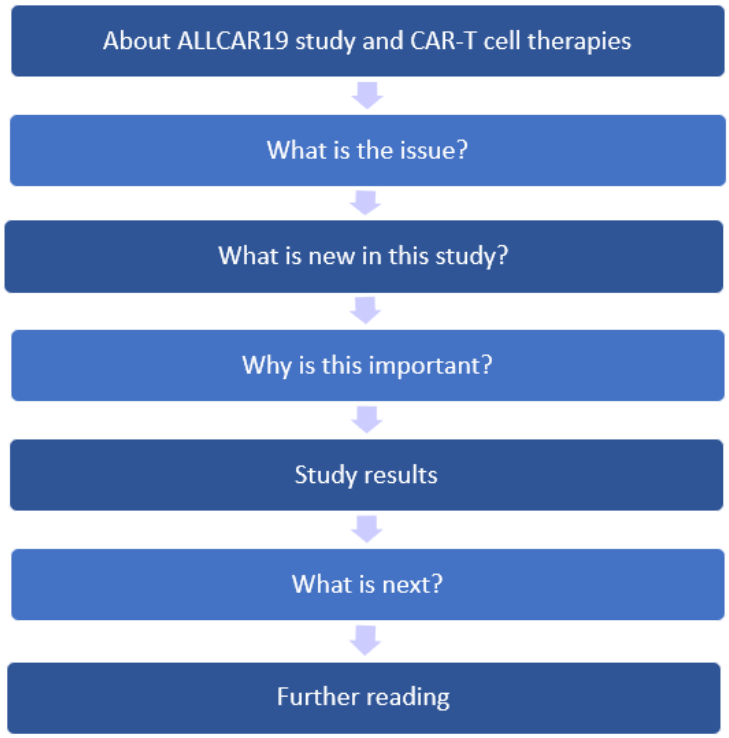
New CAR T-cell therapy (ALLCAR19) for adults with relapsed/ refractory B-cell Acute Lymphoblastic Leukaemia shows promise as a stand-alone treatment

Author: Marina Mitsikakou, PhD student with Claire Roddie at the UCL Cancer Institute
Lay review: Patient and Public Research Panel members and Linda von Nerée, Patient and Public Involvement Lead, NIHR Blood and Transplant Research Unit at UCL

'While CAR T therapy is very effective for some patients, current CAR T-cell treatments have limitations. In the ALLCAR19 study we addressed two main problems of CAR-T therapy in adults with relapsed B-cell Acute Lymphoblastic Leukaemia as there is no licensed treatment in this age group for this type of cancer.'
Professor Karl Peggs, Chief Investigator of the ALLCAR19 study and Co-Director of the Blood and Transplant Research Unit in Stem Cells and Immunotherapies at UCL

'As both scientists and doctors, we are delighted with the results; they are important because they show the new CD19 CAR design allows for the safe treatment of CAR T-Cell therapy to adult patients with relapsed B-ALL. Moreover, this treatment may allow patients to have long-term remissions with no other treatment.'
Dr Claire Roddie, Associate Professor at UCL Cancer Institute, consultant haematologist at UCLH and Director of the Blood and Transplant Research Unit in Stem Cells and Immunotherapies at UCL

Overview of content



About ALLCAR19 study and CAR T-cell therapies

The ALLCAR19 study is a Chimeric Antigen Receptor (CAR) T-cell therapy and belongs to the rapidly evolving field of T-cell immunotherapies, that make the own immune system cells more capable of fighting cancer. Patients with B-cell Acute Lymphoblastic Leukaemia (B-ALL) took part in the study at three hospitals in the UK, if their cancer had returned or got worse (relapsed) or did not respond to available treatments

(refractory). Twenty patients took part in this phase 1 study with the aim of finding out about side effects (toxicity), and what happens to the treatment in the body *(for more information on the ALLCAR19 study see section 'Further reading', links 1, 2 and 3)*. The American Society of Clinical Oncology (ASCO) recently published the ALLCAR19 study in the Journal of Clinical Oncology (JCO) *(for the published article see section 'Further reading', link 4)*.

Key facts about the ALLCAR19 study

Why this study?

Approved CAR T-cell therapies can cause intolerable side effects for adults with relapsed/ refractory B-cell Acute Lymphoblastic Leukaemia (B-ALL), especially if patients are older and/or have other health conditions. For many of these patients cancer returns when CAR T-cells are no longer present in the body. The ALLCAR19 study addressed these two major limitations of current CAR-T therapy:

1. Over-activation of the immune system leading to intolerable side effects.
2. Lack of survival (persistence) of CAR T-cells.

What is new?

1. New CAR T-cell model (AUTO 1) for treatment.
2. Adapted study design – treatment given in two doses instead of one.

How was it done?

ALLCAR19 study tested if:

1. The new CAR T-cell model works better, increasing the persistence of CAR-T cells.
2. The changed study design (treatment in two doses) avoids over-activation of the immune system.

What are the results?

The new CAR T-cells and changed trial design showed better outcomes for adult patients with relapsed/refractory B-ALL.

What is next?

1. FELIX study to confirm results in a larger number of patients.
2. ALLCAR19 Extension study to include patients with other B-cell cancers (e.g. Lymphomas and Chronic Lymphocytic Leukaemia).

For CAR T-cell therapy (Figure 1), scientists use T-cell lymphocytes, a type of white blood cell in the immune system. T-cell lymphocytes recognise micro-organisms that cause illness (pathogens) or cells that have been infected with such micro-organisms and destroy them. Based on this ability of T-cells, scientists engineer the patient's own T-cells in the laboratory to express a new protein that allows the T-cells to be redirected to seek out, attack and destroy specific cancer cells. The protein that allows the T-cells to find cancer cells is a receptor called a Chimeric Antigen Receptor (CAR). T-cells that have been engineered to carry this protein are called CAR T-cells (Figure 2).

Figure 1. How CAR T-cell therapy works. (Starting from the human figure and following the pink arrow) Patient's T-cells are collected from the blood, engineered in the laboratory to carry the CAR protein and allowed to multiply. They are then given back to the patient. In the body, the CAR T-cells will travel through the blood, they will recognise cancer cells and they will destroy them.

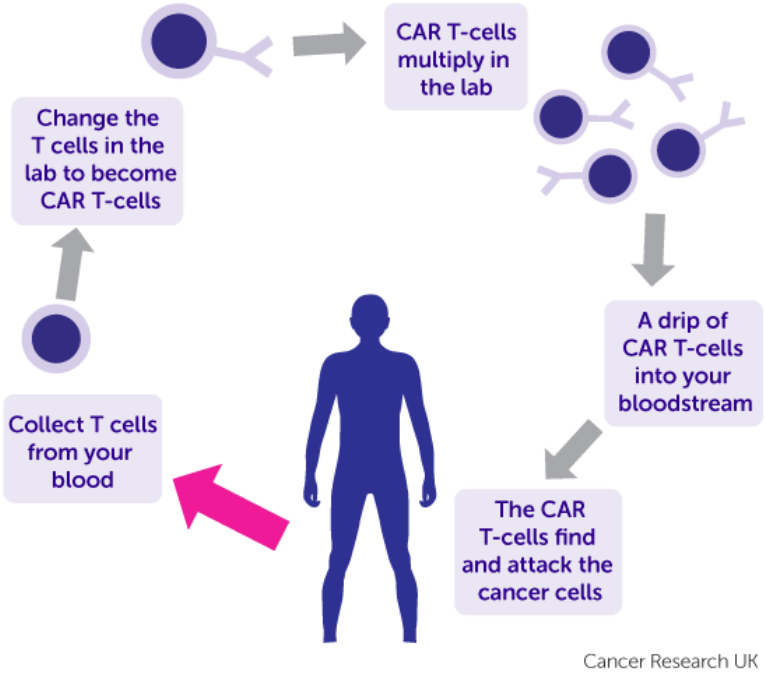
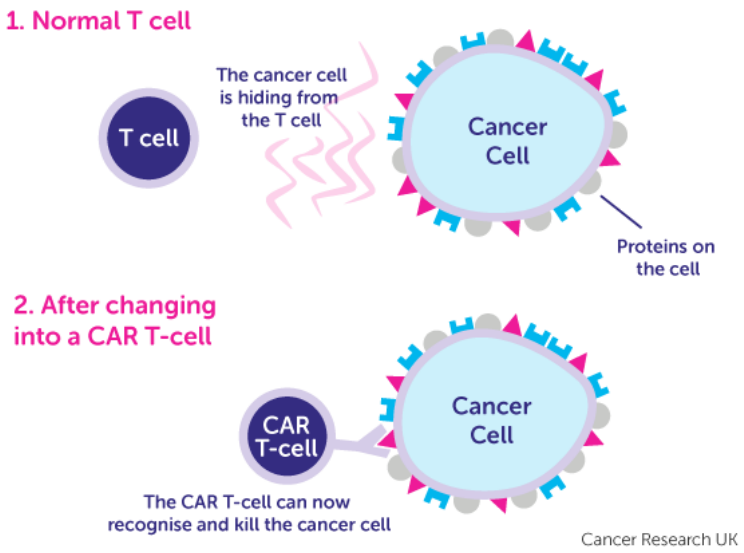


Figure 2. How CAR T-cells work. 1. In the body, T-cells cannot recognise cancer cells because they are missing a tool that will identify the cancer cells and will then notify the T-cells to destroy them. 2. Patient's own T-cells are engineered in the laboratory to carry this tool (the CAR, shown as a light purple Y shape) that recognises protein molecules on the surface of the cancer cells (shown as pink triangles). Once the CAR attaches to its protein molecule, complex biological procedures command the T-cell to kill the cancer cell.



In B-ALL, the CAR recognises a protein named CD19 on the surface of the leukemic cancer cells. Once the CAR recognises the CD19 protein, it signals to the T-cell to attack and kill this cancer cell *(for more information on CAR-T therapy see section 'Further reading', links 5 and 6)*.

CD19-directed CAR T-cell therapies target different blood cancer types and have been approved in the USA by the Food and Drug Administration (FDA), in Europe by the European Medicines Agency (EMA) and in the

UK by the National Institute for Health and Care Excellence (NICE). One of these therapies is Tisagenlecleucel (sold under the brand name Kymriah from the pharmaceutical company Novartis), which treats paediatric and young adult patients up to 25 years of age with relapsed or refractory (r/ r) B-ALL *(see Appendix 1)*. However, when Kymriah was used for the treatment of adult r/ r B-ALL patients, it had significant toxic side effects.

What's the issue?

Current CAR T-cell therapies are very effective, but like most treatments, they have limitations. Two major limitations are the associated toxicity and the inability of the CAR T-cells to survive for long periods of time in the body following infusion into the patient (lack of persistence). These two issues have proven particularly hard to resolve in adult r/ r B-ALL patients and hence there is still no approved treatment for adults with this cancer type in the UK.

What's new?

A team of scientists led by Dr Martin Pule at the UCL Cancer Institute worked on addressing these issues, focusing on the biological features of the CAR and on the trial design. They developed a new CAR named AUTO1, which they thought to:

- Have fewer toxic side-effects and
- Survive in the patient's body for longer periods of time (persistence) than other commercially available CARs.

The ALLCAR19 study team, researchers and medical professionals, used the AUTO1 CAR for patients taking part in the ALLCAR19 study together with a split dose design (giving CAR T-cells in two doses instead of one).

Why is this important?

Toxicity and lack of persistence result from the over-activation of the immune system when the CARs are attacking the cancer cells. When the immune system encounters a pathogen, it gets activated (immune response) and small proteins called cytokines are released. Cytokines coordinate a fine-tuned and effective immune response by helping the cells of the immune system to communicate and interact with each other and to produce more cytokines as needed. Normally, the initial response of the immune system is slow. That's because a rapid immune response, where over-activation of the immune system and excessive production of cytokines occur, can lead to hyperinflammation which can lead to shock, organ damage and even death.

During CAR T-cell therapy, the engineered CAR T-cells are returned in the patient's body where they all encounter their target cancer cells at the same time. This results in the activation of a large number of cells and the production of cytokines from a large number of cells at the same time, which is similar with an unwanted rapid immune response. Excessive production of cytokines can lead to severe side effects. Simultaneously, the longer a CAR T-cell stays in contact with its target cancer cell, the more 'tired' (exhausted) the CAR becomes. Exhausted CARs cannot function properly and cannot persist in the patient's body. This lack of persistence can lead to relapse.

In an attempt to mimic more closely the normal interaction of T-cells with their targets during a slow initial immune response, Dr Martin Pule's team suspected that if a CAR connects to its target less tightly, it will then be able to leave its target more quickly. This shorter interaction of the CAR T-cells with the cancer cells could lead to a decreased production of cytokines and to less 'tired' CAR T-cells. It could therefore decrease toxicity and improve CAR T-cell persistence. Based on the above, the novel AUTO1 CARs that Dr. Pule's team developed have the ability to bind their target leukemic cells less tightly and to disconnect from them (off-rate) faster than other CD19-directed CARs that have been used so far for B-cell malignancies (one of which is B-ALL). Thus, AUTO1 was called a 'fast off-rate CAR'.

To further reduce toxic side effects, the team adjusted the first dose of the treatment depending on the severity of the disease and the second dose depending on side-effects experienced after the first dose. This helped to reduce side effects in two ways:

1. Less AUTO1 CARs were given to patients with many cancer cells to prevent the over-activation of the immune system
2. The second dose was either delayed or omitted if patients experienced severe or prolonged toxicity after the first dose, preventing further toxic side effects.

In conclusion, both changes (the fast off-rate of the AUTO1 CARs that were used at the ALLCAR19 study, together with the administration of the treatment in two doses) improved the outcomes of CAR T-cell therapy for adult patients with r/ r B-ALL.

Study results

During the ALLCAR19 study 20 patients were treated with the fast off-rate AUTO1 CAR, showing the following results:

- All patients experienced only mild to moderate toxic side effects that resolved quickly.
- 85% of the patients achieved Complete Response (CR) at 1 month after treatment.
- 70% of the patients were still in CR at 3 months after treatment.
- 68.5% of the patients showed no signs of disease or need for additional treatment at 6 months after AUTO1 CAR therapy (Event-Free Survival, EFS).
- 75% of the patients had persistent AUTO1 CAR in their blood at a median *(see Appendix 1)* of almost 6 months after treatment.
- The Overall Survival (OS) at 1 year after treatment was 63.8%.

In summary, AUTO1 showed limited toxic side effects, excellent persistence (longer survival of CAR T-cells), and high remission rates (absence of cancer cells), which in some cases were maintained for over 24 months without the need for other treatment *(for more information on the meaning of clinical trial results see section 'Further reading', link 7)*.

What's next?

The above findings are now confirmed in the larger FELIX study that is sponsored by Autolus Limited, a UCL spin-off company. FELIX is a Phase Ib/II global registration study that is designed to enrol adult r/ r B-ALL patients across some of the leading academic and non-academic centres in the United States, Spain, and the United Kingdom *(for more information see section 'Further reading', links 8, 9 and 10)*.

AUTO1 CAR T-cells are also named Obecabtagene Autoleucel or Obe-cel. The UK Medicines and Healthcare products Regulatory Agency (MHRA) included Obe-cel in the Innovative Licensing and Access Pathway (ILAP). An ILAP helps to speed up the process for medicines to make them available to patients faster. Obe-cel also received an orphan drug designation (financial support from the government to produce drugs treating medical conditions that are rare) by the FDA in the US and Priority Medicines (PRIME) designation by the EMA *(see Appendix 1)*. Autolus expects to present data from FELIX Phase II in 2022.

In addition, the ALLCAR19 study has been extended to include adult patients with cancer types other than r/ r B-ALL. These include:

- r/ r Diffuse Large B-cell Lymphoma (DLBCL)
- r/ r Chronic Lymphocytic Leukaemia / Small Lymphocytic Lymphoma (CLL/ SLL) and
- r/ r indolent B-cell Non-Hodgkin Lymphoma (iB-NHL).

As for r/ r B-ALL, there are limited treatment options for the above cancer types. AUTO1 CAR (Obe-cel) could offer hope where other treatments have failed for even more patients and their families.

The graphic below summarizes the challenges addressed in the ALLCAR19 study.

Further reading

1. ALLCAR19 Trial: *https://clinicaltrials.gov/ct2/show/NCT02935257*
2. BBC News at Ten (7th January 2022) section on ALLCAR19 starting at 24:03 minutes: *https://www.youtube.com/watch?v=P6mkKZ9S-cc&t=2s*
3. Written piece on BBC News Health for ALLCAR19: *https://www.bbc.co.uk/news/health-59771464*
4. Research published in JCO: *Roddie et al, DOI: 10.1200/JCO.21.00917 Journal of Clinical Oncology 39, no. 30 (October 20, 2021) 3352-3363 (https://ascopubs.org/doi/full/10.1200/JCO.21.00917)*
5. The UCL CAR T-cell programme: *https://www.ucl.ac.uk/cancer/research/ucl-car-t-programme*
6. NHS England information on CAR T-cell therapy: *https://www.england.nhs.uk/cancer/cdf/car-t-therapy/*
7. Cancer Research UK (CRUK) – Meaning of Clinical Trial Results: *https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/clinical-trial-results/what-do-clinical-trial-results-mean-0*
8. FELIX Trial: *https://www.clinicaltrials.gov/ct2/show/NCT04404660*
9. Cancer Research UK (CRUK) on FELIX Trial: *https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-car-t-cell-therapy-for-people-with-b-cell-acute-lymphoblastic-leukaemia-felix-obe-cel#undefined*
10. Autolus Limited: *https://www.autolus.com/*

Funding for this study

1. UK National Institute for Health Research (NIHR)
2. NIHR University College London Hospitals (UCLH) Biomedical Research Centre (BRC)
3. NIHR Blood and Transplant Research Unit (BTRU) in Stem Cells and Immunotherapy at University College London (UCL)
4. NHS Blood and Transplant (NHSBT) Research Unit
5. Cancer Research UK (CRUK) London Centre
6. CRUK core grant

Conflicts of Interest: The study authors declare no conflicts of interest.

Image credits: Cancer Research UK (CRUK), https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/immunotherapy/types/CAR-T-cell-therapy

Appendix 1. Abbreviations and terms explained.

Abbreviation	Term	Explanation
-	Acute (for cancer)	A cancer that develops very quickly.
B-ALL	B-cell Acute Lymphoblastic Leukaemia	A bone marrow and blood cancer with high numbers of abnormal, immature B-cells.
-	B-cells	A type of white blood cell that is part of our immune system and normally protect us from invaders/ germs.
CAR	Chimeric Antigen Receptor	A synthetic molecule that recognises specific molecules (proteins) on cancer cells and attaches to them.
CAR-T	Chimeric Antigen Receptor (CAR) T-cell	A T-cell engineered with an additional synthetic receptor (CAR) that allows it to find and destroy cancer cells.
CAR-T therapy	Chimeric Antigen Receptor (CAR) T-cell therapy	A type of T-cell immunotherapy which involves collecting, engineering, and returning the patient's own T- cells to treat their cancer.
CD19	Cluster of Differentiation 19	A protein which is abundant on the surface of abnormal (cancerous) and healthy B-cells.
-	Chronic (for cancer)	A cancer that tends to develop slowly.
CLL	Chronic Lymphocytic Leukaemia	A bone marrow and blood cancer with high numbers of abnormal B-cells.
-	Diffuse (for cancer)	Spread out cells rather than grouped together when they are seen under a microscope.
DLBCL	Diffuse Large B-cell Lymphoma	A lymphatic system cancer with high numbers of abnormal, larger than healthy and diffused B-cells. DLBCL is a type of fast-growing Non-Hodgkin Lymphoma.
-	Indolent (for cancer)	Indolent lymphomas spread and grow slowly (slow-growing) and have fewer symptoms.
iB-NHL	indolent B-cell Non-Hodgkin Lymphoma	A lymphatic system, slow-growing cancer with high numbers of abnormal, immature B-cells.
-	Leukaemia	A cancer that starts in the bone marrow or blood.
-	Lymphoma	A cancer that starts in the lymphatic system, a part of our immune system that normally protects us from invaders/ germs and tries to destroy old or abnormal cells.

-	Median	In statistics, the median is the value separating the higher half from the lower half of a data set. It may be thought of as 'the middle' number in a sorted, ascending or descending, list of numbers.
-	Orphan drug	An orphan drug is developed to treat very rare medical conditions, whose rarity means it would not be profitable to produce treatments for them without government assistance. The conditions are referred to as orphan diseases.
PRIME	Priority Medicines	An EMA scheme to enhance support for the development of medicines that target an unmet medical need. The scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier.
r/ r	relapsed/ refractory	• relapsed: cancer returning or becoming worse. • refractory: cancer not responding to available treatment options.
r/ r B-ALL	relapsed/ refractory B-cell Acute Lymphoblastic Leukaemia	B-ALL that has returned and/ or became worse and/ or did not respond to available treatments.
r/ r CLL	relapsed/ refractory Chronic Lymphocytic Leukaemia	CLL that has returned and/ or became worse and/ or did not respond to available treatments.
r/ r DLBCL	relapsed/ refractory Diffuse Large B-cell Lymphoma	DLBCL that has returned and/ or became worse and/ or did not respond to available treatments.
r/ r iB-NHL	relapsed/ refractory indolent B-cell Non-Hodgkin Lymphoma	iB-NHL that has returned and/ or became worse and/ or did not respond to available treatments.
r/ r SLL	relapsed/ refractory Small Lymphocytic Lymphoma	SLL that has returned and/ or became worse and/ or did not respond to available treatments.
SLL	Small Lymphocytic Lymphoma	SLL that starts in the lymphatic system instead of the bone marrow or blood. SLL is a type of iB-NHL.
-	T-cells	A type of white blood cell that is part of our immune system and normally protect us from invaders/ germs.