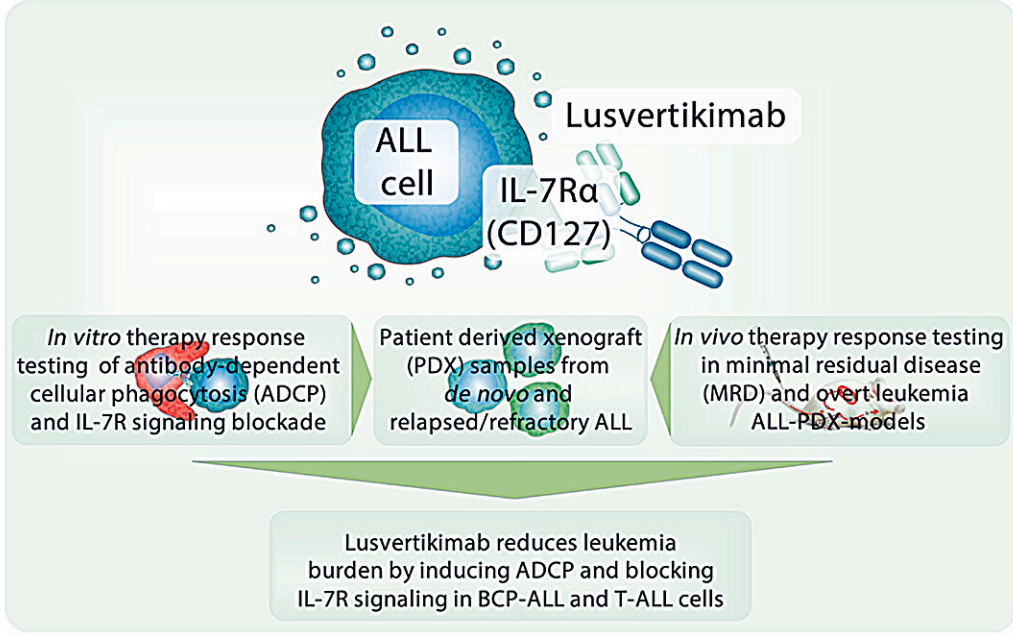


New antibody harbors great potential for fighting blood cancer


July 1 2024

IL-7R α (CD127)-Directed Immunotherapy in B-Cell Precursor (BCP) and T-Cell Acute Lymphoblastic Leukemia (T-ALL)



Conclusion: IL-7R immunotherapy with lusvertikimab shows *in vivo* efficacy in BCP- and T-ALL xenografts in correlation with CD127 surface expression levels, especially when combined with polychemotherapy.

Lenk et al. DOI: [10.1182/blood.2023021088](https://doi.org/10.1182/blood.2023021088)



Credit: *Blood* (2024). DOI: [10.1182/blood.2023021088](https://doi.org/10.1182/blood.2023021088)

Acute lymphoblastic leukemia (ALL) is the most common cancer in children. This form of blood cancer, which also occurs in adults, is caused by malignantly degenerated precursor cells of certain white blood cells (B-cell precursors or T-cells) that divide in an uncontrolled manner. This usually quickly leads to a reduction in bone marrow function and impaired blood formation.

Depending on the cell of origin, this results in B-cell precursor ALL (BCP-ALL) or T-cell ALL (T-ALL). If left untreated, ALL can lead to death within a short period of time.

Despite the severity of the disease, children today often have a good chance of recovery and survival. Various very effective chemotherapies are currently available for treatment.

However, due to their toxicity even for [healthy cells](#), these can cause severe side effects. In addition, about 15%–20% of patients suffer relapses with more limited treatment options.

Scientists from the Faculty of Medicine at Kiel University and the Department of Pediatrics and Adolescent Medicine I at the University Hospital Schleswig-Holstein (UKSH), Kiel Campus, are collaborating with the French company OSE Immunotherapeutics and researchers from other locations in Germany to find new treatment strategies, in particular different variants of immunotherapy for the treatment of ALL.

In a recent [study](#) published in *Blood*, they investigated the antibody Lusvertikimab, which is directed against the interleukin-7 receptor and is already used clinically in the treatment of autoimmune diseases.

They were able to show that the antibody can kill leukemia cells very efficiently: Lusvertikimab showed high preclinical efficacy in almost all samples tested. In some cases, the antibody even caused complete elimination of the leukemia.

Antibody also shows promise for ALL

The Translational ALL Research team at the ALL-BFM Reference and Study Center at UKSH, Kiel Campus, is looking for additional immunotherapeutic treatment options for childhood leukemia. Part of the research deals with the identification of so-called immunotherapy targets, i.e., certain proteins on [cancer cells](#) to which therapeutic antibodies can dock according to the lock-and-key principle in order to either kill them or interrupt pathological signaling pathways.

Researchers are currently discussing such a novel target in ALL: The interleukin-7 receptor, a protein on the [cell surface](#) that is involved in the formation of B and T cells in healthy organisms.

"However, if certain gene mutations or dysregulations are present, the cellular signaling pathways controlled by the IL-7 receptor can also be involved in the development of blood cancer and contribute to the proliferation of cancer cells and suppression of programmed cell death," explains Dr. Lennart Lenk, Co-Head of the Translational ALL Research Group at the Department of Pediatrics and Adolescent Medicine I at the Kiel University and UKSH.

One part of the IL-7 receptor in particular, the so-called α chain or CD127, appears to be a particularly promising target structure in ALL. The researchers found that CD127 is detectable on the cell surface in up to 85% of ALL patients. According to the researchers, it has already been shown in principle that these mechanisms can be interrupted with the help of artificial antibodies.

"However, there is still no clinically available immunotherapy based on IL-7R for the treatment of ALL," says Lenk, who is also active in the CATCH-ALL research group. This requires the successful development and testing of antibodies, which is very complex and takes several years.

The new study, on the other hand, is based on an existing antibody that is at an advanced stage of development and clinical testing, but was originally developed for a different purpose. "The IL-7R antibody Lusvertikimab was developed to suppress pathological activities of B and T cells in autoimmune diseases such as ulcerative colitis and Sjögren's syndrome.

"Despite the completely different disease patterns, the IL-7 receptor is important in autoimmune diseases and ALL, too.

"This coincidence gives us the great advantage of having a ready-made antibody that has previously been tested for its tolerability in humans, which saves us several years of development time," said Professor Denis Schewe, initiator of the study in Kiel and new Head of Pediatric Oncology and Hematology at Dresden University Hospital.

Model trials confirm efficient fight against cancer cells

In order to test the effect of Lusvertikimab in ALL, the researchers tested blood cancer cells from children and adults with leukemia in so-called patient-derived xenograft (PDX) models, which can serve as patient "avatars."

"These experiments showed that if only a few ALL cells are present in the blood, the antibody is able to combat them very effectively and even eradicate the leukemia cells," says Schewe, Co-initiator of the CATCH-

ALL research group. These results are particularly promising for T-ALL, for which there are hardly any immunotherapeutic approaches to date.

In a second step, the research team examined the situation in advanced disease stages in the PDX model. At this stage, it is much more difficult for the antibody to exert its effect. "Even in advanced leukemia, however, we were still able to observe a significant reduction in leukemia cells in 95% of cases," emphasizes Schewe.

The research team was also able to experimentally determine how the antibody works under laboratory conditions.

"We were able to prove that Lusvertikimab can cause the death of cancer cells by blocking the IL7 receptor. We also observed a second mechanism, which consists of attracting 'scavenger cells' such as macrophages to the tumor cells. The more CD127 is present on the cell surface, the more efficiently they destroy the cancer cells," explains Lenk.

Due to the combined effects, the researchers refer to this as a dual mode of action. According to Lenk, it may be possible in future to expect Lusvertikimab to be particularly effective in patients with a high CD127 level, which is easy to measure.

Clinical trials with ALL patients as the next goal

In the near future, the Kiel research team together with partner institutions plans to transfer the newly gained knowledge to clinical trials. In principle, there is always the restriction that the results obtained in the mouse model are not directly transferable to humans. For example, it must first be verified whether the tolerability and non-toxic properties of the antibody can also be confirmed in ALL patients,

according to the researchers.

"Overall, we see the new research results as a promising approach to developing improved treatment options for ALL in the future, which are particularly relevant in cases of relapse.

"With the new immunotherapeutic approach, we hope to be able to offer additions and possibly also alternatives to the current repertoire of chemotherapeutic agents in the future in order to treat particularly vulnerable patients more gently and effectively," says Professor Martin Schrappe, Director of the Department of Pediatrics and Adolescent Medicine I at Kiel University and UKSH and also a CATCH-ALL member.

More information: Lennart Lenk et al, The IL-7R antagonist lusvertikimab reduces leukemic burden in xenograft ALL via antibody-dependent cellular phagocytosis, *Blood* (2024). [DOI: 10.1182/blood.2023021088](https://doi.org/10.1182/blood.2023021088)

Provided by Kiel University

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