



Acute Lymphoblastic Leukaemia (ALL) – Brief Information

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Acute Lymphoblastic Leukaemia (ALL) – Brief Information

1. General disease information

Acute lymphoblastic leukaemia (ALL) is a malignant cancer that arises within the haematopoietic system. ALL usually originates from the *bone marrow*, where the blood cells are produced. It is characterised by an overproduction of impaired white blood cells.

Healthy blood cells reproduce and regenerate at a normal, balanced rate. They undergo a complex maturation process. ALL interferes with this process: The white blood cells (*leukocytes*) are unable to mature into functional cells and instead multiply rapidly and uncontrollably. This disturbs normal blood cell formation, so that healthy white blood cells, red blood cells (*erythrocytes*), and platelets (*thrombocytes*) can no longer be produced to the extent that is necessary.

Lack of red blood cells (*anaemia*), *infections*, and bleeding tendencies can result and may be the first signs of acute leukaemia. Since ALL is not limited to one specific region of the body, but can spread from the bone marrow into the blood and the *lymphatic system*, it can affect all organs and organ systems and is, therefore (like all *leukaemias*), known as a malignant systemic disease.

ALL progresses rapidly. The spread of leukaemia cells and the resulting damage to other body parts can cause serious diseases, which – without the appropriate treatment – are lethal within a few weeks or months.

2. Incidence

Comprising about 80 % of childhood leukaemias, acute lymphoblastic leukaemia (ALL) is the most common form of leukaemia in children and adolescents. It accounts for approximately 22 % (one fifth) of all cancers in this age group. According to the German trial centres, about 550 to 600 children and adolescents aged 0 to 17 years are newly diagnosed with ALL in Germany each year. In general, ALL can occur at any age, including adults. However, the frequency of ALL is highest in children between 1 and 5 years of age, with boys being slightly more affected than girls (gender ratio: 1.4:1).

3. Types of ALL

ALL is mainly characterised by a malignant transformation of immature precursor cells of *lymphocytes*. This transformation can occur during every stage of cell development (differentiation), thereby affecting various subtypes of lymphocytes as well as their precursors. For this reason, there are various forms of ALL. So-called B-ALL subtypes, for example, are based on progenitor cells of *B lymphocytes*, while T-ALL forms from precursors of *T lymphocytes*. A degeneracy in the early development stages is characterised by the prefix "pre" or "pro".



This results in the following ALL-subtypes:

- Pro-B-ALL (also pre-pre-B-ALL)
- Common B-ALL
- Pre-B-ALL
- Mature B-ALL (or B-AL)
- Pro-T-ALL
- Pre-T-ALL
- Cortical (intermediate) T-ALL
- Mature T-ALL

The classification of the ALL subtypes listed above is based on the results of a special *immunological* laboratory test (*immunophenotyping*). An even more precise characterisation can be done based on the *genetic* features of the leukaemia cells. It is important to know that there are multiple forms of ALL, because when it comes to the course and prognosis of this disease, there are differences between each type to some extent. These differences are considered during the selection of a treatment plan.

4. Causes

The causes of acute lymphoblastic leukaemia (ALL) are largely unknown. It is known so far that the disease arises from the malignant transformation of precursor *lymphocytes*, and also, that this transformation can be associated with genetic alterations of these cells. Why these genetic alterations exist and why they cause the disease in some children but not in others, remains to be discovered.

For example, there is a known *gene mutation* in ALL that can be found in some newborns, even if they do not present with the disease until years later. Furthermore, not every child with this kind of genetic mutation will suffer from ALL. This suggests that, in addition to genetic and *immunological* factors, the *immune system* as well as environmental influences can play a role in pathogenesis. It seems that many factors must come together for ALL to occur.

It is also known that children with certain inherited or acquired immunodeficiencies [see *immunodeficiency*] as well as young patients with chromosomal alterations have a higher risk of developing acute leukaemia than their healthy peers. Hereditary concomitant diseases promoting the development of ALL are, for example, *Down syndrome*, *Fanconi anaemia*, *Bloom syndrome*, *Louis-Bar syndrome* (ataxia telangiectasia) and *Li-Fraumeni syndrome*. Since these (very rare) diseases are associated with a predisposition to develop cancer, they are also called *cancer predisposition syndromes*.



Also, exposure to *radioactive radiation* and *X-rays*, certain chemicals and drugs as well as certain viruses have been reported to play a role in the development of leukaemia. However, for most patients no specific cause for the development of ALL can be identified.

5. Symptoms

The health problems (symptoms) caused by ALL usually develop within only a few weeks. They mainly occur due to the increase of malignant cells within the bone marrow as well as their spread into other organs and tissues. The uncontrolled production of leukaemia cells in the *bone marrow* increasingly suppresses the production of normal blood cells.

Children and adolescents suffering from ALL initially experience general symptoms such as fatigue, pain, and pallor. This is due to the lack of red blood cells (*anaemia*), the function of which it is to carry oxygen to cells throughout the body. The lack of functional white blood cells (i.e. *lymphocytes* and *granulocytes*) prevents pathogens from being attacked and eliminated properly, thereby causing *infections* and fever. Another frequent symptom is bleeding, for example, under the skin (bruises, petechiae) or from mucous membranes such as the gums, owing to impaired *blood coagulation* as a result of low platelet counts.

The growth of leukaemia cells in the marrow of the long bones can cause bone and joint pain, especially in the limbs (arms and legs) and back. This pain can be so intense that the affected child may refuse to walk or run. The malignant cells can also spread into the liver, spleen, and *lymph nodes*. Therefore, these organs may enlarge and subsequently cause problems, such as abdominal pain. In general, all organs can be affected by ALL. If ALL spreads to the brain and its *meninges*, patients may suffer from headache, visual disturbances, nausea, vomiting, and other central nervous system impairments

The most important *symptoms* are summarized as follows:

- fatigue, exhaustion, weariness, malaise
- pallor (caused by the lack of red blood cells, *anaemia*)
- increased risk of bleeding, for example, frequent spontaneous nose bleeding, gum bleeding (for example while brushing teeth), excessive bruising, pinpoint, round and red spots on the skin (petechiae); rare: cerebral haemorrhage (due to lack of platelets)
- fever and/or frequent nonspecific infections (due to the lack of white blood cells, neutropenia)
- enlarged *lymph nodes* (for example, in neck, armpits, groin)
- abdominal pain and loss of appetite (due to the enlargement of spleen and/or liver)
- bone and joint pain (mostly limbs and back)
- headache, visual disturbances, vomiting, cranial nerve palsies (if the central nervous system is involved)



- shortness of breath (due to the enlargement of the *thymus gland* or of lymph nodes in the chest area)
- enlargement of testicle(s)

Good to know: The type and degree of symptoms of ALL vary individually. It is also important to know that the occurrence of one or more of these symptoms does not necessarily mean that they are caused by leukaemia. Many of these symptoms also occur in benign diseases that have nothing to do with leukaemia. However, if these symptoms occur or recur frequently or persist, a doctor should be consulted as soon as possible. If acute leukaemia is diagnosed, treatment must be started promptly.

6. Diagnosis

If the doctor, based on the young patient's history (*anamnesis*) and *physical examination*, suspects acute leukaemia, he or she will first initiate a blood test. If the results promote the diagnosis of an acute leukaemia, a sample of the bone marrow (*bone marrow puncture*) is required for confirmation. For bone marrow tests and other diagnostic procedures, the doctor will refer the patient to a children's hospital with a paediatric oncology program (paediatric oncology unit).

6.1. Blood and bone marrow tests

Blood and bone marrow tests are needed to confirm the diagnosis of leukaemia as well as to determine the type. The tests include microscopic (*cytomorphological*), *immunological*, *cytogenetical* and *molecular genetical* laboratory analysis of blood and bone marrow samples that distinguish ALL from other kinds of leukaemia (such as AML) and, furthermore, allow to define the specific subtype of ALL. The immunological and genetic characteristics of the cells are playing an increasingly important role in this context.

Knowing the exact subtype of ALL is necessary for appropriate therapy planning, because different forms of ALL have different cellular and *molecular* characteristics and they also vary regarding their response to treatment and, thus, *prognosis*.

6.2. Tests to assess spread of the disease (staging)

Following the diagnosis of ALL and its subtype, it is important to know whether the leukaemia cells have spread to additional body compartments (other than the bone marrow), including the brain, liver, spleen, *lymph nodes*, testicles, or bones. Therefore, various imaging techniques, such as *ultrasound*, *X-ray examination* and possibly also *magnetic resonance imaging (MRI)* and *computed tomography (CT)*, may be used to evaluate spread of the disease. To find out whether the central nervous system (brain and spinal cord) is affected, a sample of cerebrospinal fluid is taken and analysed for leukaemia cells (*lumbar puncture*).



6.3. Additional diagnostics before treatment begins

For treatment preparation, tests on the patient's cardiac function (*electrocardiography* [ECG] and *echocardiography*) and brain function (*electroencephalography*, EEG) are performed. Furthermore, additional bloodwork is needed to assess the patient's general health condition and to determine the patient's *blood group* (essential in case a *blood transfusion* may be necessary during the course of treatment). Also, the functions of certain organs (such as kidneys and liver) need to be evaluated by blood tests in order to rule out potential metabolic disorders that can have negative impact on the treatment. Having collected all this information prior to treatment helps the doctors later to detect and thus treat treatment-induced changes earlier.

Good to know: Not all the tests listed above need to be done for every patient. Contrariwise, the patient's individual situation may require additional diagnostic procedures that have not been mentioned in this chapter. Therefore, you should always ask your doctor, based on the information above, which test your child needs and why.

Psychosocial Care

A child's cancer is a stressful situation for the whole family. The psychosocial team of the clinic or later the aftercare facility provides advice and support to patients and their relatives from diagnosis to completion of treatment as well as during aftercare. Don't hesitate to take advantage of this offer. It is an integral part of the treatment concept of all paediatric oncology centres in many countries. Here you will find comprehensive information on this.

7. Treatment planning

After the diagnosis has been confirmed, therapy is planned. In order to design an individual, risk-adapted treatment regimen for the patient, certain factors influencing the patient's chance of recovery (prognosis) – called risk factors or prognostic factors – are being considered during treatment planning (risk-adapted treatment strategy).

Important *prognostic factors* are the subtype of ALL (see chapter „Types of ALL“), *genetic* changes in ALL cells, the number of leukaemia cells in the blood, the response of the disease to treatment, and the patient's age.

The exact knowledge of the ALL type helps the caregiver team to assess how sensitive the leukaemia cells might be to the *chemotherapy* and thus, how intensely patients need to be treated in order to keep the risk of relapse as low as possible. Extent of the disease and response to treatment impact the decision whether, aside from chemotherapy, additional treatment methods (for example cranial *radiation* or *high-dose chemotherapy* followed by *stem cell transplantation*) are necessary to increase the probability of cure.

All these factors are included in treatment planning in order to achieve the best outcome possible for each patient. Hence, each individual clinical situation is crucial for assigning a patient to a treatment group (standard risk, medium risk, high risk group) and for choosing the optimal treatment protocol.

8. Treatment

Treatment of children and adolescents with acute lymphoblastic leukaemia (ALL) should take place in a children's hospital with a paediatric oncology program. Only in such a treatment centre, highly experienced and qualified staff (doctors, nurses and many more) is guaranteed, since they are specialised and focus on the diagnostics and treatment of children and teenagers with cancer according to the most advanced treatment concepts. The doctors (such as oncologists, radiologists, surgeons) in these centres collaborate closely with each other. Together, they treat their patients according to treatment plans (protocols) that are continuously optimised. The goal of the treatment is to achieve high cure and low rates of side effects.

8.1. Treatment methods

- **Chemotherapy** is the major backbone of ALL treatment. It uses drugs (so-called cytostatic agents) that can kill fast-dividing cells, such as cancer cells, or inhibit their growth, respectively. Since one cytostatic agent alone may not be capable of destroying all the leukaemia cells, a combination of *cytostatics* that function in different ways are usually given (polychemotherapy).
- **Targeted therapy:** For patients with certain *chromosomal* aberrations in their leukaemia cells (*Philadelphia chromosome*-positive ALL and *ABL*-class fusion positive B-ALL) continuous treatment with a so-called *tyrosine kinase* inhibitor (such as imatinib) is recommended in addition to chemotherapy. It blocks (inhibits) the protein altered by the chromosomal aberration, which is responsible for the uncontrolled growth of the leukaemia cells. Cell division is being inhibited and the malignant cells die (*apoptosis*). For certain groups of patients, an *antibody*-based therapy may be considered in addition to chemotherapy, for example with blinatumomab, a synthetic bispecific antibody (bispecific T-cell engager, BiTE). It binds to a *receptor* protein (CD19) on B cells – and hence also on B-cell leukaemia cells – as well as to a receptor (CD3) on *T lymphocytes* (the body's own immune cells), which results in an elimination of the leukaemia cells.
- **Radiation therapy** of the brain (cranial irradiation) is used in very rare cases in addition to *chemotherapy*. However, *radiotherapy* is increasingly reduced and hence its indication currently subject to change.
- **Stem cell transplantation:** For some patients, *high-dose chemotherapy* (and, partly, total body irradiation) followed by *allogeneic stem cell transplantation* may be an option. In the case of a first-time diagnosis, this may be the case, for example, if there is a clearly increased risk of the disease to relapse and a suitable donor is available. The goal of treatment is to eliminate the leukaemia cells in the body as extensively as possible, so that the *bone marrow* can resume its function as a blood cell-producing organ.

The intensity and duration of chemotherapy (as well as, where appropriate, the option of a targeted therapy), the need for radiotherapy and/or stem cell transplantation, as well as the *prognosis* of the disease, depend on the subtype of ALL, on how extensively the leukaemia cells have spread throughout the body, whether the patient tolerates the treatment, and whether the leukaemia responds to it (see *chapter "treatment planning"*). In order to prevent or adequately manage the



side effects of the intensive therapy, specific supportive care regimens have been established and now represent an important and efficient component of ALL treatment.

Note for patients with mature B-ALL (B-AL): This ALL subtype is not treated like the other forms of ALL. Patients with mature B-ALL will receive a treatment similar to that of mature B-cell *Non-Hodgkin lymphoma* and are therefore not included in the following chapters. Information on Non-Hodgkin lymphoma can be found [here](#).

8.2. Course of treatment (chemotherapy)

Treatment of children and teenagers with ALL consists of different steps. These steps (or phases) have different purposes. Therefore, they vary regarding their duration, treatment intensity, and drug combinations. Each treatment period follows a different treatment plan (protocol), and each treatment plan is adapted to the patient's individual situation. The protocol the doctors decide to use for a patient depends, for example, on the subtype of ALL, the results of the staging, and other individual factors that are important for the patient's risk of recurrent disease. As a rule of thumb, the doctors will recommend more intense treatment if your child has a relatively high risk of relapse.

Usually, treatment will take about a total of two years, in particular if the disease responds sufficiently to therapy and no relapse occurs. There will be both times spent as inpatient (about six months total with discharges in between) and outpatient (about one and a half years).

The major elements of ALL treatment are:

- **Pretreatment (preliminary phase):** In many treatment protocols for ALL, induction therapy begins with the so-called *cytoreductive* pre-phase. It serves to initiate therapy and aims at reducing the often initially heavy burden of leukaemia cells gradually. This relatively gentle start helps the doctors to keep the metabolic products released by the dying leukaemia cells under control, which is important, because such metabolites can seriously harm the patient's organs, especially the kidneys (so-called *tumour lysis syndrome*).
- **Induction therapy:** The first therapy phase, induction therapy, consists of an intense phase of chemotherapy using a combination of different agents. It aims at eliminating most of the leukaemia cells, thereby inducing *remission* in a short period of time. Induction therapy usually takes about five to eight weeks.
- **Consolidation / intensification therapy:** The consolidation or intensification therapy is also an intensive chemotherapy, partially using different combinations of agents and higher dosages. The goal is to consolidate the remission achieved by induction therapy by further eliminating leukaemia cells in order to reduce the risk of recurrent disease. The intensity of treatment is based on the patient's individual risk of relapse; accordingly, this treatment phase may take between weeks and months. It is also designed to reach the *central nervous system* (CNS) and the testes (so-called extracompartment therapy; *see below*).
- **CNS therapy (extracompartment therapy):** Major part of all the intensive treatment phase, in particular of the consolidation/intensification phase, is the treatment of the central nervous

system (CNS). The CNS therapy is extremely important, since ALL affects the CNS in most patients, even if no leukaemia cells are detectable in the cerebrospinal fluid. Most chemotherapeutic agents cannot pass the blood-brain barrier. Therefore, treatment is performed using high doses of certain agents that can pass this barrier due to their specific characteristics. Also, chemotherapy is given directly into the spinal canal via *lumbar puncture (intrathecal chemotherapy)*. For some (few) patients, cranial *radiotherapy* may become an option, for example, if central nervous system involvement has been proven.

- **Reinduction therapy:** Aside from the treatment phases described above, another intensification strategy, the reinduction therapy, has proven to be an effective approach in ALL patients. Reinduction aims at completely destroying leukaemia cells, thereby reducing the risk of recurrent disease as much as possible. The reinduction phase can last between weeks and months depending on the risk group the patient has been assigned to. In case of longer treatment times, for example for high-risk patients, short intensive phases of therapy alternate with more moderate ones in order to ensure the patient's recovery between courses.
- **Maintenance therapy:** This last phase of treatment is designed to eliminate all the leukaemia cells that may not be detectable but still have survived despite intensive treatment. The intensity of chemotherapy is much less than in the other phases. Also, the patient is mainly *outpatient* and may even continue with kindergarten or school. This phase of treatment is usually continued until a total treatment time of two years has been achieved.

Typical *cytostatics* in ALL treatment are, for example, prednisone (PRED) or dexamethasone (DEXA), vincristine (VCR), daunorubicin (DNR), asparaginase (ASP), methotrexate (MTX), cyclophosphamide (CPM), cytarabine (ARA-C), 6-mercaptopurine (6-MP), etoposide (VP-16), and thioguanine (TG).

Note: Depending on the trial, the terminology of the different treatment phases as well as their duration and design may vary. Also, new targeted treatment approaches (such as immunotherapy with antibodies) may be examined in the context of clinical studies.

8.3. Therapy in case of recurrent disease (relapse)

In case of recurrent disease (relapse), which occurs in about 15 % of ALL patients, treatment options consist of *chemotherapy*, *radiation therapy*, and *stem cell transplantation*. The majority of patients receive an intensified chemotherapy regimen aiming at *remission*, followed by an *allogeneic stem cell transplantation*. In some patients, remission may be achieved by chemotherapy only. Radiotherapy is given in case of *central nervous system* and/or testicular involvement. Patients whose disease does not respond to conventional treatment approaches (refractory or secondary ALL relapse), may benefit from new substances with different mechanisms of action, which are currently being investigated in various clinical trials.

In certain scenarios, *immunotherapy* using antibodies or *CAR T cells* can be considered. For example, the bispecific *antibody* blinatumomab (see the chapter "Treatment methods") is given to patients with a bone marrow relapse of B-precursor ALL during consolidation therapy (in particular

prior to a stem cell transplant). Under certain conditions, patients with multiple relapses of B-ALL or with B-ALL that does not respond to standard therapy (refractory B-ALL), respectively, may receive *CAR T-cell therapy* ([for more information on CAR T cell therapy see here](#)).

In clinical trials, the monoclonal antibody inotuzumab coupled with a toxic compound (antibody-drug conjugate) is currently being tested in certain patients with (CD22-positive) precursor B-ALL [see *monoclonal antibodies*]. While the antibody binds to the CD22 receptor protein on the leukaemia cells, the drug is released, thereby killing the malignant cells. Other patients, too, whose disease does not respond to conventional treatment approaches (refractory or secondary ALL relapse) may benefit from new substances with different mechanisms of action, which are currently being investigated in various clinical trials.

9. Therapy optimising trials and registries

In Germany, diagnosis and treatment of almost all children and adolescents with acute lymphoblastic leukaemia (ALL) are performed according to the treatment plans (protocols) of "*therapy optimising trials*", so named because the treatment concepts of such trials are continuously being optimised based on the latest medical knowledge and the experience with former protocols. Therapy optimising trials are standardised and controlled studies that aim at steadily developing and improving treatment possibilities for cancer patients. They are usually applied in numerous treatment centres, not only in Germany but also abroad (multicentric and international studies).

Patients who are not included in any trial, either because they suffer disease while there is no trial available or because they do not, for some reason, fit into one of the existing trials, are often included in so-called **registries**. The patients are generally treated according to the recommendations of the trial centre, thus receiving the current best therapy available.

Currently, the following therapy optimising trials are open for children and adolescents with ALL in Germany:

- **Trial ALLTogether1:** international therapy optimising study of the newly founded European consortium ALLTogether for children, adolescents and adults (between 0 and 45 years of age) with newly diagnosed ALL. The worldwide largest study group, which also includes the CoALL study centre located in Hamburg, is examining new treatment concepts considering therapy intensification as well as therapy reduction based on the patient's individual risk of relapse and by using multiple randomization arms. In Germany, the ALLTogether1 trial has been open since April 1, 2022 (principal investigator: Mats Marshall Heyman, MD, PhD, Karolinska University Hospital, Stockholm). The German chair is Prof. Dr. med. Gabriele Escherich (CoALL study centre) at the University Hospital (Universitätsklinikum) Hamburg-Eppendorf.
- **Registry ALL-BFM:** Since 1 May 2024, children and adolescents with a first diagnosis of ALL (and under the age of 18) have been eligible for inclusion in the ALL-BFM registry (after the AIEOP-BFM ALL 2017 study was closed for patient enrolment, *see below*). The main purpose of the registry is to record and analyse medical data, regardless of whether the patient is participating in a clinical trial or not. Treatment centres throughout Germany are involved in the



study. The registry centre is located at the University Hospital Schleswig-Holstein (Campus Kiel) under the direction of Prof. Dr. med. Gunnar Cario.

- **Registry CoALL 2020** (CoALL stands for Cooperative ALL Trial): children and adolescents under the age of 18 who are not treated within the ALLtogether1 trial can be registered with the CoALL 2020 Registry. The registry accepts children and adolescents with any type of ALL since May 2020 (as a transitory solution after study COALL-08-09 was closed for patient recruitment). It also includes patients with ALL as a secondary malignancy as well as with non-Hodgkin lymphoma. Therapy recommendations within the registry correspond to the standard therapy of the ALLtogether trial. Chair of registry and study centre is Prof. Dr. med. Gabriele Escherich (MD, PhD), University Hospital Hamburg-Eppendorf.
- **Trial Interfant 21**: international trial for infants in the first year of age with newly diagnosed acute lymphoblastic leukaemia (B-precursor ALL or B-cell ALL with mixed phenotype and *KMT2A* rearrangement); The aim of the trial opened in Germany in 2024 is to improve treatment outcomes in terms of event-free survival compared to the results achieved in the INTERFANT-06 trial. The German study centre is located at the University Hospital Hamburg-Eppendorf (principal investigator: Prof. Dr. med. Gabriele Escherich).
- **Registry ALL SCT FORUM 2022** : national registry for patients (under 21 years of age) with a high or very high risk of relapse, for whom *allogeneic stem cell transplantation* is an option. The interim registry has been open since 13/09/2022, being sequel to the trial ALL SCTped 2012 FORUM (which was closed in 2022). Transplant centres throughout Germany are participating. The study director in charge is Prof. Dr. med. Peter Bader at the Johann-Wolfgang-Goethe University Hospital, Frankfurt.
- **Trial IntReALL HR 2010**: international, multicentric therapy optimising trial for children and adolescents (under 18 years of age) with a first high-risk relapse of ALL (B-precursor- or T-cell-ALL, high-risk patients). Numerous paediatric oncology centres throughout Germany as well as in other European and non-European countries participate in this trial. The study centre is located at the Department of Paediatric Oncology and Haematology of the Charité Berlin (Study Director: Prof. Dr. Arend von Stackelberg).
- **Observation Trial ALL-REZ**: this trial collects data of recurrent disease patients (under 18 years of age) that are not included in above-mentioned study, such as children and adolescents with a second relapse or a first but high-risk relapse of ALL (principal investigator: Prof. Dr. Arend von Stackelberg, Department of Paediatric Oncology and Haematology of the Charité Berlin).

The following therapy optimisation studies have been closed to new patients for some time and are currently in the follow-up or evaluation phase:

- **Trial AIEOP-BFM ALL 2017**: From mid-2018 to the end of March 2024, the international therapy optimising trial AIEOP-BFM ALL 2017 was available for the treatment of children and adolescents (aged 0 to 17 years) with first diagnosis of ALL (patient recruitment for children with B-precursor ALL already closed on 31/08/2023). In contrast to the preceding trial (AIEOP-BFM ALL 2009), this trial also considers children in their first year of life. Multiple paediatric oncology

centres in Germany, other European countries, Israel and Australia have been participating in this trial. German study centre: University Hospital Schleswig-Holstein, Campus Kiel; principal investigator: Prof. Dr. med. Martin Schrappe. **Note:** *The study is currently in the follow-up phase and will be analysed once this phase is completed.*

- **Trial EsPhALL2017/COGAALL1631:** From 15/11/2019 until 30/09/2024, this international, multicentric therapy optimising trial was open for the treatment of children and adolescents between 1 and 21 years of age with Philadelphia chromosome-positive ALL (patient admission in Germany). Numerous paediatric oncology centres in Germany and other countries have been participating in this trial. The German study centre is located at the University Hospital (Universitätsklinikum) Schleswig-Holstein (Campus Kiel); the principal investigator is Prof. Dr. med. G. Cario. **Note:** *Since the end of patient uptake in September 2024, newly diagnosed patients have been registered in the ALL-BFM registry. The study is currently in the follow-up phase and will be analysed once this phase is completed.*

Please note: The treatment protocols developed by the AIEOP-BFM study group and the CoALL and ALLTogether study groups are designed for the same group of patients (patients with newly diagnosed ALL, aged 0 to 17 or 1 to 17, respectively) and only differ but slightly. The choice between the two trial protocols or resulting recommendations, respectively, is made by the local treatment team, depending on which of the two protocols the respective treatment centre is specialised in. Since April 2022, the CoALL study group – as one of nine study groups in total – has been participating in the new phase III study of the international ALLTogether consortium.

Please note that patients with mature B-ALL (B-AL) are not considered here, since they receive a treatment for mature B-cell *Non-Hodgkin lymphoma*.

The major goal of therapy optimising trials is to continuously improve the treatment and, thus, the outcome of all ALL patients and to minimise treatment-related side effects. The experience with a previous trial will be incorporated into the subsequent protocol, thereby providing continuous optimisation and knowledge gain.

10. Prognosis

The chances of cure (prognosis) for children and adolescents with acute lymphoblastic leukaemia (ALL) have significantly improved due to the immense progress in diagnostics and treatment over the last four decades. Today's modern diagnostic procedures and the use of intensive, standardised polychemotherapy protocols combined with optimised supportive care regimens currently result in 10-year survival rates of about 90 %. Hence, ALL is among the best treatable malignancies.

However, for children with unfavourable *prognostic factors*, such as nonresponse to therapy and/or certain hard-to-treat ALL subtypes, survival rates are considerably lower than 90 %. That also applies to patients who are either under one year of age or over ten years old.

About 90 of the 550 to 600 children and adolescents (approximately one in seven patients) newly diagnosed with ALL in Germany per year develop recurrent disease (relapse). Recurrent disease most frequently appears during the first two to three years after the initial diagnosis, while it is rather



rare after five years following first diagnosis of ALL. The prognosis is generally worse than during the initial treatment, although in a subset of patients treatment success can still be achieved. The 5-year survival rates in children and adolescents with ALL relapse are currently at about 50 to 60 %. Under the current *therapy optimising trials* and future studies, the chances of cure are continually improved for these patients.

Note: The survival rates mentioned in the text above are statistical values. Therefore, they only provide information on the total cohort of patients with childhood ALL. They do not predict individual outcomes. Acute leukaemias can show unpredictable courses, in both patients with favourable and patients with unfavourable preconditions.

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Glossary

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| allogeneic stem cell transplantation | transfer of stem cells from a donor to a recipient. The prerequisite for an allogeneic transplant is that the tissue characteristics of the donor and recipient are largely identical. The stem cells are obtained from the blood or bone marrow. |
| anaemia | „lack of blood“; reduction of the red blood pigment (haemoglobin) and/or the proportion of red blood cells (haematocrit) in the blood below the normal value typical for a given age. Signs of anaemia include palor, headache, dizziness, and fatigue. |
| anamnesis | medical interview, a patient’s history, development of signs of illness; the type, onset and course of the (current) symptoms as well as any risk factors (e.g. hereditary diseases) are evaluated during a medical interview. |
| antibody | Antibodies are proteins from the group of globulins, which the bodys immune system forms as a defensive reaction to invading foreign substances or foreign structures (antigens). The antibodies bind specifically to these antigens and lead (in various ways) to the elimination of the pathogen. Antibodies are produced by a group of white blood cells, so-called B lymphocytes, which are known as "plasma cells" at the stage of antibody production. |
| apoptosis | programmed cell death; form of cell death, which is triggered by various mechanisms in the cell itself; this can happen naturally in the context of cellular aging, but also, for example, in response to cell damage (e.g. caused by cytostatics, radiotherapy). |
| B lymphocytes | subtype of lymphocytes; they develop in the bone marrow and are responsible for the recognition of pathogens and the formation of antibodies. |
| blood coagulation | phased solidification of the liquid blood; intact blood clotting is important, for example, in haemostasis and wound healing during or after surgery. Impaired blood clotting leads to an increased tendency to bleed and/or prolonged bleeding time (e.g. after an injury). Increased blood clotting can cause thrombosis, for example. |
| blood group | hereditary, usually stable, structural characteristics (blood group antigens) of blood components (e.g. AB0 blood groups) located on the cell walls of blood and other tissue cells; |



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| blood transfusion | transfer of blood (whole blood) or blood components (e.g. red blood cells or platelets) from a donor to a recipient |
| Bloom syndrome | rare hereditary disorder characterized by growth disorders, pigmentation defects, photosensitivity, fertility disorders, increased susceptibility to infections and increased risk of cancer (leukaemias and solid tumors); the affected patients develop several tumours in the first two years of life, which are rare in the rest of the population. Bloom syndrome is therefore one of the cancer predisposition syndromes. |
| bone marrow | site of blood formation; spongy tissue with a strong blood supply that fills the cavities inside many bones (e.g., vertebrae, pelvic and thigh bones, ribs, sternum, shoulder blade, and collarbone); in the bone marrow, all forms of blood cells develop from blood progenitor cells (blood stem cells). |
| bone marrow puncture | removal of bone marrow tissue to examine the cells; during the puncture, a few milliliters of liquid bone marrow are drawn from the pelvic bone or sternum into a syringe with the help of a thin hollow needle. The puncture is performed under local anaesthesia in older children; a sedative may also be administered (sedation). For smaller children, a short period of anesthesia may be appropriate. |
| cancer predisposition syndrome | genetic disorders that can include malformations and intellectual disability in addition to an increased risk of tumors; according to current knowledge, about 10% of childhood and adolescent cancers develop due to a known hereditary change or cancer predisposition syndrome. Cancer predisposition syndromes include Louis Bar syndrome (= ataxia telangiectatica), Beckwith-Wiedemann syndrome, Down syndrome, Hoppel-Lindau syndrome, Li-Fraumeni syndrome, MEN syndrome, neurofibromatosis and WAGR syndrome. The familial form of retinoblastoma is also part of it. |
| CAR T cells | the body's own immune cells (T cells, T lymphocytes) that have been genetically modified in the laboratory and are used in immunotherapy (CAR T-cell therapy) to recognise and destroy cancer cells. |
| CAR T-cell therapy | immunotherapy for the treatment of cancer patients, based on the genetic modification of specific immune cells (T lymphocytes) from the patient; these cells are extracted from the patient, treated in the laboratory and then returned in a modified form as CAR T cells. |



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| central nervous system | comprises the brain and spinal cord and is separated from the so-called peripheral nervous system; as a central organ of integration, coordination and regulation, it serves to process external sensory impressions as well as stimuli produced by the organism itself. |
| chemotherapy | here: use of drugs (chemotherapeutic agents, cytostatics) for the specific inhibition of tumor cells in the organism |
| chromosomal | referring to the chromosomes, carriers of the genetic material (see chromosomes) |
| computed tomography | imaging, X-ray diagnostic procedure; it produces an image by computer-controlled evaluation of a large number of X-rays from different directions. This makes it possible to produce sliced images of body parts (tomograms, transverse or longitudinal sections of the human body) |
| cytomorphological | referring to the shape and structure of the cells (under the microscope); the cytomorphological assessment of bone marrow and blood smears is part of the basic diagnosis if a blood disease, such as leukemia, is suspected. |
| cytoreductive | cyt-: part of the word meaning „cell“; reductive means „reducing“; decreasing the number of cells |
| cytostatics | drugs that inhibit cell growth; cytostatics can affect the metabolism of different types of cells, thereby destroying them and/or preventing them from multiplying. Cells that divide frequently are particularly affected. |
| Down syndrome | congenital disorder associated with maldevelopment of tissues and organs, mental retardation that varies from person to person, short stature and malformations in the facial area; patients with Down syndrome also have an increased risk of developing cancer, especially leukaemia. Down syndrome is caused by a chromosomal alteration: chromosome 21 is present in every cell of the body in three copies instead of two (Trisomy 21). As a result, tissues and organs grow more slowly, remain immature, age faster and have malformations. |
| echocardiography | ultrasound examination of the heart to check its performance (cardiac function); the position or structure of the heart valves and walls, the wall thickness of the heart muscle, the size of the heart and the ejected blood volume (pumping function of the heart) are examined and assessed, among other things. |



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| electrocardiography | method of measuring the electrical activity of the heart |
| electroencephalography | method of recording the electrical activity of the brain; the electroencephalogram (also abbreviated EEG) is the graphical representation of this electrical brain activity. Its evaluation can provide evidence of brain dysfunctions. |
| erythrocytes | red blood cells, the most abundant cells in the blood, they are mainly used to transport oxygen in the body; erythrocytes are formed in the bone marrow (erythropoiesis). The red blood pigment (haemoglobin) inside the erythrocytes is responsible for binding and transporting the oxygen absorbed in the lungs. If red blood cells are not present in sufficient quantities or, due to a lack of haemoglobin, are not functional, it is referred to as anaemia. |
| Fanconi anaemia | hereditary haematopoietic disorder; it is mainly characterized by a progressive dysfunction of the bone marrow, which leads to a reduced formation of blood cells (bone marrow insufficiency), as well as by chronic anaemia and a high risk of cancer (especially for acute myeloid leukaemia). Other concomitant symptoms include skeletal malformations (e.g. short stature, malformations of the thumbs and arms). Fanconi anemia is one of the cancer predisposition syndromes. At the cellular level, there is an increased chromosomal fragility; this leads to chromosomal changes and, as a result, to disorders of cell cycle control. |
| gene | unit of genetic information in the genome of living organisms; a gene contains the genetic information – the blueprint – for a specific gene product (protein or RNA). In most organisms, the entirety of all genes, the genome, is present as a deoxyribonucleic acid chain (DNA), which forms the chromosomes in the cell nucleus. The information of a gene is mediated by a certain sequence of the nucleic acid building blocks adenine, guanine, cytosine and thymine. |
| genetic | concerning the (level of) inheritance or genes; inherited |
| granulocytes | subgroup of white blood cells (leukocytes); they are mainly responsible for defending against bacteria and other pathogens (such as viruses, parasites and fungi); granulocytes are also involved in allergic and inflammatory reactions, as well as pus formation. Granulocytes make up about 60 – 70% of the leukocytes in the blood. Due to their differently colourable granules and their different tasks, they are divided into three subtypes: neutrophils (90 %), eosinophils (2 – 4 %) and basophilic |



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| | <p>granulocytes (up to 1 %). The neutrophils (neutrophils for short) play the most important role in the defense against infections.</p> |
| high-dose chemotherapy | <p>the use of a particularly high dose of cell growth-inhibiting drugs (cytostatics); in the case of cancer, it aims to destroy all malignant cells. Since the haematopoietic system in the bone marrow is also destroyed, the patients own or foreign blood stem cells must then be transferred (autologous or allogeneic stem cell transplantation).</p> |
| immune system | <p>the bodys own system for maintaining a healthy organism by defending against foreign substances and destroying abnormal body cells (e.g. cancer cells); the immune system has the ability to distinguish between self and foreign or dangerous and harmless; mainly the organs of the lymphatic system as well as cells distributed throughout the body (e.g. leukocytes) and molecules (e.g. immunoglobulins) are involved.</p> |
| immunodeficiency | <p>congenital or acquired disorder of the immune system that results in a weakening of the bodys immune response; this leads to the fact that pathogens and consequently infections cannot be sufficiently or adequately fended off.</p> |
| immunological | <p>associated with the structure and function of the bodys own defense system (immune system); includes the recognition and defense mechanisms of an organism for foreign and endogenous substances and tissues.</p> |
| immunophenotyping | <p>a diagnostic method in which certain proteins (antigens) are searched for on the surface of cells using various special methods and monoclonal antibodies; the most commonly used method for detecting individual antigens is flow cytometry.</p> |
| immunotherapy | <p>a form of treatment that affects the immune system with the aim of fighting off or fighting tumours or other diseases</p> |
| infection | <p>penetration of the smallest organisms (e.g. bacteria, viruses, fungi) into the body and subsequent multiplication within it. Depending on the characteristics of the microorganisms and the immune system of the infected person, various infectious diseases can occur after infections.</p> |
| intrathecal chemotherapy | <p>administration of cell growth-inhibiting drugs (cytostatics) into the cerebrospinal fluid (CSF) canal, which contains the CSF</p> |
| leukaemia | <p>malignant disease of the blood forming (haematopoietic) system and the most common cancer in children and adolescents (about 33%); depending on the origin of the malignant cells,</p> |



a distinction is made between lymphoblastic and myeloid leukaemias. Depending on the course of the disease (fast or slow), a distinction is made between acute and chronic leukaemias.

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| leukocytes | white blood cells; they serve as cells of the immune system, defending against pathogens and fighting infections. In addition, they remove the cell debris produced by the decay of body cells. Leukocytes include granulocytes (with 60 – 70 %), lymphocytes (20 – 30 %) and monocytes (2 – 6 %). Leukocytes are mainly produced in the bone marrow. This process is called leucopoiesis. |
| Li-Fraumeni syndrome | cancer predisposition syndrome characterized by the increased occurrence of various solid tumours within a family; in childhood and adolescence, tumours of the adrenal glands, as well as soft tissue sarcomas, leukaemias and CNS tumours are most commonly observed, in adulthood mainly bone tumours (osteosarcomas), breast cancer and lung tumours. In most cases, there is a change (mutation) of the so-called tumour suppressor gene TP-53 (protein p53). |
| Louis-Bar syndrome | hereditary disease; it is mainly characterized by degeneration of the central nervous system (CNS), an impairment of the immune system (immunodeficiency), dilated blood vessels of the eyes and skin (so-called telangiectasias) and an increased risk of cancer (so-called cancer predisposition syndrome). Degeneration of the CNS is associated with various neurological disorders, such as movement disorders (ataxia) and abnormal eye movements. The immunodeficiency often causes recurrent infections. |
| lumbar puncture | puncture of the spinal canal in the lumbar spine, e.g. to remove cerebrospinal fluid (CSF) or for the purpose of administering medication (so-called intrathecal treatment); in the case of cancer, a sample and examination of cerebrospinal fluid can be used to detect malignant cells; in the case of increased intracranial pressure due to a CNS tumour, cerebrospinal fluid removal (CSF) is also used to relieve pressure. |
| lymph nodes | small lenticular to bean-shaped organs that are part of the body's immune system and are located in many parts of the body; they serve as filter stations for the tissue water (lymph) of a region of the body and contain cells of the immune system. |
| lymphatic system | collective term for lymphatic vessels, lymphatic vessel trunks, lymph nodes, lymphatic tissues (lymphocytes in connective |



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| | tissue, mucous membranes, glands) and lymphatic organs (spleen, pharyngeal tonsils, bone marrow, thymus gland). |
| lymphocytes | subgroup of white blood cells that are responsible for the body's own defenses, especially the defense against viruses; there are B and T lymphocytes. They are formed in the bone marrow, but partly only mature to full functionality in the lymphatic tissue (e.g. lymph nodes, spleen, thymus gland). They eventually enter the blood via the lymphatic vessels, where they take over their respective tasks. |
| magnetic resonance imaging | diagnostic imaging method; very precise, radiation-free examination method for the visualization of structures inside the body; with the help of magnetic fields, cross-sectional images of the body are generated, which usually allow a very good assessment of the organs and many organ changes. |
| meninges | layers of connective tissue that protectively envelop the brain; the three meninges are joined to the outside by the skull bones. In the area of the spinal cord, the meninges merge into the three-layered spinal cord membrane, which surrounds the rest of the central nervous system. |
| molecular | at the level of molecules |
| monoclonal antibodies | antibodies produced by the derivatives of a single B lymphocyte (cell clone) that are completely identical; they can be genetically engineered for diagnostic and therapeutic purposes and target a small molecular segment (epitope) of a specific antigen. |
| mutation | alteration of genetic material; it can arise without any identifiable external cause (so-called spontaneous mutation) or be caused by external influences (induced mutation). External influences include, for example, ionizing radiation or certain chemical substances (mutagens). If somatic cells are affected, it is referred to as a somatic mutation, and if germ cells are affected, it is referred to as a generative mutation. Somatic mutations are not heritable, while germ cell mutations can lead to hereditary damage. Depending on the extent of the change (single or multiple genes, larger chromosome segments or complete chromosomes), a distinction is made between point and block mutations as well as numerical and structural chromosomal aberrations. |
| Non-Hodgkin lymphoma | a large group of malignant diseases of the lymphatic system, which can provoke lymph node swelling as a main feature; like |



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| | <p>Hodgkin lymphoma, NHL is a malignant lymphoma. It accounts for about 7 % of malignant diseases in childhood and adolescence.</p> |
| outpatient | <p>non-inpatient medical care: the patient does not stay overnight in the medical facility for diagnostic and/or treatment center, but can go home the same day.</p> |
| Philadelphia chromosome | <p>A genetically altered, shortened chromosome 22 that promotes the development of cancer; it arises through the exchange of gene segments between chromosomes 9 and 22 [translocation t(9;22)]. In this process, the BCR gene on chromosome 22 combines with the ABL gene (a tyrosine kinase gene) on chromosome 9 to form the BCR-ABL fusion gene. The altered gene causes the formation of an equally altered protein (an altered tyrosine kinase), which triggers uncontrolled proliferation of the affected cell. The Philadelphia chromosome is named after the place where it was discovered.</p> |
| physical examination | <p>an important part of diagnostic examinations; includes palpation and listening to certain body organs as well as testing reflexes to obtain indications of the nature or course of a disease.</p> |
| prognosis | <p>prediction of the course and outcome of a disease / prospect of recovery</p> |
| prognostic factors | <p>factors that allow an approximate assessment of the further course of the disease (i.e. the prognosis);</p> |
| radiation | <p>controlled use of ionizing (high-energy) radiation for the treatment of malignant diseases</p> |
| radioactive radiation | <p>radiation produced by the decay (nuclear decay) of radioactive substances; these are substances with unstable atomic nuclei that spontaneously transform by releasing energy. The energy released is emitted as ionizing radiation (high-energy particles and/or gamma radiation).</p> |
| radiotherapy | <p>controlled use of ionizing (high-energy) radiation for the treatment of malignant diseases</p> |
| receptor | <p>specialised stimulus-receiving structure of the organism that serves to facilitate communication between the organism and its environment or between the cells of an organism; these include, for example, sensory cells, which receive external stimuli (such as smell, taste, light, colour, pressure) and transmit them to the nervous system. However, receptors also refer to molecular structures (proteins or protein complexes) on and in body cells. These can, for example, specifically bind certain messenger</p> |



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| | <p>substances (such as hormones, neurotransmitters) and transmit them into or within the cell. This process triggers a reaction in the cell, e.g. the production of a chemical substance or cell division (biochemical signalling processes). Receptors on certain immune cells (lymphocytes), known as antigen receptors, can recognise specific antigens and trigger an immune response.</p> |
| remission | <p>temporary or permanent decrease or disappearance of the signs of cancer.</p> |
| stem cell transplantation | <p>transfer of haematopoietic stem cells after conditioning chemotherapy, radiation or immunosuppression of the recipient; the stem cells can be obtained either from the bone marrow or from the bloodstream. In the first case, the procedure of their transfer is called bone marrow transplantation, in the second case peripheral stem cell transplantation. Depending on the type of donor, a distinction is made between two forms of SCT: allogeneic SCT (stem cells from a foreign donor) and autologous SCT (own stem cells).</p> |
| symptom | <p>sign of illness</p> |
| T lymphocytes | <p>subtype of lymphocytes (a form of white blood cells); they develop in the thymus gland and are responsible for the so-called cellular immune response; T lymphocytes play an important role in the direct defense against viral and fungal infections and control the activities of other immune cells (e.g. granulocytes).</p> |
| therapy optimising trial | <p>a controlled clinical trial (study) that aims to provide the best possible treatment for patients and at the same time to improve and develop treatment options; therapy optimisation is aimed not only at improving the chances of recovery, but also at limiting treatment-related side effects and long-term effects.</p> |
| thrombocytes | <p>blood cells that are responsible for haemostasis; they ensure that, in the event of an injury, the walls of the blood vessels are sealed within a very short time, thus stopping the bleeding.</p> |
| thymus gland | <p>organ belonging to the lymphatic system below the thyroid gland; part of the body's own defence system and significantly involved in the development of the immune system, especially during childhood; from puberty onwards, it loses its size and importance.</p> |
| tumour lysis syndrome | <p>metabolic changes due to tumour cell death as a consequence of cancer treatment, usually with large masses or cell counts, after chemotherapy; the changes are manifested by increased uric acid, potassium and phosphate levels, as well as a decrease</p> |



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| | <p>in serum calcium concentrations, which can result in acute renal failure.</p> |
| tyrosine kinase | <p>enzymes from the protein kinase family; they particularly contribute to the transmission of signals within a cell and are important for embryonic development as well as the regeneration and maintenance of tissues. Functional disorders can play a role in the development of cancer, among other pathological conditions.</p> |
| ultrasound | <p>an imaging technique used to examine organs, in which ultrasound waves are sent through the skin into the body; at tissue and organ boundaries, the sound waves are reflected back, picked up by a receiver (transducer) and converted into corresponding images with the help of a computer.</p> |
| X-ray examination | <p>imaging procedure that uses X-rays to visualize organs or parts of organs</p> |
| X-rays | <p>high-energy electromagnetic radiation, discovered by W. C. Röntgen in 1895; X-rays can partially penetrate matter, so that insights into the interior of the human body are possible, among other things. Since X-rays have an ionising effect (ionising rays), they can also change matter, e.g. damage cells and possibly cause cancer. In diagnostics, X-rays are used to examine certain parts of the body. Depending on the type of irradiated tissue, the radiation is intercepted (absorbed) to varying degrees and displayed on a film plate as a two-dimensional image. Since every X-ray examination is associated with a certain amount of radiation, particularly sensitive parts of the body (such as gonads) must be protected. In the context of X-ray therapy (e.g. radiotherapy), very high-energy X-rays are used to kill tumour cells.</p> |