

CAR T cells

This information is about CAR T-cell therapy, a type of targeted treatment used for certain types of high-grade (fast-growing) lymphoma.

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What are CAR T cells?

CAR T cells use your own **immune system** to try to destroy lymphoma cells.

Lymphocytes are types of white blood cell that your body produces to help you fight infection and disease, including cancer. They are part of your immune system. Lymphocytes include T lymphocytes (T cells) and B lymphocytes (B cells), and these have different roles in your immune system.

If any of your own cells become abnormal, they are normally recognised as different by T cells and destroyed by your immune system. When a cancer (such as a lymphoma) develops, it means that the immune system, for some reason, has not detected the abnormal cancerous cells or has not been able to get rid of them. Cancer cells also develop ways to prevent the immune system attacking them. For example, some cancer cells make special proteins on their surface that tell T cells not to attack them.

In CAR T-cell therapy, your own T cells are collected and genetically modified (changed) in a laboratory. These changes allow them to recognise and kill lymphoma cells that are otherwise not detected by your immune cells. The genetically modified T cells are known as 'CAR T cells'. After they have been modified, the CAR T cells are grown in the laboratory until there are enough of

them to treat your lymphoma. They are then given back to you, like a blood transfusion.

The parts of a CAR T cell

When CAR T cells are made, a 'chimeric antigen receptor' (CAR) is joined onto your T cells by genetic engineering in a laboratory. The CAR is made up of several parts. These usually include:

- An **antigen receptor**, which is the part that is designed to attach to a specific target on cancer cells.
- **Stimulation signals** and **activation signals**, which help the CAR T cells to multiply and survive in your body.

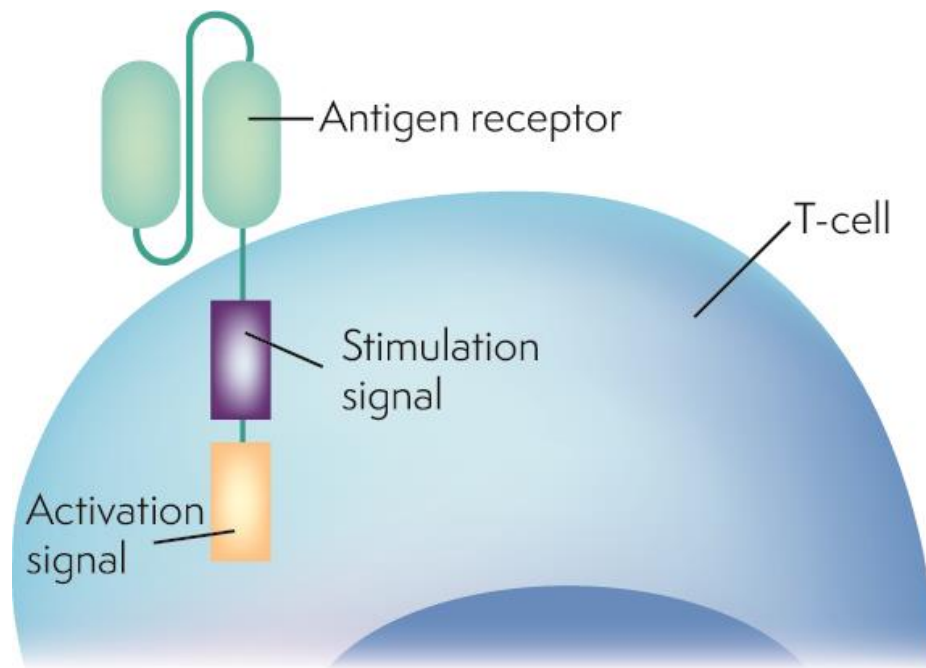


Figure: A CAR T cell

When a CAR T cell binds to a cancer cell in your body, it sends signals to tell your immune system to destroy the cell.

The various types of CAR T cell have different antigen receptors so they can target specific types of cancer cell. New CAR T cells are in development that have other parts added to them to help them survive in your body or to help switch them off if they cause problems in your body.

Who can have them?

Two types of CAR T-cell therapy are **approved in Europe** for some people with high-grade (fast-growing) lymphomas:

- tisagenlecleucel (Kymriah®) for some people with **diffuse large B-cell lymphoma (DLBCL)** who have had two or more previous courses of treatment but their lymphoma has relapsed (come back) or was refractory (did not respond to treatment)
- axicabtagene ciloleucel (Yescarta®) for some people with relapsed or refractory DLBCL or **primary mediastinal large B-cell lymphoma (PMBL)**, who have had two or more previous courses of treatment
- brexucabtagene autoleucel (Tecartus®) for some people with relapsed or refractory mantle cell lymphoma who have had previous treatment with a BTK-inhibitor (for example, ibrutinib).

Several CAR T-cell treatments are being tested in clinical trials in these and other **types of lymphoma**. Use our searchable database to see if there's a clinical trial that might be suitable for you at [Lymphoma TrialsLink](#).

Note: CAR T cells are being tested and may be approved for other types of cancer, but this information is specifically about lymphoma.

Are they available on the NHS in the UK?

Axicabtagene ciloleucel and tisagenlecleucel are available on the NHS in the UK. Brexucabtagene autoleucel is available on the NHS in England and Wales. At the time of writing, it has not been assessed for use on the NHS in Scotland.

CAR T-cell therapy can only be given at approved treatment centres with the facilities and staff to administer it safely. If you are eligible for CAR T-cell therapy, you might have to travel some distance to have it.

CAR T-cell therapy is a very intensive type of treatment and you have to be fit enough to have it. Even if you are suitable for this treatment, it is not always possible for you to have it for several reasons, for example:

- It may not be possible for your medical team to collect enough T cells from you to make the treatment.
- The laboratory might not be able to successfully make the treatment.

Your health might worsen while the treatment is being made, and you might no longer be well enough to have it.

In these cases, your specialist will consider what other treatment options are available for you.

Benefits

CAR T-cell therapy is a new type of treatment, so little is known about its long-term effects or whether any response the lymphoma has to the treatment will last long-term. Initial results from clinical trials are very encouraging, particularly for people who have few other treatment options after having standard treatments.

Benefits of axicabtagene ciloleucel

Around three-quarters of 101 people treated with axicabtagene ciloleucel in a clinical trial responded to treatment, with half overall having a complete response (the lymphoma was completely cleared). People who had a complete response were more likely to stay in remission (no evidence of lymphoma). The people included in the trial had DLBCL or PMBL, including DLBCL that had **transformed** (changed) from follicular lymphoma, **double-hit or triple-hit DLBCL** and people with **high-grade B-cell lymphoma not otherwise specified**. All of the people included in the trial had previously received treatment and their lymphoma either hadn't responded or had relapsed after at least two courses of treatment.

Benefits of tisagenlecleucel

Around half of 68 people treated with tisagenlecleucel in a clinical trial responded to treatment, with around a third overall having a complete response. As with axicabtagene ciloleucel, the response to tisagenlecleucel seems to be lasting in those who had a complete response. The people included in this trial all had DLBCL (including DLBCL that had transformed from follicular lymphoma) and had all received at least two previous courses of treatment.

Benefits of brexucabtagene autoleucel

Almost all (93%) people treated with brexucabtagene autoleucel in a clinical trial responded to treatment. Around two in three people had a complete response. After a year of follow-up, over half the people treated were still in remission. The people in this trial had mantle cell lymphoma and had received up to five previous treatments, including a type of targeted drug called a BTK-inhibitor (for example, ibrutinib).

How are they given?

CAR T-cell treatments have to be made individually for each person. This process can take several weeks. You might be able to have other treatments,

such as **chemotherapy**, to keep your lymphoma under control while the CAR T cells are being made.

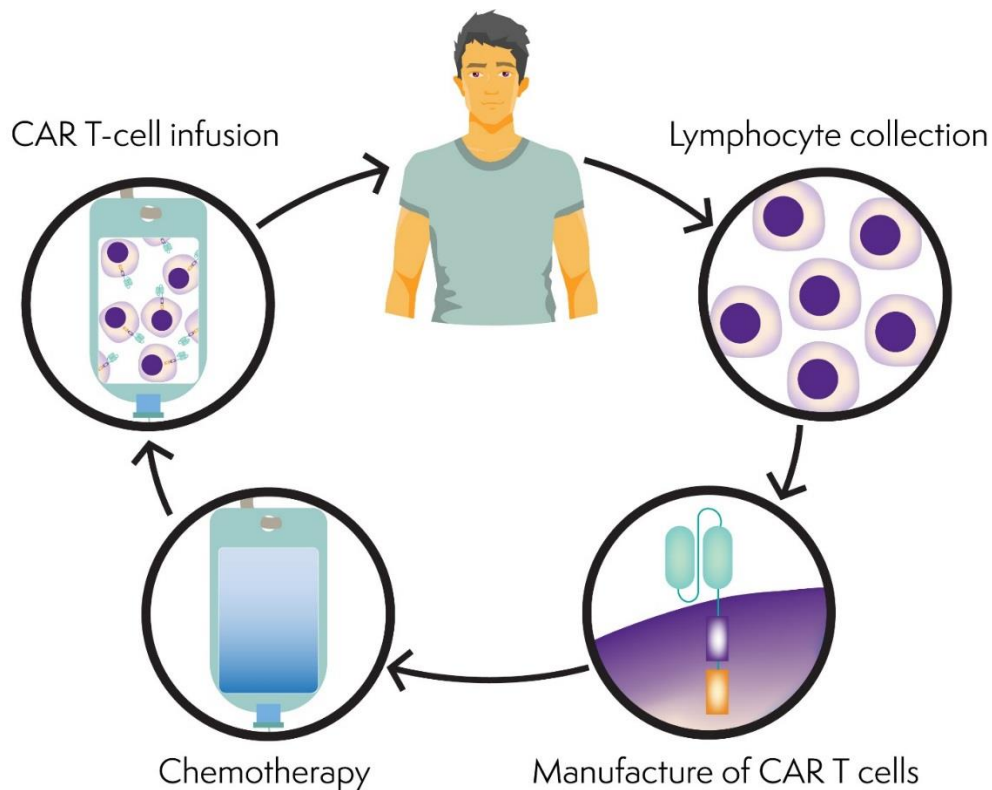


Figure: The CAR T cell treatment process

Step 1: Lymphocyte collection

Your lymphocytes are collected so that the T cells can be modified in the laboratory. This collection process is called 'leukapheresis'. In leukapheresis, your blood is taken from a line (thin tube) in one arm, and passed through a machine. The machine separates the lymphocytes (T cells and other types of lymphocyte) from your blood and collects them. The rest of your blood is returned to your bloodstream through another line. Only lymphocytes that are in your blood can be collected through this process, so not all of your lymphocytes are taken.

Step 2: Manufacture of CAR T cells

The T cells are modified and allowed to multiply in the laboratory until there are enough cells to make the treatment effective. You need lots of CAR T cells in your body so that they can survive, multiply even more and destroy most or all of the cancer cells.

Making CAR T cells is complicated and usually takes several weeks.

Your doctor needs to check that you are still well enough to have the CAR T-cell treatment when it is ready. Some people get more unwell while the CAR T-cell treatment is being made, as their lymphoma might get worse. If you are no longer well enough to have this treatment when it has been made, your doctor might delay your treatment or discuss other treatment options with you.

Step 3: Chemotherapy

If you are still well enough and your CAR T cells have been made successfully, you have chemotherapy to reduce the number of white blood cells in your body. This is to make room for the CAR T cells to multiply in your body. The chemotherapy is given over a few days.

Step 4: CAR T-cell infusion

You usually have only one treatment with CAR T cells. Some people in clinical trials had a second treatment with CAR T cells, but most people had a single treatment. A single treatment should contain enough cells to treat your lymphoma.

The CAR T cells are given intravenously (into a vein).

You are monitored carefully in hospital during and after the treatment. You need to stay close to the hospital you were treated in for at least a month after treatment in case you develop side effects.

Possible side effects

All medicines can cause **side effects** (unwanted effects of treatment). As CAR T cells are a new type of treatment, more information about possible side effects is still being gathered.

This is not a complete list of side effects that have been reported. Ask your **medical team** for the most up-to-date information about possible side effects. Ask all the questions you have. You also need to tell your medical team about any other conditions you have and any medicines, supplements or complementary therapies you are taking before you start any new treatment.

CAR T-cell treatments can cause serious side effects and the treatment is only given in hospitals with the facilities and staff to treat these side effects effectively. You are given treatments to help manage serious side effects before you have the CAR T-cell infusion. These may include paracetamol and antihistamines.

You are monitored closely at the treatment centre as an in-patient for at least a week after having CAR T-cell treatment, and you should look out for new symptoms for at least 4 weeks after having CAR T-cell treatment. You have to

stay close to the treatment centre during this time. You should contact your medical team promptly if you have any changes to your health – they will give you more details about what to look out for and who to contact.

Common side effects of CAR T cells, which can affect more than 1 in 5 people, include:

- **cytokine release syndrome**
- fever and chills
- low blood pressure and low oxygen levels
- nervous system problems, which might include brain problems (encephalopathy), headache, twitching or shaking (tremor), and dizziness
- rapid heart rate (tachycardia) and changes in heart rhythm (arrhythmia)
- fatigue (extreme tiredness)
- cough
- digestive symptoms such as **nausea, vomiting**, reduced appetite, **diarrhoea and constipation**
- **febrile neutropenia** (fever associated with a drop in the number of neutrophils you have – a type of white blood cell that fights infection) and infections.

The most serious of these side effects are described in more detail below.

Cytokine release syndrome

One of the most common and serious complications of CAR T-cell treatments is 'cytokine release syndrome' (CRS). This can happen when CAR T-cell treatment causes a massive immune reaction in your body. This reaction causes the white blood cells affected by the treatment to release substances called 'cytokines' into your blood. Cytokines are proteins that help cells communicate with each other. When they are released, they can signal to other cells to come and help with an **immune response**. When lots of cytokines are released at once, too many immune cells might be activated at the same time, overwhelming your body.

Symptoms of CRS include fever, chills, low oxygen levels in your body, rapid heart rate and low blood pressure. You are most likely to develop symptoms a couple of days after the CAR T-cell infusion, but they have been known to develop up to 12 days after the infusion.

Almost everyone treated with CAR T-cell treatments experiences some level of CRS due to the way this treatment works. Most cases are mild, and easily treated. Severe, life-threatening reactions can occur. If you have a severe reaction, you might need to be admitted to intensive care for treatments to

help with your symptoms, such as oxygen and fluids. You might also be given a drug called ‘tocilizumab’, which can dampen down the immune response.

Other immune system side effects

As CAR T-cell treatment affects your immune system, you might be at greater risk of infection, including serious infections, after having this treatment. Your white blood cell counts might be low and some people have very low B-cell levels, and low antibody levels (antibodies are proteins that B cells produce to help you fight infection). These problems can make it difficult for your body to fight infections. You might be given drugs such as antibiotics to prevent or treat infections. If you have very low antibody levels, you might need **immunoglobulin replacement therapy** (infusions of antibodies).

Your medical team can advise you whether your previous **vaccinations** are still effective, and whether they recommend any vaccinations for you depending on your individual circumstances.

Nervous system problems

Most people treated with CAR T-cell treatments experience nervous system problems within a few days of treatment, although problems can develop up to 8 weeks after treatment. Nervous system problems are usually mild and get better over a couple of weeks. Most commonly, problems develop with the way your brain works, and you may experience headaches, shaking, dizziness, confusion, difficulty sleeping or problems with your speech. Life-threatening problems such as swelling of your brain can develop. Treatments such as steroids can be given if you develop troublesome nervous system problems.

Your medical team will be aware of the signs and symptoms of these side effects and will monitor you closely.

Precautions

If you have certain other conditions, you might not be able to have CAR T-cell treatment or you might be monitored more carefully. You need to be fit to have this type of treatment.

CAR T-cell treatment has not been approved for use in people under 18 with lymphoma.

People who are pregnant should not usually have CAR T cells during their pregnancy in case it could harm the unborn baby. Your doctor might also advise that you do not breastfeed until you have recovered from the treatment.

Discuss your treatment options with your doctor if you think you might be pregnant.

References

The full list of references is available on request. Please email publications@lymphoma-action.org.uk or call 01296 619409 if you would like a copy.

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