

PATIENT INFORMATION SHEET – PART 1

Trial title: A randomized trial for adults with newly diagnosed acute lymphoblastic leukaemia

Short title: UKALL14

Version: 2.1

Date 17.05.2010

Introduction

You are being invited to take part in a research trial. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the trial?

The purpose of this trial is to find out more about how best to treat patients with Acute Lymphoblastic Leukaemia (ALL). The more people who take part in these studies, the better the information that we are able to obtain and the more quickly we are able to improve treatment for future patients. For many years the Medical Research Council (MRC) have run trials in Leukaemia with the National Cancer Research Institute (NCRI). Over the years this approach has led to a steady improvement in the treatment of leukaemia. This trial will be run by the NCRI and the Cancer Research UK & UCL Cancer Trials Centre (UCL CTC).

Your doctor will, by now, have explained what Acute Lymphoblastic Leukaemia is, how it will affect you, and what treatment is needed. You will know whether your leukaemia is of the “B-cell” or “T-cell” type. This information sheet provides details about the trial that we are inviting you to take part in. There is some background information given about the treatment of ALL in general, so that you can see where the treatment you might receive as part of this trial will be different from standard treatment that you would receive anyway.

The trial asks questions about 4 specific issues in ALL treatment which will be explained below. The rest of the treatment you will receive will be standard treatments that you would receive anyway, whether or not you participate in the trial. There is a flowchart attached to Part 1 of this patient information sheet that clearly sets out the standard and trial treatments for reference.

Standard ALL treatment

The standard treatment for ALL consists of chemotherapy drugs to destroy the leukaemia cells. The treatment is divided into stages, which are the same for both B cell and T cell types: each stage has been given a name to help doctors and patients keep track of where they are in the treatment.

- (i) Initial chemotherapy treatment, called induction, is given to achieve disease remission, which means that your bone marrow function and blood counts return to normal and when doctors

look under the microscope they can't see any leukaemia cells. Induction therapy is given in 2 parts, called 1 and 2.

- (ii) Immediately after induction therapy patients are given further chemotherapy called Intensification, aimed at preventing leukaemia cells from getting into the fluid around the brain and spinal cord. Not all patients will receive this treatment.
- (iii) Consolidation treatment is more chemotherapy treatment. Patients who are already in remission must be given more therapy in order to prevent the disease relapsing (coming back). Not all patients will receive this treatment.
- (iv) Maintenance treatment is a lower dose chemotherapy, which is given as an out-patient treatment – mostly as tablets but sometimes as 3 monthly injections. This is also used to prevent the leukaemia coming back. Not all patients will receive this treatment.
- (v) Stem Cell Transplant (also known as bone marrow transplant) for patients who have a suitable donor and are at the highest risk of relapsing. **Patients who receive stem cell transplantation don't always have intensification, consolidation and maintenance as well.**

Trial question 1: Assessing a new form of an standard drug; L-asparaginase

During the initial (induction) phase of treatment, all trial patients will be given a drug called Pegylated-asparaginase, this is a form of a standard drug (L-asparaginase) that is always used in the treatment of ALL. This new pegylated form is hoped to be better for the patient than the standard L-asparaginase treatment and may be more convenient. Many hospitals in the UK are already using the new form of this drug but information on its risks and benefits have not been collected before in a systematic way in such a large group of patients. We want to make sure we don't just adopt this new form of the drug without taking the opportunity to study its use carefully.

Trial question 2: does the addition of new drugs in the initial (induction) phase of treatment lead to a better outcome?

The main purpose of the UKALL14 trial is to investigate whether new drugs, given with the standard initial induction therapy for ALL can improve the long-term outcome for patients. The drug treatments we are studying have already been used before, either in patients with other diseases or in small numbers of patients with ALL, but we are not certain whether adding one or more of these drugs to best available standard treatments will improve the outcome. Therefore, we are asking if you would be prepared to have one or more of these drugs added to the best available standard induction treatment by a process of 'randomisation'. By this we mean that neither you nor your doctor chooses whether you get one of the new drugs but that choice is made by a computer, similar to tossing a coin.

In this trial, there are 3 new drugs to be tested in the induction stage of treatment. 2 of them apply only to B cell ALL and one only to T cell ALL.

B cell ALL: 2 new drugs called Rituximab and Epratuzumab are to be tested, the "toss of the coin" or randomisation will determine if you get one or both of these drugs with standard treatment or best standard treatment without new drugs.

T cell ALL: 1 new drug called Nelarabine is to be tested. The "toss of the coin" will determine if you get the new drug with standard treatment or best standard treatment without the new drug.

Trial question 3: Who will benefit most from a stem cell transplant (also known as bone marrow transplant)?

Stem cell transplant is a widely used treatment for ALL. Presently, there are no firm rules about who should have a stem cell transplant. Different hospitals within the UK often make different decisions about who should and should not have a transplant. Within this trial we have developed some firm guidelines about who should have a transplant based on assessing the 'risk' level of your leukaemia.

If you participate in the UKALL14 trial, your trial doctors will make a decision about whether or not you have a stem cell transplant and which of the 2 types of transplant you receive ("myeloablative", i.e. high dose, or "non-myeloablative") depending on 3 things: donor type, risk of relapse and age as detailed below.

- A. If you have a sister or brother who is a tissue type matched donor, it will be recommended that you go ahead for a transplant regardless of your risk of relapse. If you are aged 40 years or less at trial entry, this will be myeloablative (a high dose transplant which includes total body irradiation). If you are older than 40 at trial entry this will be non-myeloablative.
- B. If you do not have a matched sibling donor your risk of relapse will determine whether or not you are recommended for a transplant. Your relapse risk following induction therapy will be assessed using a number of special tests done in the weeks following your diagnosis and by your leukaemia cell count at diagnosis.
 - i. If you are considered to be at low risk of relapse you will continue with intensification, consolidation and maintenance chemotherapy and will not be recommended for a transplant.
 - ii. If you are considered to be at high risk of relapse your trial doctor will recommend you for a transplant (if we can find a matched unrelated donor for you). If you are aged 40 years or less at trial entry, this will be myeloablative (high dose including total body irradiation) transplant. If you are older than 40 at trial entry this will be non-myeloablative.

Trial question 4: Does the drug palifermin help protect myeloablative (high dose) transplant recipients against getting a sore mouth?

Everyone who has a transplant using the myeloablative (high dose including total body irradiation) regimen will be able to take part in a "toss of the coin" (randomisation) to receive one of two different dosing schedules of the drug Palifermin. All patients who take part in this question, will receive the drug. This drug is used to help the very sore mouth that the transplant treatment can cause and it is known to be effective. However, it is expensive and can be difficult to administer as it needs to be given on several days. Here, we are testing whether giving the same amount of drug on a more convenient schedule, over less days, is equally effective as the standard daily schedule.

Why have I been invited?

You have been chosen to take part because you have ALL. Patients from hospitals all across the UK and Eire will also be invited to take part in this trial. In all, we expect approximately 960 patients to take part.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

Consent

If you agree to take part, you will be asked to sign a consent form. You may have already started your initial treatment by this time with a dose of steroid by mouth or be about to start.

Initial treatment: induction

For all patients, the first four weeks of induction treatment (phase 1) will be a combination of chemotherapy drugs, which has been used for over 15 years. In total this first period of treatment (phase 1 and phase 2 induction) lasts for about 8 weeks. You will be in hospital some, or possibly, all of this period. Your induction treatment may be accompanied by one of the new trial drugs or not, depending on the outcome of the randomization as described above. Induction treatment is usually highly successful in initially treating leukaemia so that 'remission' is obtained and more than 9 out of 10 people will go into remission after initial treatment. A bone marrow test at the end of each of the 2 phases of your induction therapy will allow your doctor to give you information on how well the treatment has worked.

The additional drugs being tested for B-cell ALL patients are not chemotherapy drugs, but antibodies against markers expressed on the surface of your leukaemia cells. These drugs will be given as injections directly into the vein once a week for 4 weeks during the first part of induction. The injections will be given by your regular nurses taking care of you on the wards.

For those people with T cell ALL who are going to receive the extra drug, this will be given as an extra course of treatment after both phases of induction. It will be given intravenously on 3 consecutive days, by your regular nurses. It may be given as either an in- or an out-patient's treatment, depending on how well you are feeling.

Assessment of the outcome of initial treatment and determination of your "risk status"

At the end of your initial treatment, regardless of whether you receive the new drugs or not, we will give you an assessment of whether you are "high risk".

We know that Induction treatment needs to be 'consolidated', to prevent your leukaemia from coming back.. There are two ways of doing this – either by further chemotherapy or by stem cell transplantation (also known as bone marrow transplantation). Patients who are "high-risk" will be assigned to stem cell transplant wherever possible. This might not always be possible – a donor might not be available or you may not be fit enough to have a transplant. Also, you are free to decide not to have a transplant, even if it is recommended by the trial.

How is my risk status determined?

A blood and bone marrow sample will be taken at the beginning of your treatment and used to find out whether you have a marker which we can use to follow the outcome your leukaemia treatment using a very sensitive special test called "minimal residual disease testing" (in most cases this test would be done as part of standard treatment). We will also look to see if your leukaemia has genetic alterations known as "cytogenetic abnormalities" You will then have bone marrow and blood tests after each treatment course to look at your response to treatment and sensitive tests for evidence of leukaemia using genetic methods.

Initial treatment: intensification

Immediately after induction, patients will receive drugs to treat any leukaemia cells which may be in their nervous system (intensification). These are given through small injections into the spine called lumbar punctures and are part of standard treatment and not part of the trial. This treatment may not be given to some patients, depending on the type and timing of a stem cell transplant.

Looking for a stem cell /bone marrow donor

With your and their permission, all full siblings (sisters and brothers) will be tested to see if they have a matched tissue type to you. If your siblings are not a match, we may seek an unrelated donor depending on your risk status. By the time you come to the end of induction, most patients will know whether a donor is available or not.

What happens if my leukaemia is “high risk”?

If you are high risk, knowing that your leukaemia is at considerable risk of returning, even if you are in remission now, we will recommend you have a stem cell transplant even if you do not have a matched sibling. This transplant will be part of the trial and we will assess the benefits of using an unrelated donor, from a register, for your transplant. Depending on your age (older or younger than 40 at trial entry) we have 2 ways of doing the transplant. We know that the transplant can be a very hard treatment to tolerate in older people and we plan to find out if using a more gentle form of transplant preparation (conditioning regimen) for the transplant can be as effective as the high dose treatments we usually use.

Your transplant may be accompanied by the new dosing schedule of Palifermin mentioned above depending on what conditioning regimen you have and the result of the randomization.

What happens if my leukaemia is “standard risk”?

If your leukaemia is standard-risk, i.e. nothing about your disease makes us worried that you are at high risk of relapsing, you will be recommended to stay on standard treatment unless you have a brother or a sister who can be a stem cell (or bone marrow) donor.

Expenses & Payments

You will not receive any payment or reimbursement of expenses for taking part in this trial. The doctors and nurses working on this trial at your hospital will not get any payment for putting you in to the trial.

What will I have to do?

You will be in hospital for much of your treatment. You will also have side effects which can make you feel unwell and unable to carry on work for a while. These side effects occur in all standard chemotherapy for ALL. Almost all of the drugs you will be treated with will be the standard treatment for ALL unless you are ‘randomized’ to get one of the new drugs to be tested during induction therapy or during transplant.

You will be prescribed a number of different drugs throughout your treatment which will be explained to you. It is very important that you take these drugs as they are prescribed to you.

What are the alternatives for diagnosis or treatment?

ALL is a rapidly advancing type of leukaemia which, without treatment, is usually fatal within a few weeks. If you were not on this trial, you would receive one of the standard treatments that are

included in this trial. Additionally, you may also be recommended to have a stem cell transplant, depending on your doctor's assessment of your risk of relapsing. You also have the option of not receiving any treatment at all although this is not recommended.

What are the possible disadvantages and risks of taking part?

Everyone who agrees to take part will receive standard treatment. Some people will receive additional drug treatments to standard ones. We hope that the additional treatments might mean your chance of having a long term future without leukaemia is higher. However, we are not certain of that and this is the reason why we are doing a trial. Outside of a trial, these new drugs are not licensed for the treatment of ALL and would not be prescribed to you, so by entering the trial, there is a chance you might receive a new drug which might be of benefit to you. It is also possible that the new drug would neither benefit nor harm you and the outcome would be the same as if you had standard treatment only. Finally, although we don't think this will be the case, we can't be absolutely sure that the new drugs won't cause additional side effects and complications and make your outcome worse. The side effects and leukaemia responses of all patients on trial will be closely followed both by the trial doctors and coordinators and by an independent data and safety monitoring committee. If there is any evidence that the trial drugs are much better or much worse than the standard treatment, the trial will be stopped.

What if I am breastfeeding, pregnant or planning to become pregnant?

Breastfeeding or pregnant women will not be eligible to take part in the trial. If you are breastfeeding or pregnant, you need to discuss this with your doctor straight away before starting any treatment for your leukaemia. Male patients may consider the option of sperm banking before treatment. Women of childbearing age will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. Women who could become pregnant must use an effective contraceptive during the course of this trial and for 12 months after the trial. Likewise, men on the trial should use effective contraceptive during the trial and for 12 months after to prevent their partner from becoming pregnant because their sperm may have been damaged by the chemotherapy. Women should not breastfeed for 12 months following the trial..

What are the side effects of any treatment received when taking part?

Unfortunately, all of the available treatment options for acute lymphoblastic leukaemia have side effects. The degree and severity of these will differ from person to person. However, most patients will experience the following at some stage during treatment and would do if they were receiving standard chemotherapy for ALL outside the trial. There is also a small risk that you might die as a result of your treatment for leukaemia.

- Hair loss – most patients lose some or all of their hair. It will grow back once the therapy is finished.
- Low red blood cell counts resulting in tiredness and dizziness and shortness of breath. You will receive regular blood transfusions to overcome these symptoms.
- Low platelets (the cells that make your blood clot) resulting in an increased risk of bleeding and bruising. You will receive platelet transfusions to counteract this and you should be careful not to cut or bang yourself while your platelets are low.
- Low white blood cell counts resulting in a high risk of infection. If you have a temperature or feel unwell, you should tell your trial doctor or nurse immediately so they can start you on antibiotics. Infections can occasionally be life threatening.
- Nausea and vomiting – medications are given with your treatment to prevent or alleviate this.
- Sore mouth – medications are given with your treatment to prevent or alleviate this.

- Diarrhoea.
- Temporary or permanent infertility. Your medical team will discuss treatment options with you before starting treatment.

Your medical team will monitor you closely for side effects and you should report any side effects to them. Blood transfusions and/or other medications will be prescribed to prevent or reduce these.

The side effects of the antibody drugs which are given for patients with “B” type ALL are generally mild and some of these can be reduced with medicines. Side effects can begin during the first dose of the drug and may continue for a few hours afterwards, but are usually milder with following doses. Specifically the side effects of the antibodies might include the following:

- Flu-like symptoms: These can include a high temperature, chills, weakness, muscle aches, tiredness, dizziness and headaches. They can occur while the rituximab is being given, but do not usually last long.
- Low blood pressure: This may happen during the infusion, so your blood pressure will usually be regularly checked. People who normally take medicines to lower their blood pressure may be advised by the doctor to take these at least 12 hours before rituximab is given.
- Feeling sick (nausea) and occasional vomiting: Your doctor can now prescribe very effective anti-sickness drugs to prevent or greatly reduce nausea and vomiting. If the sickness is not controlled, or if it continues, tell your doctor. They can prescribe other anti-sickness drugs that may be more effective.
- Allergic reactions: You may have a slight allergic reaction to rituximab. Signs of this include skin rashes and itching, a feeling of swelling in the tongue or throat, irritation of the nasal passages, wheezing, a cough and breathlessness. You will be monitored closely during your treatment, but let your nurse or doctor know if you have any of these symptoms. To help reduce the chance of developing an allergic reaction, antihistamines can be given before the infusion. The infusion can also be slowed down or stopped until the reaction is over.

Specifically, the side effects of Nelarabine which might be given to patients with the T cell type of ALL can include:

- weakness, dizziness, extreme sleepiness.
- confusion or clumsiness;
- lack of balance or coordination;
- weakness or trouble walking;
- numbness and tingling in the hands, fingers, feet, or toes;
- problems with buttoning clothes or picking up small items with your fingers;
- blurred vision;
- seizure (convulsions);

Your transplant doctor will explain the side effects of a stem cell transplant to you in detail if and when it is decided that you should have a transplant. Specifically, the side effects of stem cell transplantation might include the the problems detailed below:

- Immediate problems occur due to side effects of the transplant treatment. These usually resolve within a couple of weeks. A very sore mouth and throat is common, along with a high temperature due to the suppression of your white blood cells.
- Later on problems can continue after you have left hospital:

(To be printed on hospital headed paper)

- Continued infections due to the suppression of your immune system
- Graft versus host disease (this is a particular illness that occurs when the transplanted donor cells 'reject' cells in your body after your transplant)

Patients aged 40 years or under at the time of trial entry eligible for stem cell transplantation will be treated with a myeloablative conditioning regimen, this includes total body irradiation. These patients will undergo a CT scan or a test dose before the total body irradiation. This will allow the doctors to work out what dose they should give the patient in order to protect the patient's organs, such as lungs, as much as possible. The combination of total body irradiation and CT scan or test doses is standard treatment for ALL and does not represent any additional exposure to radiation above a patient who is not on the trial being treated with the same procedure. One CT scan is equivalent to about 4 years of natural background radiation exposure. This level of exposure is very unlikely to put you at significant health risk. We all have a one in five chance of getting a fatal cancer even if we never have an x-ray, so this CT scan represents a very small addition to this underlying risk from all causes.

What are the possible benefits of taking part?

We hope that all the treatments given will help you. The aim of the trial is to compare benefits of different treatments, since we genuinely do not know if adding the new treatments will help. The information we get from this trial may help us to treat future patients with ALL better.

What happens when the trial stops?

If the trial finishes while you are still receiving treatment you will continue to be treated on the trial protocol until your allocated treatment is completed.

Contact for further information

If you have any concerns or questions about this trial, please contact [Local investigator name and contact number] who will be pleased to give you further information.

In the event of medical emergencies out of hours you should contact [local contact].

This completes Part 1 of the Information Sheet

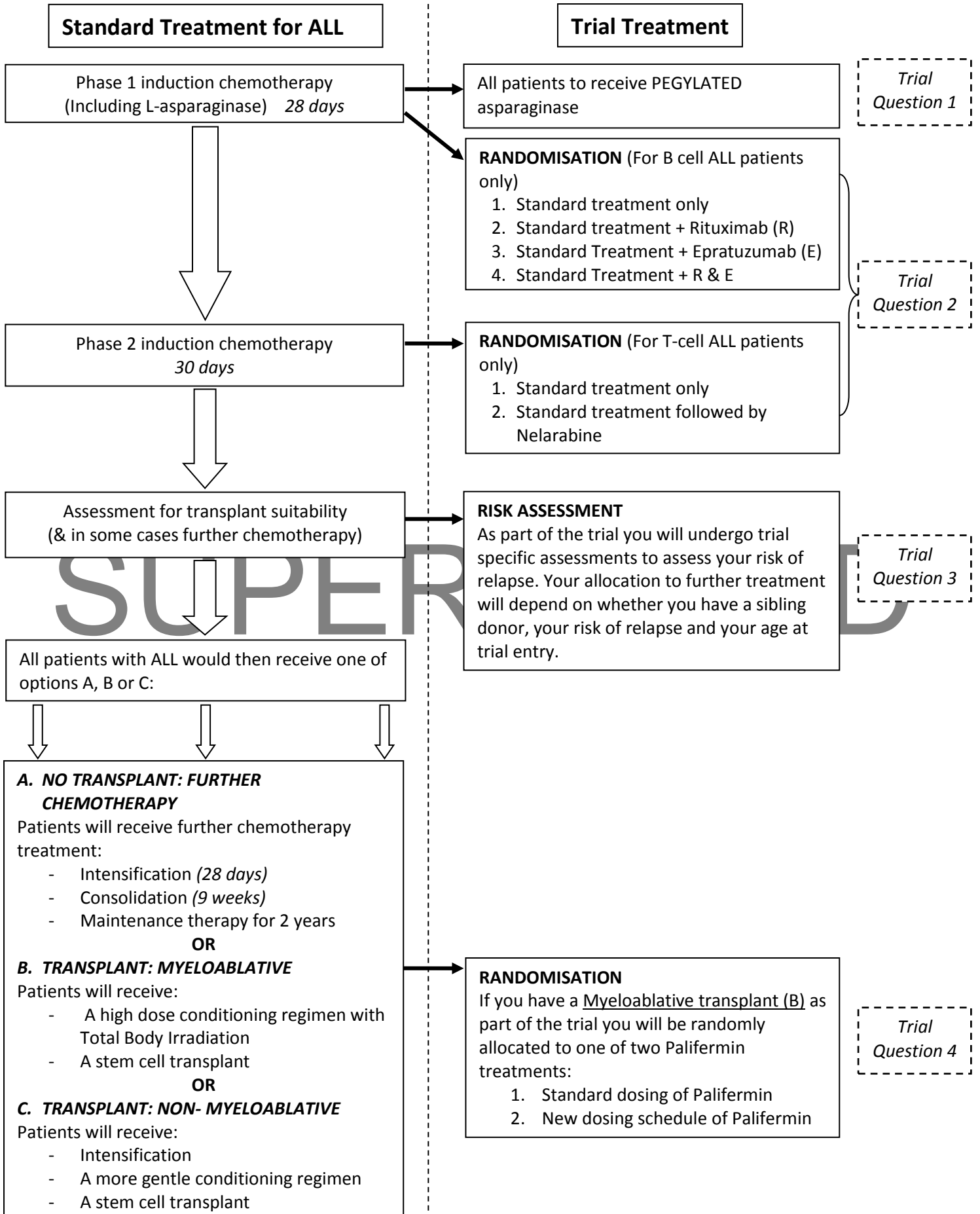
If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Thank you for reading this information.

PLEASE SEE NEXT PAGE FOR:

UKALL14 Flowchart showing standard treatment for ALL patients plus additional trial treatment

UKALL14 Flowchart showing standard treatment for ALL patients plus additional trial treatment



PATIENT INFORMATION SHEET – PART 2

Trial title: A randomized trial for adults with newly diagnosed acute lymphoblastic leukaemia

Short title: UKALL14

Version: 2.1

Date 17.05.2010

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment or drug that is being studied. If this happens, your trial doctor will tell you about it and discuss with you whether you want to continue in the trial. If you decide to withdraw from the trial the Cancer Trials Centre (UCL CTC) will be informed and your care will continue at your current hospital. If you decide to continue in the trial you will be asked to sign an updated consent form.

Also, on receiving new information your trial doctor might consider it to be in your best interests to withdraw you from the trial. He/she will explain the reasons and arrange for your care to continue at your current hospital.

What will happen if I don't want to carry on with the trial?

You can withdraw from the trial at any time without giving a reason and this will not affect the standard of care you receive. If you withdraw from the trial we will still need to use the data collected up to your withdrawal. Or, you may also withdraw from treatment but keep in contact with us to let us know your progress, allowing us to continue to collect information about your disease and response to treatment.

What if there is a problem?

Every care will be taken in the course of this clinical trial. However if you are harmed by taking part, University College London (UCL), as sponsor, will provide non-negligent compensation (i.e. compensation without the need to prove that there has been negligence). If, however, you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this trial, you should ask to speak to the researchers, who will do their best to answer your questions (*contact number*). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital and from the Department of Health website: http://www.dh.gov.uk/en/Managingyourorganisation/Legalandcontractual/Complaintspolicy/NHScomplaintsprocedure/DH_4080897

Please ask your trial doctor if you would like more information about this.

Will my taking part in this trial be kept confidential?

If you consent to take part in a research trial such as this one, relevant aspects of your medical records will be sent in confidence to UCL CTC. The UCL CTC, like the NHS, is registered under the data protection act to hold patient information in secure storage, to be accessed only by

appropriate staff involved with this trial. Occasionally, trained staff from UCL CTC or regulatory authorities will need to visit the hospital to review your notes to check that the information being provided is correct. Information collected for the trial from your medical notes will also be passed to the local Registry, the Regional Cancer Registry, the Leukaemia Research Cytogenetic Group and appropriate central trials offices. Information collected for the trial may also be used by investigators working on the trial outside the EU, possibly in the United States. In all cases personal details will be treated with the strictest security and confidentiality. Small samples of your blood and bone marrow will also be sent to named personnel in other NHS hospitals for further analysis. At all times your details will be handled by fully trained staff and will remain confidential. No individual patients will be identified when the results of the trial are published. Your General Practitioner will however be informed of your participation in the trial.

What will happen to any samples I give?

Blood samples taken for the trial will be collected and processed in exactly the same way as other samples taken in your hospital. Small samples of your blood and bone marrow will also be sent to named personnel in other NHS hospitals for further analysis. We will request that any surplus samples left over may be donated to a cell bank and we will ask for you to agree to this on the consent form. However you are within your rights to refuse to donate any leftover samples. In this instance, any leftover samples will be destroyed after analysis.

Will any genetic tests be done?

Yes, as mentioned in part 1, we will test to see if your leukaemia has any 'cytogenetic abnormalities' that may influence the treatment. These genetic tests are only done on your leukaemia cells. The genetic changes we find in your leukaemia cells are not changes taking place in the rest of your body.

What will happen to the results of the research trial?

The results of the trial will not be available until all patients taking part have completed the trial, this should be in the next few years, depending on the rate of subject entry to the trial. This will allow time to recruit enough patients and to follow them up for a sufficient period of time. The results will then be published in scientific journals and presented at national and international meetings. It will not be possible to identify you in any publication or presentation of the research findings. If you wish, you may contact your trial doctor to obtain a copy of the results.

Who is organising and funding the research?

This trial is being organised by the National Cancer Research Institute (NCRI) subgroup on Acute lymphoblastic Leukaemia in Adults and will be run by the Cancer Research UK & UCL Cancer Trials Centre (UCL CTC). The funding is provided by Cancer Research UK.

The new drugs being tested in this trial (Epratuzumab, Rituximab, Nelarabine & Palifermin) are being provided free of charge by Immunomedics, Roche, GlaxoSmithKline & Biovitrum.

Your hospital may receive financial reimbursement if they choose to use a particular brand of granulocyte colony-stimulating factor for supportive care called Lenograstim.

Who has reviewed the trial?

This trial has been reviewed by Cancer Research UK, the Charing Cross Hospital Research Ethics Committee. It has also been reviewed at your hospital by the Research & Development Department.

Further information and contact details

(To be printed on hospital headed paper)

If you have any questions about this trial, you should contact:

Doctor:

Research Nurse:

If you have any questions about research in general, you can contact Macmillan Cancer Support who are an independent organisation providing support and counselling to help people live with cancer.

They can be contacted at Macmillan Cancer Support, 89 Albert Embankment, London, SE1 7UQ
Telephone 020 7840 7840 or visit their website at <http://www.macmillan.org.uk>

Thank you for reading this information sheet.

SUPERSEDED