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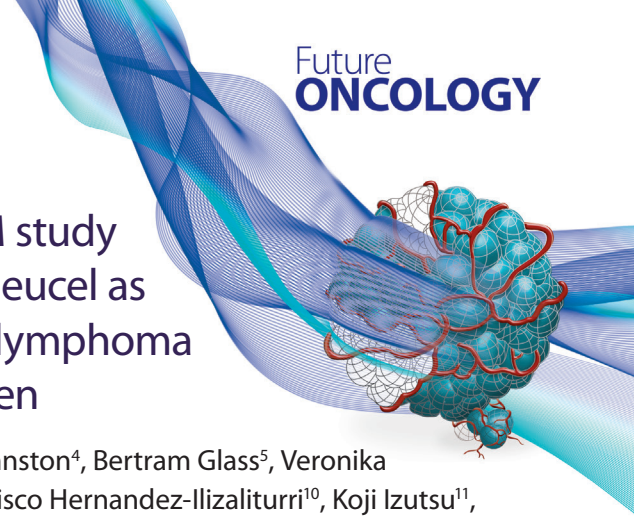
Plain Language Summary of Publication

Future ONCOLOGY



Plain language summary of the TRANSFORM study primary analysis results: lisocabtagene maraleucel as a second treatment regimen for large B-cell lymphoma following failure of the first treatment regimen

Jeremy S Abramson[1], Scott R Solomon[2], Jon Arnason[3], Patrick B Johnston[4], Bertram Glass[5], Veronika Bachanova[6], Sami Ibrahimi[7], Stephan Mielke[8], Pim Mutsaers[9], Francisco Hernandez-Ilizaliturri[10], Koji Izutsu[11], Franck Morschhauser[12], Matthew Lunning[13], Alessandro Crotta[14], Sandrine Montheard[14], Alessandro Previtali[14], Ken Ogasawara[15] and Manali Kamdar[16]

Full affiliation information can be found at the end of this plain language summary.

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Summary

What is this summary about?

People diagnosed with a disease called large B-cell **lymphoma** (LBCL) may experience return, or early relapse, of their disease within the first year after receiving and responding to their first (first-line) treatment regimen. Others may have **primary refractory** disease, meaning that the disease either did not respond to first-line treatment at all or only responded for a very brief period. Second (second-line) treatment includes immunotherapy followed by **high-dose chemotherapy** and **ASCT**, which has the potential to cure LBCL. However, if the disease does not respond to immunotherapy, people cannot receive ASCT, and less than 30% of people are cured.

Therefore, new second-line treatment options are required, such as CAR T cell therapy, which uses a person's own genetically engineered **lymphocytes**, also called T cells, to fight their lymphoma. In this article, we summarize the key results of the **phase 3 TRANSFORM clinical study** that tested if liso-cel, a CAR T cell treatment, can safely and effectively be used as a second-line treatment for people with early relapsed or primary refractory (relapsed/refractory) LBCL.

How to say (double click sound icon to play sound)...

- **Anemia:** uh-NEE-mee-uh
- **Anthracycline:** AN-thruh-SY-klin
- **CAR T:** car-TEE
- **Chemotherapy:** kee-mo-THEH-ruh-pee
- **Cytokine:** SY-tow-kine
- **Cytopenia:** SY-tow-PEE-nee-uh
- **Immunochemotherapy:** im-mew-no-kee-mo-THEH-ruh-pee
- **Liso-cel:** LY-soh-sel
- **Lisocabtagene maraleucel:** LY-soh-KAB-tuh-jeen MAR-uh-LOO-sel
- **Lymphocyte:** LIM-fow-site
- **Lymphoma:** LIM-fow-muh
- **Neutropenia:** NOO-trow-PEE-nee-uh
- **Therapeutic:** theh-ruh-PYOO-tik
- **Thrombocytopenia:** thraam-bow-sy-tow-PEE-nee-uh

A total of 184 adults with relapsed/refractory LBCL who were able to receive ASCT were randomly treated with either liso-cel or **standard of care** (SOC) as second-line treatment. SOC included **immunochemotherapy** followed by high-dose chemotherapy and ASCT.

What were the key takeaways?

Almost all (97%) people in the liso-cel group completed treatment, whereas 53% of people in the SOC group did not complete treatment, mostly due to their disease not responding or relapsing, and therefore they were not able to receive ASCT. People who received liso-cel as a second-line treatment lived longer without the occurrence of an unfavorable medical event or worsening of the disease and had a better response to treatment than those who received SOC as second-line treatment. People who received liso-cel reported **side effects** that researchers considered to be manageable, and that were known to occur with CAR T cell treatment.

What were the main conclusions reported by the researchers?

Results from the TRANSFORM study support the use of liso-cel as a more effective second-line treatment compared with SOC that is safe for people with relapsed/refractory LBCL.

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Lymphoma: Cancer that begins in the cells of the immune system.
Primary refractory: Disease progresses or worsens during treatment or immediately after stopping treatment.
High-dose chemotherapy: Chemotherapy treatment at a higher than normal dose that is designed to kill the diseased cells and as a side effect also kills the bone marrow cells.
ASCT: A procedure in which a patient's healthy stem cells (blood-forming cells) are collected from the blood or bone marrow before treatment, stored, and then given back to the patient after treatment.
Lymphocyte: A type of immune cell that fights cancer cells, viruses, and bacteria.
Phase 3 clinical study: A study that tests the safety and how well a new treatment works compared with a standard treatment.
Standard of care: Best practice or guideline for the treatment of a disease based on consensus among experts on that disease.
Immunochemotherapy: The combined use of immunotherapy and chemotherapy in the treatment of disease.
Side effects: Unintended, typically unfavorable effects of a treatment or drug.

Where can I find the original article on which this summary is based?

The original article, titled 'Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study,' was published in *Blood* in 2023. You can read the full article for free at: https://ashpublications.org/blood/article/141/14/1675/493847/Lisocabtagene-maraleucel-as-second-line-therapy

What is the purpose of this PLSP?

The purpose of this plain language summary is to help you to understand the findings from recent research.

Liso-cel is used to treat the condition under study that is discussed in this summary. Approval varies by country; please check with your local provider for more details.

Who should read this PLSP?

This article is intended for people with LBCL, families and caregivers of people with LBCL, patient advocates, and healthcare providers who treat people with LBCL.

Who sponsored the study?

The TRANSFORM study was **sponsored** by Celgene, a Bristol-Myers Squibb Company.

Sponsor: A company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information that was generated during the study.

What is large B-cell lymphoma (LBCL)?

Non-Hodgkin lymphoma is a group of cancers that affects a type of white blood cell called lymphocytes. These cells are part of the body's immune system that protect against illness and disease. LBCL is a type of non-Hodgkin lymphoma that affects a type of lymphocyte called B cells. Normal B cells produce antibodies, which act like defenders that bind to bacteria and viruses, disabling the invaders or marking them for other immune cells to remove. Relapsed/refractory LBCL (as defined in TRANSFORM) is disease that has returned within 12 months of starting and initially responding to the first treatment regimen (called early relapse). However, when LBCL does not respond to first-line treatment at all or only responds for a very brief period of 3 months or less, the disease is called primary refractory.

How is relapsed/refractory LBCL typically diagnosed and treated?

Antibody: A protein component of the immune system that recognizes bacteria, viruses, and cancer cells and neutralizes them.

Chemotherapy regimen: One or more chemotherapy drugs that people with cancer receive as part of their treatment.

Diagnosis and management

LBCL is diagnosed by blood tests, and response to treatment is evaluated according to a scoring system agreed on by experts called the Lugano 2014 criteria.

- Using this system helps to ensure that different doctors consistently apply the same criteria to evaluate LBCL

First-line standard of care (SOC) treatment

First-line SOC treatment of LBCL is immunochemotherapy, which is made up of an **antibody** targeting a protein called CD20 on the surface of B cells (a type of white blood cell) given in combination with a **chemotherapy regimen** containing an anthracycline, a class of medicine used to treat cancer.

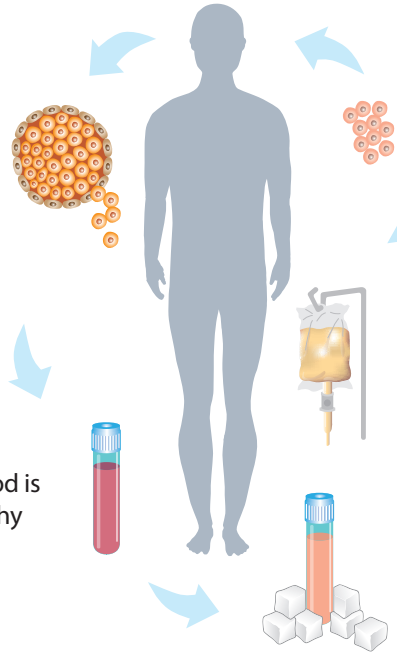
- If the disease does not respond or only responds for a period of time, it is considered relapsed/refractory to first-line treatment, and the second-line treatment process is started

Second-line SOC treatment

Second-line SOC treatment of relapsed/refractory LBCL begins with immunochemotherapy followed by high-dose chemotherapy and then ends with ASCT. This has been the standard second-line treatment for decades.

- ASCT is a procedure that begins with a person's own healthy stem cells being collected from the bone marrow or bloodstream before they undergo high-dose chemotherapy. It then ends with their own healthy stem cells being reinfused back into them to replace the blood-forming cells that were destroyed by high-dose chemotherapy
- Only those who respond (disease completely or partially removed) to immunochemotherapy qualify for high-dose chemotherapy and ASCT
- Up to half of all people living with relapsed/refractory LBCL will not be eligible to receive potentially life-saving ASCT because they do not respond to immunochemotherapy
- Less than 30% of people with relapsed/refractory LBCL whose lymphoma returns early are cured (healed of disease) with ASCT

Understanding the role of high-dose chemotherapy and ASCT in relapsed/refractory LBCL



1. A person's bone marrow or blood containing healthy stem cells (special human cells that are able to develop into many different cell types) is collected
2. The bone marrow or blood is processed to purify healthy stem cells
3. Stem cells are stored frozen until used
4. High-dose chemotherapy is given to remove the disease (in this case LBCL), but also has the side effect of reducing the person's level of nondiseased blood-forming cells
5. The person's melted stem cells are then given to replace the cells removed by the high-dose chemotherapy

What is liso-cel and how does it work?

Liso-cel is a personalized chimeric antigen receptor (CAR) T cell therapy. CAR T cell therapy is a treatment where CARs (proteins that are designed to bind to cancer cells) are combined with T cells (cells that kill cancer). The T cells are collected through a blood sample and are then combined in the laboratory with CARs. This is then put back into the person's blood stream. The CAR helps the T cells find and kill cancer cells.

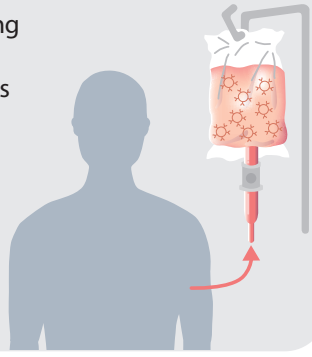
Liso-cel is approved for the treatment of relapsed/refractory LBCL as a:

- Second-line treatment (used after initial treatment has failed) in the United States, European Union, Japan, and Switzerland
- Third-line treatment (used after 2 previous courses of treatment have failed) in the United States, European Union, Japan, Switzerland, and Canada

How is liso-cel made?

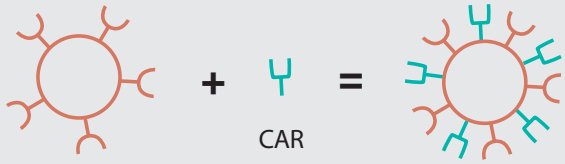
1

White blood cells (including T cells) are collected from a person's blood (a process called leukapheresis)



2

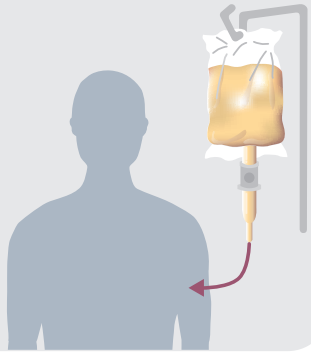
T cells are combined with CARs to make CAR$^+$ T cells that can then recognize a specific protein, CD19, found on lymphoma cells



Regular T cell CAR$^+$ T cell

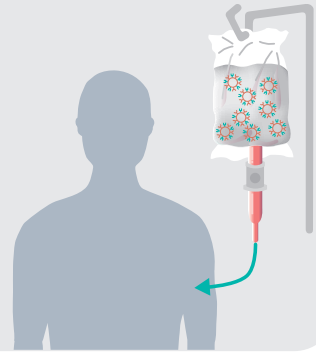
3

The person receives chemotherapy to reduce their level of whie blood cells, thus preparing the body for receiving CAR$^+$ T cells and increasing their effectiveness



4

The CAR$^+$ T cells are given back to the same person, where they seek out and recognize lymphoma cells expressing CD19 and stop them from growing and kill them

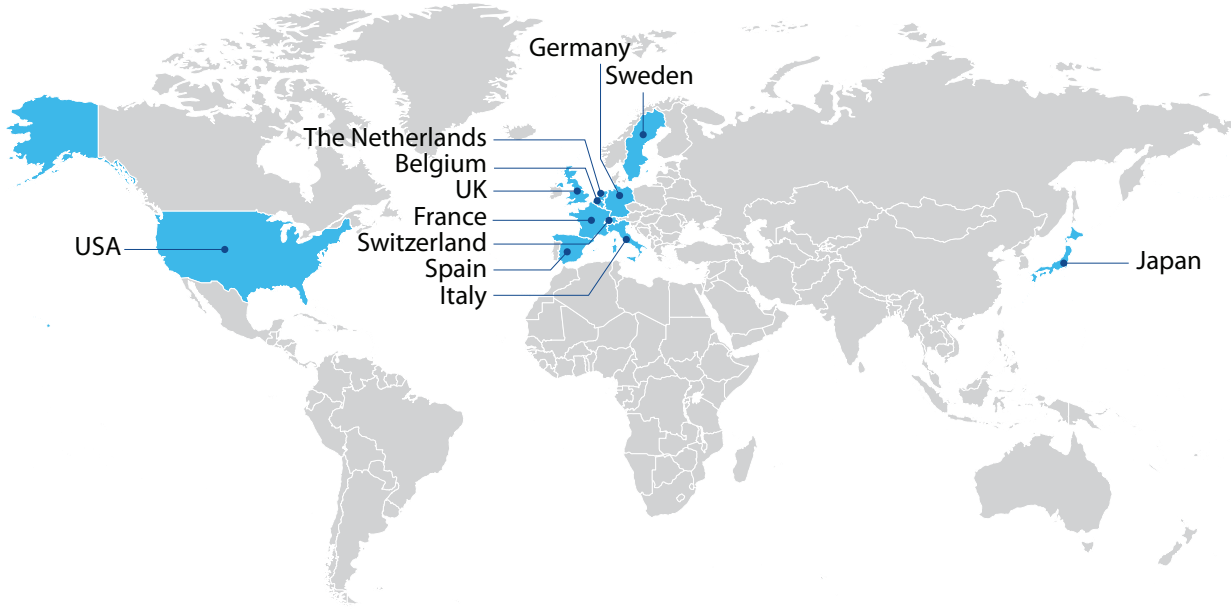


Where did the study take place and who took part?

This study was initiated in July 2018, with main results collected in or before May 2022. It is still ongoing but is no longer recruiting participants. This study was conducted at 53 study sites worldwide, including the United States, Belgium, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, Switzerland, and the United Kingdom.

The study included:

- People between 18 and 75 years of age who had LBCL that relapsed (returned) within 12 months after or was refractory (did not respond) to first-line treatment
- People whose disease responded to immunochemotherapy and were therefore able to receive high-dose chemotherapy and ASCT



What treatments were given?

A total of 184 people were randomly placed into 1 of 2 treatment groups of equal size. People received either liso-cel or SOC as second-line treatment. People and their doctors knew which treatment they received.

184 total participants

92 participants were assigned to the liso-cel group

92 participants were assigned to the SOC group

Liso-cel treatment group
infused (injected into the bloodstream) once with 100 million CAR$^+$ T cells

Bridging therapy (a single cycle of SOC chemotherapy) was allowed during the liso-cel manufacturing period in order to stabilize or reduce the extent of disease before liso-cel infusion. This meant people living with a high tumor burden (many cancer cells, large tumors, or large amount of cancer in the body) or rapidly progressing (worsening) disease could participate

SOC treatment group
received 3 cycles of immunochemotherapy followed by high-dose chemotherapy then ASCT

People in the SOC arm were allowed to cross over and receive liso-cel as a third-line treatment if their disease worsened at any time or did not respond (defined as a decrease in or disappearance of signs and symptoms of cancer) after 3 cycles of SOC chemotherapy

What did the researchers look at?

1 How long did people live with their cancer before it worsened or a new anticancer therapy was used?

This was assessed by measuring the event-free survival (EFS), defined as the time from when people were randomly divided into treatment groups until they experienced an unfavorable medical event such as death from any cause, disease progression (worsening), failure to achieve complete or partial **remission**, or start of new anticancer treatment.

Remission: Reduction or removal of disease.

2 How long did people live with their cancer before it progressed (worsened)?

This was assessed by measuring the progression-free survival (PFS), defined as the time from when people were randomly divided into treatment groups until they experienced disease progression (worsening) or death from any cause.

3 How long did people live after being randomly assigned to a group?

This was assessed by measuring the overall survival (OS), defined as the time from when people were randomly divided into groups until death from any cause, which could be due to their cancer, side effects of treatment, or a cause not related to the study.

4 Overall, did the person's disease respond by going into either complete remission (no detectable disease) or partial remission (decrease in extent of disease)?

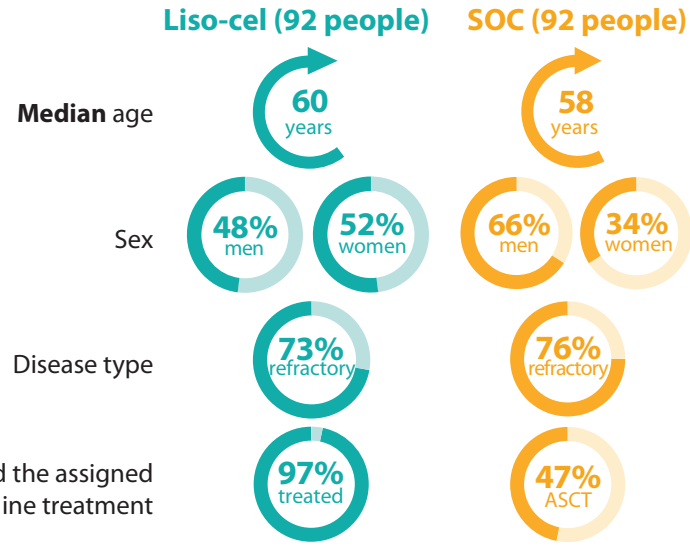
a. How many people had disease that went into complete remission (responded completely)?
b. How long did the complete or partial remission last (called duration of response, or DOR)?

5 What were the side effects of each treatment?

Side effects (unwanted or unexpected results or conditions that are possibly related to the use of a medication) were classified according to a grading system agreed on by experts associated with the National Cancer Institute called Common Terminology Criteria for Adverse Events (version 4.03). Using this system helped to ensure that different doctors consistently applied the same criteria when grading the severity and reporting side effects that emerge during and anytime after treatment.

What were the main primary results as of May 2022?

What were the characteristics of the people who participated and of their disease?

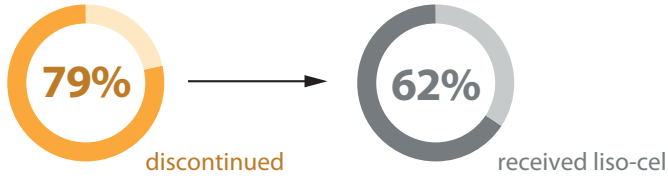


Median: The middle value in a set of measurements.

- Both treatment groups were balanced across most main characteristics
- Almost everyone in the liso-cel group completed treatment. Fewer than half in the SOC group received high-dose chemotherapy and ASCT and completed treatment

What third-line treatment did most people who discontinued second-line SOC receive?

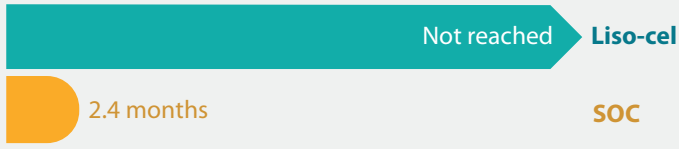
Most of the people who discontinued SOC crossed over to receive liso-cel as third-line treatment



At a median of 17.5 months after being randomly assigned to their treatment groups…

1 How long did people live with their cancer before it worsened (progressed) or a new anticancer therapy was used?

Median event-free survival (EFS)



People given liso-cel lived longer before an 'event' occurred (EFS), such as their disease progressing or worsening, starting a new anticancer therapy, or death, compared with those given SOC

Not reached: The majority of people have not yet experienced an event.

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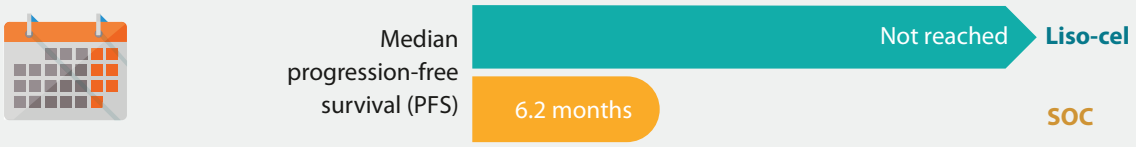
2 How long did people live with their cancer before it progressed (worsened)?

Median progression-free survival (PFS)



People given liso-cel lived longer before their disease progressed or worsened (PFS)

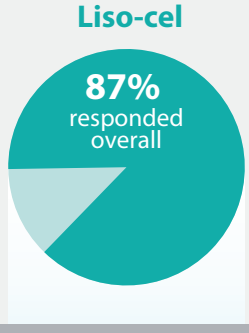
3 How long did people live after being randomly assigned to a group?

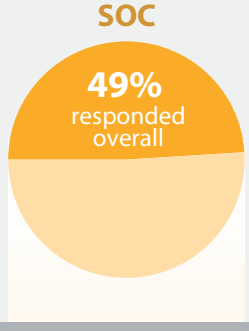
Median overall survival (OS)

- These analyses were done after 3 cycles of SOC or 5 weeks after liso-cel infusion
- A trend toward a longer total length of time people survived (OS) was observed in those who received liso-cel compared with those given SOC

4 Overall, did people's disease respond by going into either complete or partial remission?

Overall, most people's disease responded to liso-cel by going into complete or partial remission

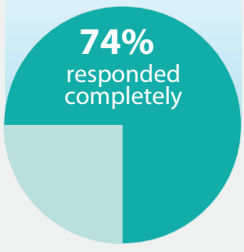


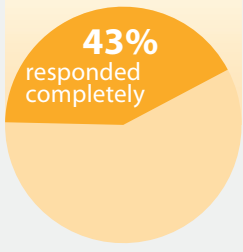


Fewer than half of those given SOC experienced complete or partial remission

a How many people had disease that went into complete remission (responded completely)?

Most people treated with liso-cel had disease that went into complete remission





Fewer than half of people treated with SOC went into complete remission

b How long did the complete or partial remission last (called duration of response, or DOR)?

Median duration of response (DOR)

Liso-cel: Not reached

SOC: 9.1 months

The response to liso-cel lasted longer than the response to SOC (DOR)

Duration of response (DOR): Length of time the disease responds to treatment without progressing or worsening.
Not reached: The majority of people's disease is still in remission and has yet to progress or worsen.

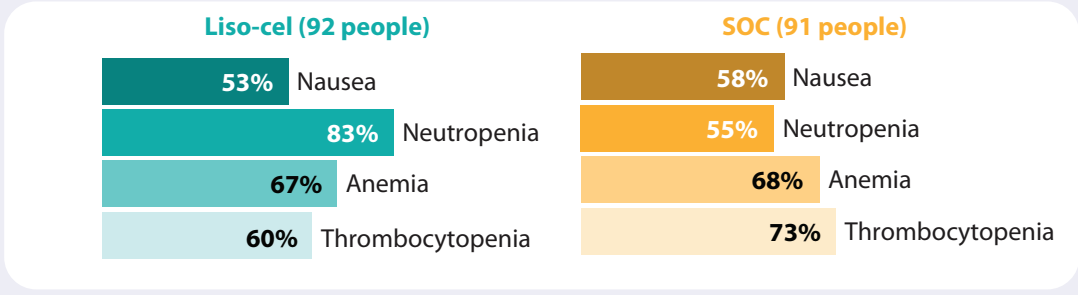
What were the side effects of each treatment?

Researchers looked at what side effects people had with treatment and graded them from 1 to 5 based on how serious they were.

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild or no symptoms	Moderate symptoms	Severe but not immediately life-threatening symptoms	Immediately life-threatening symptoms	Death

Everyone in the liso-cel group (92 people) and almost everyone in the SOC group (90 people) experienced a side effect of any severity.

Over half of people in both treatment groups experienced nausea and cytopenias (low blood cell count)
- Neutropenia (low neutrophils, a white blood cell)
- Anemia (low red blood cell count)
- Thrombocytopenia (low blood platelets needed for blood clotting)



Grade 3 and 4 side effects occurred in 85 out of 92 people in the liso-cel group, and 81 out of 91 people in the SOC group.

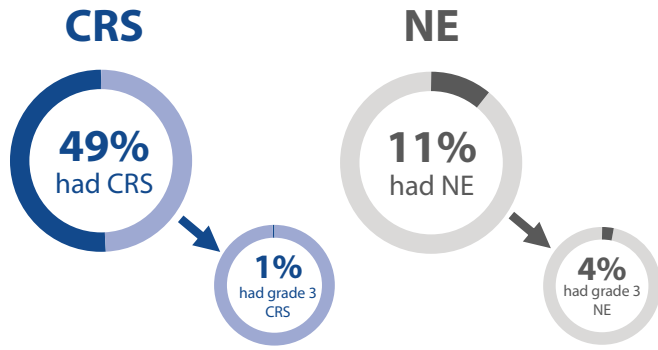
Grade 5 side effects occurred in 2 people in the liso-cel group and 2 people in the SOC group.

In both treatment groups, most severe (grade 3) or life-threatening (grade 4) cytopenias had either recovered completely or to a mild (grade 1) to moderate (grade 2) level within 2 months.

Two important side effects of CAR+ T cell therapies are cytokine release syndrome (CRS) and neurological events (NE)

- CRS occurs when a large, rapid release of messenger proteins from immune cells into the blood stimulates the immune system, which may result in side effects such as fever, nausea, headache, rashes, rapid heartbeat, low blood pressure, and/or trouble breathing
- NE may include the occurrence of confusion, delirium, loss of ability to understand or express speech, impaired movement, and drowsiness/lethargy

The median amount of time it took for CRS and/or NE symptoms to resolve was about 4 days.



Among the patients treated with liso-cel, there were no grade 4 or 5 CRS or NE

What do the results of the TRANSFORM study mean?

These results demonstrate the benefit of liso-cel over SOC in people with LBCL whose disease relapsed early or did not respond to first-line treatment.

- People who received liso-cel in the TRANSFORM study had disease that responded better to treatment and lived longer without an event occurring (EFS) or their disease progressing or worsening (PFS) compared with those who received SOC
- The overall safety of liso-cel versus SOC as second-line treatment was comparable and researchers considered side effects to be manageable
- Side effects specific to CAR T cell therapy were mild/moderate, manageable, and relatively short-lived

The results of the TRANSFORM study support the use of liso-cel as a more effective second-line treatment that is safe for people living with LBCL whose disease either relapsed early or did not respond to first-line treatment

Where can I find more information?

The original article, titled 'Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study,' was published in *Blood* in 2023. You can read the full article for free at: https://ashpublications.org/blood/article/141/14/1675/493847/Lisocabtagene-maraleucel-as-second-line-therapy

More information about the TRANSFORM study can also be found at: https://clinicaltrials.gov/ct2/show/NCT03575351

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