IntReALL – International Study for the Treatment of Childhood **Re**lapsed **A**cute **L**ymphoblastic **L**eukemia (ALL) – Standard Risk (SR)

Information for Parents

The purpose of this flyer is to inform you about the treatment for children with standard risk relapsed ALL that is widely offered, and then provide you with detailed information about an international study which aims to explore how to improve the treatment of these children. Our purpose is to help you to understand the details of this study and consider whether you wish your child to take part.

1. What is the standard treatment for children with SR relapsed ALL?

Several chemotherapy strategies have been developed to treat childhood relapsed ALL. Among those, there are two most widely used protocols in the treatment of relapsed ALL in Europe:

- The **ALL-REZ BFM protocol** (standard treatment initiated in Germany)
- The **ALL R3 protocol** (standard treatment initiated in the UK)

These protocols have never been compared with each other in the context of a research study. Each protocol has its own advantages and disadvantages yet **both produce very good outcomes.**

These protocols have similarities. First, they rely on an initial *phase of induction* which means chemotherapy is administered immediately after the diagnosis of ALL relapse; this phase is followed by other phases, known as *consolidation* and *maintenance* of chemotherapy. Second, both protocols monitor the child's level of MRD (Minimal Residual Disease), which is the amount of persisting malignant cells in the body which cannot be detected by a microscope but only by specific biotechnological methods. Children with low levels of MRD have a good chance of being cured with chemotherapy alone, while children with higher levels of MRD are eligible for HSCT (Hematopoietic Stem Cell Transplantation) as part of their treatment. Third, the drugs used in both protocols have similar side-effects.

➤ *see also: What are the possible side-effects of chemotherapy?*

These protocols have, nevertheless, some differences in the duration and administration of various drugs:

- The **ALL-REZ BFM Protocol** consists of an induction phase with short intensive treatment containing high dose methotrexate and cytarabine, a longer and less intensive consolidation phase followed by 5 additional short intensive chemotherapy courses, and a conventional maintenance therapy with 6-mercaptopurine and methotrexate.
- The **ALLR3 Protocol** consists of an induction phase with treatment that includes the anthracycline mitoxantrone, followed by a more continuous consolidation phase and a maintenance therapy including repeating intensified treatment elements with dexamethasone and viniscrine (re-induction)

2. What is the International Study for Relapsed ALL (IntReALL) that is being proposed for the treatment of my child?

The clinical trial that is being proposed for your child is the **International Study for Childhood Relapsed ALL** (IntReALL). It is the **worldwide largest international clinical trial on relapsed ALL in childhood** which seeks to discover the best treatment strategies and investigates innovative therapies for children with relapsed ALL.

This study has two aims:

a) to compare the two standard protocols (the **ALL R3 protocol** & the **ALL-REZ BFM protocol** described above) in order to determine which is the best for children with relapsed ALL, and

b) to study the effectiveness of a new drug (named **Epratuzumab**) in relapsed leukemia.

This medical research study is a **clinical trial.**

➤ *for more information about clinical trials go to: www.cci.org; www.siope.eu or www.encca.eu*

3. Who can participate in this study?

All children who are diagnosed with standard risk (SR) relapsed ALL. Your child is one of them. The more children take part, the more information can be gathered to help us improve the treatment of children with relapsed leukemia.

4. What does it mean that IntReALL is a "randomized" study?

It means that if your child takes part, then he/she will be randomly **assigned** by a computer to one of the proposed treatment arms (referred to as "arm A" or "arm B"). to follow either the ALL-REZ BFM protocol or the ALL R3 protocol *(➤ see page 1)*. Following the induction phase, a second randomization will assign patients to the respective standard consolidation therapy either with or without the new drug *Epratuzumab*.
In other words, your child will be assigned to one of the following groups:

- Standard treatment ALL-REZ BFM and consolidation **with** *Epratuzumab* (Arm A)
- Standard treatment ALL-REZ BFM and consolidation **without** *Epratuzumab* (Arm A)
- Standard treatment ALL R3 and consolidation **with** *Epratuzumab* (Arm B)
- Standard treatment ALL R3 and consolidation **without** *Epratuzumab* (Arm B)

Each **"randomization"** is done by a computer. Half of the children who participate in the study are expected to receive the new drug *Epratuzumab*.

The IntReALL study has been designed by skilled experts based on the knowledge available up to date. The safety of patients in clinical trials, such as the IntReALL study, is of utmost importance. All trial protocols have been reviewed and approved by ethics and regulatory committees.

5. How long is the treatment and what does it involve?

Regardless of the group to which your child will be randomly assigned, the treatment comprises the following four phases:

1st phase: Induction phase (treatment lasts 5 weeks)

- Very intensive therapy will be given with the aim to eradicate all – or at least most – malignant cells at the very beginning. We expect your child to remain in the hospital most of the time during this phase. At the end of this course we will check the bone marrow to assess if the disease is in remission.

2nd phase: Early Consolidation
(treatment lasts 10 weeks)

- This second load of chemotherapy is meant to consolidate the anti-cancer effect of the induction phase. During this phase, we expect your child to be hospitalized only when receiving treatment, or to deal with side-effects and possible complications as well as to recover from treatment. At the end of this phase your child's physicians will decide how to proceed with the treatment. If your child has not relapsed and has a low MRD (Minimal Residual Disease), then he/she will proceed to phase 3.

3rd phase: Late Consolidation
(treatment lasts 12–16 weeks)

- It is standard in ALL-therapy that the consolidation treatment is repeated with the intention to eradicate all possibly still existing, but not visible cancer cells.
- If the MRD measures are high, which means there are still cancer cells detectable, your child will be referred to: **Hematopietic Stem Cell Transplantation (HSCT)**

4th phase: Maintenance therapy
(treatment lasts about 90–100 weeks)

- It has been proven that after intensive treatment a longer period of less intensive treatment will improve the outcome in a considerably high number of ALL patients. As the medication in this phase will predominantly be given orally, your child will be able to stay at home most of the time and will most likely be able to take part in regular activities (such as school, sports etc. – consult your physician!).

The total duration of treatment for those patients receiving chemotherapy as late consolidation and maintenance might vary a bit due to the individual situation. If a hematopoietic stem cell transplantation should be necessary, the chemotherapy will end after the early consolidation phase.

If the disease progresses during the treatment or if side-effects are severe, your child's doctors may decide to stop the therapy before its completion. In this case, they will consult with other experts on the IntReALL study about other options or will propose palliative care. All this will be thoroughly discussed with you.

6. What is the new drug, *Epratuzumab,* and what are the side-effects?

This is a drug that was specifically produced to target certain types of leukemic cells. It was used in the past in adults and children with leukemia and had moderate effects. What remains unknown is whether Epratuzumab may improve the prognosis (possible outcome), when used in combination with chemotherapy. For this reason it will be combined either with the **respective standard consolidation** according to the standard treatment arm A (ALL-REZ BFM) or arm B (ALL R3).

This drug is easy to give, and has relatively few side effects. We expect that *Epratuzumab* will be tolerated very well with only mild reactions at the time of its administration. Side-effects may include transient chills or agitation, fever, and fatigue, and are only temporary. The drug will be given once a week via the central line for eight weeks during the early consolidation.

It is assumed that *Epratuzumab* will eliminate any residual leukemia cells left after chemotherapy and therefore may improve outcome. However, we cannot be sure unless we have proven it through this randomised study. As soon as the positive effect has been statistically confirmed, it will be recommended as standard therapy for all children with ALL relapse. If a benefit cannot be shown, it will not be further used in this indication.

7. What are other possible side-effects of chemotherapy?

Regardless of the group your child will be assigned to, you need to keep in mind that most of the drugs that are used in the treatment of childhood cancer have similar side-effects that consist of:

- **Bone marrow suppression**
  This causes increased risk of infection, anaemia and bleeding. Your child may require transfusion support to treat anaemia and the low platelet count caused by the treatment. Doctors will advise you on what precautions are required to prevent infection and inform you about how a potential infection is treated.
- **Nausea, loss of appetite, and weight loss**
  We can use strong anti-emetic drugs to minimise the nausea. We can provide help for children who are unable to eat enough.
- **Loss of hair**
  This is not permanent. The hair will grow back after treatment has finished or was stopped.

If your child has any other serious side-effects from the treatment, an alternative treatment plan will be proposed by your child's physician and you will be asked to consent to the new treatment plan. Keep in mind that the chemotherapy may also have some long term effects. As in standard treatment, there is a slight risk that fertility might be impaired and additional malignant diseases, the so-called secondary malignancies, may arise. Talk to your physician about age appropriate measures that can be taken to ensure fertility after end of treatment (such as egg- or sperm-banking or tissue preservation).

➤ *see also: Are there any risks?*

8. Will my child require more visits to the hospital?

No. Children are very closely monitored whilst receiving treatment for relapsed ALL and, if not already hospitalized, they will need to attend their treatment centre at least weekly. This is the same for patients on this study as well as on standard ALL relapse treatment.

9. Will my child require extra bone marrow tests or blood tests if he/she participates in the study?

No. All bone marrow, blood and tissue samples will be collected when the routine tests (as in standard treatment) are done to your child. So, **no additional tests** will be necessary.
We wish to take an extra few millilitres (a few teaspoons) of bone marrow when we do our routine testing. If your child is receiving *Epratuzumab,* at the time of routine blood count monitoring via your child's central line, small additional blood samples (5ml) may be required to monitor the levels of *Epratuzumab*.
We would like to ask your permission to store some of these samples to use for future research studies.

➤ *see also: Will my child's blood, bone marrow or tissue samples be stored in a "biobank" and why?*

10. Are there any risks?

To our knowledge there are **no extra risks** involved in receiving one of the randomized standard protocol arms, nor in receiving the new drug *Epratuzumab*. Side-effects are not different from the currently used standard treatment in relapsed ALL. If, however, your child has serious side-effects from the new or the standard treatment, a treatment plan will be devised by the child's consultant team.

During chemotherapy, an adolescent girl should never become pregnant nor should an adolescent boy impregnate his partner(s). Unborn babies exposed to chemotherapy have a high risk to develop malformations. Therefore, in case of sexual activity safe forms of contraception must be used.

11. Are there any benefits?

We cannot necessarily predict that the new treatment is better than the standard treatment for children with relapsed ALL. However, there are some benefits to taking part in a clinical trial, such as the IntReALL study:

- Your child may get a new treatment with the *potential* to improve outcome, which he or she could not get outside the study. The information which will be collected from your child will help to improve future treatment for children with relapsed ALL. Just like today's knowledge of cancer treatment is based on the outcome of previous clinical trials.
- If the new drug, *Epratuzumab,* proves to be effective in combination with chemotherapy, then it will be licensed for the pharmaceutical market and recommended for treatment of all children with relapsed ALL.
- National and international experts have worked together to develop the IntReALL study and your child will be monitored very closely.

12. Will my child's blood, bone marrow or tissue samples be stored in a "biobank" and why?

Before and during your child's treatment, blood, bone marrow, and possibly other tissue biopsies will be routinely taken to diagnose your child's condition and treatment progress. We plan to store all residual material from the blood, bone marrow and tissue biopsies in a so called **Biobank.** These samples will be used to understand why certain children relapse and if there are ways to provide a better therapy. For example, they will help us to determine:

a) the biological characteristics of the leukemic cells,
b) the MRD (Minimal Residual Disease) levels which can tell us more about the efficacy of the treatment,
c) the efficacy of novel drugs to kill leukemic cells,
d) mutations in your child's genes that may contribute to the development and relapse of leukemia.

The stored samples may also be used for research projects in the future. These projects will be related to the treatment, diagnosis and genetics of childhood cancer. Therefore, to make future research possible, we ask for your permission to store your child's material in the biobank and conduct other, not yet specified, scientific analyses in the future. All information about your child is protected by the national and European strict regulations on data protection. This means that all members of the staff who have access to this information are legally required to keep the information secure. Usually a patient code number is used. Thus, the samples are anonymized for anybody outside the study group.

If you give your consent, the stored samples of your child, will be accepted as a **donation.** You always have the right to see the data we have stored about your child. If you do not wish to consent to excess material being stored, any leftover specimens will be destroyed. The participation in biobanking is completely voluntary without any consequences for the treatment of your child.

13. What should I consider before consenting or not to my child's participation in the IntReALL study?

First, take the time to fully understand the information about the IntReALL study. You should not hesitate to ask questions.

Then, consider the **available options:**

a) standard treatment
b) participation in the IntReALL study.

Finally, discuss the proposed study with your spouse/partner, with your child's other parent/guardian (if you are separated, divorced or in a homosexual relationship), and of course, with your child.

There is a website ➤ *www.intreall-fp7.eu* that describes the mission and details of the study and informs about its progress in regular reports. It also contains material that you and your child may find useful.

14. What if I disagree with my child or partner about taking part in the IntReALL study?

Decision-making is a challenging process for some families. If you have different positions, listen to each other's arguments and concerns. Discuss the different views with your consultant and, if possible, a counselor or psychologist. If your child or adolescent does not want to take part in the IntReALL study, but you do, then try to understand the underlying causes of his/her objections. Some children or adolescents do not fully understand the details of the treatment, others have irrational fears and need reassurance, and those who have experienced multiple relapses may be aware of their very difficult situation and wish to maintain the present quality of life by receiving palliative care services instead of yet another treatment.

Keep in mind that in most European countries, adolescents older than 14 years of age, are informed about the IntReALL study and are expected to sign a Consent Form. In some countries their decisions have priority over those of their parents.

Do not hesitate to seek help from a counselor or psychologist to facilitate your family's decision-making process. We want you to feel that you are making the decision that is **most appropriate** for you, for your child and for your family. The psychosocial team of the hospital or our ward will be able to assist you and your child.

15. What if I decline participation in the IntReALL study? What kind of care can I expect for my child?

You are under **no obligation to take part in this study.** If you decide that you do not wish your child to participate in the study, he/she will still receive the presently best possible care.

16. What if I and/or my child change our mind and refuse further treatment?

You and/or your child can withdraw your consent to the study at any time, without giving a reason. Your child will then be entitled to the standard treatment and best possible care.

17. Who will be allowed to see my child's medical records?

By law, all information about your child and his/her illness will be kept strictly confidential. In addition, all data related to your child's participation in the IntReALL study will be used solely for research purposes, or be given to the country's regulatory body (e.g. the Office of National Statistics). Should this happen, all your child's personal details will be removed before the data is analysed so that he/she cannot be identified by name, address or medical details.

18. What if I have any questions or concerns now or later?

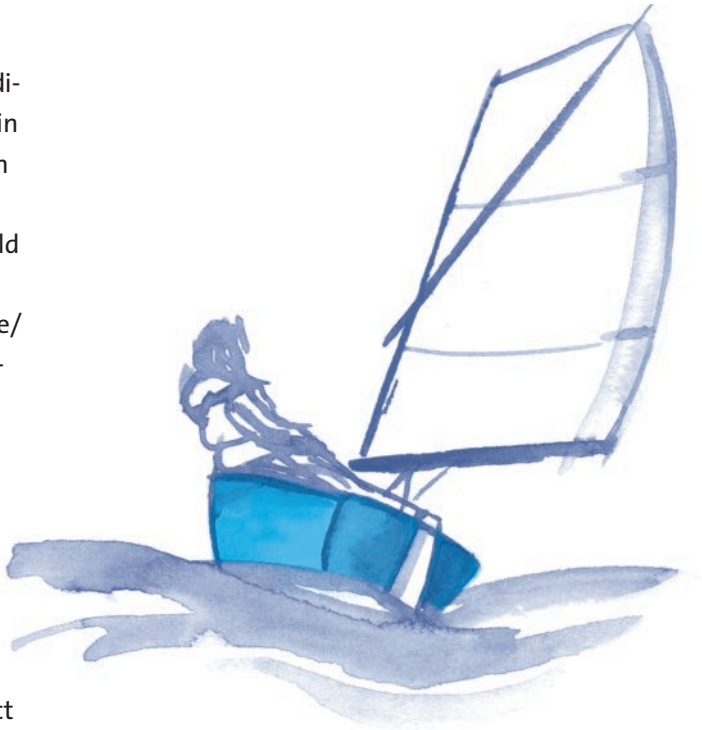
If you have any questions about the study please do not hesitate to ask anyone of the medical or research team at your treatment centre or contact the study's representatives ➤ *see details at the end of this flyer*

If you have any queries regarding the storage of your data you should contact the study's representatives ➤ *see details at the end of this flyer*

If you wish to complain about any aspect of the way you or your child have been approached or treated during the course of this study, please feel free to discuss your concerns with the treatment team, or alternatively contact the local hospital's complaints department.

19. How can I find out about the progress and results of the IntReAll study?

After the end of the study, medical researchers have the responsibility to publish the results and make them widely known so that cancer treatment can improve. Results are published in medical journals, findings are presented at national and international conferences and the progress of the study will be reported on ➤ *www.interall-fp7.eu*



20. What is the "Consent Form" I will be asked to sign?

The doctors who conduct research in new drugs must, by law, explain to you and your child or adolescent what a clinical trial involves, **before** you agree to take part. You will be asked to sign a statement, called "Informed Consent" that confirms that you have been informed about the IntReALL study, you fully understand what it involves, and you agree or disagree that your child takes part.

Names of local professionals for the IntReALL study

Names of local professionals for Biobanking

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