NETSCC, HTA

31st October 2011

ARCTIC

Attenuated dose Rituximab with ChemoTherapy In CLL:

A randomised, phase IIB trial in previously untreated patients with Chronic Lymphocytic Leukaemia (CLL) to compare fludarabine, cyclophosphamide and rituximab (FCR) with FC, mitoxantrone and low dose rituximab (FCM-miniR)

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An NIHR Portfolio Study developed in association with the NCRI CLL Subgroup

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1. KEY CONTACTS

Please direct any trial specific questions to the Senior Trial Co-ordinator in the first instance.

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Trial Randomisation

Only authorised members of staff from hospital sites with appropriate trial approvals have permission to randomise patients into the trial.

Tel.: CTRU 0113 343 8396

Reporting Serious Adverse Events (SAEs)

Complete the SAE CRF for all SAEs occurring in the trial and fax to the CTRU within 24 hours of becoming aware of the event:

Fax: CTRU: 0113 343 7985

A receipt will be sent for all received SAEs. ***If a receipt is not received within two working days contact the Senior Trial Co-ordinator.***

Reporting Suspected Unexpected Serious Adverse Reactions (SUSARs)

Complete the SUSAR CRF for all SUSARs occurring in the trial and fax to the CTRU within 24 hours of becoming aware of the event:

Fax: CTRU: 0113 343 7985

A receipt will be sent for all received SUSARs. ***If a receipt is not received within two working days contact the Senior Trial Co-ordinator***.

Reporting Pregnancies

Report all pregnancies to the CTRU Senior Trial Co-ordinator using the Notification of Pregnancy CRF.

Returning Patient Health Economics Questionnaire Booklets and In/Outpatient Hospital Forms

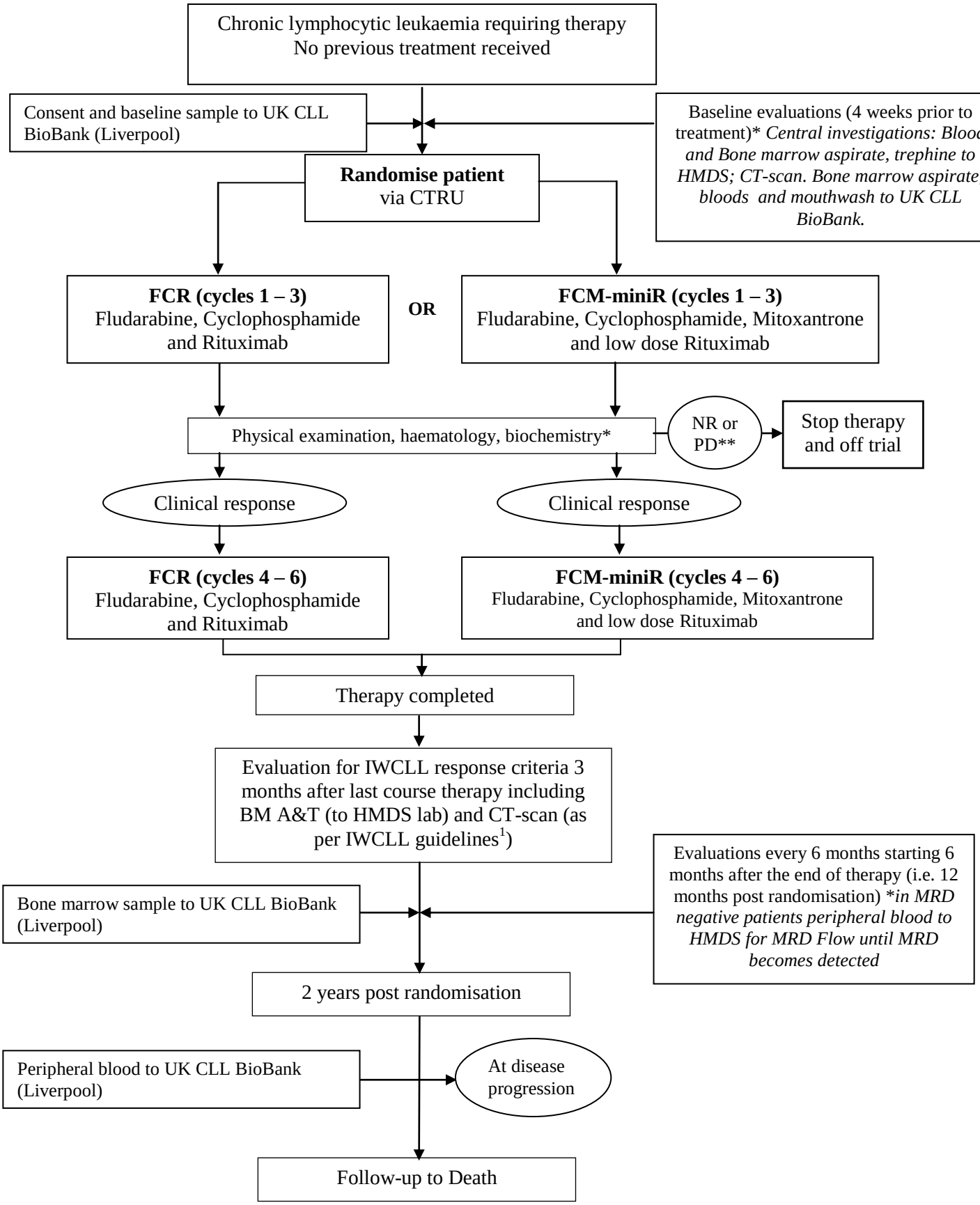
All Patient Health Economics Questionnaire Booklets and In/Outpatient Hospital Forms should be returned to the Academic Unit of Health Economics (AUHE) at the following address:

ARCTIC Trial
Academic Unit of Health Economics
Leeds Institute of Health Sciences
University of Leeds
Charles Thackrah Building
101 Clarendon Road
Woodhouse
LEEDS LS2 9LJ

In accordance with the model Non Commercial Agreement for the trial, any inconsistencies or transposition errors between the protocol and other trial documents produced at site will be the responsibility of the site.

2. CONTENTS

3. TRIAL FLOW DIAGRAM



**For more detailed information regarding the required evaluations, please refer to Section 11*
*** NR = No response; PD= Progressive Disease*

4. BACKGROUND

4.1 CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia, affecting approximately 5.0 per 100,000 population[2]. The incidence of CLL increases with age and twice as many men are affected as women. CLL results from the clonal proliferation of B-cells and is diagnosed by the pattern of expression of various cell surface antigens on the CLL cells. Patients most commonly present with lymphocytosis, lymphadenopathy, splenomegaly and systemic symptoms, such as fatigue, weight loss and malaise. The clinical course of CLL is highly variable with a median survival from diagnosis in the region of 7 years. Patients with more advanced disease (Binet stages B, C and progressive stage A) have a significantly worse survival.

4.2 THERAPY FOR CLL

It appears from the work of several groups that monoclonal antibodies, such as rituximab, synergise with cytotoxic therapy when used in combination, so that the combination is more effective than either of the agents used alone[3]. For example, randomised controlled clinical trials have demonstrated that rituximab in combination with conventional chemotherapy (CHOP) is more effective than CHOP alone in patients with diffuse large B-cell lymphoma[4].

In CLL, fludarabine combined with cyclophosphamide is one of the more frequently used combinations in second and subsequent line use[5]. Over the last few years the MD Anderson Cancer Centre have reported the use of a combination of rituximab with fludarabine and cyclophosphamide (FCR) in both previously untreated and refractory CLL[6,7,8]. The response rates for FCR are very impressive and compare extremely positively with historical controls treated with fludarabine, either alone or in combination with cyclophosphamide. Complete remission was demonstrated in 217/300 (72%), nodular partial remission in 31 (10%), partial remission in 37 (12%), no response in 13 (4%) patients, and early death in 2 (<1%) patient. Molecular remission, demonstrated by polymerase chain reaction (PCR) negativity for IgH, was documented in 42% of complete responders (Thus 42% of all previously untreated patients who received FCR achieved an MRD-negative CR). The same group also recently reported their experience with FCR in 167 patients with previously treated CLL, of whom 102 were evaluable with more than 6 months of follow-up. The median number of prior treatments was two: 14.7% of the patients had received alkylating agents only, 58.8% had been sensitive to fludarabine containing regimens and 26.4% had been resistant to fludarabine. Median follow-up is 13+ months. Using NCI criteria, 23% achieved a complete remission rate, 50% a partial remission and 21% had no response. Five of 13 patients (38%) in complete remission had undetectable IgH rearrangements by PCR. The complete remission rate based on prior therapy suggests that fludarabine-sensitive patients have a better response rate. The complete remission rates were as follows: 3/15 (20%) alkylating agents only; 18/60 (30%) fludarabine-sensitive; 2/27 (7%) fludarabine-resistant. Serious toxicities due to the treatment included 8 episodes of pneumonia, 7 episodes of neutropenic fever, 5 of sepsis and 1 prolonged myelosuppression. 26 patients have died. Recently the German CLL Study Group (GCLLSG) completed the German CLL8 trial which compared FCR to FC in patients with CLL who had previously been untreated and required therapy according to conventional criteria. The full results of this study were presented in December 2008 at the Annual Meeting of the American Society of Hematology[9]. It was reported that 811 patients were entered into the GMCLLSG CLL8 trial and randomly assigned to receive either FC or FCR. The overall response rate (ORR) was significantly higher in the FCR arm (95%; 370/390) compared to FC (88%; 328/371 (p=0.001). The complete response rate of the FCR arm was 52% as compared to 27.0% in the FC arm (p<0.0001). PFS was 76.6% at 2 years in the FCR arm and 62.3% in the FC arm (p<0.0001). FCR treatment was more

frequently associated with CTC grade 3 and 4 haematological toxicity occurring in 55% (FCR) versus 39% (FC) of all patients. The most significant difference was observed for neutropenia (FCR 33.6%; FC 20.9% p=0.0001). The incidence of CTC grade 3 or 4 infections was not significantly increased in the FCR arm (18.8% versus 14.8% in the FC arm, p=0.68). This trial has been submitted to the European Medicines Evaluation Agency (EMEA) in order to gain a product licence for rituximab combined with FC in previously untreated CLL. Thus the combination of FCR appears to be very effective in both untreated and previously treated patients with CLL.

The addition of mitoxantrone to the fludarabine-based therapy has been found to result in high response rates in a variety of indolent lymphoproliferative disorders, including follicular lymphoma[10] and mantle cell lymphoma[11]. The combination of fludarabine, cyclophosphamide and mitoxantrone has recently been reported in 60 patients who have relapsed or resistant CLL[12]. The overall response rate in this series was of 78% with 30 patients (50%) achieving a complete remission. It was of considerable importance that 10 of the patients in CR had an eradication of detectable MRD by a sensitive four-colour flow cytometric test, and that these patients had a significantly prolonged survival compared to the other patients in this series. Therefore, it appears likely that the combination of mitoxantrone with FC will yield the highest remission rates of chemotherapy-based regimes. In addition, FCM plus rituximab (FCM-R) appears to be a very promising combination in Phase II trials for CLL. The Barcelona group have reported the use of FCM-R in a non-randomised Phase II trial reporting a complete remission rate of 77% and an overall response rate of 92% in previously untreated CLL[13]. In this study 36% of the CR patients had undetectable minimal residual disease (MRD). Our group, NCRI CLL sub-group, has recently completed a randomised Phase II study including FCM and FCM-R in previously treated patients with CLL. This study recruited 52 patients with 26 in each arm and reported a 42% CR rate for FCM-R compared to a 12% with FCM ($p<0.01$) with 6 patients achieving eradication of MRD following FCM-R compared to only 3 patients with FCM[14].

The "conventional" dose of rituximab used for lymphoma of 375mg/m^2 was established in indolent lymphoma with the drug used as a single agent[15]. No formal dose finding studies have been reported in CLL and the most effective dose has not been established. Rituximab as a single agent in CLL has been reported in higher doses up to 2250mg/m^2 with no patients achieving complete remissions [16,17]. Recent evidence suggests that far smaller doses of rituximab may be effective in CLL. Doses of rituximab as small as 70mg were sufficient to achieve plasma levels in excess of those required to saturate CD20 binding[18]. In addition, small doses result in the depletion of complement activity and a marked, rapid reduction in the lymphocytosis suggesting tumour cell opsonisation and therapeutic activity. It has also been shown that the CLL cells once opsonised by rituximab are phagocytosed by macrophages where the rituximab/CD20 complexes are removed from the cell by a process of capping and then the CLL cells are released back into the circulation but without expression of CD20[18]. Therefore additional rituximab would be ineffective. Additional papers from the same group[19,20] provided further convincing evidence for the "shaving" of the CD20 antigen from CLL cells after treatment with rituximab and that smaller doses of rituximab, as low as 20mg/m^2 may be at least as effective, or perhaps more so, than the conventional doses. This is because if large doses of rituximab are given every 4 weeks there is the possibility that the expression of CD20 on the CLL cells will still be depressed by the time of further dosing and therefore little additional activity would be anticipated. However if smaller doses of rituximab, such as 100mg doses, are used then clinical activity with a transient fall in circulating CLL cells has previously been demonstrated[20] and by the time the next does of rituximab is scheduled 4 weeks later then the levels of CD20 expression will have returned to normal levels thus making further synergy between the next dose of rituximab and chemotherapy likely.

4.3 RITUXIMAB

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody, representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable regions sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on >95% of all B-cell non-Hodgkin's lymphomas (NHLs). CD20 is found on both normal and malignant B-cells, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and recruits immune effector functions to mediate B-cell lysis via the Fc domain. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells.

Median peripheral B-cell counts declined below normal following completion of the first dose, with recovery beginning after 6 months. B-cell levels returned to normal between 9 and 12 months following completion of therapy.

Of 67 patients evaluated for human anti-mouse antibody (HAMA), no responses were noted. Of 355 patients evaluated for HACA, less then 1.0% (3 patients) were positive.

Rituximab is licensed as a single agent for the therapy of refractory follicular lymphoma and in combination with CHOP chemotherapy for diffuse large B-cell lymphoma.

Rituximab is a clear, colourless liquid provided in sterile, preservative-free, non-pyrogenic, single use vials. Aseptically withdraw the necessary amount of rituximab, and dilute to a calculated concentration of 1 to 4mg/ml rituximab into an infusion bag containing sterile, pyrogen-free 0.9% Sodium Chloride or 5% Dextrose in water. For mixing the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the drug product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

4.4 MITOXANTRONE

Mitoxantrone is a synthetic anthracenedione that is structurally similar to doxorubicin and daunorubicin. It was synthesized with the aim of reducing side effects especially cardiotoxicity. It is indicated, either in combination therapy or as a single agent, in the treatment of acute non-lymphocytic leukaemia, metastatic breast cancer, hepatoma, lymphoma and paediatric sarcoma.

It inhibits DNA repair by inhibiting topoisomerase II which results in fragmentation of DNA. It is an immunosuppressive agent that may also generate free radicals, inhibit protein kinase C, cause electrostatic DNA cross-links and induce apoptosis. It is not cell cycle phase-specific but is maximally cytotoxic in the S-phase.

Oral absorption is poor. Volume of distribution is 14 L/kg with >95% plasma protein binding, 76% to albumin. It distributes into pleural fluid, kidney, thyroid, liver, heart and red blood cells but does not cross the blood brain barrier to an appreciable extent.
It is metabolized by the liver and excreted in the urine (6-11%; 65% unchanged) and faeces (25%; 65% unchanged).
Terminal half life is 23-215 hours and this is prolonged in hepatic impairment.
Clearance is 10.9-37.4L/hr/m^2 but this is decreased in the elderly.

Mitoxantrone is contraindicated if there is a history of hypersensitivity reaction to anthacyclines or mitoxantrone or if there is severe hepatic impairment.

Cardiotoxicity is cumulative across all anthracyclines and anthrcenediones and is thought to be due in part to free radical damage. It may occur during therapy or months to years afterwards and may manifest as ECG changes, an asymptomatic decrease in left ventricular ejection fraction (LVEF), cardiomyopathy and symptomatic congestive heart failure. The suggested maximum cumulative dose of mitoxantrone is 100mg/m^2.
Risk factors for developing mitoxantrone-induced cardiotoxicity include:

- high cumulative dose (>100 mg/m^2);
- previous therapy with other anthracyclines or anthracenediones;
- prior or concomitant radiotherapy to the mediastinal/pericardial area;
- pre-existing heart disease LVEF <50% or a clinically-significant reduction in LVEF;
- concomitant use of other cardiotoxic drugs.

Mitoxantrone should be used with caution in patients with myelosuppression or poor general condition. Careful supervision is recommended when treating patients with hepatic insufficiency and dose reductions should be considered in discussion with the Chief Investigator.
Topoisomerase II inhibitors, including mitoxantrone hydrochloride, when used concomitantly with other antineoplastic agents (particularly anthracyclines) and/or radiotherapy, have been associated with the development of Acute Myeloid Leukaemia (AML) or Myelodysplastic Syndrome (MDS). Treatment with mitoxantrone alone has also been associated with an increased risk of development of secondary acute myeloid leukaemia.

Sulphites, one of the exipients, can cause allergic-type reactions including anaphylactic symptoms and bronchospasm in susceptible people, especially those with a history of asthma or allergy.
Immunisation may be ineffective when given during mitoxantrone therapy. Immunisation with live virus vaccines is generally not recommended.

Amenorrhea and a typically reversible reduction in spermatogenesis have been reported. Women of childbearing potential and their partners should be advised to avoid becoming pregnant and use effective contraception during therapy and for at least six months after cessation of therapy. Breastfeeding is not recommended due to secretion into breast milk.

<u>Side effects and interactions</u>
Myelosuppression and cardiotoxicity are the main serious undesirable effects. Leucopenia is usually transient reaching its nadir at about 10 days after dosing with recovery usually occurring by the 21st day. Thrombocytopenia and anaemia occur less frequently. Myelosuppression may be more severe and prolonged in patients who have had extensive prior chemotherapy or radiotherapy or in debilitated patients.

When mitoxantrone is used as a single injection given every 21 days in the treatment of metastatic breast cancer and lymphomas, the most commonly encountered side effects are nausea and vomiting, although in the majority of cases these are mild and transient. Alopecia may occur, but is most frequently of minimal severity and reversible on cessation of therapy. Other undesirable

effects include a blue-green colouration to the urine for 24 hours after administration, increased liver enzyme levels, hyperuricaemia and tumour lysis syndrome, elevated serum creatinine, rash, onycholysis, blue discolouration of skin and nails and nail dystrophy has been reported occasionally. Reversible blue colouration of the sclerae and on-specific neurological side effects such as somnolence, confusion, anxiety and mild paraesthesia have been reported.

So far, experience has not revealed any significant drug interactions in patients who have received Mitoxantrone for treatment of cancer. The results of in vitro induction studies are inconclusive, but suggest that Mitoxantrone may be a weak inducer of CYP450 2E1 activity. Mitoxantrone may reduce quinolone absorption due to alteration of the intestinal mucosa. Therefore quinolone dose may need to be adjusted.

Mitoxantrone is a dark blue solution supplied at a concentration of 2mg/mL in 10 and 12.5mL single use vials. It should be stored at room temperature, not be frozen and be protected from light.

Dilute the required volume of Mitoxantrone Sterile Concentrate to at least 50 ml in either of the following infusion solutions: sodium chloride 0.9%, glucose 5%, or sodium chloride 0.18% and glucose 4%. The resulting solution should be administered over not less than 3 minutes via the tubing of a freely running intravenous infusion of the above fluids. Mitoxantrone should not be mixed with other drugs in the same infusion. If extravasation occurs the administration should be stopped immediately and restarted in another vein. The non-vesicant properties of mitoxantrone minimise the risk of severe local reaction following extravasation. Care should be taken to avoid contact of mitoxantrone with skin, mucous membranes or eyes.

4.5 RATIONAL FOR THE PROPOSED STUDY

The standard therapy for previously untreated CLL is currently the combination of fludarabine with cyclophosphamide (FC). The previous UK trial, LRF CLL4, demonstrated the effectiveness of oral FC. Recent studies, including a large non-randomised Phase II trial (MD Anderson Cancer Center) and a large randomised Phase III trial from the German CLL Study Group (CLL8), have demonstrated that intravenous FC plus rituximab is superior to FC alone. Initial evidence suggests that the addition of mitoxantrone to intravenous FCR produces higher remission rates. At present there is no data for the combination of rituximab with oral FC in previously untreated CLL. Our previous trial, NCRI CLL201, demonstrated the safety and potential efficacy of the addition of mitoxantrone and rituximab to oral FC (FCM-R) in previously treated patients with CLL. The dose of rituximab in the FCR schedule for CLL has not been systematically investigated. There is evidence to suggest that moderate doses of rituximab in CLL result in a loss of the target antigen (CD20) potentially impairing the efficacy of further rituximab. The use of much lower doses of rituximab appears to overcome this problem. Theoretically a tenth to a twentieth of the standard dose of rituximab may be equally or more effective. This trial is designed to assess the response rates in previously untreated patients with CLL to both rituximab with oral FC (FCR) and to low dose rituximab plus mitoxantrone with oral FC (FCM-miniR). This trial aims to assess whether mini-R in combination with mitoxantrone is a reasonable alternative to “full dose” rituximab. It is being timed to report at around the same time as NICE review rituximab for use in the treatment of CLL and if the results of this trial are positive, a larger phase III trial will be pursued which is likely to compare low dose rituximab directly with the then licensed dose.

5. AIMS AND OBJECTIVES

This trial aims to establish whether the addition of Mitoxantrone (M,) with a low dose of Rituximab (miniR), to Fludarabine (F) and Cyclophosphamide (C) – FCM-miniR, is as effective as FCR in terms of response in patients with previously untreated Chronic Lymphocytic Leukaemia.

5.1 PRIMARY OBJECTIVE

- To compare the complete response (CR) rates as defined by IWCLL criteria (Appendix B) in each treatment group

5.2 SECONDARY OBJECTIVES

- To assess the rate of eradication of detectable minimal residual disease (MRD) following treatment with FCR or FCM-miniR
- To assess the overall response rate (complete or partial remission defined by IWCLL criteria) between the treatment groups
- To assess the safety and toxicity of low-dose rituximab and mitoxantrone in combination with fludarabine and cyclophosphamide
- To develop a decision analytic cost effectiveness model to inform the design of a proposed Phase III large scale randomised controlled trial
- To assess progression free survival
- To evaluate overall survival

6. DESIGN

This is a multi-centre, randomised, controlled, open, phase II non inferiority trial in patients who are newly diagnosed with B-CLL.

Patients will be randomised on a 1:1 basis to receive one of two trial interventions, fludarabine, cyclophosphamide and rituximab (FCR) or fludarabine, cyclophosphamide, mitoxantrone and low dose rituximab (FCM-miniR).

7. ELIGIBILITY

7.1 INCLUSION CRITERIA

Patients with the following characteristics are eligible for this study:

- At least 18 years old.
- B-CLL with a characteristic immunophenotype, including small lymphocytic leukaemia (SLL).
- Binet's Stages B, C or Progressive Stage A.
- Requiring therapy by the IWCLL criteria in that they must have at least one of the following:
    i. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia.
    ii. Massive (ie, 6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
    iii. Massive nodes (ie, 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
    iv. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months as long as the lymphocyte count is over $30x10^9$/L.
    v. A minimum of any one of the following disease-related symptoms must be present:
        (a) Unintentional weight loss more than or equal to 10% within the previous 6 months.

(b) Significant fatigue (ie, Eastern Cooperative Oncology Group PS 2 or worse; cannot work or unable to perform usual activities).
(c) Fevers of greater than 38.0°C for 2 or more weeks without other evidence of infection.
(d) Night sweats for more than 1 month without evidence of infection.

- No prior therapy for CLL.
- World Health Organisation (WHO) performance status (PS) of 0, 1 or 2.
- Able to provide written informed consent.

7.2 EXCLUSION CRITERIA

Patients with the following characteristics are ineligible for this study

- Prior therapy for CLL.
- Active infection.
- Past history of anaphylaxis following exposure to rat or mouse derived CDR-grafted humanised monoclonal antibodies.
- Pregnancy, lactation or women of child-bearing potential unwilling to use medically approved contraception whilst receiving treatment and for 12 months after treatment has finished
- Men whose partners are capable of having children but who are not willing to use appropriate medically approved contraception whilst receiving treatment and for 12 months after treatment has finished, unless they are surgically sterile.
- CNS involvement with CLL.
- Mantle cell lymphoma.
- Symptomatic cardiac failure not controlled by therapy or unstable angina not adequately controlled by current therapy (in patients with a significant cardiac history the left ventricular function should be assessed and patients with severe impairment should be excluded).
- Other severe, concurrent diseases or mental disorders.
- Known HIV positive.
- Patient has active or prior Hepatitis B or C.
- Active secondary malignancy excluding basal cell carcinoma.
- Persisting severe pancytopenia (neutrophils $<0.5 \times 10^9$/l or platelets $<50 \times 10^9$/l) or transfusion dependent anaemia unless due to direct marrow infiltration by CLL.
- Active haemolysis (patients with haemolysis controlled with prednisolone at a dose 10mg or less per day can be entered into the trial).
- Patients with a creatinine clearance of less than 30ml/min (either measured or derived by the Cockcroft Gault formula [Appendix C]).

8. RECRUITMENT AND RANDOMISATION

8.1 RECRUITMENT

Patients will be recruited from multiple research centres from around the United Kingdom under the guidance of the UK CLL Forum. Research centres will be required to have obtained ethical and management approval and undertake a site initiation meeting with the CTRU prior to the start of recruitment into the trial.

The recruitment target requires that 206 patients are recruited into the trial over an 18 month period.

8.2 INFORMED CONSENT AND ELIGIBILITY

Patients will be approached during standard clinic visits for management of their disease and will be provided with verbal and written details about the trial (PISICD01). This will include detailed information about the rationale, design and personal implications of the trial. Following information provision, patients will have as long as they need to consider participation (normally a minimum of 24 hours) and will be given the opportunity to discuss the study with their family and other healthcare professionals before they are asked whether they would be willing to take part in the study.

Provision of information regarding the trial is permitted by any member of the site research team approved to do so by the Principal Investigator, although the Principal Investigator should be informed of any patients approached to participate by any other member of the site research team.

Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent. The Principal Investigator or any other clinically qualified member of the trial team who has received GCP training and who is approved by the Principal Investigator is permitted to take informed consent. The right of the patient to refuse consent without giving reasons will be respected. Further, the patient will be free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment.

A record of the consent process detailing the date of consent and all those present will be kept in the patient notes. The original consent form will be filed in the Investigator Site File, a copy of the consent form will be given to the patient and a copy will be returned to the Clinical Trials Research Unit (CTRU), at the University of Leeds.

8.2.1 Consent to the UK CLL Trials BioBank

Patients who are eligible to take part in the trial will also be eligible to have a number of biological samples sent to the UK CLL Trials BioBank. Participation within the UK CLL Trials BioBank will be discussed with patients at the same time as discussing their participation in the rest of the trial. Verbal and written details (the UK CLL Trials BioBank Patient Information Sheet) will be provided to patients. Following information provision, patients will be given as long as they need to consider participation (normally a minimum of 24 hours) and will be given the opportunity to discuss the study with their family and other healthcare professionals before they are asked whether they would be willing to have samples sent to the UK CLL Trials BioBank.

Patients who agree to have biological samples sent to the UK CLL Trials BioBank will be asked to sign an additional consent form. As for the main trial, a record of consent to this section of the trial, detailing the date of consent and all those present will be kept in the patients notes. The original UK CLL Trials BioBank Consent Form will be filed within the Investigator Site File, a copy of the consent form will be given to the patient, a copy will be returned to the UK CLL Trials BioBank at Royal Liverpool University Hospital and a copy will be returned to the CTRU at the University of Leeds.

8.3 RANDOMISATION

Following confirmation of written informed consent and eligibility patients will be randomised into the trial by an authorised member of staff at the trial research site. Randomisation will be performed centrally using the CTRU automated 24-hour telephone randomisation system. Authorisation codes and PINs, provided by the CTRU after site initiation, will be required to access the randomisation system.

The following information will be required at randomisation:

- Patient details, including initials, gender and date of birth
- Name of trial research site and site code
- Name of person making the randomisation
- Name of treating consultant
- Confirmation of eligibility
- Confirmation of written informed consent and date
- Stratification factors (see list below)
- Personal authorisation codes and PIN

Patients must complete the health economics patient questionnaire which includes the EQ-5D and SF-12 in clinic before they are informed of their treatment allocation (Section 13.1).

Direct line for 24-hour randomisation: 0113 343 8396

Patients who fulfil the eligibility criteria, and have given written informed consent, will be randomisation on a 1:1 basis to receive either FCR or FCM-miniR and will be allocated a trial number. A computer-generated minimisation program that incorporates a random element will be used to ensure treatment groups are well-balanced for the following characteristics, details of which will be required for randomisation:

- Centre
- Binet Staging (A progressive or B, C)
- Age (≤65, >65)
- Gender (M, F)

After randomisation the local hospital will:

- Provide each patient with a Trial ID card which they should be instructed to carry with them at all times and present to medical staff should they be admitted to hospital during their time on trial.

8.4 NON - RANDOMISATION

Each trial research site will be required to maintain an ongoing log of all patients screened for eligibility who are not randomised either because they are ineligible or because they decline participation. Anonymised information will be collected including:

- age
- gender
- ethnicity
- region
- date screened
- reason for ineligibility for trial participation

or

- reason for declining participation despite eligibility

or

- other reason for non-randomisation

Non Randomisation Logs are required to be sent to the CTRU every 3 months or upon their request.

9. TRIAL MEDICINAL PRODUCT MANAGEMENT

Within the trial the following are classed as Investigational Medicinal Products (IMPs):

Cyclophosphamide

Cyclophosphamide Tablets
Composition: Cyclophosphamide monohydrate BP 53.50mg equivalent to 50mg anhydrous cyclophosphamide.
Generic supply of Cyclophosphamide as determined by individual hospital sites; please refer to the trial supplied Summary of Product Characteristics for the brand being used.

Cyclophosphamide Solution for Infusion
Composition: Cyclophosphamide monohydrate, powder for solution for injection or infusion.
Generic supply of Cyclophosphamide as determined by individual hospital sites; please refer to the trial supplied Summary of Product Characteristics for the brand being used.

Fludarabine

Fludara Oral Tablets
Composition: Fludarabine phosphate 10mg
Supply of Fludarabine as determined by individual hospital sites; please refer to the trial supplied Summary of Product Characteristics for the brand being used.

Fludarabine Solution for Infusion
Composition: Fludarabine phosphate 50mg
Supply of fludarabine as determined by individual hospital sites; please refer to the trial supplied Summary of Product Characteristics for the brand being used.

Mitoxantrone

Mitoxantrone concentrate for solution for infusion
Composition: Each millilitre of concentrate contains 2 mg mitoxantrone (as hydrochloride).
Each 10 ml vial contains 20 mg mitoxantrone (as hydrochloride).
Generic supply of Mitoxantrone as determined by individual hospital sites; please refer to the trial supplied Summary of Product Characteristics for the brand being used.

Rituximab (MabThera)

MabThera solution for infusion
Composition: Rituximab 100mg/10ml or 500mg/50ml
Ordered by individual hospital as a routine stock item. Please refer to the trial supplied Summary of Product Characteristics.

Within the trial the following is classed as a Non-Investigational Medicinal Product (NIMP).

Lenograstim

Please refer to the trial supplied Summary of Product Characteristics.
Granocyte should be ordered from AAH Hospital Services as a routine stock item; it will be supplied at hospital contract prices under NHS terms and conditions.

9.1 LABELLING AND IMP HANDLING

All IMPs (fludarabine, cyclophosphamide, mitoxantrone and rituximab) will be off the shelf supplies. There is no requirement to ring fence off the shelf general hospital supplies of these IMPs.

Pharmacy will be responsible for labelling fludarabine and cyclophosphamide in accordance with the requirements of the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994.

The CTRU will provide labels for rituximab and mitoxantrone in line with Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 (amended 2006). The pharmacy will be responsible for completing individual patient details on each label and the application of the labels.

Please refer to the ARCTIC Pharmacy and IMP Study Site Operating Procedure for full details of the trial IMP management requirements.

10. TREATMENT DETAILS

The following section of the protocol describes treatment for patients with FCR and FCM-miniR.

10.1 ROUTINE TESTS BEFORE EACH CHEMOTHERAPY CYCLE

Within 1 week prior to Day 1 of each treatment cycle, each patient will be assessed for their suitability for treatment. Please see Section 11.4 for details.

10.2 TREATMENT REGIMEN DETAILS

Patients will be randomised to receive 6 cycles of either FCR or FCM-miniR according to the following regimens:

Fludarabine, cyclophosphamide and rituximab (FCR):

Fludarabine	Oral*	24mg/m^2/day	Days 1 to 5
Cyclophosphamide	Oral*	150mg/m^2/day	Days 1 to 5
Rituximab	Intravenous	375mg/ m^2	Day 1 **(Cycle 1)**
Rituximab	Intravenous	500mg/m^2	Day 1 **(Cycle 2-6)**

Cycles of FCR are repeated every 28 days for a total of 6 cycles. (See Appendix D for body surface area calculation).

G-CSF (eg. Lenograstim 263µg/day) for days 7 to 13 is recommended for all subsequent cycles in patients who have to have a previous dose delay due to neutropenia or an infection associated with neutropenia during previous courses of therapy (see Section 10.5 c).

The treatment of patients with a BSA > 2.2m^2 should be as per your local policy.

*Patients should be questioned regarding nausea and vomiting or diarrhoea occurring with the prior cycle of therapy and if this is present then the fludarabine and cyclophosphamide should be given via the intravenous route due to concerns over drug absorption. Intravenous fludarabine (25mg/m^2/day for 3 days) and cyclophosphamide (250mg/m^2/day for 3 days) regimens is recommended if the oral regimen is not tolerated. Patients should be prescribed anti-emetics as per

local policy. If a patient misses a dose, the dose should be taken later provided the patient remembers within 12 hours. If the patient does not remember within 12 hours, the missed dose should be omitted. Doses should NOT be doubled to make up for missed doses. Compliance with oral administration of fludarabine and cyclophosphamide should be recorded in the patient diary card.

Fludarabine, cyclophosphamide, mitoxantrone and low dose rituximab (FCM-miniR)

Fludarabine	Oral*	24mg/m^2/day	Days 1 to 5
Cyclophosphamide	Oral*	150mg/m^2/day	Days 1 to 5
Mitoxantrone	Intravenous	6mg/m^2/day	Day 1
Mini Rituximab	Intravenous	100mg	Day 1

Cycles of FCM-miniR are repeated every 28 days for a total of 6 cycles. (See Appendix D for body surface area calculation).

G-CSF (eg. Lenograstim 263µg/day) for days 7 to 13 is recommended for all subsequent cycles in patients who have to have a previous dose delay due to neutropenia or an infection associated with neutropenia during previous courses of therapy (see Section 10.5 c).

The treatment of patients with a BSA > 2.2m^2 should be as per your local policy.

*Patients should be questioned regarding nausea and vomiting or diarrhoea occurring with the prior cycle of therapy and if this is present then the fludarabine and cyclophosphamide should be given via the intravenous route due to concerns over drug absorption. Intravenous fludarabine (25mg/m^2/day for 3 days) and cyclophosphamide (250mg/m^2/day for 3 days) regimens is recommended if the oral regimen is not tolerated. Patients should be prescribed anti-emetics as per local policy. If a patient misses a dose, the dose should be taken later provided the patient remembers within 12 hours. Doses should NOT be doubled to make up for missed doses. Compliance with oral administration of fludarabine and cyclophosphamide should be recorded in the patient diary card.

10.3 ADMINISTRATION OF RITUXIMAB

If at the first treatment cycle the total lymphocyte count is > 25 x 10^9/l, the rituximab dosage should be split in view of concerns of cytokine release and severe immediate toxicity, as per one of the following schedules:

Dose split schedule A

- Cycle 1 - 100mg is given on day 1 and the remainder of the 375mg/m^2 (i.e. 375mg/m^2 minus 100mg) is given on day 2.
- Cycles 2-6 - if the lymphocyte count remains above 25 x 10^9/l then, at the clinician's discretion, the rituximab dose can be split, with 100mg given on day 1 and the remainder of the 500mg/m^2 given on day 2. If the lymphocyte count is <25 x 10^9/l then the whole dose should be given on day 1 without splitting the dose.

Dose split schedule B

- Cycle 1, 50mg/m2 is given on day 1 and 325mg/m2 is given on day 2.
- Cycles 2-6. If the lymphocyte count remains above 25 x 109/l then, at the clinician's discretion, the rituximab dose can be split, with 125mg/m2 given on day 1 and 375mg/m2 given on day 2. If the lymphocyte count is <25 x 109/l then the whole dose should be given on day 1 without splitting the dose.

Note: This is not required in patients receiving FCM-miniR.

Rituximab should be administered in an environment where full resuscitation facilities are immediately available, and under close supervision of an experienced haematologist/oncologist. Patients should receive premedication with paracetamol and anti-histamines 30-60 minutes prior to infusion of rituximab. **Rituximab must not be administered as an intravenous bolus injection.**

Infusion rates: Sites are permitted to follow local practice when determining the rituximab infusion rates although it is recommended that sites use the dose rates given in the most recent version of the SPC. Further guidance is given below.

First infusion: The recommended initial dose is 50mg/hr for the 30 minutes. During the administration of rituximab, vital signs such as heart rate, respiratory rate and blood pressure should be monitored every 15 minutes during the first hour of infusion and then once an hour. If there are no adverse events, the dose rate may be escalated in 30 minute intervals, with increment steps of 50 mg/hr to a maximum of 400 mg/hr. Patients may experience transient fever and rigors with the infusion. If this occurs, the antibody infusion should be temporarily discontinued and treatment administered if necessary. Also if there is a significant fall in systolic blood pressure (30mmHg or more) or bronchospasm (or similar reaction) then the rituximab infusion should be temporarily interrupted. Following resolution of symptoms, the infusion may recommence initially at half the previous rate.

Subsequent infusions: If there are no adverse events seen the recommended infusion rate at the start of following infusions is 100mg/hr and increased by 100mg/hr increments at 30 minute intervals, to a maximum of 400mg/hr.

Following the infusions the intravenous line should be continued for one hour so that drugs may be administered intravenously if necessary.

It is recommended that the speed of infusion be halved if the following adverse events occur:

- Fevers > 38.5C
- Chills – mild, moderate
- Mucosal swelling – mild, moderate
- Hypotension (drop in systolic BP) > 30mmHg

10.4 ROUTINE CONCOMITANT THERAPY

All patients should receive prophylaxis against pneumocystis carinii pneumonia (PCP) with co-trimoxazole 960mg bi-daily (bd) Monday/Wednesday/Friday or 480mg daily. Patients who are allergic to co-trimoxazole should receive an alternative, such as dapsone (100mg OD) or nebulised pentamidine (monthly). PCP prophylaxis should continue throughout treatment and for at least 2 months after the last course of treatment.
Aciclovir 400mg bd as prophylaxis against Herpes virus reactivation is also recommended for all patients.
Allopurinol 300mg/day is recommended for at least the first 28 days of therapy.

All blood products should be irradiated for patients in both arms of the trials.

It is recommended that after randomisation, but before starting the allocated schedule, Binet stage C patients (Hb <10g/dl and/or platelets $<100x10^9$/l not due to autoimmune phenomena) should be

given prednisolone - 30mg/m^2 daily for 3 weeks, plus 1 week tailing off, followed 1 or 2 weeks later by the randomised therapy.

10.5 MANAGEMENT OF TOXICITY – Delays and Dose Reductions

a) **Infusion related adverse reactions (rituximab only)**

- Temporarily stop infusion and when the reaction has resolved restart at half the speed of infusion if the following adverse events occur:
  - Fevers > 38.5C
  - Chills – mild, moderate
  - Mucosal swelling – mild, moderate
  - Hypotension (drop in systolic BP) > 30mmHg

b) **Impaired Renal Function**

- Fludarabine should not be given to patients with a creatinine clearance of less than 30ml/min (exclusion criteria). Patients with a creatinine clearance of less than 30ml/min can have a delay of treatment for up to 4 weeks but should be withdrawn from the study if their creatinine clearance does not improve to above 30ml/min.
- At the physician's discretion, patients with a creatinine clearance between 30-60ml/min should have 50% the dose of fludarabine. The cyclophosphamide dose does not need to be reduced when the creatinine clearance is above 30ml/min.
- Levels of creatinine should be monitored carefully in further cycles and, eventually, doses may be gradually increased.
- Refer to Appendix C for details of creatinine clearance calculation.

c) **Neutropenia**

- At 28 days, if the neutrophils are <1.0 x 10^9/l due to trial chemotherapy, rather than due to bone marrow involvement, treatment should be delayed for up to two weeks, with 25% reduction in dose of subsequent cycles (except in the case of isolated neutropenia not on G-CSF when the full dose of chemotherapy may be used if G-CSF is being added for the first time). Rituximab will not be dose reduced.
- Patients who have a neutrophil count of <1.0 x 10^9/l at day 28 of any cycle of therapy should receive G-CSF (rHuG-CSF) for the next and all subsequent cycles of chemotherapy. It is recommended that G-CSF (preferably lenograstim) should be given at a dose of 263μg/day from days 7 to 13 for each subsequent cycle of therapy.
- If further grade 3-4 neutropenia occurs after 25% dose reduction, a further reduction to 50% of the original doses is allowed.
- If at Day 28 of the subsequent cycle with G-CSF support the neutrophils are >1.0 x 10^9/l the full dose of chemotherapy should be given with continuing G-CSF support.
- At the second occurrence of neutropenia treatment should be delayed for up to two weeks, with 25% reduction in dose of all subsequent cycles.
- If treatment is delayed by longer than 2 weeks the patient's ongoing treatment within the trial is permitted and should be discussed with the Chief Investigator or a Co-Investigator (Protocol Section 1).

Management of neutropenia due to therapy:

Four weeks after last course (Day 28)	One week delay (Day 35)	Two weeks delay (Day 42)
Neut >1.0:		

Commence next cycle therapy as planned		
Neut <1.0: Delay next course of therapy and commence G-CSF 263ug/day	Neut >1.0: Commence next cycle of therapy without dose reduction but with lenograstim 263μg/day Days 7-13	
	Neut still <1.0: Continue G-CSF and delay next course therapy for a further week	Neut >1.0 Commence next cycle of therapy with 25 % dose reduction* of FCM (not rituximab) with G-CSF 263μg/day Days 7-13
		Neut <1.0 Ongoing treatment to be discussed with the Chief Investigator or Co-Investigator

* if the patient has already dose reduced by 25% previously then a dose reduction to 50% of the original doses of fludarabine, cyclophosphamide and mitoxantrone is permitted.

d) **Other haematological toxicities**

- At 28 days, if the platelets are <75 x 10^9/l due to trial chemotherapy, rather than due to bone marrow involvement, treatment should be delayed for up to two weeks, with 25% reduction in dose of subsequent cycles. Rituximab will not be dose reduced.
- If on subsequent cycles of therapy the platelets are over 100 x 10^9/l at Day 28 then the chemotherapy doses should be re-escalated to 100% dose level.
- If further grade 3-4 haematological toxicity occurs after 25% dose reduction, a further reduction to 50% of the original doses is allowed.
- If the platelet count was decreased prior to commencing the first course of therapy due to marrow involvement then the platelets should reach at least 75% of the pre-treatment level before the next, and subsequent, cycles of therapy (lower levels are permitted at the discretion of the Investigator).

10.6 WITHDRAWAL OF TREATMENT

In line with usual clinical care, cessation or alteration of treatment at any time will be at the discretion of attending clinicians or the patients themselves. All patients withdrawn from treatment **after starting trial treatment** will still attend for follow up assessments until 2 years after randomisation, unless unwilling to do so, and Case Record Forms (CRFs) will continue to be completed.

11. ASSESSMENTS / SAMPLES / DATA COLLECTION

The trial consists of a treatment period of up to six 28 day cycles (approximately 6 months without treatment delays) with either FCR or FCM-miniR. A formal assessment of response by IWCLL Criteria will be made 3 months after the end of therapy. Patients will then be followed up at 12, 18 and 24 months post randomisation or until disease progression requiring therapy if this is before 24 months post randomisation. Patients will then be followed up for survival until death as part of a long term follow up registry.

Data will be collected using paper case record forms which will be provided by, and should be submitted to, the CTRU at the University of Leeds. ***Assessments that will be collected as part of the data set are indicated in italics.***

Participating hospitals will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the CTRU, and keep copies of all completed CRFs for the trial.

Investigations in this study will use the results of centrally analysed blood and bone marrow assessments.

See Key Contacts (Section 1) for addresses for sending samples for central analysis and CRFs.

11.1 SCHEDULE OF EVENTS

Parameter	Prior to Randomisation	Baseline (up to 4 weeks before starting treatment unless indicated)	After 3 cycles of therapy	At the end of therapy	3 months post-completion of therapy (for IWCLL criteria)	12 months post randomisation	18 and 24 months post randomisation	At disease progression
Informed consent	X							
Demographic Data	X							
Health economics patient questionnaire (includes EQ-5D and SF-12)	X		X	X	X	X	X	
Medical history		X						
Serum or urine HCG		X[a]						
Assessment of disease (clinical examination)		X[b]	X		X	X	X	
CT scan		X			X	X[d]	X[d]	
ECG		X						
Vital signs (systolic BP, diastolic BP, pulse rate, temperature)		X	X	X	X	X	X	
Height (cm)		X	X	X	X	X	X	
Weight (kg)		X	X	X	X	X	X	
Body surface area (m^2)		X	X	X	X	X	X	
Performance Status		X	X	X	X	X	X	
Laboratory tests (haematology)		X	X	X	X	X	X	
Laboratory tests (biochemistry)		X	X	X				
LDH test		X						
β2M test		X						
Direct Coombs Test		X		X				
Glucose test		X						
Reticulocyte count		X		X				
Serology for Hepatitis B and C		X						
Serum immunoglobulins and electrophoresis		X						
Bone marrow (aspirate and trephine) to HMDS for flow cytometry (MRD Flow) and aspirate to UK CLL Trials BioBank		X[e]			X			
EDTA blood to HMDS for flow cytometry (MRD Flow)		X	X		X	X	X[c]	

40ml anticoagulated blood to UK CLL Trials BioBank		**X**						**X**
10ml clotted blood to UK CLL Trials BioBank		**X**						
Saliva sample to UK CLL Trials BioBank		**X**						
Concomitant diseases and medications		**X**	**Monitor throughout Study**			**X**	**X**	
Adverse events		**X**	**Monitor throughout Study**					

[a and b] Up to 2 weeks before starting treatment; [c] in patients who are MRD negative at 12 months post randomisation until MRD becomes detected; [d] if clinically indicated; [e]send to Biobank only if lymphocyte count<$10x10^9$/L,

11.2 LABELLING OF LABORATORY SAMPLES

- **Local investigations**
  Biological material samples for local analysis should be labelled using the standard hospital system and therefore will not be anonymised, this will allow the results of the investigations to be fed back to the patients' doctors.

- **Central investigations (Peripheral blood and bone marrow aspirate and trephine) to HMDS**
  Samples will be sent to the Haematological Malignancy Diagnostic Service (HMDS) at St. James's University Hospital. All samples should be labelled with the patient's trial number, date of birth, name**,** number of cycles of therapy or months follow up. Pre-printed label templates will be provided in the investigator pack for each centre.

  It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to conform with the 1998 Data Protection Act.

  Biological samples collected from patients as part of this study will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act.

  Samples should not be collected prior to taking consent. (NB: following consent, and where a bone marrow aspirate cannot be obtained, it is acceptable for trephine that had previously been taken, during the last 6 months, to be used and sent to the central laboratory).

- **Central investigations (anti-coagulated blood, clotted blood, bone marrow aspirate and saliva sample) to UK CLL Trials BioBank**
  The UK CLL Trials BioBank aims to identify biomarkers that predict therapeutic response to the treatments being evaluated. Patients entering the study are therefore requested to donate blood bone marrow (if a low lymphocyte count, see 11.1)and saliva samples prior to commencement of therapy. Additional samples are requested at specific points thereafter. These samples will be used for a range of studies of direct relevance to the treatment of CLL. Data resulting from analysis of samples sent to the BioBank will be fed back to the CTRU for integration with the clinical data set. Details of what samples to collect when and where to send them are given in Section 11.3, 11.7 and 11.9. It should be noted that the UK CLL Trials Biobank is a generic resource which is available to serve all national CLL trials. As such, it has its own ethical approval for the purposes described above, including Patient Information Sheet and Consent Form, which should be used in addition to those provided for the main study.

11.3 BASELINE ASSESSMENTS

Baseline assessments are to be performed within four weeks prior to the start of treatment unless otherwise indicated. Assessments given in *italics* will be collected as part of the data set:

- ***Complete medical history:*** (*Detailed history of CLL, baseline clinical conditions*)
- ***Pregnancy test:*** (*Serum or urine HCG in women of child bearing potential* ***within 2 weeks*** *prior to starting treatment*)
-

- ***Complete physical examination:*** (*Systolic and diastolic blood pressure, pulse rate, height, weight, body surface area* (Appendix D), *B symptomsand WHO performance status* (Appendix A).
- ***Local Haematology and Biochemistry:***
    - *FBC(Hb, platelets, WBC count, ANC neutrophils, ALC lymphocytes)*
    - *U&E's (sodium, potassium, calcium (adjusted), urea, urate, serum creatinine, creatinine clearance), LFT's (bilirubin, alkaline phosphatase, ALT, total protein, albumin), LDH, β_2M, glucose, reticulocyte count)*
    - *Serum immunoglobulins and electrophoresis*
    - *Direct Coombs test*
    - *Serology for Hepatitis B and C and HIV*
- ***Central investigations:***

  In addition, the following samples will be sent for central analysis,

    - ***Bone marrow aspirate and trephine*** The first draw of bone marrow aspirated should be put in EDTA and used for MRD flow cytometry (the less the marrow is diluted with blood the more accurate the assessment of involvement by CLL). The marrow aspirate and, if possible, the trephine biopsy in formalin should be sent to:

      Haematological Malignancy Diagnostic Service
      Level 3, Bexley Wing
      St. James's University Hospital
      Beckett Street
      Leeds, LS9 7TF

      The second draw of bone marrow aspirated should be sent to:

      UK CLL Trials BioBank
      Division of Haematology
      2nd Floor Duncan Building
      Royal Liverpool University Hospital
      Prescot Street
      Liverpool
      L7 8XP

    - ***5 to 10ml blood*** in EDTA to Haematological Malignancy Diagnostic Service, (HMDS) (address above) for flow cytometry

    - ***40ml anticoagulated blood*** *to*:

      UK CLL Trials BioBank
      Division of Haematology
      2nd Floor Duncan Building
      Royal Liverpool University Hospital
      Prescot Street
      Liverpool
      L7 8XP

    - ***10ml clotted blood*** to the UK CLL Trials BioBank (address above)
    - ***Saliva sample*** to the UK CLL Trials BioBank (address above)

- ***Chest X-ray (if required)***

- ***CT-scan (thorax, abdomen and pelvis)***
- ***Electrocardiogram***

- ***Assessment of disease*** *(Must be performed* ***within 2 weeks*** *prior to the patient starting treatment. Clinical assessment of lymph node disease; the size of the largest lymph nodes in each nodal area should be measured in centimetres in 2-dimensions. If appropriate clinically, CT-scan to assess lymph node disease should be performed).*

In addition the patient will complete the health economics patient questionnaire which includes the EQ-5D and SF-12 (Section 13.1).

11.4 ROUTINE TESTS BEFORE EACH CHEMOTHERAPY CYCLE

Patients will be assessed for their suitability for treatment within 1 week prior to Day 1 of each chemotherapy cycle according to standard clinical practice. Details of these assessments will not be collected as part of the trial data set.

Patients should be weighed prior to each cycle of treatment but the BSA (Appendix D) should only be re-calculated if the weight changes by greater than 10% (loss or gain).

11.5 EVALUATIONS AFTER 3 CYCLES OF THERAPY

Patients will be evaluated after 3 cycles of chemotherapy and the following investigations should be undertaken. Assessments given in *italics* will be collected as part of the trial data set:

- ***Complete physical examination:*** (*Systolic and diastolic blood pressure, pulse rate, height, weight, body surface area* (Appendix D) *, B symptoms and WHO performance status* (Appendix A)*).*
- ***Local Haematology and Biochemistry*** **:**
    - *FBC(Hb, platelets, WBC count, ANC neutrophils, ALC lymphocytes)*
    - *U&E's (sodium, potassium, calcium (adjusted) urea, urate, serum creatinine, creatinine clearance) , LFT's (bilirubin, alkaline phosphatase, ALT, total protein, albumin)*
- ***Central investigations:***
  In addition, the following samples will be sent for central analysis:
    - ***5 to 10ml blood*** in EDTA to Haematological Malignancy Diagnostic Service, (HMDS) (address above) for flow cytometry
- ***Assessment of disease***
  Patients will be formally assessed by full clinical examination. Patients who have no response or progressive disease (according to the IWCLL criteria – Appendix B*) will stop therapy.*

In addition the patient will complete the health economics patient questionnaire which includes the EQ-5D and SF-12 (Section 13.1).

11.6 EVALUATIONS AT THE END OF THERAPY

Patients will be evaluated at the end of therapy and the following investigations should be undertaken. Assessments given in *italics* will be collected as part of the trial data set:

- ***Complete physical examination:*** (*Systolic and diastolic blood pressure, pulse rate, height, weight, body surface area* (Appendix D), *B symptoms and WHO performance status* (Appendix A)*).*

- ***Local haematology and biochemistry :***
    - *FBC(Hb, platelets, WBC count, ANC neutrophils, ALC lymphocytes)*
    - *U&E's (sodium, potassium, calcium (adjusted) urea, urate, serum creatinine, creatinine clearance) , LFT's (bilirubin, alkaline phosphatase, ALT, total protein, albumin), Direct Coombs Test, reticulocyte count*

In addition the patient will complete the health economics patient questionnaire which includes the EQ-5D and SF-12. (Section 13.1)

11.7 EVALUATIONS 3 MONTHS AFTER THE END OF THERAPY

Patients will be evaluated for response to treatment and assessment of minimal residual disease 3 months after the end of therapy, according to the IWCLL Response Criteria (Appendix B). This visit should be timed 3 months after Day 1 of the patient's final cycle of treatment. The following investigations should be undertaken. Assessments in *italics* will be collected as part of the trial data set:

- ***Complete physical examination:*** (*Systolic and diastolic blood pressure, pulse rate, height, weight, body surface area* (Appendix D), *B symptoms and WHO performance status* (Appendix A)*).*
- ***Local haematology:*** *FBC (Hb, platelets, WBC count, ANC neutrophils, ALC lymphocytes*)
- Serum immunoglobulins
- ***Central investigations:***
  In addition, the following samples will be sent for central analysis:

    * ***Bone marrow aspirate and trephine*** The first draw of bone marrow aspirated should be put in EDTA and used for MRD flow cytometry (the less the marrow is diluted with blood the more accurate the assessment of involvement by CLL). The marrow aspirate and, if possible, the trephine biopsy in formalin should be sent to:

      Haematological Malignancy Diagnostic Service
      Level 3, Bexley Wing
      St. James's University Hospital
      Beckett Street
      Leeds, LS9 7TF

      The second draw of bone marrow aspirated should be sent to:

      UK CLL Trials BioBank
      Division of Haematology
      2nd Floor Duncan Building
      Royal Liverpool University Hospital
      Prescot Street
      Liverpool
      L7 8XP

    * ***5 to 10ml blood*** in EDTA to Haematological Malignancy Diagnostic Service, (HMDS) (address above) for flow cytometry

- ***CT-scan (thorax, abdomen and pelvis)***

- ***Assessment of disease***

Clinical assessment of lymph node disease should be performed. The size of the largest lymph nodes in each nodal area should be measured in centimetres in 2-dimensions. A CT-scan to assess lymph node disease should be performed.

In addition the patient will complete the health economics patient questionnaire which includes the EQ-5D and SF-12. (Section 13.1)

11.8 EVALUATIONS AT 12, 18 AND 24 MONTHS POST RANDOMISATION OR UNTIL DISEASE PROGRESSION REQUIRING THERAPY

Patients will be evaluated at 12, 18 and 24 months post randomisation or until disease progression requiring therapy if this is before 24 months post randomisation. The following investigations should be undertaken. Assessments given in *italics* will be collected as part of the data set

- ***Complete physical examination:*** (*Systolic and diastolic blood pressure, pulse rate, height, weight, body surface area* (Appendix D), *B symptoms and WHO performance status* (Appendix A)*).*
- ***Local haematology:*** *FBC (Hb, platelets, WBC count, ANC neutrophils, ALC lymphocytes*)
- ***Assessment of disease***
  Clinical assessment of lymph node disease should be performed. The size of the largest lymph nodes in each nodal area should be measured in centimetres in 2-dimensions. If appropriate clinically, CT-scan to assess lymph node disease should be performed.

For all patients at 12 months post randomisation and for patients who are MRD negative 12 months post randomisation until MRD becomes detected:

- ***Central investigations:***
  The following samples are needed for central investigations:

  - ***5 to 10ml blood*** in EDTA to Haematological Malignancy Diagnostic Service, (HMDS) for flow cytometry

    Haematological Malignancy Diagnostic Service
    Level 3, Bexley Wing
    St. James's University Hospital
    Beckett Street
    Leeds, LS9 7TF

All patients will be followed up in terms of progression-free survival until 2 years post randomisation or death if sooner.

In addition the patient will complete the health economics patient questionnaire which includes the EQ-5D and SF-12. (Section 13.1)

11.9 EVALUATIONS AT DISEASE PROGRESSION

Patients will be evaluated at disease progression. The following investigations should be undertaken. Assessments given in *italics* will be collected as part of the data set:

- ***Central investigations:***
  The following samples are needed for central investigations:

* ***40 ml anti-coagulated blood*** sent to:

UK CLL Trials BioBank
Division of Haematology
2nd Floor Duncan Building
Royal Liverpool University Hospital
Prescot Street
Liverpool
L7 8XP

11.10 ANNUAL FOLLOW UP

Patients will be followed up for survival on an annual basis until death as part of a long term follow up registry.

11.11 ASSESSMENT OF EFFICACY

A clinical assessment of response will be made after 3 cycles of therapy (either FCR or FCM-miniR). Patients with evidence of progressive disease will stop therapy and will be deemed to have failed treatment.
A formal assessment of response, including minimal residual disease status, by IWCLL Criteria will be made 3 months after the end of therapy (FCR or FCM-miniR).

11.12 RESPONSE TO TREATMENT

Disease will be evaluated according to the IWCLL criteria given in Appendix B.

11.13 MEASUREMENT OF DISEASE PROGRESSION

Disease progression will be defined using the IWCLL criteria given in Appendix B. Progressive disease during or after therapy is characterised by at least one of the following:

- Lymphadenopathy
- An increase in the liver or spleen size by 50% or more and the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.
- Transformation to a more aggressive histology (eg, Richter syndrome). Whenever possible this diagnosis should be established by lymph node biopsy.
- Occurrence of cytopenia (neutropenia, anaemia, or thrombocytopenia) attributable to CLL.

11.14 ADVERSE AND SERIOUS ADVERSE EVENTS

Complete the AE CRF for all AEs occurring in the trial and report via the usual data management routes.

Complete the SAE CRF for all SAEs occurring in the trial and fax to the CTRU within 24 hours of becoming aware of the event (see Section 12).

Complete the SUSAR CRF for all SUSARs occurring in the trial and fax to the CTRU within 24 hours of becoming aware of the event:

11.15 PREGNANCIES

All pregnancies, suspected pregnancies and pregnancies in the female partners of male participants must be reported immediately to the CTRU (Senior) Trial Co-ordinator using the Notification of Pregnancy CRF. Female participants who become pregnant should be withdrawn from the trial treatment immediately. Any congenital abnormality or birth defect resulting from the pregnancy should be reported as a Serious Adverse Event.

11.16 DEATHS

Up to 24 months post randomisation
All deaths must be recorded on the Death Form and sent to the CTRU within 5 days of notification to the site trial research team. The date of death and cause of death will be collected.

After 24 months post randomisation
Deaths occurring after 24 months post randomisation should be collected as part of the long term follow up registry.

Treatment related mortality (TRM) must be faxed immediately to the CTRU. See Section 12.6 for further details. Where the cause of death is uncertain this should be classed as a SUSAR, a Suspected Unexpected Serious Adverse Reaction CRF is completed and reported to the CTRU in accordance with the trial pharmacovigilance procedures (Section 12).

11.17 DEFINITION OF THE END OF TRIAL

The end of the trial is defined as the date of the last patient's last treatment visit plus 30 days. Long term follow up for purposes of the Main REC and Research Governance to one month after the last patient's last trial follow up visit constitutes the non-interventional phase of the trial. Subject to the set-up of the CLL Trials Registry, patients will be followed up annually for life.

12. PHARMACOVIGILANCE PROCEDURES

12.1 GENERAL DEFINITIONS

12.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with this treatment and can include;

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests.

In addition the following criteria may be used in order to collect protocol-defined *reportable adverse events* which do not meet the criteria for serious (Section 12.1.2):

- requires medical or surgical intervention to prevent permanent impairment of function or permanent damage to body structure.

12.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is defined in general as 'any untoward medical occurrence or effect that:

- results in death,
- is life-threatening*,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- consists of a congenital anomaly or birth defect or
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.'

*the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical judgement should be exercised in deciding whether an SAE is serious in other situations. Important SAE/SARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardize the subject may require intervention to prevent one or the other outcomes listed in the definition above, should also be considered serious.

Where an SAE is deemed to have been related to an IMP used within the trial the event is termed as a Serious Adverse Reaction (SAR).

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a Serious Adverse Reaction which also demonstrates the characteristics of being unexpected, the nature and severity of which is not consistent with the information about the medicinal product in question set out;
(a) in the case of the product with a marketing authorisation, in the summary of product characteristics for that product,
(b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

12.2 OPERATIONAL DEFINTION AND REPORTING AEs

All adverse events, both related and unrelated to the treatment of CLL will be collected for all patients and will be evaluated for duration and intensity according to the National Cancer Institute Common Terminology Criteria for Adverse Events V3.0 (NCI-CTCAE). A copy is provided in the Investigator Site File and may be obtained at:

http://ctep.cancer.gov/forms/CTCAEv3.pdf

Published date: August 9, 2006

AEs will be collected from randomisation until 30 days after the last dose of treatment with FCR or FCM-miniR.

Information about AEs, whether volunteered by the patient, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded on the CRF.

12.3 OPERATIONAL DEFINTION – SERIOUS ADVERSE EVENTS

12.3.1 Events not classed as SAEs

The following events **will not** be recorded as SAEs within this trial:
Hospitalisation for:

- Routine treatment or monitoring of the studied indication not association with any deterioration in condition.
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition.
- Admission to hospital or other institution for general care, not associated with any deterioration in condition.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions for serious as given above and not resulting in hospital admission.
- Disease progression
- Deaths attributable to CLL beyond 30 days of the last administration of the study agent

12.3.2 Expected SAEs

The following events **will be** classed as expected SAEs within this trial and therefore will not be reportable as SUSARs:

Expected SAEs related to CLL:

- Infections requiring intravenous antibiotics
- Blood product support necessitating admission to hospital

Expected SAEs common to all treatments:

- Anaemia
- Neutropenia
- Thrombocytopenia
- Infections requiring intravenous antibiotics
- Gastrointestinal upset

Expected SAEs for specific drugs/treatments:

When determining whether an SAE is expected or not, please refer to the version of the SPC supplied in the Investigator Site File or the latest updated version as instructed by the CTRU.

Drug/treatment	Examples of expected SAEs
Mitoxantrone	Alopecia (<5% of patients) Blue-green colouration to the urine Cardiotoxicity Discoloration of skin and nails Elevated serum creatinine Extravasation Hyperuricaemia Increased liver enzymes Myelosuppression Nail dystrophy Nausea Neurological side effects (somnolence, confusion, anxiety, mild parathesia) Onycholysis Rash Tumour lysis syndrome Vomiting
Cyclophosphamide	Amenorrhoea Anaemia Anorexia

	Cardio-toxicity at high doses Cystitis Interstitial pulmonary fibrosis Nausea Pigmentation of palms, nails and soles Vomiting
Fludarabine	Anorexia Chills Cough Diarrhoea Fever Nausea Malaise Oedema Peripheral neuropathy Pneumonia Pulmonary toxicity Rash Renal impairment Visual disturbances Vomiting Weakness
Rituximab	Arrhythmias Cytokine release syndrome (severe dyspnoea, accompanied by bronchospasm and hypoxia, in addition to fever, chills, nausea, rigors, urticaria, and angioedema). Hypotension Mucosal swelling Weight changes

12.4 RECORDING AND REPORTING SAEs AND SUSARs

All SAEs / SUSARs / Related Unexpected SAEs occurring whilst on trial must be recorded on the SAE or SUSAR Form and faxed to the CTRU within 24 hours of the research staff becoming aware of the event. Once all resulting queries have been resolved, the CTRU will request the original form be posted to the CTRU and a copy to be retained on site:

For each SAE / SUSAR / Related Unexpected SAE, the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates if applicable)
- action taken
- outcome
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether or not the event would be considered expected or unexpected

Any follow-up information should be faxed to the CTRU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached.

Fax Number for reporting SAEs and SUSARs:
0113 343 7985

12.5 RESPONSIBILITIES

Principal Investigator:

1. Checking for SAEs when patients attend for treatment.
2. Medical judgment in assigning to SAEs:
   - Seriousness
   - Causality
   - Expectedness
3. To ensure all SAEs are recorded and reported to the CTRU and to provide further follow up information as soon as available.
4. To report SAEs to local committees in line with local arrangements.

CTRU:

1. Expedited reporting of SUSARs to Competent Authority (MHRA in UK), Main REC and Sponsor within required timelines.
2. Preparing annual safety reports to Competent Authority, Main REC and Sponsor
3. Notifying Investigators of SUSARs that occur within the trial.
4. Preparation of investigator notifications relating to SUSARs and annual updates to the SPC

Chief Investigator (or nominated individual in CI's absence):

1. Assign causality and expected nature of SAEs where it has not been possible to obtain local assessment.
2. Review all SAEs for seriousness, expectedness and causality. All SUSARs or increase in trends or severity of SARs will be identified and expeditedly reported to the MREC, MHRA and Sponsor.
3. Review all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and CI / Sponsor review with regards to SUSAR status, local assessment will not be overruled, but CI / Sponsor may add comments prior to expedited reporting.
4. Chief Investigator to assign code to all SAEs suspected to be related to trial treatment using the MedDra Body System Organ Class coding, prior to submission of annual safety reports.

Trial Management Group (TMG):

1. The Trial Management Group will review cumulative reports of all SAEs on a monthly basis to identify patterns or trends of events or identify safety issues which would not be apparent on an individual basis.
2. To immediately notify CTRU of any increase in the incidence or severity of any SARs.

Trial Steering Committee (TSC):

1. In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

Data Monitoring and Ethics Committee (DMEC):

1. In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

12.6 OPERATIONAL DEFINITION OF TREATMENT RELATED MORTALITY (TRM)

Treatment Related Mortality is defined as any death during or within one month of the last chemotherapy treatment which is not due to other causes.

Treatment Related Mortality is assessed for each death occurring whilst a patient is on the trial. Each death is recorded on the Death CRF; where the death is suspected to be related to the trial treatment it is faxed to the CTRU within 24 hours of notification to the research team. Where the treatment related death (TRD) is also classed as a SAE, a Serious Adverse Event CRF is completed and reported to the CTRU in accordance with the trial pharmacovigilance procedures (Section 12). NB: Where the cause of death is uncertain this should be classed as a SUSAR, a Suspected Unexpected Serious Adverse Reaction CRF is completed and reported to the CTRU in accordance with the trial pharmacovigilance procedures (Section 12).

Fax Number for reporting TRDs: 0113 343 7985

13. ECONOMIC EVALUATION

The focus of the economic evaluation alongside this trial will be the development of a decision analytic cost effectiveness model to inform the design of the proposed Phase 3 large scale randomised controlled trial. The Research Fellow in Health Economics will work closely with the clinical co-investigators to develop a comprehensive model of the long term clinical pathway for CLL patients treated with FCR and FCM-miniR respectively. The pathways will be used to derive a comprehensive list of the evidence required to parameterise the cost effectiveness model. Focussed systematic search strategies of published and grey literature will then be undertaken. Where multiple sources of evidence are available, the data will be synthesised if it is methodologically appropriate to do so; otherwise a preferred data source will be chosen and the rationale for that choice recorded.

In line with recommended best practice, the model will adopt the perspective of the UK NHS and Personal Social Services budget. The time horizon of the analysis will be lifetime. Costs and outcomes will be discounted at 3.5% per annum. The outcome measure for the analysis will be the Quality Adjusted Life Year (QALY)[21]. The effectiveness data from the trial will be synthesised with existing evidence where it exists. Parameter uncertainty will be assessed using probabilistic sensitivity analysis. The results of the model will be presented as expected incremental cost effectiveness ratios; cost effectiveness acceptability curves and expected net benefit, assuming lambda =£20,000 per QALY.

We will undertake Expected Value of Information analysis to assess the value of undertaking further research to reduce the decision uncertainty. We will use analysis of covariance to assess the contribution of each parameter to the total uncertainty around the expected cost effectiveness. Expected Value of Partial and Sample information will be used to quantify the value, from reduced decision uncertainty, of undertaking (a) a Phase 3 trial with different sample sizes; and (b) research into other parameters in the cost effectiveness analysis[22].

Secondary analyses will adopt a societal perspective taking into account direct patient expenditures such as over the counter medicines and supplements and the indirect costs associated with each

intervention (time away from work for the patient). There is currently substantial uncertainty about the best method for estimating productivity costs. If this uncertainty has been resolved at the time of analysis we will adopt the recommended method, if not we will undertake sensitivity analysis to demonstrate the impact of using friction cost based estimate rather than human capital based estimates of productivity costs.

Unit costs for health service resources will be obtained from national sources such as the Personal Social Services Research Unit (PSSRU), the British National Formulary (BNF) and National Health Service (NHS) Reference Cost database. Where national costs are not available the finance departments of trusts participating in the study will be asked to provide local cost data. The mean of these costs will be used as the unit cost estimates in the analysis.

13.1 HEALTH ECONOMICS QUESTIONNAIRES

NHS resource use associated with each treatment modality will be collected via the CRFs (investigations, drugs, referrals for other services) and health economics patient questionnaires. The questionnaires will also be used to collect data on out-of-pocket expenses associated with their condition and indirect costs (time away from work for the patient).

The questionnaires also contain the EQ-5D, a measure of health related quality of life, that is very simple instrument to complete and will be used in the estimation of QALYs; and the SF-12, a short, validated survey that measures general health status and includes physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role functioning emotional, and mental health. The questionnaires are designed to allow tick-box completion where ever possible.

13.1.1 Timing and administration of health economics patient questionnaires

All patients will be asked to complete the health economics patient questionnaires; the questionnaires will be administered **during clinic** at the following time points:

- Baseline (**Prior** to the patient being informed of their randomisation allocation)
- After 3 cycles of therapy
- At the end of therapy
- 3 months after the end of therapy
- Every 3 months after the end of therapy until 2 years post randomisation (ie at 6, 9, 12, 15, 18 , 21 and 24 months post randomisation).

If the patient progresses prior to the 2 year post randomisation time point, questionnaires should be administered during clinic every 3 months from disease progression up to 1 year post disease progression.

In order to maintain confidentiality, patients will be provided with an envelope in which to seal their completed questionnaire before returning it to the clinician. All original questionnaires will be returned to the CTRU by the participating research centre.

14. ENDPOINTS

14.1 PRIMARY ENDPOINT

- Proportion of patients achieving a Complete Response (CR), as defined by IWCLL criteria (see Appendix B)

14.2 SECONDARY ENDPOINTS

- Proportion of patients with undetectable minimal residual disease
- Overall response rate defined as complete or partial remission by IWCLL Criteria (see Appendix B).
- Safety and toxicity
- Economic evaluation
- Progression-free survival at 2 years (defined in section 11.13)
- Overall survival at 2 years

14.3 STUDY DEFINITIONS

- Response: Response is assessed by the IWCLL criteria as defined in Section 11.12 and Appendix B.
- Minimal residual disease: A negative MRD is defined as the presence of < 0.01% CLL cells in the blood or bone marrow.
- Safety and toxicity: Reported based on adverse events, as graded by CTCAE V3.0, and determined by routine clinical assessments at each centre.
- Economic evaluation: See section 13 for further details.
- Progression free survival: Time from randomisation to first documented evidence of disease progression or death. Patients who do not progress will be censored at the last date they were known to be alive and progression free.
- Overall survival: Time from randomisation to date of death. Patients still alive at the time of analysis will be censored at the last date they were last followed up.

15. STATISTICAL CONSIDERATIONS

15.1 SAMPLE SIZE

206 patients are required.

From previous studies it is anticipated that FCR will produce response rates of at least 50%. In particular, the results from the German CLL study group presented at the American Society of Haematology conference 2008, show a 52% complete response rate with FCR[9]. We anticipate that FCM-miniR will actually have a superior response rate to FCR. This is based on, firstly, our assumption from previously discussed data[18] that miniR is as good, or nearly as good as full dose rituximab, and, secondly, the hypothesis that mitoxantrone increases the response rate when added to FCR. We therefore hypothesise that FCM-miniR may increase the response rate by approximately 10%. If this is the case, and FCM-miniR really has a 10% better response rate when compared with FCR, a non-inferiority phase IIB trial is practicable. Under this assumed 10% difference in favour of FCM-miniR, to have 80% power to show non-inferiority, where this is defined as FCM-miniR being not more than 10% worse in terms of response rate than FCR, would require the randomisation of 98 patients per arm, 196 in total[23].

To account for a 5% dropout, we will randomise 206 patients (103 per arm). This approach uses a one-sided 97.5% CI, i.e. α (type I) error rate of 2.5%, equivalent to a conventional α of 5% for the superiority setting[23]. In addition, if FCM-miniR is really 10% superior to FCR in terms of response rate, we will have about 30% power to show this with the randomisation of 206 patients.

15.2 PLANNED RECRUITMENT RATE

In order to recruit 206 patients over an 18 month period, the recruitment target is 11-12 patients per month.

16. STATISTICAL ANALYSIS

16.1 GENERAL CONSIDERATIONS

Statistical analysis is the responsibility of the CTRU Statistician. The analysis plan outlined in this section will be reviewed and a final statistical analysis plan written before any analysis is undertaken. The analysis plan will be written in accordance with current CTRU standard operating procedures and will be finalised and agreed by the following people: the trial statistician and supervising statistician, the Chief Investigator, the CTRU principle investigator and the senior trial coordinator. Any changes to the finalised analysis plan, and reasons for changes, will be documented.

All analyses will be conducted on the intention-to-treat (ITT) population (as defined in the statistical analysis plan), where patients will be included according to the treatment they were randomised to. A per-protocol analysis, where patients will be included according to the treatment they received, will be considered for the primary endpoint if there are a considerable number of protocol violators. For the primary analysis, equal weighting will be given to both the ITT analysis and per-protocol analyses, as the ITT is likely to be the least conservative approach when testing non-inferiority. The safety population will consist of all patients who receive at least one dose of trial treatment.

An overall one-sided 2.5% significance level will be used for the primary response analysis. A two-sided 5% significance level will be used for all superiority efficacy endpoint comparisons.

16.2 FREQUENCY OF ANALYSES

Interim reports summarising safety and short term efficacy data will be presented to the Data Monitoring and Ethics Committee (DMEC) in strict confidence at approximately yearly intervals or as soon as sufficient data have been accrued to make them meaningful. A single formal interim analysis is planned on the primary endpoint when half the number of patients (103) has reached their primary endpoint. The DMEC, in the light of the interim reports and of any advice or evidence they wish to request, will if necessary report to the Trial Steering Committee if there are concerns regarding the safety or efficacy of the trial treatment.

Apart from the interim analysis to the DMEC, no other formal analyses are planned until after the trial is closed to accrual and the required number of patients has been randomised. Final analysis will be carried out on all but the survival endpoints when the response data is available for all patients, approximately 9 months after the close of recruitment. The survival endpoints will be analysed two years after the close of recruitment and subsequently updated as appropriate, and formally at 5 years after the close of recruitment.

16.3 PRIMARY ENDPOINT ANALYSES

- Proportion of patients achieving a Complete Response (CR), as defined by IWCLL criteria

The proportion of patients who have at least a CR will be summarised by treatment group, and the lower limit of the 95% confidence interval (one-sided type I error rate of 2.5%) for the difference in

the proportions of patients achieving a CR between the treatment groups reported. This will be obtained using one-sided binary logistic regression to adjust for the minimisation factors, excluding centre. This lower limit will be compared with the non-inferiority margin of 10%.

16.4 SECONDARY ENDPOINT ANALYSES

- Proportion of patients with undetectable minimal residual disease

The proportion of patients who are MRD negative following treatment will be summarised by treatment group and the lower limit of the 95% confidence interval (one-sided type I error rate of 2.5%) for the difference in the proportions of patients achieving MRD negativity between the treatment groups reported. This will be obtained using one-sided binary logistic regression to adjust for the minimisation factors, excluding centre. This lower limit will be compared with a non-inferiority margin of 10%.

- Overall response rate defined as complete or partial remission by IWCLL Criteria

The proportion of patients who have at least a PR will be summarised by treatment group and the lower limit of the 95% confidence interval (one-sided type I error rate of 2.5%) for the difference in the proportions of patients achieving an overall response between the treatment groups reported. This will be obtained using one-sided binary logistic regression to adjust for the minimisation factors, excluding centre. This lower limit will be compared with a non-inferiority margin of 10%.

- Progression-free survival

Progression free survival will be calculated from date of randomisation to date of first documented evidence of disease progression or death from any cause. Patients not reaching disease progression or death at the time of analysis will be censored at the last date known to be alive and progression-free. Cox regression analysis will be used to analyse time to progression accounting for the minimisation factors, excluding centre. 97.5% one-sided confidence intervals on the hazard ratio will be presented to evaluate non-inferiority of FCM-miniR to FCR. Progression-free survival curves will be calculated using the Kaplan Meier method, adjusted for the minimisation factors[24], excluding centre, and adjusted hazard ratios and corresponding 95% confidence intervals will be calculated.

- Overall survival

Overall survival will be calculated from date of randomisation to date of death from any cause. Patients who are alive at the time of analysis will be censored at the last date known to be alive. Cox regression analysis will be used to analyse overall survival accounting for the minimisation factors, excluding centre. 97.5% one-sided confidence intervals on the hazard ratio will be presented to evaluate non-inferiority of FCM-miniR to FCR. Overall survival curves will be calculated using the Kaplan Meier method, adjusted for the minimisation factors[24], excluding centre, and adjusted hazard ratios and corresponding 95% confidence intervals will be calculated.

- Safety and toxicity

Safety analyses will summarise the adverse event rates and laboratory changes, the number of NCI toxicity grades for laboratory parameters and treatment-related mortality rates. Safety data will be presented by treatment group and relationship to study treatment or underlying CLL.

- Economic evaluation

Details are given in Section 13 and a separate analysis plan will be written before analysis is performed.

16.5 SUBGROUP ANALYSES

Exploratory analyses may be carried out to assess whether the risk of the patient (good or standard) is prognostic of the primary outcome. Good risk CLL is defined as V_H mutated excluding V_H3-21 cases, and standard risk CLL is defined as V_H unmutated or V_H3-21 cases but excluding patients with >20% 17p deleted cells.
Subgroup analyses may, by chance, generate false negative or positive results. Those carried out will be interpreted with caution and treated as hypothesis-generating.

17. DATA MONITORING

17.1 DATA MONITORING AND ETHICS COMMITTEE

An independent Data Monitoring and Ethics Committee (DMEC) will review the safety and ethics of the study. The committee will review serious adverse events and other safety or ethical issues at least 3-monthly. Detailed unblinded reports containing safety and short-term efficacy summaries will be prepared by the CTRU for the DMEC at approximately yearly intervals. The formal interim analysis on the primary endpoint will be reported to the DMEC after half the number of patients (103) has reached their response timepoint.

17.2 DATA MONITORING

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of patients, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to patient notes at the participating hospital sites and the collection of copies of consent forms and other relevant investigation reports. A Trial Monitoring Plan will be developed and a Meeting Group Monitoring Schedule including primary endpoint and safety data will be defined and agreed by the Trial Management Group (TMG) if necessary.

17.3 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by patients during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts.

18. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

18.1 QUALITY ASSURANCE

The trial will be conducted in accordance with the principles of Good Clinical Practice in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework (*and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 for studies conducted in Scotland),* and through adherence to CTRU Standard Operating Procedures (SOPs).

CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify the CTRU of a serious breach (as defined by Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument

2006/1928) that they become aware of. A "serious breach" is a breach which is likely to effect to a significant degree –

a) the safety or physical or mental integrity of the subjects of the trial; or
b) the scientific value of the trial.

For further information, the Investigator should contact the Senior Trial Co-ordinator at the CTRU.

18.2 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996. Informed written consent will be obtained from the patients prior to registration into the study. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a main Research Ethics Committee (main REC) and the appropriate Site Specific Assessor for each participating centre prior to entering patients into the study. The CTRU will provide the main REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

19. CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- consent from patients to record personal details including name, date of birth, postcode, NHS ID, hospital ID
- appropriate storage, restricted access and disposal arrangements for patient personal and clinical details
- consent from patients for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- consent from patients for the data collected for the trial to be used to evaluate safety and develop new research.
- patient name will be collected on the consent form when a patient is randomised into the trial, but all other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two patient identifiers, usually the patient's initials and date of birth.
- where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the patient's name must be obliterated by site before sending
- where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU

If a patient withdraws consent from further trial treatment and / or further collection of data, their data and samples will remain on file and will be included in the final study analysis.

The trial staff at the participating site will be responsible for ensuring that any data / documentation sent to the CTRU is appropriately anonymised as per instructions given by CTRU in accordance with the trial procedures to conform with the 1998 Data Protection Act.

20. ARCHIVING

At the end of the trial, data will be securely archived in line with the Sponsor's procedures for a minimum of 15 years. Data held by the CTRU will be archived in the Leeds Sponsor archive facility and site data and documents will be archived at the participating centres. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be confidentially destroyed.

21. STATEMENT OF INDEMNITY

This trial is sponsored by The Leeds Teaching Hospitals NHS Trust and The Leeds Teaching Hospitals NHS Trust will be liable for negligent harm caused by the design of the trial. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under this duty of care.

As this is a clinician-led study, there are no arrangements for no-fault compensation; however, usual product liability will be covered by the manufacturer under the Consumer Protection Act 1987.

22. STUDY ORGANISATIONAL STRUCTURE

22.1 RESPONSIBILITIES

Chief Investigator - The Chief Investigator will have responsibility for the design and set-up of the trial, the investigational drug supply and pharmacovigilance within the trial.

Clinical Trials Research Unit – The CTRU will have responsibility for conduct of the trial in accordance with relevant GCP standards and CTRU SOPs.

22.2 OPERATIONAL STRUCTURE

Chief Investigator – The Chief Investigator is involved in the design, conduct, co-ordination and management of the trial

Trial Management Group - The TMG, comprising the Chief Investigator, CTRU team and co-investigators will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and supporting applications for Site Specific Assessments, (iv) submitting a CTA application and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) appointing and facilitating the TSC and DMEC, (vii) reporting of serious adverse events, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development.

Clinical Trials Research Unit - The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, ICH GCP and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006 including, randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition the CTRU will support main REC, Site Specific Assessment and R&D submissions and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

Trial Steering Committee – The Trial Steering Committee, with an independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, patient safety and consideration of new information. It will include an Independent Chair, not less than two other independent members. The Chief Investigator and other members of the TMG will attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC): The DMEC will review the safety and ethics of the trial by reviewing interim data during recruitment. The Committee will meet or communicate via teleconference approximately annually.

23. PUBLICATION POLICY

The trial will be registered with an authorised registry, according to ICMJE Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributor ship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- and final approval of the version to be published
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the end of the trial, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee or the Chief Investigator. In addition, individual collaborators must not publish data concerning their patients which is directly relevant to the questions posed in the trial until the main results of the trial have been published and following written consent from the Sponsor.

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APPENDIX A PERFORMANCE STATUS SCALE

Activity performance description	Score
Fully active, able to carry out all normal activity without restriction.	**0**
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e. g. light house work, office work.	**1**
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	**2**
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	**3**
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	**4**

APPENDIX B IWCLL RESPONSE CRITERIA

For a complete version of the IWCLL Guidelines for the diagnosis and treatment of chronic lymphocytic leukaemia: a report from the International Workshop on Chronic Lymphocytic Leukaemia updating the National Cancer Institute Working Group 1996 guidelines visit:

http://bloodjournal.hematologylibrary.org

Definition of response, relapse, and refractory disease

Assessment of response should include a careful physical examination and evaluation of the blood and marrow (Tables 3,4).

5.1. Complete remission (CR)

CR requires all of the following criteria as assessed at least 2 months after completion of therapy:

5.1.1. Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x 10^9/L (4000/µL). In clinical trials, the presence of minimal residual disease (MRD) after therapy should be assessed (see section 5.9). The sensitivity of the method used to evaluate for MRD should be reported.

5.1.2. Absence of significant lymphadenopathy (eg, lymph nodes >1.5 cm in diameter) by physical examination. In clinical trials, a CT scan of the abdomen, pelvis, and thorax is desirable if previously abnormal. Lymph nodes should not be larger than 1.5 cm in diameter.

5.1.3. No hepatomegaly or splenomegaly by physical examination. In clinical trials, a CT scan of the abdomen should be performed at response assessment if found to be abnormal before therapy or if physical examination is inconclusive at the time of evaluation.

5.1.4. Absence of constitutional symptoms.

5.1.5. Blood counts above the following values: *5.1.5.1. Neutrophils more than 1.5 x 10^9/L (1500/µL) without need for exogenous growth factors.*

5.1.5.2. Platelets more than 100 x 10^9/L (100 000/µL) without need for exogenous growth factors.

5.1.5.3. Hemoglobin more than 110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin.

5.1.6. For patients in clinical trials (Table 3), a marrow aspirate and biopsy should be performed at least 2 months after the last treatment and if clinical and laboratory results listed in sections 5.1.1 through 5.1.5 demonstrate that a CR has been achieved.

Table 3. Recommendations regarding the response assessment in CLL patients

Diagnostic test	Section of guidelines	General practice	Clinical trial
History, physical examination	5.1.2, 5.1.3, 5.1.4, 5.2.2, 5.2.3, 5.3.1, 5.3.2	Always	Always
CBC and differential count	5.1.1, 5.1.5, 5.2.4, 5.3.3, 5.3.5	Always	Always
Marrow aspirate and biopsy	5.1.6	At cytopenia of uncertain cause	At CR or cytopenia of uncertain cause
Assessment for minimal residual disease	5.9	NGI	Desirable
Ultrasound of the abdomen*	5.1.2, 5.1.3, 5.2.2, 5.2.3, 5.3.1, 5.3.2	Possible, if previously abnormal	NGI
CT scans of chest, pelvis, and abdomen	5.1.2, 5.1.3, 5.2.2, 5.2.3, 5.3.1, 5.3.2	NGI	Recommended if previously abnormal and otherwise with a CR

General practice is defined as the use of accepted treatment options for a patient with CLL who is not enrolled in a clinical trial.

NGI indicates not generally indicated.

* Used in some countries to monitor lymphadenopathy and organomegaly.

To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent.

In some cases, lymphoid nodules can be found, which often reflect residual disease.[55,56] These nodules should be recorded as "nodular PR." Moreover, immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or until peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment. A marrow biopsy should be compared with that of pretreatment marrow. In general practice, the use of a marrow biopsy for evaluating a CR is at the discretion of the physician.

In clinical trials aiming at maximizing the CR rate, the quality of the CR should be assessed for MRD by flow cytometry (see section 5.9) or by immunohistochemistry (IHC).

5.1.7. A controversial issue is how best to categorize the response of patients who fulfil all the criteria for a CR (including the marrow examinations described in section 5.16) but who have a persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity. We recommend that these patients be considered as a different category of remission: CR with incomplete marrow recovery (CRi). For the definition of this category, CRi, the marrow evaluation (see section 5.1.6) should be performed with scrutiny and not show any clonal

infiltrate. In clinical trials, CRi patients should be monitored prospectively to determine whether their outcome differs from that of patients with detectable residual disease or with noncytopenic CR.

5.2. Partial remission (PR)

PR is defined by the criteria described in sections 5.2.1, 5.2.2, or 5.2.3 (if abnormal before therapy), as well as one or more of the features listed in section 5.2.4. To define a PR, these parameters need to be documented for a minimal duration of 2 months (Table 4). Constitutional symptoms persisting for more than 1 month should be recorded.

Table 4. Response definition after treatment for patients with CLL, using the parameters of Tables 1 and 3

Parameter	CR*	PR*	PD*
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease ≥50%	Increase ≥50%
Hepatomegaly	None	Decrease ≥50%	Increase ≥50%
Splenomegaly	None	Decrease ≥50%	Increase ≥50%
Blood lymphocytes	< 4000/µL	Decrease ≥50% from baseline	Increase ≥50% over baseline
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi (5.1.6).	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B			
Platelet count	> 100 000/µL	> 100 000/µL or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils†	> 1500/µL	> 1500/µL or > 50% improvement over baseline	

Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system (or marrow).

* CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above criteria of group A or group B has to be met.

†Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).

‡These parameters are irrelevant for some response categories.

5.2.1. A decrease in the number of blood lymphocytes by 50% or more from the value before therapy.

5.2.2. Reduction in lymphadenopathy (by CT scans in clinical trials[57] or by palpation in general practice) as defined by the following: *5.2.2.1. A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy.*

5.2.2.2. No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2 cm), an increase of less than 25% is not considered to be significant.

5.2.3. A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan (in clinical trials) or palpation (in general practice).

5.2.4. The blood count should show one of the following results: *5.2.4.1. Neutrophils more than 1.5 x 10^9/L (1500/µL) without need for exogenous growth factors.*

5.2.4.2. Platelet counts greater than 100 x 10^9/L (100 000/µL) or 50% improvement over baseline without need for exogenous growth factors.

5.2.4.3. Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

5.3. Progressive disease

Progressive disease during or after therapy is characterized by at least one of the following:

5.3.1. Lymphadenopathy. Progression of lymphadenopathy is often discovered by physical examination and should be recorded. In CLL, the use of CT scans usually does not add much information for the detection of progression or relapse.[58] Therefore, the use of imaging methods to follow CLL progression is at the discretion of the treating physician. Disease progression occurs if one of the following events is observed:

Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates.

An increase by 50% or more in greatest determined diameter of any previous site.

5.3.2. An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.

5.3.3. An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.

5.3.4. Transformation to a more aggressive histology (eg, Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.

5.3.5. Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL. *5.3.5.1. During therapy.* Cytopenias may occur as a side effect of many therapies and should be assessed according to Table 5. During therapy, cytopenias cannot be used to define disease progression. Each protocol should define the amount of drug(s) to be administered with such cytopenias.

Table 5. Grading scale for hematologic toxicity in CLL studies

Grade*	Decrease in platelets† or Hb‡ (nadir) from pretreatment value, %	Absolute neutrophil count/µL§ (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

* Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

†Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is < 20 x 10^9/L (20 000/µL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20 x 10^9/L [20 000/µL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

§If the absolute neutrophil count (ANC) reaches < 1 x 10^9/L (1000/µL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1 x 10^9/L (1000/µL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

5.3.5.2. After treatment. The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100 x 10^9/L (100 000/µL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

5.4. Stable disease

Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease (which is equivalent to a nonresponse).

5.5. Treatment failure

Responses that should be considered clinically beneficial include CR and PR; all others (eg, stable disease, nonresponse, progressive disease, or death from any cause) should be rated as a treatment failure.

5.6. Time to progression, progression-free survival, and overall survival

Time to progression (TTP) is defined as the time from study entry until objective disease progression (see section 5.3). Progression-free survival (PFS) is defined as the time from study entry until objective disease progression or death. Overall survival is defined as the time from study entry until death from any cause, and is measured in the intent-to-treat population.

5.7. Relapse

Relapse is defined as a patient who has previously achieved the above criteria (sections 5.1 and 5.2) of a CR or PR, but after a period of 6 or more months, demonstrates evidence of disease progression (see section 5.3).

5.8. Refractory disease

Refractory disease is defined as treatment failure (as defined in section 5.5) or disease progression within 6 months to the last antileukemic therapy. For the definition of "high-risk CLL" justifying the use of allogeneic stem cell transplantation,[59] the disease should be refractory to a purine analog-based therapy or to autologous hematopoietic stem cell transplantation.

5.9. Minimal residual disease

The complete eradication of the leukemia is an obvious desired endpoint. New detection technologies, such as multicolor flow cytometry and real-time quantitative PCR, have determined that many patients who achieved a CR by the 1996 NCI-WG guidelines have detectable MRD. Although eradication of MRD may improve prognosis, prospective clinical trials are needed to define whether additional treatment intended solely to eradicate MRD provides a significant benefit to clinical outcome. The techniques for assessing MRD have undergone a critical evaluation and have become fairly standard.[60] Either 4-color flow cytometry (MRD flow) or allele-specific oligonucleotide PCR is reliably sensitive down to a level of approximately one CLL cell in 10 000 leukocytes. As such, patients will be defined as having a clinical remission in the absence of MRD when they have blood or marrow with less than one CLL cell per 10 000 leukocytes. The blood generally can be used for making this assessment except during the period within 3 months of completing therapy, particularly for patients treated with alemtuzumab, rituximab, and other antibodies targeting CLL. In such cases, it is essential to assess the marrow for MRD. Therefore, future clinical trials that aim toward achieving long-lasting CRs should include at least one test to assess MRD because the lack of leukemia persistence using these sensitive tests seems to have a strong, positive prognostic impact.[61–63]

APPENDIX C – CREATININE CLEARANCE (COCKCROFT GAULT FORMULA)

Creatinine clearance (ml/min) for males = (140-age) x weight[kg] x 1.23/serum creatinine (µmol/l)

Creatinine clearance (ml/min) for females = (140-age) x weight[kg] x 1.04/serum creatinine (µmol/l)

APPENDIX D – BODY SURFACE AREA CALCULATION

BSA [m2] = weight [kg]$^{0.425}$ x height [cm]$^{0.725}$ x 0.007184

APPENDIX E - GLOSSARY OF TERMS

ADCC	Antibody Dependent Cellular Cytotoxicity
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
ß$_2$M	ß$_2$microglobulin
BP	Blood Pressure
BSA	Body Surface Area
CDC	Complement Dependent Cytotoxicity,
CDR-grafted	Complementarity Determining Region-grafted
CHOP	Cyclophosphamide, Doxorubicin, Oncovin and Prednisolone
CLL	Chronic Lymphocytic Leukaemia
CNS	Central Nervous System
CR	Complete Response
CRF	Case Record Form
CT	Computerised Tomography
CTA	Clinical Trials Authorisation
CTC	Common Toxicity Criteria
CTRU	Clinical Trials Research Unit
DFS	Disease Free Survival
DMEC	Data Monitoring and Ethics Committee
ECG	Electro-Cardiogram
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FC	Fludarabine and Cyclophosphamide
FCM	Fludarabine, Cyclophosphamide and Mitoxantrone
FCM-R	Fludarabine, Cyclophosphamide, Mitoxantrone and Rituximab
FCM-miniR	Fludarabine, Cyclophosphamide, Mitoxantrone and low dose Rituximab
FCR	Fludarabine, Cyclophosphamide and Rituximab
FISH	Fluorescent In Situ Hybridisation
GCSF	Granulocyte Colony Stimulating Factor
HAMA	Human Anti-Mouse Antibody
Hb	Haemoglobin
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HMDS	Haematological Malignancy Diagnostic Service
IB	Investigator Brochure
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
IMP	Investigational Medicinal Product
IWCLL	International Workshop on Chronic Lymphocytic Leukaemia
LDH	Lactate dehydrogenase
LFTs	Liver function tests
LREC	Local Research Ethics Committee
Main REC	Main Research Ethics Committee
MHRA	Medicine and Healthcare Products Regulatory Agency
MRD	Minimal Residual Disease
NCI	National Cancer Institute
NHL	Non Hodgkin's Lymphoma
NICE	National Institute for Health and Clinical Excellence
NK cells	Natural Killer Cells

NR	No Response
PCR PCP	Polymerase Chain Reaction Pneumocystis Pneumonia
PD	Progressive Disease
Plts	Platelets
PR PS	Partial Response Performance Status
SAE SAR SPC	Serious Adverse Event Serious Adverse Reaction Summary of Product Characteristics
SUSARs	Suspected Unexpected Serious Adverse Reactions
U&Es	Urea & Electrolytes
U/S	Ultra-Sound
WBC	White Blood Cells
WHO	World Health Organisation