymphoma, primary mediastinal LBCL, and follicular lymphoma (FL) grade 3B who have: <ul style="list-style-type: none"> • Refractory disease or relapse within 12 months of first-line chemoimmunotherapy [Jun. 2022] • Refractory disease or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age [Jun. 2022] • Relapsed or refractory disease after 2 or more lines of system therapy [Feb. 2021]
Carvykti [®] (ciltacabtagene autoleucel)	\$555,310	Janssen Pharmaceutical Companies of Johnson & Johnson and Legend Biotech	Adults with relapsed or refractory multiple myeloma (MM) after 4 or more prior lines of therapy [Feb. 2022]
Kymriah [®] (tisagenlecleucel)	\$593,533 \$488,927	Novartis	<ul style="list-style-type: none"> • Children and young adults (up to 25 years old) with B-cell acute lymphoblastic leukemia (ALL) [Aug. 2017] • Adults with diffuse large B-cell lymphoma (DLBCL) [May 2018] • Adults with transformed follicular lymphoma (TFL) [May 2022]
Tecartus [®] (brexucabtagene autoleucel)	\$462,000	Kite Pharma, Inc., a Gilead Company	<ul style="list-style-type: none"> • Adults with mantle cell lymphoma (MCL) [Jul. 2020] • Adults with B-cell acute lymphoblastic leukemia (ALL) [Oct. 2021]
Yescarta [®] (axicabtagene ciloleucel)	\$503,580	Kite Pharma, Inc., a Gilead Company	<ul style="list-style-type: none"> • Adults with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma (HGBL), and DLBCL arising from follicular lymphoma (FL) after 2 or more lines of systemic therapy [Oct. 2017] • Adults with relapsed or refractory follicular lymphoma (R/R FL) after 2 or more lines of systemic therapy [May 2021] • Adults with large B-cell lymphoma that is refractory to or relapses (R/R LBC) within 12 months of first-line chemoimmunotherapy [Apr. 2022]

Other Advanced Cellular Therapies

Name	Wholesale Acquisition Cost (WAC) ³	Manufacturer	Indication [FDA Approval Date]
Amtagvi® (lifileucel)	\$562,000	Iovance Biotherapeutics, Inc.	Adult patients with unresectable or metastatic melanoma previously treated with other medications [January 2024]
Tecelra® (afamitresgene autoleucel)	\$727,000	Adaptimmune Therapeutics	Adults with metastatic or unresectable synovial sarcoma who have received prior chemotherapy [August 2024]

What is the total cost of Advanced Cellular Therapy treatment?

In addition to the wholesale acquisition cost (WAC) noted in the previous chart, there are additional costs associated with Advanced Cellular Therapy administration and in some cases, costs for an inpatient admission due to serious side effects that may result from receiving an Advanced Cellular Therapy treatment. Based on the risk and incidence of serious side effects reported in clinical trials and the hospital admission that may be required to manage these side effects, the total cost of care for a single course of treatment may range from \$700,000 to more than \$1 million.⁴

A 2018 Institute for Clinical and Economic Review study found that despite the high price of CAR T-cell therapies in B-cell cancers, they are priced in alignment with their clinical value.



Embarc Benefit Protection®

Separate from Advanced Cellular Therapies, other life-changing gene therapies continue to receive FDA approval. The high cost of these therapies threatens access if plans cannot afford to cover them. The Embarc Benefit Protection network solution offers a way to make certain gene therapies more affordable and accessible for clients and members, and can be added regardless of the underlying network. Embarc Benefit Protection is not included as part of the Cigna LifeSOURCE Transplant Network, but is available separately from Payer Solutions. For more information, please contact your Payer Solutions sales representative.



1. Johnson & Johnson. (2022, February 28). "U.S. FDA Approves CARVYKTI™ (ciltacabtagene autoleucel), Janssen's First Cell Therapy, a BCMA-Directed CAR-T Immunotherapy for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma." www.jnj.com/u-s-fda-approves-carvykti-ciltacabtagene-autoleucel-janssens-first-cell-therapy-a-bcma-directed-car-t-immunotherapy-for-the-treatment-of-patients-with-relapsed-or-refractory-multiple-myeloma.

2. Fernandez, C.R. (2021, November 10). "A Cure for Cancer? How CAR-T Cell Therapy is Revolutionizing Oncology." Labiotech.eu. www.labiotech.eu/in-depth/car-t-therapy-cancer-review/#.

3. WAC as of April 2022, subject to change.

4. Prime Therapeutics. (2021, April 12). "Prime Therapeutics' study shows total cost of care for CAR-T plus post-treatment events can exceed \$1 million." [Press release]. www.primetherapeutics.com/news/prime-therapeutics-study-shows-total-cost-of-care-for-car-t-plus-post-treatment-events-can-exceed-1-million/#.

Refer to your plan documents for costs and complete details of your plan's transplant coverage.

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