(Form to be on hospital/institution headed paper)

INCA TRIAL

A multicentre randomised phase II clinical trial of Inotuzumab Ozogamicin plus Rituximab and CVP (IO-R-CVP) versus Gemcitabine plus Rituximab and CVP (Gem-R-CVP) for the first line treatment of patients with diffuse large B cell lymphoma who are not suitable for anthracycline containing chemotherapy

IRAS No.: 106985

PATIENT INFORMATION SHEET

INCA

We would like to invite you to take part in a clinical trial for patients with diffuse large B cell lymphoma (DLBCL).

- Before you decide if you would like to take part, one of your doctor's team will go through this patient information sheet with you and answer any questions you may have so that you understand why the research is being done and what it would involve for you.
- Please take as much time as you need to read the information carefully and discuss it with friends, relatives and others if you wish. Ask us if there is anything unclear or if you would like more information and take your time to decide whether or not you wish to take part.
- You are free to decide if you want to take part in this trial. If you choose not to take part, this will not affect the care you receive from your doctor.
- You can decide to stop taking part in the study at any time without giving a reason.
- If you decide to take part, we will ask you to sign a form to give your consent for the study.

Brief summary of the INCA trial

We are testing whether a new drug, **Inotuzumab ozogamicin (IO),** given together with rituximab, cyclophosphamide, vincristine and prednisolone, is a safe and effective treatment for patients with DLBCL who cannot be treated with standard therapy due to heart problems or other serious health problems. The new drug combination is called **IO-R-CVP**.

Half of the patients in the trial will be treated with IO-R-CVP. The other half of patients will also be treated with rituximab, cyclophosphamide, vincristine and prednisolone, but instead of the new drug IO, they will have gemcitabine. This drug combination is called **Gem-R-CVP** and is commonly used to treat DLBCL patients with heart problems or other serious health problems.

Patients will be chosen randomly which drug combination to receive (the new IO-R-CVP or the standard Gem-R-CVP).

As **IO** is a new drug we cannot anticipate all side effects you may experience. You will be closely monitored by your doctor who will give you medication for the side effects if needed and may delay or change the dose of the trial drugs you are administered.

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How to contact us

If you have any questions about this trial, please talk to your trial doctor or members of the research team:

<Trial Doctor Name>

<Contact phone number>

<Research Nurse Name>

< Contact phone number

1 What is the purpose of the study?

This study is trying to find a better treatment for cancer patients with a type of lymphoma called diffuse large B cell lymphoma, often shortened to DLBCL. It is a form of cancer that mainly affects the body's lymph nodes but sometimes also involves other parts of the body, especially the bone marrow.

The standard treatment for DLBCL is a combination of chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine, and prednisolone) with rituximab (a newer type of immunotherapy drug). This drug combination is called R-CHOP. However it is not a suitable treatment for DLBCL patients with heart problems as one of the drugs (doxorubicin) can harm the heart. This is why many DLBCL patients with heart problems are given the drug combination without doxorubicin (called R-CVP). R-CVP sometimes controls DLBCL but rarely cures it. For this reason we need to find treatments that are less toxic than R-CHOP but more effective than R-CVP.

Recently a trial showed that adding another chemotherapy drug called gemcitabine to the R-CVP combination is safe and effective in treating DLBCL patients with heart problems. This drug combination is called Gem-R-CVP.

Inotuzumab ozogamicin (IO) is a new cancer drug which consists of an antibody (targeting the lymphoma cells) with attached chemotherapy drug (which kills the targeted lymphoma cells).

The INCA trial aims to find out whether giving inotuzumab ozogamicin (IO) with R-CVP is an effective treatment for patients with DLBCL who cannot be treated with R-CHOP due to heart problems. This combination is called IO-R-CVP.

The study will compare one group of patients receiving the new IO-R-CVP combination with a group of patients receiving the existing Gem-R-CVP combination. Patients will be allocated to one of the two groups at random (this is called randomisation).

Randomised trials are done when there are several treatment options but we don't know which one is best. Randomisation, is done by a computer, to ensure that people in each group are equally matched for disease characteristics and any features which could influence the outcome of treatment. Thus the only difference between the two groups will be the allocated treatment.

This means that neither you nor your doctor can choose whether you get the new IO-R-CVP combination or the existing Gem-R-CVP combination.

2 Why have I been invited?

We have invited you to take part in this study because you have been diagnosed with DLBCL but your doctors think that it would not be safe to treat the lymphoma with R-CHOP because of your heart problems or other serious health problems.

Patients from other hospitals across the UK have been invited to take part in this study. We aim to have 132 people taking part in this trial.

3 Do I have to take part?

No. It is up to you to decide.

The clinical team will go through this information sheet with you, explain what is involved in taking part and answer any questions you may have. You will be able to take this information sheet home with you and think about taking part. You are free to discuss the information with anyone you wish including your family and friends.

If you decide to take part in the INCA trial, we will ask you to sign a consent form.

You can withdraw from the study at any time without giving a reason and this will not affect the standard of care you receive from your doctor.

If you decide not to take part, this will not affect your medical treatment in any way and your doctors would decide on the best combination of drugs to treat the DLBCL.

4 What will happen if I take part?

Consent and screening:

If you would like to take part in this study, we will ask you to sign a consent form.

We will then carry out some screening tests to find out if you meet all of the entry criteria for the study.

The screening tests are routine investigations that you would have as part of your standard care even if you decide not to enter the study. If you do enter the study, you may already have had some of the tests carried out before you sign the consent form. The tests will be the same for all of the people entering the study.

The screening tests and investigations will include:

- Collection of information about your medical history.
- A physical examination will be done by your doctor. This will include measurement of vital signs (including blood pressure, temperature and pulse), height and weight, an examination of your lymph nodes, and an assessment of the size of your liver and spleen. The examination will assess the spread of the disease as well as your general health status.
- Blood samples will be taken (about 2 tablespoons) to assess your blood count, biochemistry (including tests to check liver and kidney function), and to check for different viruses including hepatitis B, and hepatitis C. Your blood may also be tested for HIV.
- Biopsy – this is usually a sample of tissue from a lymph node, and is used to diagnose DLBCL. If you have already had a biopsy, it does not need to be repeated for the study.
- Bone marrow biopsy – this involves inserting a needle into the back of your pelvis and taking a small amount of bone marrow fluid and bone marrow tissue. This is carried out under local anesthetic and is important to determine the spread of the lymphoma. Bone marrow biopsies are a standard test in most hospitals for patients with newly-diagnosed DLBCL.
- A sample of cerebrospinal fluid may be taken to check for lymphoma cells. This involves inserting a needle between the bones in your lower spine and drawing out a small sample of fluid. Not all patients will need to have this test.
- Tests to determine the function of your heart such as electrocardiograms, echocardiogram or MUGA scan.
- Further tests for kidney function using urine or blood samples will be needed if your kidney function is impaired.
- CT scan – a scan of your neck, chest, abdomen, and pelvis will need to be performed to find out and measure the spread of disease in your body. This may already have been done as part of your standard care, but if it was done more than 5 weeks ago, the scan may need to be repeated because it is important to have the most up to date results. A CT scan is a special type of x-ray, which builds up a three-dimensional picture of the inside of the body. You may have an injection of a dye called 'contrast medium' that will help make the tissues in your body show up better in the scan. The scan is painless, and takes about 20 minutes. It involves lying on a bed that moves through a short tunnel, which contains the scanner. Your doctor may decide to perform a PET-CT instead of a CT scan and may choose to perform other imaging (e.g. an MRI) if needed. A PET-CT combines a CT scan and a PET scan into one scan to give more detailed information. The PET part uses a very small amount of an injected radioactive drug to show where cells are active in the body.
- If you are a woman who could become pregnant, we will ask you to have a pregnancy test.

We will also ask you to complete a questionnaire about your quality of life. Your doctor will ask you about any previous illnesses and level of any disability you may have. This is called a functionality assessment.

With your permission, we would like to collect a sample of tissue from your biopsy and additional blood samples, to be sent to central laboratories for research. The extra blood samples would be collected at the same time as your routine blood samples. There is more information about this research (including how the samples will be labelled) in **section 16** of this information sheet. You will be asked to sign a consent form if you are happy to give these samples.

Treatment

Steroids

The majority of patients will have steroids (prednisolone) which are taken in tablet form at home before starting trial treatment. If your doctor feels that you do not need steroids this will be explained to you by your doctor.

If you are considered to be in good enough health to go ahead with the next treatments, you will be allocated randomly (as explained in section 1) to one of the two different study groups (also called treatment arm): the new IO-R-CVP combination or the existing Gem-R-CVP combination.

Trial treatment

The exact treatment that you will receive (described further below) will depend on which treatment arm you are randomly allocated, but the treatments in each arm last for the same period of time.

You will initially receive 3 cycles of treatment, each one given 21 days (3 weeks) apart.

After 3 cycles of treatment you will have another CT scan (or PET-CT scans (with or without MRI scans) if your doctor has decided to perform PET-CT scans) to assess your response to treatment. You will also

be asked to complete a questionnaire regarding your quality of life and your doctor will complete a functional assessment with details about any previous illnesses and any disability you may have.

If the scan shows that the DLBCL is responding to the treatment, you will go on to receive another 3 cycles of treatment given every 3 weeks, followed by 2 doses of rituximab on its own, also given 21 days apart.

This means that your treatment will take approximately 24 weeks in total.

New treatment arm IO-R-CVP:

If you are allocated to IO-R-CVP you will need to come to hospital three times during each cycle: for treatment on days 1 and 2 of the cycle, and also on day 8 for assessments in line with patients on the other treatment arm. We are asking you to visit the hospital on day 8 as well in order that the information we collect about side effects between the two treatments is equal.

The drugs are given as follows:

Day 1 of each treatment cycle:

- Rituximab – given as a slow infusion through a drip into a vein
- Cyclophosphamide – given as an injection into a vein
- Vincristine – given as an infusion into a vein

Day 2 of each treatment cycle:

- Inotuzumab ozogamicin – given as an infusion into a vein

Days 1 - 5 of each treatment cycle:

- Prednisolone – given as tablets to be taken for the first 5 days of each treatment cycle (the first day will be given to you at the hospital, but you will take the tablets at home on days 2 to 5)

In addition, you will need to take a number of other medications to treat or prevent side effects during the treatment, these will be determined by your trial doctor and may include an injection of a growth factor called G-CSF to boost your body's immune system and reduce the risk of infections.

After completing the 6 cycles of IO-R-CVP treatment you will then receive 2 infusions of rituximab treatment (each cycle of rituximab is also 21 days long). The rituximab may be given to you as a slow infusion through a drip into a vein on day 1 of each cycle.

Control arm Gem-R-CVP:

If you are allocated to Gem-R-CVP you will need to come to hospital twice during each cycle for treatment, on days 1 and 8 of the cycle.

The drugs are given as follows:

Day 1 of each treatment cycle:

- Rituximab – given as a slow infusion through a drip into a vein
- Cyclophosphamide – given as an injection into a vein
- Vincristine – given as an infusion into a vein

Day 1 and Day 8 of each treatment cycle:

- Gemcitabine – given as an infusion into a vein on the first and eighth day of each treatment cycle

Days 1 - 5 of each treatment cycle:

- Prednisolone – given as tablets to be taken on the first 5 days of each treatment cycle (the first day will be given to you at the hospital, but you will take the tablets at home on days 2 to 5)

In addition, you will need to take a number of other medications to treat or prevent side effects during the treatment. These will be determined by your trial doctors and will include an injection of a growth factor called G-CSF to boost your body's immune system and reduce the risk of infections.

After completing the 6 cycles of Gem-R-CVP treatment you will then receive 2 infusions of rituximab treatment (each cycle of rituximab is also 21 days long). The rituximab may be given to you as a slow infusion through a drip into a vein on day 1 of each cycle.

Hospital visits

During treatment:

The details of visits to the hospital during treatment will depend on which treatment arm you are randomly allocated to receive.

In the IO-R-CVP arm you will need to attend hospital for treatment on the 1st and 2nd day for 6 cycles and then the 1st day for a further 2 cycles. You will also need to visit the hospital on day 8 of each cycle for us to collect information about any side effects of your treatment.

In the Gem-R-CVP arm you will need to attend hospital for treatment on the 1st and 8th day for 6 cycles and then the 1st day for a further 2 cycles.

Mid-way through your chemotherapy and after finishing your treatment you will be required to come back to hospital for tests to measure how effective the treatment has been.

Follow up visits after completing treatment:

You will be asked to attend regular hospital visits for follow-up so we can assess your response to treatment in the same way doctors would see you if you weren't participating in the study.

You will be seen every 3 months for the first year after treatment, every 4 months in the second year, every 6 months in the third year and annually thereafter.

Trial duration

The trial treatment consists of 6 cycles of treatment plus 2 further cycles of rituximab treatment. Each cycle lasts 21 days (3 weeks). Treatment will take approximately 24 weeks (about 6 months) in both arms of the trial.

After the trial treatment has been completed, we will ask you to come to hospital for regular follow-up visits as part of the trial for at least 3 years.

It may not be possible to learn everything we can from the trial within the 3 years of follow up. Rather than make you attend clinic for many years, we would like your permission to collect health information about you in the future from registries such as the National Cancer Registration and Analysis Service, NHS Information Centre's Medical Research Information Service (MRIS), the Health and Social Care Information Centre (for patients in England), NHS Wales Informatics Service (Wales) or the Information Services Division (Scotland). In order to collect this information we would need to use some of your personal identifiers (such as initials, date of birth and NHS number).

Please see the flowchart on the next page summarising the trial treatment, follow up and investigations performed.

5 What will I have to do?

It is important that you attend for all scheduled appointments for treatment and clinic visits.

These visits will include blood tests, physical examinations, measurement of vital signs, completion of questionnaires, CT scans (or PET-CT scans (with or without MRI scans), measurement of your heart function (only measured after the end of treatment) and a repeat bone marrow biopsy (after the end of treatment) if the cancer was present in your bone marrow at the start of the study.

If you are on the IO-R-CVP arm you will also need to have ECGs performed before each cycle of treatment.

The exact schedule of your clinic visits and treatment appointments will depend on which treatment you are receiving but you should be prepared to spend longer at the hospital for some visits.

Taking part in this study does not place any restrictions on your daily way of life, although you will probably suffer fatigue and may have some side-effects. These problems are common in many cancer patients being treated with drugs, whether or not they are in research studies.

Other drugs while on trial treatment

There are restrictions relating to what other drugs you can take during the study. Your doctor will explain which drugs should be avoided. Please let your doctor or nurse know which medicines you are taking before you start the study, and during the study, so they can check if there are any possible interactions between these medications and the study treatment. Your doctor may ask you to change your regular medications if they cannot be taken with the study medication. You will also need to check with your doctor before taking additional/new medicines (e.g. bought over the counter anti-inflammatory/pain killers such as aspirin, paracetamol, indometacin) and/or herbal medicines.

6 What is the drug that is being tested?

This study is testing a new combination of drugs called inotuzumab ozogamicin, rituximab, cyclophosphamide, vincristine, and prednisolone (IO-R-CVP). This will be compared to a combination of drugs called gemcitabine, rituximab, cyclophosphamide, vincristine, and prednisolone (Gem-R-CVP).

- **Inotuzumab ozogamicin** is a new type of anti-cancer treatment. It is an antibody treatment that is targeted against lymphoma cells. In addition to being an antibody treatment, it also has a chemotherapy drug attached to it that it delivers directly into the lymphoma cells to kill the lymphoma cells with reduced side effects compared to traditional chemotherapy.
- **Rituximab** is an antibody treatment that has been used for a number of years in the treatment of various types of lymphoma, especially DLBCL. It targets the lymphoma cells and has been shown to be very effective especially when used in combination with chemotherapy drugs.
- **Cyclophosphamide** and **Vincristine** are established chemotherapy drugs.
- **Prednisolone** is a steroid drug that is very effective in the treatment of lymphoma and is included in most treatment combinations used in the treatment of DLBCL.

- **Gemcitabine** is an established chemotherapy drug that has recently been shown to be effective and safe when added to R-CVP in the treatment of DLBCL in patients with heart problems.

INCA TRIAL

Treatment and Investigations Summary

Consent
You agree to take part in the trial after reading this information sheet and sign a consent form

Screening
Tests to check if you are eligible for the trial

Investigations

- Physical examination
- Medical history
- Blood samples
- Lymph node biopsy
- Bone marrow biopsy
- Electrocardiogram and/or
- Echocardiogram and/or MUGA
- CT scan or PET-CT scan
- Urine analysis
- Pregnancy test (if appropriate)
- Lumbar puncture if needed

Steroids
You may be asked to take steroids for up to 28 days.

- Performance Status
- QoL questionnaires
- Functionality assessment

Treatment
If you are considered to be in good health you will be allocated randomly to one of the two treatments arms

IO-R-CVP Arm (new combination)

Day 1:
Cyclophosphamide (iv infusion)
Vincristine (iv infusions)
Rituximab (iv infusion)
Day 2:
Inotuzumab ozogamicin (iv infusion)
Days 1-5:
Prednisolone (tablets at home)
Days 4-12 (if needed):
G-CSF

Each cycle is 21 days
Maximum of 6 IO-R-CVP cycles
Followed by 2 cycles with
Rituximab only on Day 1

GEM-R-CVP Arm (control)

Day 1:
Cyclophosphamide (iv infusion)
Vincristine (iv infusions)
Rituximab (iv infusion)
Gemcitabine (iv infusion)
Days 1-5:
Prednisolone (tablets at home)
Day 8:
Gemcitabine (iv infusion)
Days 9-17 (if needed):
G-CSF

Each cycle is 21 days
Maximum of 6 Gem-R-CVP cycles
Followed by 2 cycles with
Rituximab only on Day 1

- Physical examination
- Performance Status
- Blood samples
- Electrocardiogram (IO-R-CVP arm before each cycle, and all patients at end of treatment
- CT scan after the 3rd cycle
- QoL questionnaires after the 3rd cycle and at the end of all treatment
- CT or PET-CT at the end of all treatment
- Bone marrow biopsy at the end of all treatment if needed

Follow up
Out-patient clinic 3 monthly during the first year, 4 monthly during the second year, 6 monthly during the third year and annually thereafter

- Physical examination
- Performance Status
- CT or PET-CT at 3 months and 1 year
- QoL questionnaires at 6 and 24 months

7 What are the alternatives for treatment?

Some doctors would use R-mini CHOP (which has a lower dose of doxorubicin) in some carefully selected patients, but not in patients with severe heart problems.

Some doctors would use the R-CVP combination which is very safe but is not considered to be effective enough to lead to a cure in most patients with DLBCL.

Most other treatment options include adding other anti-cancer drugs to R-CVP. Gem-R-CVP has been the most carefully studied of the alternatives in the UK, which is why we are using it in the INCA study.

You should discuss all your treatment options with your doctor before you decide to take part in this study. You may decide that you do not want to take part in this study, but whatever you decide to do, this will not affect your rights to receive the best medical care from your doctor.

8 What are the possible disadvantages and risks of taking part?

Taking part in this study will mean that you may have extra tests to assess the effect of treatment on your disease.

- Bone marrow biopsy

You will have a bone marrow biopsy before taking part in the trial which is a standard staging test for lymphoma. You will be required to have another bone marrow biopsy at the end of treatment if the result of your first bone marrow sample showed cancer cells were present.

- CT and PET/CT scans

Taking part in this study means you will have up to 5 CT (or PET/CT) scans to assess the extent of your disease. These scans use ionising radiation which can cause cell damage and this is associated with a small increase in the natural risk of incurring cancer. The ionising radiation dose from each CT scan is equivalent to the radiation dose received from 5-10 years of naturally occurring background radiation exposure. The radiation dose from a PET-CT is similar or lower than a CT scan.

CT scanning is a usual part of lymphoma treatment and you would typically have 4-5 scans as part of treatment. Participation in this study is likely to expose you to up to 1 additional CT scan. However the increased radiation exposure from the additional scan is very unlikely to have any detrimental effects on your health.

- Blood samples

With your permission, we would like to take some blood to be analysed at laboratories outside your hospital as part of this trial. This will mean we would take more blood than usual when you have some of your routine blood tests. You would not be subjected to any more needles than you would if you were treated in the standard way. More information about these tests is in **section 16** of this information sheet.

- Questionnaires

As an important part of this study is to find out how the treatments affects your life, we will ask you to complete questionnaires about your quality of life before, during and after your treatment. This may make some of your clinic appointments longer than if you were not taking part in the study but you will not need to attend hospital any more frequently. You would not routinely complete such questionnaires if you were not participating in this study.

Before agreeing to take part in the study you should check that any private medical insurance you have will not be affected by your participation in the study.

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

All drugs have side effects. If side effects occur and cause you problems, your treatment doses can often be adjusted, so please make sure that you inform your trial doctor about any side effects that you are experiencing.

It is unlikely that you will experience all of the side effects listed in this section, or even many of them, but we cannot predict which ones you will experience, or how serious they may be. You may experience a less common reaction not listed here. If you have a severe reaction, we may discontinue the study treatment and recommend alternative treatments. In general most are short term and will begin to go once treatment has stopped.

Common Chemotherapy Side effects (more than 1 in 10 patients):

- General: tiredness, lethargy, fatigue, change in mood, loss of facial/head/bodily hair, nail changes, loss of fertility
- Digestive system: mouth ulcers, change in sense of taste, constipation, diarrhoea, vomiting
- Lowered blood counts: this may result in infection, tiredness, clotting or bleeding problems
- Skin: rashes, soreness, itchiness, flakiness
- Nerves: tingling or numbness sensations, change in hearing

Inotuzumab ozogamicin and gemcitabine side effects

Some of the expected possible side effects for the two drugs added to the R-CVP backbone of treatment are as follows:

Incidence*	Inotuzumab ozogamicin side effects	Gemcitabine side effects
>50%	Lowered blood counts Constipation Fatigue Infection	**>10% occurrence** Lowered blood counts Nausea/vomiting Abnormal liver function Blood or Protein in the urine Skin rashes Hair loss Shortness of breath Flu- like symptoms (including sweating, malaise and other symptoms listed) Weight loss Swelling including facial swelling
10-50%	Abnormal liver function Nausea Loss of appetite Fever Chills Headaches Abdominal pain Diarrhoea Vomiting Sore mouth (including inflammation of mouth/lips) Bleeding	
<10%	Infusion reaction Change in ECG reading (which is a measurement of heart trace) Abdominal distention Accumulation of protein-like fluid in the abdomen Excessive uric acid in blood	Headache Altered sleep patterns Cough Nasal irritation Diarrhoea Mouth ulcers Sore mouth (including inflammation of mouth/lips) Constipation Fever Chills Weakness Loss of appetite Itching Back pain Muscle pain

*An incidence of <10% means that less than 1 patient in 10 would experience the side effect. An incidence of 50% means that 1 in every 2 patients would experience the side effect.

Inotuzumab ozogamicin

In previous studies with inotuzumab ozogamicin some patients developed severe liver problems. This can happen during and after treatment. Some of these cases have been fatal. However such cases are extremely rare and your clinician will monitor your liver function closely during and after treatment.

R-CVP side effects

Some of the known side effects for the drugs used in the R-CVP regimen are as follows (all patients receive these drugs plus either inotuzumab ozogamicin or gemcitabine):

Incidence*	R-CVP side effects
>50%	Hair loss Infusion reactions to rituximab (especially to the first infusion)
10-50%	Infections Loss of appetite Heart changes Constipation Nausea/vomiting Mouth ulcers Fluid retention Tingling or numbness in the hands/feet Rashes Fever Chills Headache Weakness Menstrual periods temporarily stop
<10%	Lowered blood counts Blood in the urine Mouth ulcers Eye irritation Abdominal cramps Shortness of breath Diarrhoea Sore throat Weight loss Abnormal liver Kidney and pancreas function Abnormal blood pressure Visual disturbances

Rituximab

The Medicines and Healthcare products Regulatory Agency (MHRA), the government body that checks the safety of drugs, has warned that a very small number of people treated with rituximab for non-Hodgkin's lymphoma developed a dangerous brain infection called Progressive Multifocal Leukoencephalopathy 'PML'. Some of these people died. But doctors don't know for sure if rituximab caused the illness. In some cases, the infection happened more than one year after people stopped rituximab treatment. This is extremely rare and in patients who have received rituximab for a variety of indications (i.e. not just non-Hodgkin's lymphoma patients) it only occurs in approximately 1 in every 20,000 cases. Your clinician is aware of this risk and will take necessary steps to monitor you for any signs and symptoms of PML.

The company that make Rituximab have warned that a very small number of people (<1/10,000) taking Rituximab for lymphoma and leukaemia have developed severe skin reactions known as Stevens-Johnson syndrome. This syndrome is not specific to Rituximab, a number of other drugs are known to cause it. However, although it is usually treatable it can be severe and some of these people died. The skin reaction can happen during treatment with Rituximab, or in the first few months after finishing treatment. The main symptoms are a rash and blistering of the skin. If you develop a rash during or after your Rituximab treatment, please contact your study doctor immediately.

Gemcitabine

The company that make gemcitabine have warned that a very small number of people (<1/10,000) taking gemcitabine for lymphoma as a single drug or in combination with other chemotherapy agents have developed posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences. The main symptoms are high blood pressure and seizure activity but other symptoms include a headache, tiredness, confusion and blindness. PRES is typically reversible in most cases with appropriate treatment. Your clinician is aware of this risk and will take necessary steps to monitor you for any signs and symptoms of PRES.

Patient Contact Card

You will be asked to take home a patient contact card with you to carry while you are on treatment. This will give details of the study treatment and contact details for your hospital and should be shown to any other doctors who may treat you while you are taking study treatment.

If you would like any further information on the potential side effects of the drugs please speak to your doctor and they may be able to provide further information leaflets on the individual drugs.

Please tell your doctor if you have any side effects at any time throughout the study.

10 Harm to the unborn child

For women:

Please share this information with your partner if appropriate.

- Some of the chemotherapy drugs used in this trial are known to be harmful to unborn babies. It is also possible that these drugs may be present in breast milk. If you are pregnant or breast-feeding you will not be able to take part in the trial.
- If there is a chance that you could become pregnant, you will be asked to take a pregnancy test before entering the trial to ensure you are not pregnant.
- You must agree to use at least 1 form of contraception during your treatment (e.g. hormonal contraception, intrauterine device (IUD) or intrauterine system (IUS). This must continue for the time you are receiving treatment and for 12 months after you finish your treatment. If you or your partner have been sterilized or you will practice absolute and complete abstinence you will not need to use one of the above methods. If you do become unexpectedly pregnant during the trial, you must inform your trial doctor immediately. We would discuss referral for specialist counselling on the possible risks to yourself and your unborn baby.

For men:

Please share this information with your partner if appropriate.

- It is possible that the trial medicine will affect sperm or semen and therefore you should not father a child during the trial, or for a safety period of 12 months after trial treatment.
- If your partner might become pregnant you must advise her to use at least 1 reliable form of contraception during treatment and for 12 months afterwards (as described above). You should also use condoms during treatment and for 12 months afterwards.
- If your partner becomes pregnant during the trial, or within 12 months of your stopping treatment, you must tell your trial doctor immediately. We would discuss referral for specialist counselling on the possible risks to your partner and your unborn baby.
- We recommend that male patients wanting to father children should preserve unexposed sperm

prior to commencing treatment and this should be discussed with your doctor.

For women and men:
Pregnancies occurring during or following trial treatment will need to be monitored and followed up; in order to do this a pregnancy monitoring information sheet and consent form will be provided.

If you are uncertain about what contraception measures to use please discuss this with your doctor.

11 What are the possible benefits in taking part?

You may or may not benefit. Half the people in the study will receive the current best available treatment. The others will receive a treatment that we think may be more effective, but we do not know this. We are asking patients in both arms to complete questionnaires and, if possible, to donate samples. That is why the information we get will help us to improve the treatment of people with DLBCL in the future, but we cannot promise you that taking part in the study will help you specifically.

12 What happens when the trial stops?

At the end of the study your clinical trial doctor will determine how often they need to review you. If your disease does not respond well enough to treatment, or if your disease comes back at any time, your local doctors will decide what the best treatment for you is at that time.

Results from the study are often presented at medical meetings and published in medical journals to ensure that as many doctors as possible find out about the results. This is how studies such as this can improve the treatment and care of patients with DLBCL. You will never be identified in any publications.

If you wish to see the published results of this study, you should ask your clinical trial doctor. A summary of results will be made available to you by your clinical trial doctor once the results have been published. You will also be able to find out about the results of the trial from the Lymphoma Association and Cancer Research UK's Cancerhelp website.

13 Expenses and Payments

You will not receive any payment if you enrol in this study.

14 What if there is a problem?

Any complaint about the way you have been dealt with during the clinical trial or any possible harm that you might suffer will be addressed. Detailed information concerning this is given in **section 16** of this information sheet.

15 Will my participation in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Detailed information concerning this is given in **section 16** of this information sheet.

If you think you are interested in taking part in the trial, please read the additional information in section 16 before making your decision.

16 More information about taking part

What if relevant new information becomes available?

Sometimes during the course of a research project, new information about a treatment being studied becomes available. If this happens, your doctor will tell you and discuss whether you should continue in the study or not. If you decide not to carry on, your doctor will make arrangements for your care to continue. If you decide to continue in the study you may be asked to sign an updated consent form.

We will tell you if the study is stopped for any other reason, and your doctor will again arrange your continuing care.

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

You can withdraw from trial treatment at any time but we would like to continue to collect information about you through your doctor so that we know about your progress following trial treatment.

Wherever possible, any stored blood or tissue that can still be identified as yours will be destroyed if you wish.

What if there is a problem?

Every care will be taken in the course of this clinical study. However, in the unlikely event that you are injured by taking part, compensation may be available. If you suspect that the injury is the result of the Sponsor's (University College London) or the hospital's negligence then you may be able

to claim compensation. After discussing with your clinical trial doctor, please make the claim in writing to Dr Andrew McMillan who is the Chief Investigator for the INCA trial and is based at Nottingham City Hospital. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this. Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. You should discuss this possibility with your clinical trial doctor in the same way as above.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side-effects you may have experienced due to your participation in the clinical study, the normal National Health Service complaints mechanisms are available to you. Please ask your clinical trial doctor if you would like more information on this. Details can also be obtained from the Department of Health website: http://www.dh.gov.uk.

You can also talk to the Patients Advisory Liaison Service (PALS). Their contact details can be found at the end of this leaflet.

Will my taking part in this trial be kept confidential?

Yes, all information collected about you during the course of the research will be kept strictly confidential.

Details about you, your treatment, any side-effects you have, how the cancer responds and how you are during and following study treatment will be recorded in your medical notes.

Information relevant to your participation in the study will be passed to the Cancer Research UK & University College London Cancer Trials Centre (UCL CTC)**.** This will include your initials, date of birth and NHS number.

This study will be registered under the UK Data Protection Act 1998 through UCL. All information held at UCL CTC will be stored securely and handled according to these data protection requirements. When you join the study you will be assigned a study number by UCL CTC. Your study data held at UCL CTC will be linked by this number. This study number will also be used to link your study data to any tissue or blood samples you agree to being collected and sent to relevant central laboratories. Your name will never be used in any reports about the study.

The study information collected will be used to help improve our knowledge of treating DLBCL and may also be shared with other researchers in the future to help answer other important questions. This information would be shared anonymously and if appropriate, additional ethics approval would be obtained.

If you consent to take part in the research, any of the information collected about you may be inspected by the company who are providing the medication for the IO-R-CVP arm, inotuzumab ozogamicin by Pfizer Ltd, by the sponsor of the study (University College London) and their representatives, as well as the UCL CTC who are coordinating the study. These inspections are solely for the purposes of the research and analysing the results. Your records may also be looked at by the regulatory authorities or ethics committees to check that the study is being carried out correctly.

The organisations listed above will keep information about you confidential. Your hospital doctor will tell your GP about your participation if you agree to enter the study and the CTC may also use information from the NHS Information Centre and the Medical Research Information Service (MRIS) to follow your progress if this is not available from your hospital or General Practitioner.

What will happen to any blood and tissue samples I give?

The researchers involved in this study are also interested in doing research on blood and tissue samples to try and discover more about your cancer and the way it behaves. The collection of these samples is required as it is an important part of the study.

All samples taken will only be used for cancer research. The samples will be stored at two central laboratories. The samples will be kept until they are either used up or destroyed after 15 years. The samples may also be used in future scientific studies in cancer, and some of these studies may involve collaborations with scientists from other countries.

You will be asked to provide consent for the following components of the research.

Samples to learn more about DLBCL (required)

Two of the samples we are asking you to donate will be used to learn more about DLBCL. These

samples will be sent to researchers at Haematological Malignancy Diagnostic Service (HMDS) in Leeds. Samples will be labelled with your study number, your initials and date of birth.

- Tissue sample: You will be asked to provide a sample from the biopsy taken when you were diagnosed with DLBCL to look at your type of cancer, carry out genetic research and look for other important markers. The genetic research will involve looking at variations in genes due to DLBCL, which may influence the way patients respond to treatment.
- A single blood sample taken during screening to be stored and used for future ethically approved research into DLBLC, which may include genetic research.

Samples for FLT-3 research (optional)

The collection of samples for FLT-3 is important for research into how to reduce infections in patients treated with chemotherapy. It is not compulsory to take part in this research and if you decline you can still participate in the trial. These samples will be sent to researchers at the Paterson Institute for Cancer Research in Manchester. Samples will be labelled with your study number, your initials and date of birth.

This research will be looking at a gene called FLT-3. Studies in a small number of patients have suggested that levels of FLT-3 may tell us how likely a patient is to develop infections after chemotherapy. We would like to study this further in a larger number of patients being treated with chemotherapy and growth factor injections. This knowledge may help us to monitor side-effects of treatment and to identify patients who could benefit from additional measures to reduce the risk of chemotherapy related infection in future.

You will be asked to donate 4 blood samples for this study. The amount of blood taken each time will be 10 - 20ml (2-4 teaspoons). Every effort will be made to take the blood samples at the same time as your routine blood tests are taken but you may need to make additional visits to have the samples taken. Blood samples will be taken at Screening, Cycle 1 day 3 and day 8, and Cycle 2 day 1.

Will any genetic tests be done?

Yes, some of the optional samples will be used for genetic tests. However, these tests look at the genetics of your cancer cells, not your normal cells. This is because we know that cancer makes changes to genes and these can influence the way people respond to treatment – if we can understand these changes better, we may be able to improve treatment and supportive care for patients.

Who is organising and funding the research?

The study is funded by the pharmaceutical company Pfizer Ltd, who are also providing inotuzumab ozogamicin free of charge for the IO-R-CVP arm. The study is endorsed by Cancer Research UK and is being run by Cancer Research UK & UCL Cancer Trials Centre, London.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect the interests of any patients that may take part. This trial has been reviewed and granted a favourable opinion by a Research Ethics Committee (NRES Committee Yorkshire & The Humber - Leeds East). It has also been approved by the Research and Development department at your hospital and the Cancer Research UK Clinical Trials Advisory and Awards Committee (CTAAC).

Sources of further information and Contact details

Macmillan Cancer Support who are an independent organisation providing support and counseling to help people live with cancer:
Freephone: 0808 808 00 00
Website: http://www.macmillan.org.uk/

Cancerhelp (Cancer Research UK) who provide all aspects of information for people with cancer:
Telephone: 020 7061 8355
Freephone: 0808 800 1234
Website: http://www.cancerhelp.org.uk

Bloodwise (previously Leukaemia and Lymphoma Research) provide information for people affected by leukaemia and lymphoma:
Telephone: 020 7405 0101
Email: patientinfo@beatbloodcancers.org
Website:http://beatbloodcancers.org/patient-information

The Lymphoma Association are an independent organisation providing support and information for people affected by lymphoma:
Freephone: 0808 808 5555
Website at http://www.lymphomas.org.uk/info/

Patient Advisory and Liaison Service (PALS) provide information about the NHS and help with health-related queries and can help to resolve concerns or problems when you are using the NHS. You can visit their central website at http://www.pals.nhs.uk/ or ring your local PALS contact using the contact details given below.

Useful contacts:

Your doctor ..... Tel: .....

Your nurse ..... Tel: .....

Your local PALS ..... Tel: .....

Thank you

Thank you for considering taking part in this trial and for taking the time to read this patient information sheet, which is yours to keep. If you decide to take part in the trial, you will also be given a copy of your signed consent form.