TO BE PRINTED ON LOCAL HOSPITAL HEADED PAPER

Patient Information Sheet

Study Title: A phase IIa study of rituximab and varlilumab in relapsed or refractory B-cell malignancies

This study or trial is also known as RiVa, which is a shorter name.

We would like to invite you to take part in a research trial

Your doctor or nurse has given you this information sheet because they would like you to think about taking part in the RiVa trial.

You are being invited to take part in the RiVa trial because you have a particular type of cancer called B-cell lymphoma which develops when the body makes abnormal B-lymphocytes (a type of white blood cells that fight infection), and your lymphoma has returned (relapsed) or not responded (refractory) to treatment and your doctors are considering further treatment for you.

Before you decide whether or not to take part, it is important for you to understand as much as possible about what is being done and what is involved, so:

- Please take the time to read this information carefully. You may also wish to discuss it with your family and friends before making up your mind
- Please feel free to ask your doctor any questions you may still have after reading this information sheet

Do I have to take part? No. It is entirely up to you if you take part in the trial or not. If you choose not to take part, the care you get from your own doctors will not be affected in any way.

If I start the trial, can I stop if I want to? Yes. If you choose to take part in the trial, you are free to stop at any point without giving a reason – the standard of your care will not be affected.

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If you have any questions about this trial or would like to discuss it further, please contact:

[local investigator name]

[contact details]

This document does not provide general information about lymphoma. For more information about lymphomas and lymphoma treatment, please ask your medical team or contact one of the following organisations:

The Lymphoma Association	0808 808 5555	www.lymphomas.org.uk
Cancer Research UK	0808 800 4040	www.cancerresearchuk.org

Important things you need to know about RiVa

- The RiVa trial is being done so that we can find out more about a new drug (medicine) that might improve the treatment of patients who have their lymphoma return or not respond to initial treatment. In particular, we wish to see if adding the new drug to one of the usual types of therapy used for returned or non-responding lymphoma, can improve the outcome of treatment.
- All patients in the RiVa trial will receive rituximab. This is a standard treatment for your type of cancer. In addition, all patients will receive the new drug called varlilumab.
- All of the drugs used in this trial can cause side-effects; however, you will be closely monitored and any side-effects will be treated.
- You will need to sign a consent form before taking part in the trial to confirm that you understand it and agree to take part.
- We would like your permission to collect, store and analyse samples of your blood and lymphoma tissue so we can learn more about who may benefit from this treatment.
- Women who might still be able to become pregnant will need to take a pregnancy test before being accepted on the trial. Pregnant women will not be able to take part in the trial.
- All patients enrolled in the study **must** be willing to use adequate contraception while taking part in the trial.
- You can stop taking part in the trial at any time, without giving a reason and without affecting the care or benefits that you receive.

1. Why we are doing the RiVa trial?

The RiVa trial is a **Phase IIa** study, where we are looking at whether varlilumab might increase the effectiveness of rituximab in B-cell lymphoma. The trial will include 40 people whose B-cell lymphoma has returned or does not respond to initial treatment. We hope the information collected from this trial will help us design better treatments in the future, and that people with the same cancer as you, might benefit.

2. Who is the trial for?

There are different things that your doctor will take into account to make sure that the RiVa trial is suitable for you. They will check things like your blood count, how well your kidneys and liver work and whether you are suitable for more intensive treatment or not.

The RiVa trial is for people with B-cell lymphoma whose cancer has returned or has not responded to your first or second treatment, and who are not fit enough for more intensive treatment.

3. More about the trial medicine

If you decide to take part in the RiVa trial, you will be treated with commonly used anti-cancer antibody, rituximab. This part of the treatment is one of a few options the doctor could treat you with if you were not taking part in this trial. We are trying to find out more about the effect of adding the new drug, varlilumab, to rituximab. Half of the trial patients will be assigned at random by a computer to Arm A. Arm A patients will receive varlilumab on day 2 of cycle one. Arm B patients will receive the same dose of varlilumab but on day 8 for cycle one. All further cycles of treatment will be exactly the same for all patients.

What exactly is the medicine that is being tested? Doctors know that cancers are very good at hiding themselves from detection by our immune system. Cancer cells are also able to suppress our immune system, making it less effective in killing the cancer cell. Rituximab is an anti-cancer antibody that can directly bind to a marker on normal and cancerous B-cells, thereby revealing the cancer cells to the immune system. On the other hand, varlilumab is an anti-cancer antibody that boosts the immune system's ability to kill the cancer cells revealed by rituximab.

The trial is investigating whether the combination of these two drugs will improve the treatment of your lymphoma.

Has varlilumab been given to people before? Yes, this drug has been given to patients with the same disease as you in studies. The RiVa trial is the next step towards developing this drug in combination with other chemotherapies to improve their effect, for use in patients with lymphoma. Varlilumab has been found to be effective in other cancers but is currently being investigated further in patients with the intention of obtaining a product licence. Rituximab has been approved for use in other B-cell lymphomas in the US and Europe.

How do the doctors decide how much varlilumab I will get? In the RiVa trial, doctors will be treating 40 patients with returning or non-responding B-cell lymphoma at the dose recommended from previous studies. During the trial, the trial team will be performing further checks on safety and any side effects from the treatment combination of varlilumab with rituximab. The doctors will also look at the effect the treatment will be having on your lymphoma and immune system.

4. What will I have to do if I decided to take part?

Screening

If you decide that you would like to take part in the RiVa trial, your doctor will ask you to sign the informed consent form. After you have provided informed consent, the trial team will need to do some tests to make sure that you are fully suitable to take part - this is called screening. These tests include a review of your medical history, review of medications you are currently taking, physical examination, pregnancy test (if appropriate), CT scan, ECG, collection of blood samples (1 tablespoon of blood) for laboratory analysis, a bone marrow biopsy (if appropriate), and a tumour biopsy.

It is possible that after these tests are reviewed, you may not be able to take part in this study. Or even though you may meet all the criteria for participation, your study doctor may decide not to enrol you in to this study (for example, the study doctor might think you are not well enough to participate). In this situation, your study doctor will discuss other treatment options with you.

Treatment period

After screening you will need to attend repeated clinic visits in order to receive your medicines, have examinations and provide samples. As part of your standard treatment, your doctor will assess the extent of your cancer (e.g. by CT scan and the newer type PET/CT scan) and we will collect this information. The trial team will also need to know the details of other medicines that you take during the trial. You will also be asked some extra questions about how you are feeling and if you have noticed any side effects from your treatment. Most of the tests and procedures carried out during screening will be repeated during the treatment period.

Routine blood samples will be taken when you attend the hospital in order to monitor your progress. During your treatment, extra blood samples will need to be taken so that the levels of varlilumab and rituximab in your blood can be checked (this is called pharmacokinetics).

In order to collect more information about how the drug works (pharmacodynamic and translational studies), we would like your permission to collect, store and test some further samples of blood which will be collected at various points throughout treatment and at the end of the trial.

You can find more about the trial samples in Section 8, 'More about the trial samples'.

If you decide to take part in the RiVa trial, you will need to attend more clinic visits than if you were receiving different treatment for your returned or non-responding lymphoma: this is to enable the trial team to check that you are okay and to take further blood samples for analysis.

You will have another CT scan 2 weeks after completion of the treatment. You may have other scans as per your hospitals normal practice.

Follow-up visits

When you complete the trial treatment, you will begin the last part of the study, the follow-up period. During this 12-month period, you will visit the hospital every 2 months. During the follow-up visits, your study doctor will continue to assess your health condition. It is important to know, for example, if you have recovered, developed an illness or suffered an important adverse event. As part of this, you will have a blood sample taken and may have another CT scan. At the end of the trial, you will be followed up by your physician as per standard NHS care.

5. What is the treatment schedule?

Each treatment cycle is 14 days and you will have up to 6 cycles of treatment. You will receive rituximab in each cycle and varlilumab in every other cycle.

Cycle 1:

	Day					
Drug	**1**	**2**	**3**	**4**	**5**	**8**
Rituximab	√					
Varlilumab – Arm A		√				
Varlilumab – Arm B						√

Cycle 3 and 5:

Drug	Day					
	1	2	3	4	5	
Rituximab	√					Every 14 days for 6 cycles
Varlilumab – Arm A		√				
Varlilumab – Arm B		√				

Cycle 2, 4 and 6:

Drug	Day					
	1	2	3	4	5	
Rituximab	√					Every 14 days for 6 cycles
Varlilumab – Arm A						
Varlilumab – Arm B						

Rituximab – This will be given on day 1 of each cycle by infusion (a 'drip') in to your vein. You will receive the recommended dose for this treatment.

Varlilumab – Arm A – Varlilumab will be given on day 2 of every other cycle, during cycles 1, 3 and 5. You will receive the standard dose for this regime by infusion (a 'drip') into your vein.

Varlilumab – Arm B – Varlilumab is given every other cycle, during cycles 1, 3 and 5. During cycle 1, varlilumab will be given on day 8, during cycles 3 and 5 varlilumab will be given on day 2. You will receive the standard dose for this regime by infusion (a 'drip') into your vein.

Other medicines – You will be given other medicines to reduce the risk of infusion reactions to rituximab and varlilumab.

Will this treatment schedule change? It could change. Some of the most common reasons the schedule may change are:

- At each stage, your doctor must be satisfied that you are well enough to continue receiving treatment. If you are not well enough, your schedule of treatment may change a little or stop, depending on the exact situation. Your doctor will discuss these with you on an ongoing basis throughout the trial.
- Sometimes during the course of a trial, new information becomes available about the trial medicine. If this happens, it may or may not affect your treatment schedule. If anything changes that might affect your treatment, your doctor will discuss this with you and you can decide if you want to continue with the trial. You may be asked to sign an updated consent form.

6. What are the possible side effects?

As with most medicines, the medicines used in this trial can cause unwanted side effects. This information sheet does not list all of the known side effects, only the most common.

Please be aware that you may experience a side effect(s) that we do not yet know about: if you suffer from something that you think may be caused by the trial medicines, please contact your trial doctor/nurse.

Potential risks associated with study treatment are listed below. It is also possible that other side effects not listed below may occur following study treatment. Side effects may be mild or very serious, may last a long time or cause permanent bad effects, or could even result in death. It is possible that side effects may require medications or other treatment. For more information about risks and side effects, ask your study doctor.

Everyone taking part in the study will be watched carefully for any side effects. You should be sure to talk to your study doctor about any side effects that you have while taking part in the study.

VARLILUMAB

	Side effects associated with varlilumab	
Frequent (occurring in more than 20% of patients)	• Fatigue	
Less likely (occurring in 20% or fewer of patients)	• Rash (10%) • Nausea (feeling sick) (13%) • Vomiting (8%) • Itching (10%) • Low lymphocyte (white blood cell) count (6%) • Anaemia (4%)	• Decreased appetite (9%) • Diarrhoea (8%) • Headache (7%) • Infusion reaction (7%) • Joint pains (6%) • Fever (6%)
Rare but serious (occurring in 3% or fewer of patients)	• Bronchospasm (wheezing)	• Inflammation of the kidneys
Other potentially serious side effects	• Infusion-related reactions (fever, chills, nausea, dizziness, vomiting, headache, sweating, flushing, itching, skin rash, hives, runny nose, sneezing, cough, fatigue, joint pain, muscle pain, swelling of arms or legs, soreness or swelling at disease sites, and chest pain. Severe reactions may include tongue or throat swelling, wheezing or difficulty breathing, fluid or inflammation in the lungs, low blood pressure	• Hair loss, loss of pigmentation (colour in the skin) • Severe inflammation of the gastrointestinal tract • Changes in blood cells • Changes in organs of the endocrine system (collection of glands that produce hormones that regulate metabolism, organ function, sexual function, reproduction, sleep, and mood, among other things) • Inflammation of the eye

RITUXIMAB

Rituximab is known to cause the following side effects, though not in all patients:

	Side effects associated with rituximab	
Less likely (occurring in 20% or fewer of patients)	• Anaemia • Fewer white blood cells	• Tumour lysis syndrome, which means that your cancer cells die and release their contents into your blood stream. This may be mild (resulting in changes in blood tests) to severe (resulting in kidney damage) • Immune system problems (including inflammation of the eyes, nerves, blood vessels, joints, or lining of the lungs)
Rare but serious (occurring in 3% or fewer of patients)	• Reactions of the lining of the mouth, nose and eyes (includes peeling, rashes, blisters and open sores) • Worsening of hepatitis B • Worsening of pre-existing heart problems, including heart failure, heart attack, irregular heartbeat, and angina	• Progressive multifocal leukoencephalopathy (PML), an infection of the brain that can cause brain damage, memory loss, trouble thinking, blindness, and death. • Bowel obstruction and rupture
Other potentially serious side effects	• Infusion-related reactions (fever, chills, nausea, dizziness, vomiting, headache, sweating, flushing, itching, skin rash, hives, runny nose, sneezing, cough, fatigue, joint pain, muscle pain, swelling of arms or legs, soreness or swelling at disease sites, and chest pain. Severe reactions may include tongue or throat swelling, wheezing or difficulty breathing, fluid or inflammation in the lungs, low blood pressure	• Increased risk of infections • Interaction with vaccinations • Heart failure • Irregular heartbeats • Lung problems (scarring or inflammation) • Developing hepatitis B

Varlilumab combined with rituximab

Varlilumab combined with rituximab for the treatment of cancer has not been studied in another trial. The side effects of the combination may be similar to what has been identified in other trials separately evaluating varlilumab or rituximab, or the side effects of the combination may be different. There also may be new side effects of the combination that are not yet known that may occur. You should tell your doctor or nurse right away about any possible side effects you experience with this combination treatment.

7. What will happen at the end of the trial?

You will have an end of treatment clinic visit 2 weeks after the completion of cycle 6. After the completion of cycle 6, you will be followed up every 2 months for one year as part of the trial. You will then be followed up by your physician as per standard NHS care.

8. More about the trial samples

In the trial, you will have a biopsy at screening and on day 8 of cycle 1. These biopsies are extremely important to help doctors understand how the treatment works or fails, and how we might make it better. Specifically, we are analysing the behaviour of the cancer cells and how the immune system responds with treatment to understand how the drug works in the body (these studies are called pharmacodynamic and translational studies). We will also collect blood samples for pharmacodynamic tests. These samples will be sent to the Southampton Tissue Bank for storage and will be analysed at the WISH Laboratory at Southampton General Hospital. This information, along with the other results collected in this trial, will be used to get a better understanding of lymphoma, how treatment works and how it interacts with lymphoma.

If your tumour does not respond to the treatment then a further optional biopsy will be requested with your permission.

Within the trial we will need to take a number of additional blood samples from you at regular time points, please ask your trial team for exact details. We need to take these blood samples at specific times throughout the trial after you have received rituximab and varlilumab so that we can assess the level of drug in your blood over time (this is called pharmacokinetics). Some of these samples will be sent to the Southampton Tissue Bank for storage and will be analysed at the WISH Laboratory. Other pharmacokinetic blood samples will be sent to Celldex Therapeutics in the USA for analysis.

All of your samples will be coded: this means that your samples will be labelled with a code number, not your name. Neither you nor your relatives will be contacted about them once they have been taken.

With your consent, any remaining samples may be used in future ethically approved studies. You can agree to this or decline on the informed consent form.

9. What are the possible benefits, risks and disadvantages of taking part in the trial?

Clinical trials are designed to reduce the risks and increase the benefits to the people who take part, regardless of which treatment they get. However, we cannot guarantee any specific treatment benefits or that there are no risks involved when taking part in a clinical trial.

Possible benefits:

- You will be helping to further our knowledge of how to treat cancer and this will benefit society and others with the same condition in the future.

Possible risks/disadvantages

- The trial treatment may not control your lymphoma.
- There may be some unpleasant side effects (please see section 6 for more information).
- There could be risks to your child if you, or your partner, are or become pregnant, or breastfeeding (please see section 11 for more information).
- You will need to attend more clinic visits.
- You will provide more blood samples and undergo more tumour biopsies than if you were not taking part in the trial. These can cause pain, bruising, infection or inflammation at the sampling site, and may make you feel faint.

Radiation Risks

- During the trial, you will have contrast enhanced CT scans and PET/CT scans. These scans are part of your routine care. If you take part in this study, you will not undergo any additional contrast enhanced CT scans or PET/CT scans. These tests use ionising radiation to provide your doctor with images of your tumour. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. The chances of this happening to you are the same whether you take part in this study or not.

Risk Explanations:

A **contrast enhanced CT scan** involves radiation, using X-Rays to get a detailed image of the body area. The main risk of the radiation is there is a small chance it may cause a cancer many years after exposure. It is considered that for a patient with your medical condition this represents a very small risk. The CT scans also require an injection of a dye to help show up your organs and any tumours that might be present, which some patients may have an allergic reaction to. In certain patients, it could cause kidney damage and it is recommended that if you have previously experienced problems, you let your doctor know.

In comparison, for a **PET/CT scan**, an injection with a radioactive isotope is given to you. The PET/CT scanner detects how much of the isotope your body absorbs and uses a computer to create an accurate image of the scanned body area. As with CT scans, this involves radiation which has a small chance of causing cancer many years after exposure, though it is higher than a CT scan due to the extended time within the scanner. It is considered that for a patient with your medical condition this represents a very small risk.

10. What are the alternative treatments?

If you prefer not to take part in the RiVa trial, your doctor will be able to discuss all treatment options with you. Please be reassured that it is entirely up to you whether or not you decide to take part in the RiVa trial. If you decide not to take part, the standard of your care will not be affected in any way.

11. More about contraception and pregnancy during the trial

We realise that it is very unlikely that female trial participants will become pregnant. However, it is important that we provide the following information:

Women

If you are pregnant or breast feeding, you will not be able to enter the RiVa trial. Women who are of child bearing potential will need to have a negative pregnancy test at screening (prior to starting treatment). Please be aware that if you become pregnant during the trial, you will not be able to continue taking part in the trial.

You must also agree to use one very effective form of contraception and one effective form (see below) from the start of your trial treatment, throughout the trial and for 12 months after finishing treatment.

Men

If your partner is pregnant or breast-feeding, we advise you to use barrier method contraception (condom) to make sure that the baby is not exposed to the trial drug.

If you have a partner of child bearing potential, you must agree to use one very effective form of contraception (see below) from the start of your trial treatment, throughout the trial and for 12 months after finishing treatment. You must refrain from any sperm donation from the start of your trial treatment, throughout the trial and 12 months after finishing treatment.

Suitable very effective contraceptive methods include:

- Oral, injected or implanted progesterone-only hormonal contraception (with inhibition of ovulation)
- Oral, intravaginal, or transdermal combined (oestrogen and progesterone containing) hormonal contraception (with inhibition of ovulation)
- Intra-uterine device (IUD)
- Intra-uterine hormone releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Abstinence

Suitable effective contraceptive methods include:

- Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Condom
- Cap, diaphragm or sponge with spermicidal gel

**** If you or your partner becomes pregnant during the trial, you must tell your trial doctor immediately because we will need to follow the pregnancy to check that the trial drug has not caused any problems. ****

Future fertility – chemotherapy can affect your ability to have children in the future so you may wish to discuss this, and the possibility of storing eggs/sperm, with your doctor.

12. Other questions you may have about the trial

What does informed consent mean?

No one can enter you in the trial without your permission. To help you decide if taking part in a trial is right for you, the trial doctor/nurse should discuss the trial with you in depth. The most important thing is that you should feel satisfied that you know enough about the trial to make an informed decision. You should feel free to ask as many questions as you need to. In addition, you should be given as much time as you need to make your decision – you should not feel rushed.

If you decide to take part in the trial, you will be asked to sign a consent form which confirms that you agree to take part.

What if I change my mind?

If you decide to take part in the RiVa trial, then you are still free to withdraw at any time without giving a reason. This will not affect your future care in any way but we would still like to know how you are, and with your permission, will request this information from your doctor. This is so that the overall quality of the study is not impaired. Please let your doctor know if you wish to withdraw and he/she will carry on your care in the normal way.

If you withdraw, you will be asked to clarify which part of the trial you are withdrawing from. You may withdraw from some parts or all parts. Depending on your response, we will know what information we can keep and whether we can still collect information on your progress.

Will my details be kept confidential?

Yes. If you decide to take part in the RiVa trial, any data collected and any results produced will not identify you personally. Information collected during the trial may be transferred within or outside of the European Economic Area and the Sponsor is responsible for ensuring compliance with the UK Data Protection Act of 1998 and protection of your privacy. Non-identifiable data, managed by the Southampton Clinical Trials Unit, will be held on servers located in the EU and USA. Access to this data will be strictly controlled and all applicable Data Protection legislation will be abided by. In collaboration with the Southampton Clinical Trials Unit, a selection of laboratories across the UK will have strictly controlled access to your anonymised data. This information will contribute to a better understanding of this disease and will be used by investigators who will not have access to any data that will identify you. The data may also be used in future, ethically approved studies to further enhance our understanding of your disease. There are no additional visits or investigations required. You can agree to this or decline on the informed consent form.

With your permission, we will tell your General Practitioner (GP) that you are taking part in the RiVa trial. Your medical records will be available to those involved in your clinical care and authorised individuals from the Sponsor or the Sponsor's delegates from the Southampton Clinical Trials Unit and Regulatory Authorities.

Expenses and Payment

You will not receive any payment for taking part in this trial nor will your traveling expenses be reimbursed.

What happens if something goes wrong?

If you decide to take part in the RiVa trial and feel concerned about any part of the trial at any point, you should contact your research doctor/nurse as soon as possible. Your clinical research team will do their best to help you and answer your questions.

If you wish to complain, or have any concerns about the way you have been approached or treated during the RiVa trial, the normal NHS complaints system will be available to you. Please be aware that if you are harmed as a result of taking part in the RiVa trial, there are no special compensation arrangements. If you are harmed because of someone's negligence, you may be able to take legal action but you may have to pay your own legal costs.

If you have private medical insurance you may wish to check with your provider before agreeing to take part in this trial to make sure that your participation will not affect your cover.

Who is organising and funding the trial?

This is an academic trial coordinated by the Southampton Clinical Trials Unit. The trial is funded by Cancer Research UK and by Celldex Therapeutics Ltd (the manufacturer and supplier of varlilumab). The Sponsor is University Hospital Southampton NHS Foundation Trust.

What will happen to the results of the trial?

At the end of the trial, any results will be analysed and presented at national or international meetings, and will also be published in a medical journal. You will not be personally identified in anyway in any reports or publications that come from the RiVa trial. A lay version of the trial results will be prepared and made available for patients and members of the public, please ask your doctor.

13. Contact information

If you have any further questions about your illness or available treatments please discuss them with your doctor. If at any stage you have questions about the RiVa trial, or would like to discuss your participation in more detail, please contact:

Doctor's name: *(Insert)*

Name of treatment centre: *(Insert)*

Telephone number: *(Insert)*

Further information about cancer, treatments and taking part in trials can be found on the Cancer Research UK website: www.cancerresearchuk.org

Macmillan Cancer Support can also provide support and information: http://www.macmillan.org.uk/