

St. James's Hospital HOPE Directorate Stem Cell Transplant Unit

Patient Information Leaflet for Chimeric Antigen Receptor Therapy (CAR T)

Name of Patient: (Print Name)

MRN:

Introduction and Background

Chimeric Antigen Receptor Therapy sometimes referred to as “engineered cell therapy” or “immune effector cell therapy”.

Chimeric antigen receptor (CAR) T cell therapy is a novel treatment for some types of cancers. It is a form of immunotherapy, a type of treatment that helps your immune system recognise and destroy cancer cells. CAR T cell therapy changes some of your body's own T cells (part of your immune system) to improve their ability to fight your cancer.

How CAR T Therapy Works:

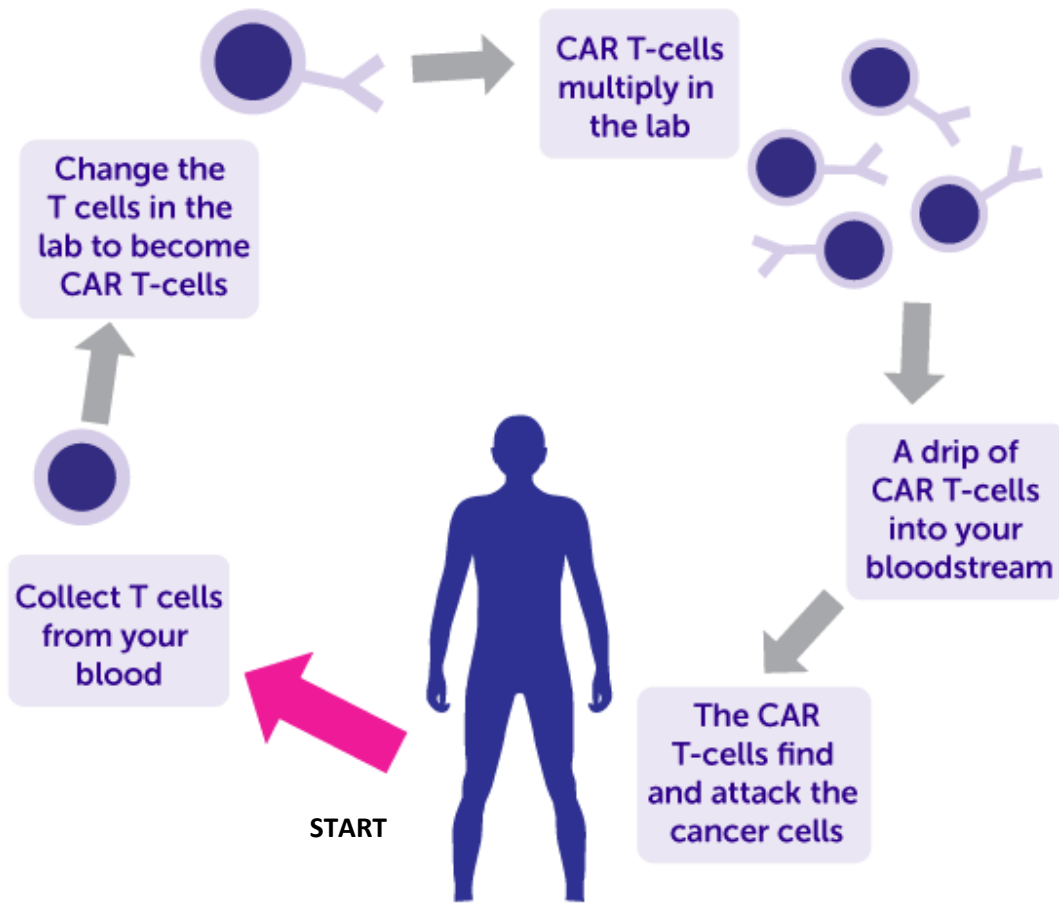
The immune system is made up of specific cells and organs, including T cells, which protect your body from infections, disease, and cancer. CAR T cell therapy modifies your own T cells to improve their ability to fight certain types of cancer. In this process T cells are collected from your blood. They are then sent to a specialist laboratory, where they will be modified to produce special receptors called **chimeric antigen receptors (CARs)**. When these CARs are re-infused into your body (intravenous infusion), these CARs help your T cells find and destroy the cancer cells.

To prepare for this treatment, you will be carefully assessed by the Haematology team in St James's hospital to determine if CAR T Cell therapy is appropriate for treating your cancer. At this meeting you will meet the Consultant Haematologist and the CAR T Nurse Co-Ordinator. You will be asked to bring a family member/ friend to this consultation also.

We encourage you to ask your consultant haematologist or CAR T Co-Ordinator questions to ensure you understand the process, the risks and benefits associated with this treatment, and the resources available to you.

The diagram below demonstrates the treatment process.

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Preparing for CAR T Cell Therapy

There are many things to consider as you prepare for CAR T cell therapy at St. James's Hospital. In this section, we outline the preparative testing and screening required, the cell collection and manufacturing process, your inpatient stay after your cells are returned to you and the post discharge care.

There are many team members involved in your care. In addition to the people you meet during the process, there are many others working behind the scenes who contribute to your care.

Evaluation Tests and Screening

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You will have a series of tests and assessments to evaluate your health as you prepare for CAR T cell therapy. Testing may include some or all of the following,

- Physical exam
- Lung Function Tests
- Echocardiogram
- ECG
- Chest X-Ray
- Creatinine Clearance (24-hour urine collection to study Kidney function)
- PET CT Scan
- Bone Marrow Biopsy
- Blood Tests -
 - Full Blood Count
 - Coagulation Screen
 - Ferritin
 - Renal liver and Bone Profile
 - Blood Group
 - Viral screening to include Hepatitis and HIV screen

The Treatment is divided into two stages:

1. Apheresis (The process of collecting your T Cells also called an MNC (A) product)

To start the CAR T cell therapy process, we need to collect your T cells so we can send them for processing. Your team will use an *apheresis machine* to collect your T cells. Collecting the T cells is called Apheresis.

To collect the T cells, a needle will be put into a vein in each arm. One of these needles takes the blood from you, the other is to allow the blood that is not required as part of the T cell collection to be returned to you. During the collection, you cannot move your arms as freely as normal as a lot of movement could displace these needles. Your arms will be placed in a comfortable, supported position beforehand. Once the T cells are collected the needles will be removed. You may notice some bruising and tenderness around the needle area but this should clear up within a few days. If your veins are

St. James's Hospital HOPE Directorate Stem Cell Transplant Unit

too small or not suitable, you may need to have a temporary line put into a large vein. This line or tube is called a central line. This vein can be located in your neck, upper chest or groin. This procedure is performed in the X-Ray department. A local anaesthetic is given first and X-rays are taken to guide the catheter into your vein. As this is like minor surgery, you will need to sign a consent form. But any risks will be explained to you beforehand.

The catheter will be left in place until all the cells are collected and will then be removed. Again, once removed, the area around the catheter may be tender and may also bruise. But this should clear up within a few days.

This machine contains a centrifuge that spins your blood at high speed. You will notice on the day of your harvest that the machine makes a low humming noise like a washing machine spinning. The spinning allows your blood to separate into layers. The layer with the T cells is selected and collected into a sterile bag by the machine. All the kits used in the machine containing the lines and bag are disposable, so no blood actually comes in contact with the inside of the machine. The collection process takes approximately 4 – 6 hours and is normally done as an outpatient appointment.

Once the cells are collected, they are sent to a pharmaceutical company for manufacture. This process modifies your cells to express a receptor specific to your type of cancer. This can take up to four weeks. In rare circumstances the manufacturing process fails and it is not possible to generate any CAR-T cells for treatment. If appropriate we may organise another apheresis procedure. Your CAR-T team will discuss this with you in detail.

The consultant may decide to give you some form of treatment to control your cancer when the CAR-T cells are being manufactured. This is called Bridging Therapy and your consultant and CAR T Co-Ordinator will discuss this with you. This therapy can potentially be administered in your local hospital; again your Consultant and CAR T Co-Ordinator will discuss this with you. Once your CAR T cells have been returned to the laboratory in St James's Hospital your Co-Ordinator will arrange the next stage of your treatment.

2. Lymphodepletion and Infusion of CAR T cells



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At this stage you will be admitted to St James's Hospital. The total inpatient stay is normally 2 – 3 weeks.

Lymphodepletion therapy, the destruction of lymphocytes including T cells by chemotherapy, is usually three days of treatment. This treatment creates room in your immune system to allow the new cells to expand and multiply. You will then have a two-day rest period before your CAR T cells are re-infused.

Prior to the start of the treatment, a central line, also known as a PICC line or a Hickman line, will be inserted into a major vein in the neck, arm or the chest to allow the administration of various drugs, blood and platelet transfusions and the infusion of your CAR T cells. There are risks associated with the insertion of a central line. The risks involved will depend on the type of line you have inserted. You will be provided with information related to the risks involved, prior to giving your consent to this procedure. The insertion of a central line may be done by your referring hospital prior to your admission to St James's Hospital.

The day you receive your CAR T cells is known as Day 0 (Zero), this is because your medical team measure your recovery starting from this day. One of the laboratory scientists will bring your cells from the lab to your bedside where they will be thawed in a water bath. These cells will then be reinfused through your central line. The infusion process usually takes no more than 15 minutes.

You will need to stay in the hospital for approximately two weeks following cell reinfusion and your team of doctors and nurses will monitor you closely during this time.

Possible Side Effects or Reactions Associated with CAR T Cell Therapy:

CAR T cell therapy is associated with the side effects listed below. You may develop some or all of these side effects. The most common of each of these side effects will be described in detail within this information leaflet.

Please note that there may be other side effects that are not listed below.

St. James's Hospital HOPE Directorate Stem Cell Transplant Unit

COMMON	UNCOMMON
<ul style="list-style-type: none"> • Infection • Cytokine Release Syndrome • Central nervous system problems (ICANS) • Anaemia and Bleeding • Tumour Lysis syndrome • B cell Aplasia 	<ul style="list-style-type: none"> • Liver and Kidney problems • Pain • Heart problems • Digestive system problems • Skin rashes and hair problems • HLH • Bladder problems • Fertility • Secondary Cancers

Infection:

Your blood count may be very low in the weeks following lymphodepletion therapy, resulting in an increased risk for infection. You will be monitored closely during this time and will be treated with antibiotics if you develop a high temperature. Bacterial infections are most common. Viral or fungal infections can also occur. Occasionally people can become very ill with infection and develop "Sepsis" which may result in a low blood pressure or difficulty breathing and can require admission to the intensive care unit for closer monitoring.

Cytokine Release Syndrome:

In some patients the immune system may become activated as the CAR T cells travel through the body. Substances called cytokines are released into the system. This can make you feel like you have the flu, with a high fever and/or chills. Other signs and symptoms that may occur include a drop in your blood pressure and some difficulty in breathing and confusion. These symptoms can range from mild to severe. These symptoms normally occur within the first 10 days after the infusion of the CAR-T cells. Your healthcare team will monitor you frequently for these symptoms. You may need oxygen, intravenous fluids and other medications to control the release of these cytokines. In some cases, you may require admission to the intensive care unit to help control these symptoms.

ICANS (Immune effector cell associated neurotoxicity syndrome):

St. James's Hospital HOPE Directorate Stem Cell Transplant Unit

You may experience neurological complications ranging from mild to severe confusion, difficulty with communication and co-ordination or seizures. Onset normally occurs 7-10 days after the CAR T cells have been infused, but can occur at any stage. You will have frequent neurological assessments to monitor for these side effects as an inpatient. Because of this you should not drive or operate heavy machinery for eight weeks following CAR –T Infusion.

Anaemia and Bleeding: (reduction in the number of blood cells). The lymphodepletion chemotherapy decreases the cells in the bone marrow resulting in anaemia (decreased red blood cells) and a severe decrease in white cells and platelets. This means that you will be at risk of severe bleeding, which can on occasion be fatal. You may require transfusions of red cells and platelets.

Tumour Lysis syndrome:

In some cases lymphodepletion may destroy a large amount of tumour. When these cells die the contents of the cells are released into your bloodstream. This can result in build-up of fluids and salts in your blood and can possibly lead to kidney damage as your kidneys try to get rid of them from your body. Your medical and nursing team will monitor you closely for signs of this and will intervene as needed. This may involve the administration of fluids and medications to help your body clear these excess minerals and protect your kidneys.

B Cell Aplasia:

CAR T cell therapy cannot differentiate between malignant and non-malignant cells therefore they destroy some of your normal B cells. B Cells make antibodies which help fight infection. Intravenous substitutions of immunoglobulins can be given to manage this. Your team will check your bloods regularly to see if this is required.

Liver and Kidney problems:

Chemotherapy drugs used in lymphodepletion can damage the liver and kidneys. Kidney damage can also be caused by antibiotic therapy and some other drugs. As mentioned previously, Tumour Lysis Syndrome can also affect your kidney function. The healthcare team monitors the amount of fluids going in and the amount coming out (Urine, diarrhoea). The team will also monitor your liver and kidney function daily by doing specific blood tests. There are many measures the team can take to reduce liver and kidney damage including giving you extra fluids intravenously and re-evaluating your drug therapy.

St. James's Hospital HOPE Directorate Stem Cell Transplant Unit

Pain:

Pain occurs when tissues or nerves are inflamed. Pain can be caused by:

- infection
- mouth sores
- intestinal problems

Pain medicines are used to relieve any pain experienced.

Heart problems:

Heart, or cardiac, problems are not common after CAR T cell therapy but they can occur. Certain chemotherapy drugs, such as cyclophosphamide (Cytoxan), can cause the heart to work less efficiently. They can also cause inflammation of the tissue around the heart (called pericarditis). If you develop cardiac problems the healthcare team may carry out additional cardiac investigations such as a repeat echocardiogram.

Digestive System problems:

Digestive system problems can occur. These problems happen because tissues in the mouth, stomach and intestines are sensitive to the drugs used in the lymphodepletion. Digestive system problems include;

- inflammation and sores in the mouth (called stomatitis or oral mucositis)
- nausea
- vomiting
- loss of appetite
- weight loss
- diarrhoea

Digestive problems can be managed in different ways. Your healthcare team may give you special mouthwashes or lozenges and pain medicines for a sore mouth. They may also prescribe medicines to control diarrhoea, nausea and vomiting. The healthcare team will also talk to you about good mouth care during and after treatment.

St. James's Hospital HOPE Directorate Stem Cell Transplant Unit

If you have digestive problems, try to eat small meals and snacks. The team may also suggest nutritional or food supplements if you have trouble eating. If you are not managing to eat enough, you may be given a special fluid through the central venous catheter to make sure you get enough nutrition. This is called parenteral nutrition or total parenteral nutrition (TPN).

Skin and hair problems:

Certain drugs for CAR T cell therapy can cause a skin rash. These rashes are temporary and will normally improve once your team evaluate your drug therapy. Hair loss can also occur after the Lymphodepleting therapy. Hair usually grows back within 3–6 months after treatment, but can rarely be permanent.

Haemophagocytic Lymphohistiocytosis (HLH):

HLH is an uncommon disorder caused by uncontrolled proliferation of activated lymphocytes. It is characterised by lymphocytes and macrophages secreting high amounts of inflammatory cytokines. HLH clinically manifests with fever, enlargement of liver and spleen, enlarged lymph nodes, yellow discoloration of skin and eyes, skin rash, elevated ferritin levels and cytopenias and may be fatal.

Bladder problems:

Bladder problems can occur when chemotherapy drugs used during Lymphodepletion can cause some scarring the bladder wall. This can lead to frequent urination or blood in the urine.

Fertility problems:

Fertility problems can occur because of chemotherapy used prior to the infusion of your CAR T cells, however because of the prior treatments you received prior to CAR-T therapy this issue will have been discussed with you by your referring team.

Secondary cancers

Because the DNA in the CAR T cells have been modified, there is a risk that these changes could trigger the T Cells to divide uncontrollably potentially leading to the development of blood cancers like Leukaemia. Overall it is thought that the chances of secondary cancers are very small.

Mental Health and Psychological problems:

St. James's Hospital HOPE Directorate Stem Cell Transplant Unit

Mental health can be affected by your treatment – which can be very stressful. The chemotherapy, and periods of time in isolation can have an impact on mental health. Some chemotherapy drugs, most commonly steroids can cause severe mood disturbances such as depression or difficulty sleeping. In other people, steroids can induce a feeling of being very happy despite the events and associated illness of the transplant procedure. The health care team work closely with the psychiatry team in the hospital who specialise in working with Haematology and Oncology patients

Relapse:

The goal of CAR T cell therapy is to cure your underlying disease. Unfortunately, in some patients, the underlying disease can return after this treatment. Treatment options then may be limited depending on the previous treatments you have already received.

Care post discharge from the ward:

Recovery from CAR T therapy can take time as your immune system recovers. While every situation is different the minimum inpatient stay is approximately 10-14 days. Once you are discharged, you will be required to stay within a two-hour journey time of St James's Hospital until Day 30 post CAR T infusion approximately. You will also need to identify a care giver who can be with you at all times during this period. This person will be responsible for monitoring you for any signs of side effects, fever, infection and any neurological difficulties (e.g. confusion). They will need to notify the team immediately in St James's if you develop any of these symptoms. Your Consultant and CAR T Co-ordinator will discuss this with you in detail before you are discharged. You will have many follow up appointments post discharge, initially these will be in St James's hospital, and when your Consultant feels it is appropriate they will transfer your care back to your referring team in your local hospital. You will also undergo tests as an outpatient to ensure your therapy is working. These tests will include scans and blood tests. Your CAR T Co-ordinator will arrange these tests for you.

You will be given a patient alert card on discharge identifying that you have received CAR T Cell therapy. It is really important that you present this to any hospital/ medical professional you attend post discharge. As previously stated you should not drive or operate heavy machinery for 8 weeks post CAR T infusion.

Please read this information carefully and ask any questions you might have related to your treatment. Your Consultant and CAR T Co-ordinator will discuss details of your treatment with you. Although there

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are many side-effects mentioned in this form, each person's path is different and you may or may not experience some or all of these side-effects. Your treating consultant will explain the benefits and risks associated with CAR T therapy including rare risks, such as treatment failure and death due to complications associated with the treatment. It is important that you are informed of this information before signing the attached consent form.

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Owner: CAR T Co-ordinator : Ms E. Higgins

Approved by: Consultant Haematologist: Prof L. Bacon