# CAR-T cell treatments

## Horizons Infosheet
## Clinical trials and novel drugs

**This Horizons Infosheet contains information on CAR-T cell treatments, which are being investigated in myeloma.**

The Horizons Infosheet series provides information relating to novel drugs and treatment strategies that are currently being investigated for the treatment of myeloma. The series also aims to highlight the considerable amount of research currently taking place in the field of myeloma.

The drugs and treatment strategies described in the Horizons Infosheets may not be licensed and/or approved for use in myeloma. You may, however, be able to access them as part of a clinical trial.

### What are CAR-T cell treatments?

CAR (chimeric antigen receptor) T cell treatments are in a class of treatments called immunotherapy, which uses the body's own immune system to kill myeloma cells.

A lot of research is focusing on the potential role of the immune system in treating cancer and some myeloma drugs already in use work by affecting the immune system, such as the immunomodulatory drugs (IMiDs) lenalidomide (Revlimid®) and pomalidomide (Imnovid®).

However, CAR-T cell treatments are unlike any other immunotherapy treatments currently used in myeloma. Rather than using a drug to modify the immune system, a patient's own immune cells are collected and genetically modified in a laboratory to enable them to kill myeloma cells.

## What is the immune system?

The immune system is made up of specialised cells, tissues and proteins (including antibodies), which work together to protect the body from infection and disease. This involves protecting the body from foreign organisms such as bacteria or viruses, and from cells within the body if they become infected or abnormal.

## What are T cells?

T cells are a type of white blood cell and are one of the key components of the immune system. They are produced in the bone marrow and circulate around the body looking for any potentially harmful, infected or abnormal cells (such as cancer cells). When T cells come into contact with such a cell, they can either kill it or release chemical messengers (cytokines) to recruit other immune cells to kill it.

## How do CAR-T cell treatments work?

Myeloma cells can avoid being recognised as abnormal by the immune system, meaning that a patient's own T cells are not able to kill the myeloma cells. CAR-T cell treatments aim to get round this by boosting the ability of a patient's T cells to recognise and kill myeloma cells.

There are several steps in the process of producing and using CAR-T cells:

- The patient's blood is pumped through a machine that filters out the T cells and returns the blood to the body. This is called apheresis (see Figure 1)
- The collected T cells are genetically modified in a laboratory so that they can recognise myeloma cells
- The modified T cells are called CAR-T cells, and have a receptor on their surface that will recognise a specific protein on the surface of myeloma cells
- The modified T cells are multiplied and infused back into the patient. This is called adoptive T cell transfer (see Figure 2)

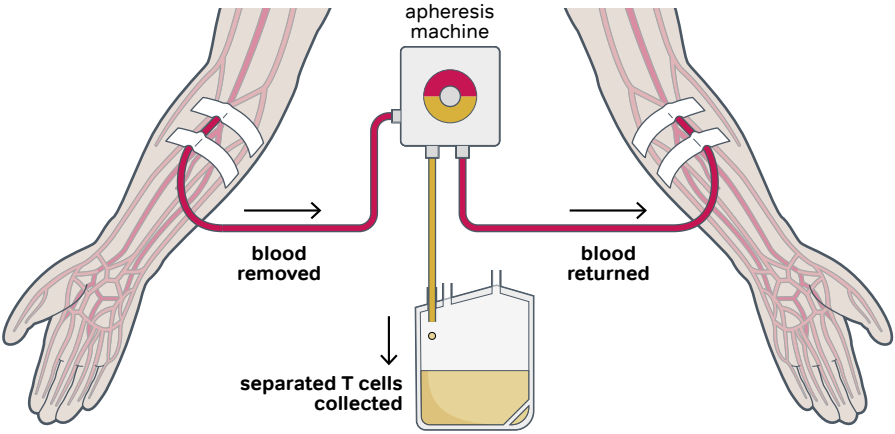


**Figure 1.** Apheresis process

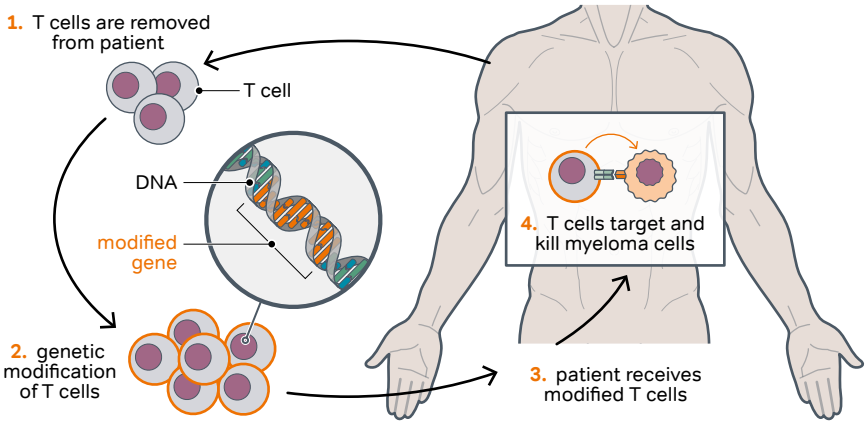


**Figure 2.** Adoptive T cell transfer process

Unlike drugs, CAR-T cells can persist in the body for a long time and can also multiply to give rise to new cells. This means CAR-T cells have the potential to provide long-term control, and are designed to be a one-off treatment. This is in contrast with standard drug treatments in myeloma which have to be given repeatedly to achieve control. However, it has been found that CAR-T cells can get 'exhausted' and stop working after a while. The myeloma cells may also 'escape' from the treatment after a while, so that the CAR-T cells can no longer recognise them. Research is looking at ways to prevent either of these things happening for as long as possible. Read more about this in the "**Future directions**" section of this Infosheet.

## What evidence exists to support the use of CAR-T cell treatments?

Several CAR-T cell treatments are being developed for use in myeloma. Two of these are:

- Idecabtagene vicleucel (Abecma®, also called ide-cel)
- Ciltacabtagene autoleucel (also called cilta-cel)

These two CAR-T cell treatments recognise a protein called BCMA on the surface of myeloma cells.

Results of trials with CAR-T cell treatments in myeloma have so far been promising, with good remission rates in relapsed or refractory myeloma patients.

In a trial of ide-cel, 128 patients with relapsed and/or refractory myeloma were treated. They had received an average of six previous lines of treatment. Three quarters of these treated patients had a partial response or better. The average time before the patients' myeloma returned was 9 months.

In a trial of cilta-cel, 97 patients with relapsed and/or refractory myeloma were treated. These patients had also received six previous treatment lines on average. Almost all of the patients responded to the treatment. In three quarters of the patients their myeloma had not returned after 12 months of follow-up.

Other smaller trials of CAR-T cell treatments have also been carried out, and shown benefits to patients.

## What are the possible known side effects of CAR-T cell treatments?

CAR-T cell treatments carry a risk of serious side effects that need expert care, including cytokine release syndrome and neurotoxic side effects. These are explained in the next paragraphs. Patients will be monitored frequently for early indications of side effects, and given rapid intensive care and supportive treatment if needed. If these side effects happen, it is usually in the first 8 weeks after the infusion, but they can develop later.

**Cytokine release syndrome (CRS)**, also called infusion reaction, happens when the modified T cells cause an excessive amount of cytokines (chemical messengers in the blood) to be released. This results in symptoms in the period after the infusion, such as fever, rapid heart rate, difficulty breathing, or lightheadedness. CRS occurs in many myeloma patients given CAR-T cell treatments. It is mild in most patients, but in some patients it may be severe. It most often happens in the first few days after the CAR-T treatment and lasts for a few days.

**Neurotoxic side effects** are side effects affecting the nervous system. These can occur in some myeloma patients given CAR-T cell treatments. Symptoms can include confusion, difficulty speaking, disorientation, or being less alert/conscious. The side effects can range from mild to very severe.

**Other possible side effects include:** reductions in blood cells (white cells, red cells and platelets). These are common after CAR-T cell treatment. They may be severe in some cases. This can lead to anaemia, increased risk of infections, or bleeding/bruising.

Because CAR-T cell treatments for myeloma are not yet in widespread use, it is possible that new side effects will emerge.

## Are CAR-T cell treatments currently available in any UK clinical trials?

Most CAR-T cell treatment clinical trials are in patients who have relapsed/refractory myeloma, and for whom existing treatment options are limited, rather than patients at earlier stages of their treatment pathway.

For an up-to-date list of UK clinical trials involving CAR-T cell treatments, visit the Myeloma Trial Finder at trials.myeloma.org.uk

To be enrolled on a clinical trial, patients have to meet certain conditions known as eligibility criteria. You should speak to your doctor in the first instance if you are interested in taking part in a trial.

If you are considering taking part in a clinical trial your doctor will discuss in detail the risks and benefits for you. They will give you detailed information to enable you to make an informed decision about whether to take part.

## Availability of CAR-T cell treatments in the UK

CAR-T cell treatments are not currently available for use in myeloma in the UK, and are only accessible to patients as part of a clinical trial.

Before a drug or treatment strategy can be widely used, it must first be authorised as a safe and effective treatment. This is usually done by the regulatory authorities at a European level and involves a review of evidence from large-scale clinical trials.

Normally, the authorised treatment must then be approved by a UK drug appraisal body before it can be routinely prescribed by NHS doctors. The treatment appraisal process differs from authorisation – it looks at how effective the newly-licensed treatment is compared with existing treatments already in use on the NHS, and decides whether the treatment offers the NHS good value for money.

The main body responsible for carrying out appraisals in England and Wales is the National Institute for Health and Care Excellence (NICE). NICE recommendations are usually adopted in Northern Ireland. Scotland's appraisal body is the Scottish Medicines Consortium (SMC).

Ide-cel has recently been conditionally authorised by the European Medicines Agency (EMA) for treatment of some myeloma patients with relapsed or refractory myeloma. This was granted on the basis of the clinical trials so far completed, but further data on effectiveness and safety are still being collected.

For more information see the **Health Technology Assessment (HTA) Infosheet** from Myeloma UK

## Future directions

CAR-T cell treatments have produced very positive results in clinical trials, in patients who have limited other treatment options.

The treatments are not suitable for all patients, however. Side effects can be severe. Treatment also involves a delay of a number of weeks while the CAR-T cells are produced. Patients are given 'bridging' treatment during this time, to keep their myeloma under control as far as possible.

A limitation of CAR-T cell treatment is that at some point the CAR-T cells can become 'exhausted' and no longer work, or the myeloma cells may 'escape' from the treatment and start to become active again.

Researchers are looking at different ways to make CAR-T cell treatments as effective and safe as possible.

Research is being done on exhaustion of CAR-T cell populations and escape of the myeloma cells. They are looking at how this happens, and how to keep the CAR-T cells working against the patient's myeloma cells for as long as possible.

The CAR-T cell treatments most advanced in development target the BCMA protein on myeloma cells (like ide-cel and cilta-cel). Larger-scale trials, including trials comparing these treatments with established myeloma drugs, are currently underway.

CAR-T cells targeting other antigens on myeloma cells are also being developed.

Although most current trials are in relapsed and/or refractory myeloma, some trials are also starting to look at using CAR-T cell treatments at earlier stages in myeloma, such as in patients who relapse quickly after their initial treatment.

Some CAR-T cell treatments are being developed that recognise two different targets. It is hoped that this will increase the chance of the CAR-T cells being able to recognise myeloma cells, and decrease the chance of the myeloma cells evolving to escape the CAR-T cells by removing the target from their surface.

Research is also being done into 'safety switches' for CAR-T cell treatments, which may help to avoid the severe adverse events that can happen in some patients.

A recent development is so-called 'off the shelf' or 'universal' CAR-T cell treatments (UCARTs). UCARTs use T cells from healthy donors, instead of using each patient's own T cells. As a result they are less costly to produce, and they also avoid the delay while CAR-T cells are manufactured for an individual patient. Clinical trials of several UCARTs are now underway.

## Key points

- CAR-T cell treatments are a new type of myeloma treatment that uses the body's own immune system to kill myeloma cells
- Some of the patient's own blood cells called T cells are taken out of the blood and modified in a laboratory
- The modified cells, called CAR-T cells, have a receptor that can recognise myeloma cells. The CAR-T cells are infused back into the patient
- Results of trials with CAR-T cell treatments in myeloma have so far been promising, and larger-scale trials are now underway
- Side effects of CAR-T cell treatments can be severe and can include infusion reactions, effects on the nervous system and reductions in blood cells (causing anaemia, increased risk of infections, or bleeding/bruising)
- CAR-T cell treatments are not yet widely available, because none have been approved in the UK for use in myeloma. However, patients may be treated with them as part of a clinical trial

## About this Horizons Infosheet

The information in this Horizons Infosheet is not meant to replace the advice of your healthcare team. They are the people to ask if you have questions about your individual situation.

For a list of references used to develop our resources, visit myeloma.org.uk/references

We value your feedback about our patient information.
For a short online survey go to myeloma.org.uk/pifeedback or email comments to patientinfo@myeloma.org.uk

## Other information available from Myeloma UK

Myeloma UK has a range of publications available covering all aspects of myeloma, its treatment and management. Download or order them from myeloma.org.uk/publications

To talk to one of our Myeloma Information Specialists about any aspect of myeloma, call our Myeloma Infoline on 0800 980 3332 or 1800 937 773 from Ireland.

The Infoline is open from Monday to Friday, 9am to 5pm and is free to phone from anywhere in the UK and Ireland.

Information and support about myeloma is also available around the clock at myeloma.org.uk

# Notes

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