INCA TRIAL

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

Trial Sponsor:	University College London
Trial Sponsor reference:	11/0475
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***Please note:** This trial protocol must not be applied to patients treated outside the INCA trial. Cancer Research UK & UCL Cancer Trials Centre (UCL CTC) can only ensure that approved trial investigators are provided with amendments to the protocol.

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1 PROTOCOL SUMMARY

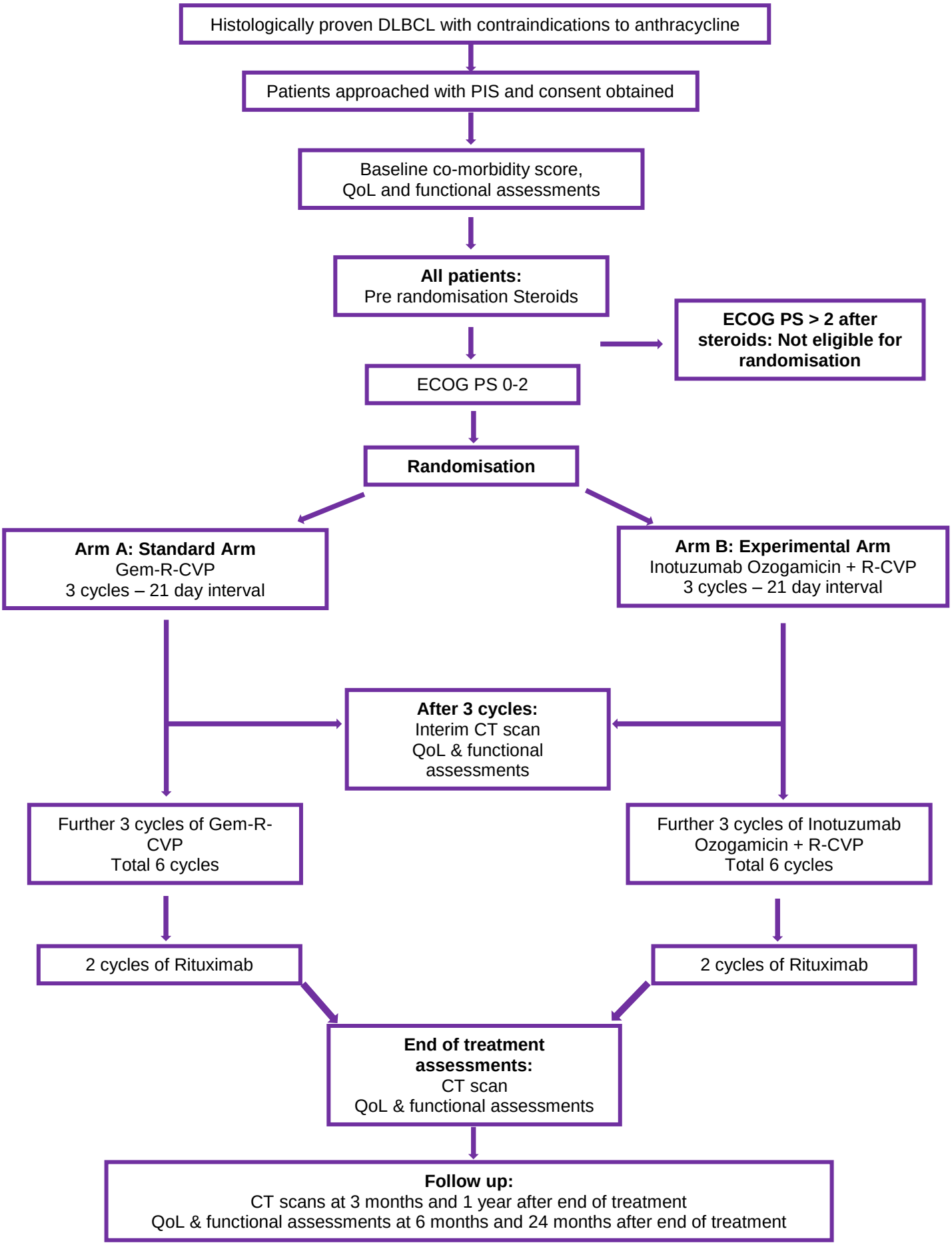
1.1 Summary of Trial Design

Title:	A multicentre randomised phase II clinical trial of Inotuzumab Ozogamicin (IO) plus Rituximab and CVP (IO-R-CVP) versus Gemcitabine plus Rituximab and CVP (Gem-R-CVP) for the first line treatment of patients with Diffuse Large B Cell Lymphoma (DLBCL) who are not suitable for anthracycline containing chemotherapy.
Short Title/acronym:	INCA
EUDRACT no:	2012-001900-39
Sponsor name:	University College London
Sponsor reference:	11/0475
Funders name:	Pfizer Limited
Funders reference:	WS1993028 (Pfizer) and A14898 (CTAAC)
Clinicaltrials.gov no:	NCT01679119
Design:	A multicentre, randomised, phase II trial comparing IO-R-CVP with Gem-R-CVP in the first line treatment of patients with DLBCL who are not fit for anthracycline-containing chemotherapy. If international sites participate they will have the option of using R-CEOP as the control arm.
Overall aim:	To determine the efficacy and safety of IO-R-CVP in patients with previously untreated DLBCL who are not-fit for R-CHOP.
Primary endpoint:	Progression free survival at 2 years from date of randomisation
Secondary endpoints:	Overall response rate Overall survival Treatment toxicity according to CTCAE v4.03 Quality of life measured by EORTC QLQ-C30 Performance status post treatment Co-morbidities of patients measured by the Cumulative Illness Rating Scale (CIRS)
Target accrual:	66 per arm (132 total)
Inclusion & exclusion criteria:	**Inclusion criteria include:** a) Age ≥18 years b) Histologically proven DLBCL with demonstration of CD20 positivity (concurrent or previous diagnosis of low grade lymphoma is permitted only if no systemic therapy has been given). Bulky Stage Ia-IV c) Unsuitable for anthracycline-containing chemotherapy due to impaired cardiac function or presence of significant co-morbidities d) ECOG PS 0-2 e) Adequate bone marrow, liver and renal function f) Life expectancy >3 months **Exclusion criteria include:** a) Stage Ia (non-bulky) b) ECOG PS >2 c) CNS involvement d) Previous low grade lymphoma treated with

	systemic therapy e) HIV, Serological evidence of active Hepatitis B or Hepatitis C infection whether acute or chronic f) Previous treatment for lymphoma (prior corticosteroids permitted) For full inclusion/exclusion criteria see section 6 (Selection of patients)
Planned number of sites:	15-25 UK sites
Target countries:	UK initially, Italy and the Netherlands
Treatment summary:	**<u>All</u> patients should receive steroids prior to randomisation into the trial** Patients may receive up to the equivalent of 1mg/kg per day of Prednisolone for a maximum of 14 days prior to randomisation. See section 8 of the protocol for further details. **Inotuzumab Ozogamicin-R-CVP arm:** D1 Cyclophosphamide 750mg/m^2 IV D1 Vincristine 1.4mg/m^2 (max 2mg) IV D1-5 Prednisolone 100mg OD Oral D1 Rituximab 375mg/m^2 IV D2 Inotuzumab Ozogamicin 0.8mg/m^2 IV* D4-12 Primary GCSF prophylaxis *Prednisolone should be given in the morning of day 2 (prior to administration of Inotuzumab Ozogamicin) and patients should be pre-medicated with paracetamol 1g (PO) and chlorpheniramine 4mg (PO) according to local policies **Gem-R-CVP arm:** D1, D8 Gemcitabine up to 1g/m^2 IV** D1 Cyclophosphamide 750mg/m^2 IV D1 Vincristine 1.4mg/m^2 (max 2mg) IV D1-5 Prednisolone 100mg OD Oral D1 Rituximab 375mg/m^2 IV D9-17 Primary GCSF prophylaxis ** **Patients with ECOG PS 0-1:** The starting dose for Gemcitabine is 875mg/m^2 (during cycle 1). If tolerated this can be escalated in cycle 2 and subsequent cycles to 1g/m^2. **Patients with ECOG PS 2:** The starting dose for Gemcitabine is 750mg/m^2 (during cycle 1). If tolerated this can be escalated in cycle 2 to 875mg/m^2. If tolerated this can be escalated in cycle 3 and subsequent cycles to 1g/m^2. See section 8 of the protocol for further details. In **both** treatment arms, cycles repeated every 21 days to a maximum of 6 cycles and followed in both arms by 2 further doses of intravenous rituximab 375mg/m^2 at 21-day intervals - day 1 of cycles 7 and 8. (i.e. 8 doses of rituximab in total).

	International sites would have the opportunity to choose an alternative control arm (R-CEOP) see section 8 (Trial treatment) for details.
Anticipated duration of recruitment:	4 Years
Duration of patient follow up:	For a minimum of two years or until death whichever occurs first
Definition of end of trial:	When all patients have completed at least two years of follow-up post last trial treatment
Translational component:	Translational studies will investigate the frequency of different sub-groups of DLBCL (ABC vs GCB), and assess the frequency of NFκB mutations in elderly patients. In addition, the frequency and prognostic significance of EBV tumoural status, assess CD22 expression levels in tumour samples by RQ-PCR and the role of FLT-3 ligand in predicting neutropenic fever will be investigated. A single 7ml EDTA blood sample will be sent to HMDS, Leeds, for future germline DNA extraction as part of future ethically approved translational studies.
Other related research:	Detailed assessment of co-morbidities using the Cumulative Illness Rating Scale (CIRS) tool prior to treatment and assessment of quality of life (EORTC QLQ-C30) and functional assessments (ADL and IADL scores) before, during and after treatment.

1.2 Trial Schema



2 INTRODUCTION

2.1 Background

The incidence of diffuse large B cell lymphoma (DLBCL) is increasing and with an expanding elderly population, the incidence will continue to rise [1]. Given that about 40% of cases of DLBCL occur in patients aged over 70 years [2] and the number of co-morbidities increases with age [3], research to investigate the optimal treatment of DLBCL in this group of patients is needed.

The optimal treatment of DLBCL is combination chemotherapy incorporating cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) in combination with the chimeric anti-CD20 monoclonal antibody rituximab. The addition of rituximab to CHOP led to significant improvements in outcome compared to CHOP alone and the initial trial demonstrating this was conducted in elderly patients aged 60-80 years [4, 5]. These results have been reproduced in other trials, confirming R-CHOP as the standard of care in DLBCL [6]. In most trials to date, 8 doses of rituximab have been added to 6-8 cycles of chemotherapy and for this reason in this trial, a total of 8 doses of rituximab will be given in both treatment arms[4, 6, 7].

Whilst R-CHOP remains the standard of care for the majority of patients with DLBCL, anthracycline use is precluded in a proportion of patients at high risk of developing cardiotoxicity, especially congestive cardiac failure. The risk of developing congestive cardiac failure is dose dependent, and increases with age and in the presence of co-morbidities (pre-existing cardiac disease, hypertension and diabetes) [8].

Alternatives to R-CHOP in patients unable to receive anthracyclines:
There is no standard of care for patients who are unfit for anthracycline treatment. It has been routine to omit the doxorubicin from R-CHOP, giving R-CVP instead. However anecdotally the outcome for patients treated with R-CVP is poor and attempts have been made to replace the doxorubicin with alternative agents.

A recent UK phase II trial investigated the safety and efficacy of adding gemcitabine to R-CVP in the first line treatment of DLBCL in a cohort of patients with significant cardiac co-morbidities precluding anthracycline use (either left ventricular ejection fraction (LVEF) ≤50% or LVEF >50% in the presence of ischaemic cardiac disease, hypertension or diabetes). This gave an overall response rate of 60% and 1 year PFS and OS of 53% and 63% respectively in a cohort of patients in whom treatment is very difficult [9].

Etoposide has been substituted for doxorubicin in the R-CEOP regimen [10]. In a retrospective study this has been reported to lead to 5 year overall survival of 49% with 57% progression free survival at 5 years. Liposomal doxorubicin has also been substituted for doxorubicin in elderly patients with DLBCL with high overall response rates and overall survival, but importantly, patients with cardiac co-morbidities were excluded from this trial [11]. Similarly, reduced doses of doxorubicin (R-mini-CHOP) were assessed in patients over 80 years old in a recent GELA study but it is not clear whether patients with cardiac co-morbidities were included in this study [12].

Inotuzumab Ozogamicin:
Inotuzumab Ozogamicin is a humanised anti-CD22 antibody conjugated to calicheamicin, a potent antitumor antibiotic. CD22 is expressed on the majority of B-cell non-Hodgkin lymphomas (NHL). As of May 2011, approximately 408 subjects have received inotuzumab ozogamicin in clinical trials, either as a single agent (3 completed or ongoing studies) in combination with rituximab (4 completed or ongoing studies), or in combination with chemotherapy. A phase I/II study evaluating the safety of inotuzumab ozogamicin in

combination with R-CVP regimen in patients with relapsed or refractory CD22+ B-cell NHL is nearing completion. The maximum tolerated dose of inotuzumab ozogamicin is 1.8 mg/m^2 based on grade 4 haematologic toxicity (thrombocytopenia and neutropenia lasting more than 7 days) reported following 2.4 mg/m^2, the highest dose tested [13].

Preliminary safety and efficacy data demonstrates that inotuzumab ozogamicin 0.8 mg/m^2 is safe and tolerable when given in combination with full dose R-CVP chemotherapy. Response rate data are highly encouraging [14]. Inotuzumab Ozogamicin cannot be added to the Gem-R-CVP regimen due to a predicted excess of severe grade III/IV haematological toxicity, especially thrombocytopenia.

Trial design:
In this randomised phase II clinical trial, patients with previously untreated DLBCL who are unable to receive anthracyclines due to co-morbidities will be randomised to either Inotuzumab Ozogamicin in combination with R-CVP, or gemcitabine in combination with R-CVP.

If international sites participate they will have the option of choosing to use R-CEOP as an alternative to Gem-R-CVP in the control arm.

Translational research questions:
A number of exploratory endpoints will investigate potentially useful clinical biomarkers in this trial.

The principal translational research questions will investigate:

- The frequency of molecularly defined subgroups of DLBCL (ABC vs. GCB) in an elderly patient population
- The frequency of somatic mutations in the NF-κB signalling pathway in DLBCL in elderly patients
- The frequency and potential predictive and prognostic value of EBV tumoural status in elderly patients with DLBCL
- Whether FLT3 ligand can be used to predict neutropenic fever. This component will be optional depending on site facilities for collection and storage of serum samples and patients' consent

For further details of translational research see section 10 (Exploratory Biological Studies).

Summary:
In summary, as the population ages there will be more patients with DLBCL who are assessed as being unsuitable to receive R-CHOP. Given that there is no internationally accepted standard of care for this group of patients there is a need to assess new regimens. The addition of the novel immunoconjugate Inotuzumab Ozogamicin to R-CVP will be assessed in this trial.

3.0 TRIAL DESIGN

Trial design:
This is a randomised phase 2 trial with an experimental arm consisting of Inotuzumab Ozogamicin added to the standard immunochemotherapy regimen of rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP). The control arm will consist of gemcitabine added to the same combination (Gem-R-CVP). If international sites participate they will be permitted to use an alternative control arm of R-CEOP.

6 cycles of either of the randomised schedules will be administered at 3 weekly intervals and will be followed by 2 further doses of rituximab at 21-day intervals in both treatment arms (i.e. 8 doses of rituximab will be given in total in both the experimental and control arms).

Primary G-CSF prophylaxis please see section 8.6.

Dose reductions according to haematological toxicity are specified in the protocol (see section 8.4 (Dose modifications)).

The main inclusion criteria will be patients of any age with biopsy proven CD20 positive diffuse large B cell lymphoma whom the investigator deems unsuitable for R-CHOP immunochemotherapy. This will include patients with cardiac impairment (LVEF≤ 50%) or co-morbidities and a LVEF of >50% as used in the Gem-R-CVP trial.

Over 90% of DLBCL cases are positive for CD22 [15]). CD22 status will be confirmed retrospectively but will not be an entry requirement as Immuno-histochemical staining of diagnostic biopsy specimens is not routinely available in all participating centres.

All patients will receive steroids prior to randomisation into the study (see section 8 for full details). All patients with a performance status of ≤2 after the steroids will be randomised between the experimental and control arm. The use of steroids has been reported to improve performance status by the DSHNHL group and therefore there is recommendation in section 8 of the protocol regarding the optimal steroid schedule [6, 15].

Cumulative Illness Rating Scale (CIRS) score will be recorded for the pre-chemotherapy assessment of co-morbidities. Quality of life assessment (EORTC QLQ-C30) will be carried out at baseline (after steroids), after 3 cycles, after 6 cycles, and at both 6 and 12 months from end of therapy. In addition, an assessment of functionality (ADL and IADL) will be made at the same time points.

Treatment arms:

All patients will receive steroids prior to randomisation unless clinically contraindicated (see section 8.2 for full details (Summary Treatment Schedule).

Patients with an ECOG performance status of ≤2 **after** steroids will be randomised in a 1:1 randomisation to:

Intervention arm (Inotuzumab Ozogamicin-R-CVP):

D1	Cyclophosphamide	750mg/m^2	IV
D1	Vincristine	1.4mg/m^2 (max 2mg)	IV
D1-5	Prednisolone*	100mg OD	Oral
D1	Rituximab	375mg/m^2	IV
D2	Inotuzumab Ozogamicin*	0.8mg/m^2	IV
*	Prednisolone should be given in the morning of day 2 (prior to the administration of Inotuzumab Ozogamicin) and patients should be pre-medicated with paracetamol 1g (PO) and chlorpheniramine 4mg (PO) according to local policies. Inotuzumab ozogamicin is light sensitive and must be protected from light during preparation and administration of the infusion using a UV protective covering (see section 8.3 for full details). The Inotuzumab ozogamicin should be infused within 1 hour at room temperature at a rate of 50 mL/hour (see section 8.3 for full details).		
D4-12	G-CSF primary prophylaxis for <u>all</u> patients e.g. filgrastim 300mcg sc od. Peg-filgrastim permitted as an alternative to daily G-CSF and dose as per local policy. G-CSF should be stopped if Neutrophils are >1.0 x 10.9/l after neutrophil nadir		

Control arm (Gem-R-CVP):

D1, D8	*****Gemcitabine	Up to 1g/m^{2*}	IV
D1	Cyclophosphamide	750mg/m^2	IV
D1	Vincristine	1.4mg/m^2 (max 2mg)	IV
D1-5	Prednisolone	100mg OD	Oral
D1	Rituximab	375mg/m^2	IV
D9-17	G-CSF primary prophylaxis for all patients e.g. filgrastim 300mcg sc od. Peg-filgrastim permitted as an alternative to daily G-CSF and dose as per local policy. G-CSF should be stopped if Neutrophils are >1.0 x 10.9/l after neutrophil nadir		

***Patients with ECOG Performance Status 0-1**: The starting dose for Gemcitabine is 875mg/m^2 (during cycle 1). If tolerated this can be escalated in cycle 2 and subsequent cycles to 1g/m^2. See section 8.2 of the protocol for further details.*

***Patients with ECOG Performance Status 2:** The starting dose for Gemcitabine is 750mg/m^2 (during cycle 1). If tolerated this can be escalated in cycle 2 to 875mg/m^2. If tolerated this can be escalated in cycle 3 and subsequent cycles to 1g/m^2. See section 8.2 of the protocol for further details.*

If grade III/IV haematological toxicity is observed, dose of gemcitabine to be reduced. See section 8.4 (Dose modifications) for further details on dose reductions.

Cycles for both arms repeated every 21 days for 6 cycles, and followed 21 days after day 1 of cycle 6 by 2 additional doses of intravenous rituximab 375mg/m^2 at 21-day intervals (i.e. patients will receive 8 doses of rituximab in total – day 1 of cycle 1 to cycle 8).

Alternative Control arm (R-CEOP): ALTERNATIVE FOR USE IN INTERNATIONAL CENTRES ONLY, NOT FOR UK SITES

D1	Rituximab	375mg/m^2	IV
D1	Cyclophosphamide	750mg/m^2	IV
D1	Vincristine	1.4mg/m^2 (max 2mg)	IV
D1-5	Prednisolone	100mg OD	Oral
D1	Etoposide	50mg/m^2	IV
D2, D3	Etoposide	100mg/m^2	Oral
D6-14	G-CSF primary prophylaxis for all patients e.g. filgrastim 300mcg sc od. Peg-filgrastim permitted as an alternative to daily G-CSF.		

Cycles repeated every 21 days for 6 cycles, and followed 21 days after day 1, cycle 6 by 2 additional doses of intravenous rituximab 375mg/m^2 at 21-day intervals (i.e. patients will receive 8 doses of rituximab in total – day 1 of cycle 1 to cycle 8).

3.1 Trial Objectives

The primary objective is to determine whether adding inotuzumab ozogamicin to R-CVP improves progression free survival when compared to Gem-R-CVP, in the first line treatment of DLBCL in patients who are not able to receive anthracycline-containing immunochemotherapy.

The secondary objectives include measuring the safety/tolerability of the regimen and to measure impact of this regimen on overall survival, response, quality of life and functionality.

3.2 Trial Endpoints

The primary endpoint is progression free survival (PFS) at 2 years from date of randomisation.

- Secondary endpoints:
    - Overall response rate (ORR)
    - Overall survival (OS)
    - Treatment toxicity according to CTCAE v4.03
    - Quality of life measured by EORTC QLQ-C30
    - Performance status post treatment
    - To gather information on the co-morbidities of patients unsuitable for anthracycline-containing chemotherapy by the Cumulative Illness Rating Scale (CIRS)

- Translational Endpoints:
    - To determine the frequency of different molecular subtypes (ABC/GCB/unclassifiable), as determined by gene expression profiling in the study population and to assess the impact of this on clinical outcomes
    - Assess the frequency of NFκB mutations in study population
    - To assess the frequency and prognostic significance of EBV tumoural status
    - To assess CD22 expression levels in tumour samples by RQ-PCR
    - To assess the role of FLT-3 ligand serum measurement in predicting neutropenic fever

3.3 Trial activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Health Research Authority (HRA) approval including Research Ethics Committee approval
- Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA)
- **'**Adoption' into NIHR portfolio
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

4 SELECTION OF SITES/SITE INVESTIGATORS

4.1 Site Selection

In this protocol trial 'site' refers to the hospital where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatment(s), imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the Research Governance Framework and the Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments)

- Data collection requirements, including adherence to CRF submission timelines as per section 11.3 (Timelines for Data Return)
- Sample collection, processing and storage requirements
- Monitoring requirements, as outline in the protocol section 14 (Trial Monitoring and Oversight and trial monitoring plan)

4.1.1 Selection of Principal Investigator and other investigators at sites

Sites must appoint an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site to lead and coordinate the work of the trial on behalf of the site. Co-investigators must be trained and approved by the PI. All investigators must be medical doctors and have experience of treating diffuse large B-cell lymphoma. The PI is responsible for the conduct of the trial at their site and for ensuring that any amendments are implemented in a timely fashion. If a PI leaves/goes on a leave of absence, UCL CTC must be informed promptly and a new PI identified and appointed by the site.

4.1.2 Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). A current, signed copy of the CV with evidence of GCP training (or copy of GCP certificate) for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

4.2 Site initiation and Activation

4.2.1 Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PI, the pharmacy lead and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site during a site visit or teleconference. Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient as per monitoring plan.

4.2.2 Required documentation

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by UCL CTC trial team:

- Trial specific Site Registration Form (identifying relevant local staff)
- Relevant institutional approvals
- A completed site delegation log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- Completed Site Contacts form (with contact information for all members of local staff)

- A signed and dated copy of the PI's current CV (with documented up-to-date GCP training, or copy of GCP training certificate)
- Trial specific prescriptions

In addition, the following agreements must be in place:

- A signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually a NHS Trust)

4.2.3 Site activation letter

Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

Once the site has been activated by UCL CTC, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol;
- all relevant site staff are trained in the protocol requirements;
- appropriate recruitment and medical care of patients in the trial;
- timely completion and return of CRFs (including assessment of all adverse events);
- prompt notification and assessment of all serious adverse events;
- that the site has facilities to provide **24 hour medical advice** for trial patients.

5 INFORMED CONSENT

Sites are responsible for assessing a patient's capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheets, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form.

Sites must assess a patient's ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved patient information sheets for the trial should be discussed with the patient.

A minimum of twenty four (24) hours must be allowed for the patient to consider and discuss participation in the trial.

Written informed consent on the current approved version of the consent form for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient notes.

Site staff are responsible for:

- checking that the current approved version of the patient information sheet and consent form are used;
- checking that information on the consent form is complete and legible;
- checking that the patient has completed/initialled all relevant sections and signed and dated the form;

- checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient;
- checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.);
- following randomisation: adding the patient trial number to all copies of the consent form, which should be filed in the patient's medical notes and investigator site file;
- following randomisation giving the patient a copy of their signed consent form, patient information sheet and patient contact card.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Patient withdrawal of consent from the trial must be explicitly documented in the source documents. Also refer to section 15.0 (Withdrawal of patients).

6 SELECTION OF PATIENTS

6.1 Screening Log

A screening log must be maintained appropriately filed at site. Sites should record each patient screened for the trial/all patients identified with DLCBL and the reasons why they were not randomised in the trial if this is the case. The log must be sent to UCL CTC when requested.

6.2 Patient Eligibility

There will be no exception to the eligibility requirements at the time of randomisation. Queries in relation to the eligibility criteria must be addressed prior to randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

Patient eligibility must be confirmed by an investigator who is suitably qualified and who has been allocated this duty, as documented on the site staff delegation log, prior to randomising the patient. Confirmation of eligibility must be documented in the patients' notes and on the randomisation CRF.

Patients must give written informed consent before any trial specific screening investigations may be carried out. Refer to section 9.1 (Pre-randomisation Assessments) for the list of assessments and procedures required to evaluate the suitability of patients prior to entry.

6.2.1 Inclusion Criteria for randomisation

- Informed written consent for the trial
- Histologically proven diffuse large B cell lymphoma (DLBCL) according to the current World Health Organisation (WHO) classification including all morphological variants. The B cell nature of the proliferation must be verified by demonstration of CD20 positivity. A concurrent (synchronous) diagnosis of low grade lymphoma (e.g. on bone marrow trephine or presence of both low grade and DLBCL in a lymph node biopsy) or previous diagnosis of low grade lymphoma which hasn't been treated with a systemic therapy is permitted.
- Bulky Stage IA (lymph node or lymph node mass ≥10cm in maximum diameter), stage IB, stage II, stage III and stage IV disease
- ECOG performance status 0-2
- Measurable disease
- Age ≥18 years
- Adequate contraceptive precautions for all patients of childbearing potential

- History of malignant disease diagnosed at any time in the past with completed radical treatment and the risk of relapsing within the next 5 years is <10%. Patients previously treated should be free of sequelae of treatment which would compromise the delivery of study drugs as compared with other eligible patients. Cases with second malignancy where eligibility is uncertain should be discussed in the first instance with the CTC.
- No previous chemotherapy, radiotherapy or other investigational drug for this indication – previous corticosteroids up to a dose equivalent to prednisolone 1mg/kg/day for up to 14 days are permitted prior to randomisation
- **EITHER**
  Unsuitable for anthracycline-containing chemotherapy due to impaired cardiac function defined by an ejection fraction of ≤50%
  OR
  Left ventricle ejection fraction >50% but in the presence of significant co- morbidities (diabetes mellitus, hypertension or ischaemic heart disease) precluding anthracycline-containing chemotherapy as determined by treating physician.
  Co-morbidities must be documented on the randomisation form and CIRS score recorded using the Cumulative Illness Rating Scale
- Adequate bone marrow function (Platelets >100x10^9/l, WBC >3.0 x10^9/l, Neutrophils >1.5x10^9/l) at time of study entry unless attributed to bone marrow infiltration by DLBCL
- Life expectancy >3 months

6.2.2 Exclusion Criteria for randomisation

- Symptomatic central nervous system or meningeal involvement by DLBCL
- Previous diagnosis of low grade lymphoma which has been treated with a systemic therapy
- Non-bulky stage IA disease
- ECOG performance status 3-4
- History of chronic liver disease or suspected alcohol abuse
- Serum bilirubin greater than upper limit of normal unless attributable to Gilbert's syndrome or haemolysis.
- Alanine and/or aspartate aminotransferase levels (ALT and/or AST) and alkaline phosphatase (ALP) greater than 2.5 times the upper limit of normal
- Glomerular filtration rate (GFR) <30ml/min. GFR calculated by Cockroft-Gault (**not** eGFR)
- Serological evidence of active hepatitis B or C infection whether acute or chronic (defined as positive anti-HCV serology; positive HBsAg). All positive HBcAb results should also be excluded on safety grounds regardless of HBsAg or HBV DNA status. Antibodies to Hepatitis B surface antigen (anti-HBs) due to a history of past vaccination is acceptable
- Known history of HIV seropositive status
- Patients with a history of Venoocclusive Disease (VOD) and Sinusoidal Obstructive Syndrome (SOS)
- Patients with a screening of QTcF interval >470msec
- Medical or psychiatric conditions compromising the patient's ability to give informed consent
- Women who are pregnant or lactating
- LVEF >50% in the absence of significant co-morbidities that preclude anthracycline use
- Patients with a history of severe allergic/anaphylactic reaction to any humanised monoclonal antibody
- Patients with serious active infection

6.3 Pregnancy and birth control

6.3.1 Pregnancy and birth control

A woman of childbearing potential (WOCBP) is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:

- undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- been postmenopausal for 12 consecutive months (i.e. who has had menses at any time in the preceding 12 consecutive months without an alternative medical cause)
- had premature ovarian failure confirmed by a specialist gynaecologist
- XY genotype, Turner syndrome, uterine agenesis

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

6.3.2 Risk of exposure to trial treatment during pregnancy

The risk to the human embryo or foetus from exposure to Inotuzumab Ozogamicin are currently unknown. When Inotuzumab Ozogamicin was given daily to pregnant rats and rabbits, maternal toxicity occurred in both species, but foetal toxicity occurred only in rats at a maternally toxic dosage. Gemcitabine has also shown reproductive toxicity in animal studies.

Cyclophosphamide and Vincristine are known to cause foetal harm, with a particular risk for women taking Vincristine in the first trimester of pregnancy. The manufacturers of these drugs state that they should not be used during pregnancy. The risks to the human embryo or foetus from exposure to Gemcitabine, Rituximab and Inotuzumab Ozogamicin are currently unknown. Administration of Prednisolone to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and affects on brain growth and development. There is currently no evidence in human studies that Prednisolone does result in an increased incidence of congenital abnormalities. However, when administered for prolonged periods or repeatedly during pregnancy, Prednisolone may increase the risk of intrauterine growth retardation. There are no adequate and well-controlled data from studies in pregnant women exposed to Rituximab. However IgG immunoglobulins are known to cross the placental barrier and transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to Rituximab during pregnancy.

6.3.3 Pregnancy testing

All women of childbearing potential who are at risk of becoming pregnant must undergo a serum pregnancy test at baseline.

6.3.4 Contraceptive advice

Due to the insufficient data on the effects of trial treatment during pregnancy and lactation, female patients of childbearing potential must consent to use one of the following highly effective methods of contraception until 12 months post last trial treatment. Methods with low user dependency are preferable, particularly where introduced as a result of participation in the trial.

Highly effective methods of effective contraception for this trial are:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - intravaginal
  - transdermal
  - progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
    - oral (e.g. desogestrel)
    - injectable
    - implantable[2]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomised partner[2,3]
- sexual abstinence[4]

1. Hormonal contraception may be susceptible to interaction with the IMP/NIMP, which may reduce the efficacy of the contraception method.

2. Contraception methods that are considered to have low user dependency.

3. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

4. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Due to the potential risk of genotoxicity and/or risk to the foetus from exposure to seminal fluid:

- Male patients (including male patients who have had vasectomies) must consent to use condoms with female partners who are WOCBP or partners who are pregnant, during treatment and until 12 months post last trial treatment.
- Male patients must also advise their female partners who are WOCBP regarding contraceptive requirements as listed for female patients who are WOCBP.

The method(s) of contraception used must be stated in the patient medical notes. The medical notes of male participants should include a statement that the female partner has been informed about contraception advice.

6.3.5 Action to be taken in the event of a Pregnancy

Female patients:

If a female patient becomes pregnant

- prior to initiating treatment, the patient will not receive trial treatment unless they elect to have a termination (please note, in such instances, termination must be the patient's own choice)
- during treatment, the patient will be withdrawn from treatment and, if they consent to pregnancy monitoring, followed up until pregnancy outcome
- after the end of the treatment (and for 12 months after discontinuing treatment), the patient will be followed up until pregnancy outcome if they consent to pregnancy monitoring.

Male patients:

If a female partner of a male patient becomes pregnant between the patient's informed consent and 12 months of the last trial treatment, the male participant can continue with the study whilst their female partner will be followed up if they have given consent to pregnancy monitoring.

Notification to UCL CTC – refer to section 12.5 for further details.

6.3.6 Long term infertility

The effect on human fertility is unknown for some of the trial drugs, although some have been shown to cause azoospermia and amenorrhoea, which may be irreversible. Infertility in patients might be temporary or permanent. Female patients also might experience an earlier menopause. Any requirement for egg and sperm preservation by individual patients should be considered as per local site policy prior to entry to the trial, and collection undertaken prior to commencing chemotherapy.

6.3.7 Lactation

It is unknown whether Cyclophosphamide, Vincristine, Gemcitabine, Rituximab and Inotuzumab Ozogamicin are excreted in human breast milk. Prednisolone is excreted in small amounts in breast milk. Infants of women receiving doses high than 40mg a day may have a degree of adrenal suppression.

Therefore, women must not breast feed during and for 12 months post last treatment administration.

7 RANDOMISATION PROCEDURES

Patient randomisation will be performed centrally at UCL CTC and this must be performed prior to commencement of any trial treatment. Patients will be allocated to a treatment arm stratified by IPI (0-2 vs. 3-5), left ventricular ejection fraction (≤50% vs. > 50%), control treatment (the control treatment offered within the patient's centre i.e. R-GCVP or R-CEOP)* and centre, using minimisation.

**Stratification by control arm will only be used in the event of international participation.*

Pre-randomisation evaluations should be carried out at sites as detailed in section 9.1 (Pre-randomisation Assessments).

7.1 Randomisation

Following pre-randomisation evaluations, confirmation of eligibility and consent of a patient at a site, the randomisation form must be fully completed and faxed to UCL CTC. These will be used to confirm patient eligibility. If further information is required UCL CTC will contact the person requesting randomisation to discuss the patient and request updated forms to be faxed.

Once eligibility has been confirmed a trial number and treatment allocation will be assigned for the patient and details should be added to the form by the site.

UCL CTC will fax confirmation of the patient's inclusion in the trial, their trial number and treatment allocation to the main site contact and pharmacy.

Randomisation telephone number:	+44 (0)20 7679 9860
Randomisation fax number:	+44 (0)20 7679 9861
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday (UK Time)

Once a patient has been randomised onto the trial they must be provided with the following:

- A copy of their signed consent form and patient information sheet
- A patient contact card. Site contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial

7.2 Initial Trial Drug Supply

Inotuzumab Ozogamicin will be provided by Pfizer Limited and distributed by Almac Clinical Services.

Cyclophosphamide, Gemcitabine, Prednisolone, Rituximab, Vincristine and G-CSF will be provided by site from hospital commercial stocks as details in the Summary of Drug Arrangements (SoDA).

Please see the current version of the SoDA for further details of drug supply and re-supply for the trial.

8 TRIAL TREATMENT

8.1 Treatment summary

For the purpose of this protocol for UK sites, the IMPs are Inotuzumab Ozogamicin and Gemcitabine. The NIMPs are the steroids, Rituximab, Cyclophosphamide, Vincristine and Prednisolone.

8.2 Summary Treatment Schedule

Both trial arms: Steroids pre-randomisation

All patients should receive steroids prior to randomisation into the trial*. Patients may receive up to the equivalent of 1mg/kg per day prednisolone for a maximum of 14 days prior to randomisation**.

The use of steroids prior to starting the randomisation treatment must be recorded in the patients' medical records and in the trial case report forms.

Ideally, there should no break between completing steroids and starting the randomised treatment, i.e. the prednisolone should continue until chemotherapy is commenced. However a gap of up to 72 hours will be permissible if logistic considerations prevent chemotherapy being started directly at the cessation of the steroids. Steroids can also be temporarily stopped for clinical reasons – e.g. in patients with diabetes who need to undergo CT scanning.

**Steroids can be omitted if patients have a clinical contraindication to steroids (e.g. a co-morbidity such as unstable diabetes/acute gastric ulceration or bleeding) as long as the ECOG is ≤2.*

***Patients on long-term low dose steroids (e.g. 10mg prednisolone daily or equivalent) for other medical conditions will be permitted to be entered into the study. Any other reasons for going over the 1mg/kg per day for 14 days must be discussed with the Trials Office in advance who will advise on the patient's eligibility.*

The following serves as guidance for the investigator for instances where patients have yet to have steroids when consulting the protocol:

It is recommended that patients may receive 60mg prednisolone for 7 days prior to starting the randomised treatment, however it may be administered for a minimum of 5 days and maximum of 14 days. The dose may be split if not tolerated as a single dose (e.g. taken 8am and 12pm daily).

Drug	Dose	D1	D2	D3	D4	D5	D6	D7
Prednisolone (po)	60mg	X	X	X	X	X	X	X

Randomised treatment

Patients with an ECOG performance status of ≤2 **after** steroids* will be randomised in a 1:1 randomisation to Gem-R-CVP or IO-R-CVP.
Steroids may be omitted due to patient having a clinical contraindication to steroids see above for further details

UK control arm (Gem-R-CVP)
Cycles repeated every 21 days for 6 cycles

Drug	Dose	Route	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Gemcitabine*	**Up to 1g /m^{2*}**	IV	X							X
Cyclophosphamide	**750mg/m^2**	IV	X							
Vincristine**	**1.4mg/m^2**	IV	X							
Prednisolone	**100mg**	PO	X	X	X	X	X			
Rituximab	**375mg /m^2**	IV	X							
G-CSF***	D9-17									

Intravenous rituximab is then given alone for 2 further doses at 21 day intervals after cycle 6, i.e. day 1 of cycles 7 and 8.

* ***Patients with ECOG Performance Status 0-1:*** *The starting dose for Gemcitabine is 875mg/m^2 (during cycle 1). If tolerated this can be escalated in cycle 2 and subsequent cycles to 1g/m^2.*

Patients with ECOG Performance Status 2: *The starting dose for Gemcitabine is 750mg/m^2 (during cycle 1). If tolerated this can be escalated in cycle 2 to 875mg/m^2. If tolerated this can be escalated in cycle 3 and subsequent cycles to 1g/m^2.*

***Vincristine maximum dose 2mg*

**** G-CSF should be stopped if Neutrophils are >1.0 x 10.9/l after* neutrophil nadir. *Pegylated G-CSF may be given as an alternative to daily G-CSF. Dose and timing of pegylated G-CSF according to local policies.*

Alternative control arm for international sites only (R-CEOP).
Cycles repeated every 21 days for 6 cycles
If international sites participate they will be required to choose one control regimen for all patients, it cannot be selected on a patient by patient basis.

Drug	Dose	Route	Day 1	Day 2	Day 3	Day 4	Day 5
Etoposide	**50mg/m^2**	IV	X				
Etoposide	**100mg/m^2**	PO		X	X		
Cyclosphosphamide	**750 mg/m^2**	IV	X				
Vincristine*	**1.4mg/m^2**	IV	X				
Prednisolone	**100mg**	PO	X	X	X	X	X
Rituximab	**375mg/m^2**	IV	X				
G-CSF**	D6-14						

Intravenous rituximab is then given alone for 2 further doses at 21 day intervals after cycle 6, i.e. day 1 of cycles 7 and 8.

**Vincristine maximum dose 2mg*

***Pegylated G-CSF may be given as an alternative to daily G-CSF. Dose and timing of pegylated G-CSF according to local policies.*

Intervention arm (IO-R-CVP)
Cycles repeated every 21 days for 6 cycles

Drug	Dose	Route	Day 1	Day 2	Day 3	Day 4	Day 5
Inotuzumab Ozogamicin	**0.8mg/m^2**	IV		X***			
Cyclophosphamide	**750 mg/m^2**	IV	X				
Vincristine*	**1.4mg/m^2**	IV	X				
Prednisolone	**100mg**	PO	X	X***	X	X	X
Rituximab	**375mg/m^2**	IV	X				
G-CSF**	D4-12						

Intravenous rituximab is then given alone for 2 further doses at 21 day intervals after cycle 6, i.e. day 1 of cycles 7 and 8.

**Vincristine maximum dose 2mg*

** G-CSF should be stopped if Neutrophils are >1.0 x 10.9/l after neutrophil nadir. *Pegylated G-CSF may be given as an alternative to daily G-CSF. Dose and timing of pegylated G-CSF according to local policies.*

*** *Prednisolone should be given in the morning of day 2 and premed with paracetamol 1g (PO) and chlorpheniramine 4mg (PO) according to local policies.* Inotuzumab ozogamicin is light sensitive and must be protected from light during preparation and administration of the infusion using a UV protective covering (see section 8.3 for full details). The Inotuzumab ozogamicin should be infused within 1 hour at room temperature at a rate of 50 mL/hour (see section 8.3 for full details).

8.3 Trial Treatment Details

Body Surface Area (BSA) should be calculated as per local practice. BSA should be recalculated in case of weight variation of greater than 10%.

Dose capping should not be performed for either IO-R-CVP or Gem-R-CVP but in cases of concern contact the UCL CTC for advice. Dose banding is allowed but must not reduce total dose by more than 10% (rounded to nearest whole percentage point from the original calculated dose).

Inotuzumab Ozogamicin:
Inotuzumab ozogamicin (CMC-544) is an antibody-targeted IV chemotherapy agent composed of a CD22-targeted antibody linked to calicheamicin, a potent cytotoxic antitumor antibiotic. It is currently unlicensed in the UK. CD22 is expressed on mature B cells. On binding to CD22, inotuzumab ozogamicin is rapidly internalised so delivering the cytotoxic agent calicheamicin into the cell resulting in cell death.

Inotuzumab ozogamicin will be given intravenously on day 2 of each cycle at 0.8mg/m^2 on the IO-R-CVP arm.

Inotuzumab ozogamicin is supplied in amber glass vials as a white, unpreserved, lyophilized cake. The vials must be stored refrigerated (2-8°C). Prior to reconstitution, allow drug vials to warm to room temperature for approximately 15 minutes.

Inotuzumab ozogamicin is light sensitive and must be protected from light during preparation and administration of the infusion using a UV protective covering. The reconstituted Inotuzumab ozogamicin solution in the syringe barrel(s) must be covered with foil if not immediately injected into the IV bag. The diluted solution of Inotuzumab ozogamicin in the IV bag must be covered (with an amber bag or covered with foil). It is recommended that all preparations are done in the pharmacy aseptic unit according to local procedures. Vials and IV bags containing reconstituted and diluted Inotuzumab ozogamicin should be gently mixed, avoiding vigorous agitation.

Dose preparation involves calculating the patient's body surface area (BSA) based on the DuBois, or equivalent formula as per local policy. This requires that an appropriate volume of Inotuzumab ozogamicin reconstituted solution be removed from vials, each of which contains a nominal volume of 4 mL at 1 mg/mL after reconstitution with 4 mL of SWFI (Sterile water for injection). The calculated dose of Inotuzumab ozogamicin should then be diluted with saline in a recommended infusion bag containing 0.9% sodium chloride injection solution to create a final volume of 50 mL for infusion. Inotuzumab ozogamicin must only be diluted with 0.9% sodium chloride solution.

If an empty IV infusion bag is being used, add a volume of sodium chloride 0.9% IV solution that is 50 mL minus the volume of Inotuzumab ozogamicin required prior to adding the reconstituted drug. Add the required Inotuzumab ozogamicin solution to the IV bag so that the final dose volume of solution in the bag is 50 mL.

If a bag containing a nominal 50 mL sodium chloride 0.9% IV solution is used, remove volume corresponding to that of Inotuzumab ozogamicin required prior to adding the reconstituted drug i.e. remove 1.5ml sodium chloride if 1.5mg is required.

If a sodium chloride 0.9% IV infusion bag contains a larger nominal volume then remove excess volume using a new syringe before adding Inotuzumab ozogamicin. The final dose volume of solution in the bag is 50mL.

Reconstituted Inotuzumab Ozogamicin / the diluted solution should be used immediately. If this is not possible please see the table below for maximum times for storage:

Storage Time Intervals for Inotuzumab Ozogamicin Drug Product Solutions			Total maximum time[a]
Reconstituted Solution	Diluted solutions		
	After start of dilution	Administration	
≤ 4 hours at 2-8 °C or use immediately	≤ 3 hours at room temperature or 2-8 °C[b]	1 hour infusion at room temperature at a rate of 50 mL/hour	≤ 8 hours

a Total maximum time allowed for the storage and administration of the reconstituted and diluted solution.
b If the dosing solution is stored at 2-8 °C, the solution should be brought to room temperature for approximately 1 hour prior to administration.

If the diluted solution (i.e. Inotuzumab ozogamicin in sodium chloride) is stored at 2 to 8 °C, the solution must be allowed to reach room temperature for approximately 1 hour prior to administration, leaving a 3 hour stability time (inclusive of 1 hour infusion time).

Note: The product must be infused within 4 hours of adding the reconstituted IO to the sodium chloride IV bag.

When infusing the product, prime the infusion line and infuse the entire contents of the bag at the rate of 50 mL/hour. IV lines may only be exposed to light for the approximate 1 hour stated for infusion; if delays in start of administration occur, or if infusions may take longer than the suggested 1 hour, lines must be protected from light.

See the Inotuzumab ozogamicin Investigational Product Manual for further details.

Flush the line with 22 mL sodium chloride 0.9% injection after the contents of the bag have been infused.

Gemcitabine:
Gemcitabine is a nucleoside analogue which has shown efficacy as single agent and also in combination with other drugs in the treatment of B cell lymphomas as well as T cell lymphoma and Hodgkin Lymphoma. Gemcitabine has been added to the R-CVP regimen in the first-line setting, delivering excellent response rates in a group of patients with cardiac co-morbidities precluding anthracycline therapy in a phase II trial [9].

Gemcitabine will be given as an i.v. infusion on day 1 and day 8 of each cycle on the Gem-R-CVP arm**.**

For patients with ECOG PS 0-1: The starting dose for Gemcitabine is 875mg/m^2 (during cycle 1). If tolerated this can be escalated in cycle 2 and subsequent cycles to 1g/m^2.

For patients with an ECOG PS 2: The starting dose for Gemcitabine is 750mg/m^2 (during cycle 1). If tolerated this can be escalated in cycle 2 to 875mg/m^2. If tolerated this can be escalated in cycle 3 and subsequent cycles to 1g/m^2.

Administration of Gemcitabine should be given according to local guidelines and policies. Prolonged infusion times should be avoided to minimise toxicity.

R-CVP and G-CSF administration in both treatment arms
Rituximab 375mg/m^2 is given as an intravenous infusion. Administration of rituximab including pre-medications and rate of administration according to local guidelines and policies. Cyclophosphamide and Vincristine should be given intravenously according to local policy. Prednisolone should be given orally in tablet form once daily as per local policy. For details of G-CSF administration please see section 8.6.

8.4 Dose Modifications

Gem-R-CVP

Haematological toxicity:
No dose adjustments or modifications based on haematological toxicity will be made for the following drugs: prednisolone, rituximab, cyclophosphamide or vincristine.

Haematological toxicity with Gemcitabine is common and dose modification should be carried out as follows:

Neutrophils

- day 1 of cycles 2-6: neutrophils ≥ $1x10^9$/l, 100% dose; neutrophils < $1x10^9$/l, defer treatment 1 week and initiate at next lower dose level upon neutrophil recovery to ≥ $1x10^9$/l

- day 8 of cycles 1-6: neutrophils ≥ $1x10^9$/l, 100% dose; neutrophils < $1x10^9$/l, omit gemcitabine and restart subsequent cycles at next lower dose level

Platelets

- day 1 of cycles 2-6: ≥ $75x10^9$/l, 100% dose; platelets < $75x10^9$/l, defer treatment 1 week and initiate gemcitabine at next lower dose level upon platelet recovery to ≥ $75x10^9$/l

- day 8 of cycles 1-6: ≥ $75x10^9$/l, 100% dose; platelets < $75x10^9$/l, omit and restart subsequent cycles at next lower dose level

Dose reduction schema:

Current dose	Dose reduction on Day 1	Dose reduction on Day 8
1g/m^2	875mg/m^2	875mg/m^2
875mg/m^2	750mg/m^2	750mg/m^2
750mg/m^2	500mg/m^2	500mg/m^2

If a patient is unable to tolerate 500mg/m^2 gemcitabine should be omitted permanently and continue with R-CVP only.

In subsequent cycles, dose of gemcitabine may be re-escalated to 750mg/m^2, then to 875mg/m^2, and subsequently to 1g/m^2 at the discretion of the local investigator provided that no grade 3 or 4 haematological toxicity was observed at the lower dose.

Non-haematological toxicity:

Neuropathy
If grade ≥2 motor or ≥3 sensory neuropathy, reduce vincristine dose to 1mg (flat dose) per cycle. If neurotoxicity increases despite this dose reduction, stop vincristine for future cycles.

Constipation
If grade 2 constipation occurs, reduce vincristine dose to 1mg (flat dose) per cycle. If greater than grade 2 omit vincristine. Investigator can reintroduce vincristine at 1mg if constipation resolves to grade 1 or better.

Hepatic impairment
In this study for elevated alanine and/or aspartate aminotransferase levels (ALT and/or AST) where the value is ≤2.5 x ULN with a normal total bilirubin there should be no dose

modifications for gemcitabine, prednisolone, rituximab, cyclophosphamide or vincristine. Sites should adhere to the SPC and manufacturer's recommendation to dose reduce vincristine by 50% for patients with a bilirubin >2.5 x ULN.

IO-R-CVP

Haematological toxicity:

No dose adjustments or modifications based on haematological toxicity will be made for the following drugs: prednisolone, rituximab, cyclophosphamide or vincristine.

Haematological toxicity with Inotuzumab Ozogamicin is common and dose modification should be carried out as follows:

Neutrophils

- day 1 of cycles 2-6: neutrophils ≥ $1x10^9$/l, 100% dose; neutrophils < $1x10^9$/l, defer treatment for up to 2 weeks and initiate at next lower dose level in subsequent cycles.

Platelets

- day 1 of cycles 2-6: ≥ $75x10^9$/l, 100% dose; platelets < $75x10^9$/l, defer treatment for up to 2 weeks and initiate at next lower dose level in subsequent cycles.

Dose reduction levels from 0.8mg/m^2 starting dose:

	Day 1
Starting dose	0.8mg/m^2
Level 1	0.5mg/ m^2

There will be no more than 1 dose level reduction of inotuzumab ozogamicin permitted. If a patient requires a 2nd dose level reduction, inotuzumab ozogamicin should be omitted permanently and continue with R-CVP only.

In subsequent cycles, dose of inotuzumab ozogamicin may be re-escalated to 0.8mg/m^2 at the discretion of the local investigator provided that no grade 3 or 4 haematological toxicity was observed at the lower dose.

Non-haematological toxicity:

Neuropathy
If grade ≥2 motor or ≥3 sensory neuropathy, reduce vincristine dose to 1mg (flat dose) per cycle. If neurotoxicity increases despite this dose reduction, stop vincristine for future cycles.

Hepatic impairment
Inotuzumab ozogamicin is known to cause hepatotoxicity, with low grade aminotransferase elevations being the most commonly reported hepatic adverse events in previous studies. Serious hepatic events of veno-occlusive disease, hepatic cirrhosis, hepatic fibrosis, nodular regenerative hyperplasia, hepatic failure, ascites, hyperbilirubinemia, and hepatitis/acute hepatitis have also been reported in <2% of cases, with some fatal events.

In this study alanine and/or aspartate aminotransferase levels (ALT and/or AST) and alkaline phosphatase (ALP) must be less than or equal to 2.5 times the upper limit of normal for both study eligibility and study drug dosing, bilirubin must not be greater than upper limit of normal for study eligibility and study drug dosing (unless attributable to Gilbert's syndrome or haemolysis).

If grade 4 alanine and/or aspartate aminotransferase levels (ALT and/or AST) occurs (irrespective of duration) or Grade 2 hyperbilirubinemia (>1.5 x ULN) ≥7 days, defer treatment for up to 2 weeks or until resolved to grade 1 or less and initiate Inotuzumab ozogamicin at the next lower dose in subsequent cycles.

In this study for elevated alanine and/or aspartate aminotransferase levels (ALT and/or AST) where the value is ≤2.5 x ULN with a normal total bilirubin there should be no dose modifications for prednisolone, rituximab, cyclophosphamide or vincristine. Sites should adhere to the SPC and manufacturer's recommendation to dose reduce vincristine by 50% for patients with a bilirubin >2.5 x ULN.

QTc Changes

If QTcF is between 471 msec and 499 msec (average of 3 ECGs), defer treatment for up to 2 weeks. If it resolves back to ≤470 msec within the 2 weeks then continue inotuzumab ozogamicin at original dose. If QTcF doesn't resolve initiate at next lower dose. If QTcF resolves continue at lower dose do not increase dose. If QTcF is >500 msec at any point inotuzumab ozogamicin should be omitted permanently and the patient should continue with R-CVP only.

Potassium/Sodium abnormalities

If any potassium or sodium abnormalities are detected these should be corrected prior to administering inotuzumab ozogamicin, and if it is thought that any concomitant medication is contributing to QTc prolongation the use of such concomitant medication should be stopped if necessary.

Constipation

If grade 2 constipation occurs, reduce vincristine dose to 1mg (flat dose) per cycle. If greater than grade 2 omit vincristine. Investigator can reintroduce vincristine at 1mg if constipation resolves to grade 1 or better.

There will be no more than 1 dose level reduction of inotuzumab ozogamicin permitted. If a patient requires a 2nd dose level reduction, inotuzumab ozogamicin should be omitted permanently and continue with R-CVP only.

8.5 Management of Overdoses, Trial treatment error or Occupational Exposure

Overdose

Administration of a quantity of a trial treatment, either per administration or cumulatively, which is in excess of the protocol specified dose. The dose can either be evaluated as overdose by the trial team at site or by the Sponsor upon review.

Overdoses should be reported on an incident report (see section 13.0). Any adverse events resulting from an overdose should be reported as an SAE (see section 12.2.2 for reporting procedures).

Trial Treatment error

Any unintentional error in prescribing, dispensing, or administration of a trial treatment while in the control of a healthcare professional or consumer. The error can be identified either by the trial team at site or by the Sponsor upon review.

Trial treatment errors should be reported on an incident report (see section 13.0). Any adverse events resulting from a medication error should be reported as an SAE (see section 12.2.2 for reporting procedures).

Occupational exposure

Exposure to a trial treatment as a result of one's professional or non-professional occupation. Occupational exposure should be reported on an incident report form (see section 13.0).

8.6 Supportive Care

Supportive medications to prevent or treat nausea, vomiting, tumour lysis syndrome, and anti-microbial prophylaxis to be given according to local policies.

Ondansetron can be given to patients as a supportive medication but the dose must not exceed 8mg bd.

Primary G-CSF prophylaxis **to be given to all patients in both treatment arms,** as once daily sub-cutaneous injections on:

- days 9-17 of each Gem-R-CVP cycle
- days 4-12 of each IO-R-CVP cycle

or, if using pegylated G-CSF, to be scheduled according to local policy.

G-CSF should be stopped if Neutrophils are >1.0 x 10.9/l after neutrophil nadir.

8.7 Concomitant medication

Patients may receive concomitant therapy deemed to provide adequate supportive care at the investigator's discretion. All medications or other treatments taken by the patient during the trial (including those initiated prior to the start of the trial) must be recorded in the patient's clinical notes and appropriate CRFs. Yellow fever and other live attenuated vaccines (including H zoster) are not recommended due to the risk of systemic, possibly fatal, disease, particularly in immunosuppressed patients. Refer to the latest version of the SmPC for rituximab, cyclophosphamide, vincristine, prednisolone and gemcitabine when giving concomitant medications to avoid cross interactions with the metabolism of these drugs and toxicity.

Other medications

The following medications should be avoided for patients in the IO-R-CVP arm as they significantly prolong QTc.

Amiodarone
Arsenic trioxide
Astemizole
Bepridil
Chloroquine
Chlorpromazine
Cisapride
Clarithromycin
Disopyramide
Dofetilide
Domperidone
Droperidol
Erythromycin
Halofantrine
Haloperidol
Ibutilide
Levomethadyl
Mesoridazine
Methadone
Moxifloxacin
Pentamidine
Pimozide
Probucol
Procainamide
Quinidine
Sotalol
Terfenadine
Thioridazine
Vandetanib

Inotuzumab Ozogamicin
It is unlikely that inotuzumab ozogamicin will inhibit the metabolic clearance of concomitant drugs that are substrates of CYP enzymes via reversible inhibition or mechanism-based inhibition. It is unlikely that inotuzumab ozogamicin will be involved in clinical induction-mediated interactions with concomitant drugs that are substrates for cytochrome P450

8.8 Pharmacy Responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the PI, who may delegate this responsibility to the local pharmacist or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the site staff delegation log.

Inotuzumab Ozogamicin supplied for the INCA trial is for INCA patients only and must not be used outside the context of this protocol.

Pharmacists should refer to the Summary of Drug Arrangements for further details on suppliers, ordering, labelling, storage, preparation and handling and destruction.

8.8.1 Temperature Excursions

All temperature excursions outside the storage conditions specified in the IB for inotuzumab ozogamicin (and the SPC for Gemcitabine if stock is ring fenced for the trial)/Summary of Drug Arrangements must be reported to UCL CTC as per the 'Pharmacy Procedure for Reporting Temperature Excursions' (see Pharmacy Site File).

Upon identifying an excursion:

- all affected trial stock must be quarantined IMMEDIATELY
- the 'Notification of Temperature Excursion' form must be completed and e-mailed to ctc.excursions@ucl.ac.uk or faxed to +44 (0)20 7679 9871.
-

Please note that UCL CTC must be informed immediately if a patient has been administered drug affected by a temperature excursion.

8.8.2 IMP accountability

The Pharmacy Lead must ensure that appropriate records are maintained.

These records must include accountability for each drug including receipt (inotuzumab ozogamicin only), dispensing, returned medication and destruction of returned/unused medication. Accountability forms will be supplied and must be used unless there is prior agreement from UCL CTC to use in-house records.

Copies of completed drug accountability logs must be submitted to UCL CTC for all trial patients upon request. Also refer to section 14.2 (Central Monitoring).

8.9 24 Hour/Out-of-Office Hours Emergency Drug-Specific Advice

Inotuzumab Ozogamicin	**24 hours**	**01304 616161 or Eumedinfo@pfizer.com**
All other IMPs and NIMPs used in this protocol	**Office hours 09:00 to 17:00 Monday to Friday, excluding Bank Holidays (UK Time)**	**Contact UCL CTC on +44 (0) 20 7679 9868 or ctc.inca@ucl.ac.uk**

8.10 Other Trial Treatments/Interventions

Central Nervous System Prophylaxis:
High risk of CNS involvement is defined as per BCSH Guidance on CNS prophylaxis in NHL and should be followed [31]. High risk is raised (>ULN) and more than 1 extranodal localisation or involvement of testicular, breast and paraspinal sites.

They should receive treatment according to local practice. Systemic methotrexate for CNS prophylaxis should **not** normally be used in this cohort of patients. All prophylactic intrathecal methotrexate injection must be given after the systemic immunochemotherapy and must be given in accordance with DOH regulations on Intrathecal chemotherapy.

Radiotherapy:
Radiotherapy to sites of residual disease or original sites of bulky disease may be given at local investigator's discretion but should not be administered within 38 days of day 1 of the last cycle of immunochemotherapy in either treatment arm.

8.11 Clinical Management after Treatment Discontinuation

If the patient is withdrawn from treatment for any reason, they should receive appropriate management at the discretion of the treating clinician. Also refer to section 15 (Withdrawal of Patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

9 ASSESSMENTS

9.1 Pre-randomisation Assessments

Patients must give written informed consent **before** any trial specific screening investigations may be carried out. The following assessments or procedures are required to evaluate the suitability of patients for the trial. These must be performed 14 days prior to randomisation except the CT scan, bone marrow biopsy, ECG and LVEF assessments which can be performed within 35 days prior to randomisation. The diagnostic biopsy (excision or core biopsy) can be performed at any time prior to randomisation.

Any time prior to randomisation

- Diagnostic biopsy with histological confirmation of DLBCL according to the current WHO classification including all morphological variants with demonstration of CD20 positivity.

Within 35 days prior to patient trial randomisation

- Contrast enhanced CT scan of the neck, thorax, abdomen and pelvis. The CT scan of the neck should be done but for those cases where it has been omitted, it does not

need to be repeated as long as a full clinical examination has been performed (ideally to also include an ultrasound/MRI) and this has been documented in the patients notes.
Note: If it is not possible to use contrast (i.e. contrast is contraindicated in the patient or a CT was previously conducted outside of the 35 day window and a repeat CT with contrast is contraindicated) then a PET-CT should be performed with other imaging e.g. MRI as clinically indicated. The method of disease assessment used should be consistent through the duration of the trial.

- Bone marrow trephine biopsy
- Electrocardiogram (ECG) including QTcF interval (average of 3 ECGs)*
- Assessment of left ventricular ejection fraction (LVEF)*
- Optional: PET-CT can also be used for staging (ideally the CT component should be contrast enhanced unless contraindicated as described above)

**To be performed within 35 days unless any clinical suspicion of a change in cardiac status warranting repeated investigation.*

Within 14 days prior to patient trial randomisation

- Medical history including concomitant diseases and treatment
- Physical examination
- Vital sign monitoring
- Height and weight
- Full blood count (FBC) to include haemoglobin, white blood cell count, absolute neutrophil count and platelet count
- Serum biochemistry (sodium, potassium, urea, creatinine, bilirubin, liver transaminases (ALT or AST), prothrombin time, alkaline phosphatase, lactate dehydrogenase (LDH), albumin, total protein, and β2 microglobulin (β2MCG))
- Virology screening to include:
    - Hepatitis B virus (HBV): hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb)
    - Hepatitis C virus (HCV): antibody serology
    - Human Immunodeficiency virus (HIV) screening suggested as standard of care, but not mandated
- Glomerular filtration rate (GFR) calculated by Cockroft-Gault (**not** by eGFR)
- Cerebrospinal fluid (CSF) examination if clinically indicated or high risk of CNS involvement. BCSH guidance on CNS prophylaxis in NHL should be followed. High risk is raised serum LDH (>ULN) and more than 1 extranodal localization or involvement of testicular, breast and paraspinal sites. CNS directed therapy may be added if in the opinion of the local PI there is a significant risk of CNS involvement.
- If female and of childbearing potential, a negative serum pregnancy test (β-human chorionic gonadotropin (β-HCG) see section 6.3.3 (Pregnancy testing) for further details

After patient has had some steroids but before randomisation (ideally should be done as close to randomisation as possible so that the best ECOG performance status is recorded)

- Documentation of baseline ECOG performance status
- Quality of life questionnaire: EORTC QLQ-C30
- Functionality assessments: ADL and IADL
- Co-morbidity score: Cumulative Illness Rating Scale (CIRS)

Exploratory Biological Studies:

- Forward diagnostic tissue block to HMDS Leeds
- A single 7ml EDTA blood sample will be sent to HMDS, Leeds, for future germline DNA extraction as part of future ethically approved translational studies

Optional

- 4.9 ml blood serum sample sent to 'The Paterson Institute For Cancer Research' Manchester for FLT-3 analysis. See the latest version of the Laboratory Handbook for further details and section 9.2 (Assessments during treatment)

9.2 Assessments during Treatment

During treatment, patients should be seen on day 1 **and** day 8 of every treatment cycle (regardless of treatment arm) and the following assessments/investigations performed:

- Physical examination
- Vital sign monitoring
- ECOG performance status
- Toxicity and adverse event assessment
- FBC to include haemoglobin, white blood cell count, absolute neutrophil count and platelet count – can be done up to 3 days before treatment
- Serum biochemistry (sodium, potassium, urea, creatinine, bilirubin, liver transaminases (ALT or AST), prothrombin time, alkaline phosphatase, lactate dehydrogenase (LDH), albumin and total protein) – can be done up to 3 days before treatment - must be done at day 1 and day 8 of each cycle
- LFT results to be known before starting each cycle of IO-R-CVP
- ECG with QTcF should be done before starting each cycle of IO-R-CVP (average of 3 ECGs)

FLT-3 ligand analysis (optional translational research component (see section 10 (Exploratory Biological Studies)).

Serum samples for this are required at the following time points:

- Baseline (between day 14 pre-randomisation and day 1 pre-treatment)
- Cycle 1 day 3 (+/- 1 day)
- Cycle 1 day 8 (+/- 1 day)
- Cycle 2 day 1 (- 1 day)

Before the 4th cycle:
In addition to the usual assessments required before starting a cycle, patients will also require the following performed before beginning cycle 4:

- Repeat quality of life questionnaire: EORTC QLQ-C30
- Repeat functionality assessment: IADL and ADL
- Contrast enhanced CT scan of chest, abdomen and pelvis (and neck if involved at baseline). PET-CT can be also be used (ideally the CT component should be contrast enhanced). The same PET-CT scanner should be used that was used at baseline if possible.
  Note: If it is not possible to use contrast (i.e. contrast is contraindicated in the patient then a PET-CT should be performed with other imaging e.g. MRI as clinically indicated.

9.3 Assessments on Completion of Trial Treatment

The following should be performed at end-of-treatment i.e. after 6 cycles of combined immunochemotherapy and 2 subsequent doses of intravenous rituximab or, if treatment stopped before this time, after last treatment received.

- Physical examination
- ECOG performance status
- Toxicity and adverse event assessment
- FBC to include haemoglobin, white blood cell count, absolute neutrophil count and platelet count
- Serum biochemistry (sodium, potassium, urea, creatinine, bilirubin, liver transaminases (ALT or AST), prothrombin time, alkaline phosphatase, lactate dehydrogenase (LDH), albumin and total protein)
- Repeat functionality assessment: IADL and ADL
- Repeat quality of life questionnaire: EORTC QLQ-C30
- Repeat assessment of left ventricular ejection fraction within 3 months of completing treatment
- Contrast enhanced CT scan of chest, abdomen and pelvis (and neck if involved at baseline). PET-CT can be also be used (ideally the CT component should be contrast enhanced). The same PET-CT scanner should be used that was used at baseline if possible.
  Note: If it is not possible to use contrast (i.e. contrast is contraindicated in the patient) then a PET-CT should be performed with other imaging e.g. MRI as clinically indicated
  The scan should be performed at end of treatment wherever possible even if 6 cycles of treatment (+ 2 additional rituximab infusions) have not been completed
- Repeat bone marrow biopsy if bone marrow was initially involved and the CT shows CR or CRu. If the end of treatment PET-CT scan is clear then a repeat bone marrow biopsy is optional.

Assessment of disease response will be according to the revised International Working Group response criteria for non-Hodgkin's lymphoma – revised Cheson criteria [17], see Appendix 2 for details.

9.4 Assessments During Follow-Up

Follow-up 3 monthly during first year, 4 monthly in the second year, 6 monthly during 3rd year, and annually thereafter with the following assessments performed:

- Physical examination
- ECOG performance status
- Contrast enhanced CT scan of chest, abdomen and pelvis (and neck if involved at baseline) at 3 months and 1 year after completion of treatment. PET-CT can be also be used (ideally the CT component should be contrast enhanced). The same PET-CT scanner should be used that was used at baseline if possible.
  Note: If it is not possible to use contrast (i.e. contrast is contraindicated in the patient) then a PET-CT should be performed with other imaging e.g. MRI as clinically indicated.
- Repeat functionality assessment: IADL and ADL at 6 & 24 months after end of treatment
- Repeat quality of life questionnaire: EORTC QLQ-C30 at 6 & 24 months after end of treatment

All efforts should be made by the Site to contact the patient's GP to assess their condition, if a patient fails to attend a clinic or cannot be followed up at site. Patients will be flagged through the Health and Social Care Information Centre to ensure long term follow-up is achieved.

Table 1, Schedule of Assessments

	Pre-randomisation[7]	Day 1 & 8 every cycle	Before 4th cycle	End of treatment	Follow-up[12]
Medical History	x				
Physical Examination	x	x	x	x	x
Vital sign monitoring	x	x	x		
Height & weight	x				
ECOG PS	x	x	x	x	x
CIRS co-morbidity score	x				
QOL: EORTC QLQ-C30	x		x	x	x[13]
Functional assessments: ADL & IADL	x		x	x	x[13]
ECG including QTcF interval	x[8]	x[14]			
Measurement of LVEF	x[8]			x	
CT scan/PET-CT	x[8]		x[10]	x[10]	x[10]
Bone marrow trephine biopsy	x[8]			x[11]	
Serum biochemistry[1]	x	x	x	x	
β2 microglobulin (β2MCG)	x				
FBC[2]	x	x	x	x	
Virology screening[3]	x				
β –HCG for pregnancy[4]	x				
CSF[5]	x				
Glomerular filtration rate (GFR)	x				
Toxicity assessment		x	x	x	x
Adverse events		x		x	
Exploratory Biological Studies					
Diagnostic tissue block & 7ml EDTA blood sample[6]	x				
FLT-3 ligand analysis *(optional)*	x	x[9]			

[1] Serum biochemistry (sodium, potassium, urea, creatinine, bilirubin, liver transaminases (ALT or AST), prothrombin time, alkaline phosphatase, lactate dehydrogenase (LDH), albumin and total protein). If any potassium or sodium abnormalities are detected these should be corrected before administering inotuzumab ozogamicin. Can be done up to 3 days before treatment. Must be done on day 1 and day 8 during treatment in both arms

[2] Full blood count to include haemoglobin, white blood cell count, absolute neutrophil count and platelet count. Can be done up to 3 days before treatment

[3] Virology screening to include HbsAg, HbcAb and HCV antibody serology. HIV screening suggested as standard of care, but not mandated.

[4] If female and of childbearing potential.

[5] CSF = Cerebrospinal fluid examination. Only if clinically indicated or lymphomatous involvement of bone marrow, orbit, nasal/paranasal sinuses, paraspinal region, testis, peripheral blood and bone.

[6] Samples sent to HMDS, Leeds.

[7] All to be performed within 14 days to date of trial randomisation with the exception of CT scan and bone marrow biopsy.

[8] Contrast enhanced CT of the neck, thorax, abdomen and pelvis and bone marrow trephine biopsy to be performed within 35 days to date of trial randomisation. PET-CT can also be used (ideally the CT component should be contrast enhanced). If it is not possible to use contrast (i.e. contrast is contraindicated in the patient) then a PET-CT should be performed with other imaging e.g. MRI as clinically indicated. ECG (average of 3 ECGs) and assessment of LVEF to be performed within 35 days unless any clinical suspicion of a change in cardiac status warranting repeated investigation.
[9] Serum samples taken at cycle 1 day 3, cycle 1 day 8 and cycle 2 day 1 if patient is participating in this sub-study and provided written informed consent.
[10] Contrast enhanced CT scan of thorax, abdomen and pelvis (neck if involved at baseline) should be carried out at the end of treatment, at 3 months and at 1 year after finishing treatment. PET-CT can also be used (ideally the CT component should be contrast enhanced). The same PET-CT scanner should be used that was used at baseline if possible. Note: If it is not possible to use contrast (i.e. contrast is contraindicated in the patient) then a PET-CT should be performed with other imaging e.g. MRI as clinically indicated.
[11] Bone marrow biopsy to be repeated at the end of treatment if marrow was involved at baseline and the CT shows CR or CRu for accurate response assessment.
[12] Follow-up: 3 monthly clinic visit during the first year, 4-monthly during the second year, 6-monthly for the third year and annually thereafter.
[13] IADL, ADL and EORTC QLQ C-30 at 6 & 24 months after end of treatment.
[14] ECG with QTcF should be done before every cycle of IO-R-CVP (average of 3 ECGs).

10 EXPLORATORY BIOLOGICAL STUDIES

A number of exploratory endpoints will be investigated in this trial exploring the use of biomarkers in clinical outcomes

Gene expression profiling of fresh frozen material has provided new insights into the biology of DLBCL. In patients treated with CHOP or CHOP like chemotherapy, unsupervised hierarchical clustering identified two distinct subgroups of the disease; one with a phenotype similar to germinal centre derived B-cells (GCB like) and one with a phenotype similar to activated peripheral B-cells (ABC like) [18]. These molecular subgroups had distinct clinical outcomes. The initial observations were extended to a larger series of tumours by the Leukaemia and Lymphoma Molecular Profiling Project [19] and the molecular model subsequently refined to a discriminator based upon the expression of just 27 genes (Rimsza, Wright et al. 2009). With the advent of R-CHOP chemotherapy, this molecular classification was found to be robust, and the inferior prognosis of the ABC-like lymphomas remained inferior with 3 year progression free survival of the ABC group 40% compared to 75% in the GCB group [20]. The frequency of molecularly defined subgroups in elderly DLBCL is unknown and the prognostic value of molecular class uncertain. Using RNA extracted from formalin fixed paraffin embedded tumour blocks, the Illumina DASL system will be used to provide whole transcriptome information from the patients tumour material for ABC/GCB classification and for exploration of additional candidate biomarkers associated with response to regimens under investigation. This system in being successfully employed for patient stratification in the NCRN REMoDL-B for younger patients with DLBCL with the procedure being performed at the Haematological Malignancies Diagnostic Service in Leeds.

Several oncogenic mechanisms distinguish the two DLBCL sub-groups [21], in particular the observation that constitutive activation of the nuclear factor-κB (NF-κB) signalling pathway appears central to cell survival in ABC-like lymphomas [22]. These tumours rely upon the CARD11/MALT1/BCL10 signalling complex to activate the central kinase in the NF-κB pathway, IκB kinase [23, 24]. More than half of ABC-DLBCL carry somatic mutations in multiple genes, including negative (A20) and positive (CARD11, TRAF2, TRAF5, MAP3K7 and TNFRSF11A) regulators of NF-kB [25]. Of these, the A20 gene, which encodes a ubiquitin-modifying enzyme involved in termination of NF-kB responses, is most commonly affected, with one third of patients displaying biallelic inactivation by mutations and/or deletions. Functional characterisation of GCB-like DLBCL cell lines has suggested that the NF-κB pathway may also be activated in a small subset of this group [26]. The induction of the NF-κB pathway appears to suppress the apoptotic effect of cytotoxic chemotherapy [27] and this may contribute to the observed differences in outcome between the biological subtypes of DLBCL. DNA extracted from FFPE blocks will be used to analyse, by PCR and direct sequencing, somatic mutations in

the NF-κB pathway to assess their frequency in the elderly population and to examine their clinical relevance (Ming Du, University of Cambridge)

FLT3 ligand is a cytokine involved in maintaining the stem cell compartment and levels rise in response to bone marrow stress. Circulating levels are easily measurable and inversely proportional to the levels of colony forming cells. In a small population of diffuse large B-cell lymphoma patients receiving standard chemotherapy, without primary GCSF prophylaxis, changes in FLT3 ligand at day 3 were found to be more sensitive than neutrophil counts in predicting febrile neutropenia (FN) at any time during chemotherapy – sensitivity 83%, specificity 53% [28]. In this trial, the population will consist of a majority of elderly patients with multiple comorbidities. It is expected that grade ¾ neutropenia rates will exceed 20% despite mandated primary GCSF prophylaxis and that this will result in a high risk of FN. Toxicity is an important secondary endpoint of this study. This exploratory analysis, measuring ELISA quantified FLT3 ligand at baseline (within 14 days of trial entry), cycle 1 day 3 & day 8 (+/- 1 day) and cycle 2 day 1, will determine if changes are predictive of neutropenia/sepsis events in this 'real world' scenario and of potential value in guiding individualised treatment modification in the future. An elevated signal at day 2/8 may inform the need for additional measures beyond GCSF alone to reduce sepsis risk (e.g. antibiotics, early review, dose reduction from cycle 2 etc.). Serum will be collected at the above time points and analysed in a GCLP accredited laboratory (Professor Caroline Dive, Paterson Institute for Cancer Research, The University of Manchester). See laboratory handbook. This component of the translational research will be optional depending on sites' facilities for serum sample collection and storage and specific patient consent.

Epstein-Barr virus-positive (EBV-positive) diffuse large B-cell lymphoma (DLBCL) of the elderly is a newly described lymphoproliferative disorder recently included as a "provisional" entity in the most current WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. The frequency and potential predictive and prognostic value of EBV tumoral status in patients with DLBCL is poorly understood. Immunohistochemistry from diagnostic material will be performed for a number of lymphoma markers along with EBV-LMP1 and in situ hybridisation for EBER (performed at HMDS).

Patient material will be centrally collated to allow for further immunohistochemical analysis. Section from the formalin fixed paraffin embedded tumour blocks will be taken for RNA and DNA extraction for transciptome and genomic analysis respectively. Material will be stored in an HTA accredited tumour bank. A translational research committee will be formed and applications welcomed for additional studies.

A single 7ml EDTA blood sample will be sent to HMDS, Leeds, for future germline DNA extraction as part of future ethically approved translational studies.

Please refer to the INCA Laboratory Manual for detailed information for processing and shipping the samples.

11 DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites on version controlled case report forms (CRFs) designed for the trial and supplied by UCL CTC. Data must be accurately transcribed onto trial CRFs and must be verifiable from source data at site. Examples of source documents are hospital records which include patient's notes, laboratory and other clinical reports etc.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, CT scan images etc.) are being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending to maintain confidentiality.

Please note that, for this trial, patients must consent to their initials, date of birth, gender and NHS number being supplied to UCL CTC. This information will be used to collect long-term follow-up of patients through the Health and Social Care Information Centre (NHS IC) Medical Research Information Service (MRIS) and to assist with follow-up via GPs.

11.1 Completing Case Report Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

All entries must be clear, legible and written in ball point pen. Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used.

The use of abbreviations and acronyms should be avoided.

Once completed the original CRFs must be sent to UCL CTC and a copy kept at site.

Pfizer Limited will be notified of any disease related deaths occurring in any patients that have been exposed to Inotuzumab Ozogamicin from treatment to 30 days post treatment.

11.2 Missing Data

To avoid the need for unnecessary data queries CRFs must be checked at site to ensure there are no blank fields before sending to UCL CTC (unless it is specifically stated that a field may be left blank). When data are unavailable because a measure has not been taken or test not performed, enter "ND" for not done. If an item was not required at the particular time the form relates to, enter "NA" for not applicable. When data are unknown enter the value "NK" (only use if every effort has been made to obtain the data).

11.3 Timelines for Data Return

CRFs must be completed at site and returned to UCL CTC as soon as possible after the relevant visit and within 1 month of the patient being seen. Sites who persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subjected to a 'for cause' monitoring visit. See section 14.3 ('For cause' on-site monitoring) for details.

11.4 Data Queries

Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Data clarification requests will be sent to the data contact at site. Further guidance on how data contacts should respond to data queries can be found on the Data Clarification Request forms.

12 PHARMACOVIGILANCE

12.1 Definitions

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6:

Adverse Event (AE)
Any untoward medical occurrence or effect in a patient treated on a trial protocol, which does not necessarily have a causal relationship with a trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment. See section 12.2.1 for AE reporting procedures.

Adverse Reaction (AR)

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between a trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (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 that hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardise the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE

See section 12.2.2 for SAE reporting procedures.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse event meeting the following criteria:

- Serious – meets one or more of serious criteria above
- Related – assessed by the local investigator or sponsor as causally related to one or more elements of the trial treatment
- Unexpected – the event is not consistent with the applicable reference safety information (RSI)

Overdose, Trial treatment error or Occupational exposure

Refer to section 8.5 for details on reporting of these events

12.2 Reporting Procedures

Adverse Event Term

An adverse event term must be provided for each adverse event. Wherever possible a valid term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 should be used. This is available online at:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Severity grade

Severity grade of each adverse event must be determined by CTCAE v4.03 (use version listed above).

Causality

The relationship between the treatment and an adverse event will be assessed.

For AEs, the local PI or designee will assess whether the event is causally related to trial treatment.

For SAEs, a review will also be carried out by the Sponsor's delegate.

Causal relationship to each trial treatment must be determined as follows:

- **None**
  There is no evidence of any causal relationship.
- **Unlikely**
  There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of a trial treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant treatments).
- **Possibly**
  There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of a trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

- **Probably**

  There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- **Definitely**

  There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

  UCL CTC will consider events evaluated as possible, probably and definitely related to be adverse reactions.

12.2.1 Reporting of Adverse Events (AEs)

All adverse events that occur between informed consent and 30 days post last trial treatment administration must be recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC using the trial specific SAE Report. Also refer to section 12.2.2 (Reporting of Serious Adverse Events (SAEs)).

Pre-existing conditions do not qualify as adverse events unless they worsen.

12.2.2 Reporting of Serious Adverse Events (SAEs)

All SAEs that occur between the signing of informed consent and 30 days post last trial treatment administration (**or after this date if the site investigator feels the event is related to a trial treatment**) must be submitted to UCL CTC by fax within **24 hours** of observing or learning of the event, using the trial specific SAE Report. All sections on the SAE Report must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

Exemptions from SAE Report submission

For this trial, the following events are exempt from requiring submission on an SAE Report, but must be recorded in the relevant section(s) of the trial CRFs:

- events that occur more than 30 days post last trial treatment administration that are not considered unless:
  - considered to be a late effect of the trial treatment
  - it is a pregnancy related event (see section 12.5)
- Disease-related events (this does not apply to disease-related deaths on the IO-R-CVP treatment arm which are reportable according to SAE reporting procedures)

Please note that hospitalisation for elective treatment, palliative care or prolongation of hospitalisation due to social/logistical reasons do not qualify as an SAE.

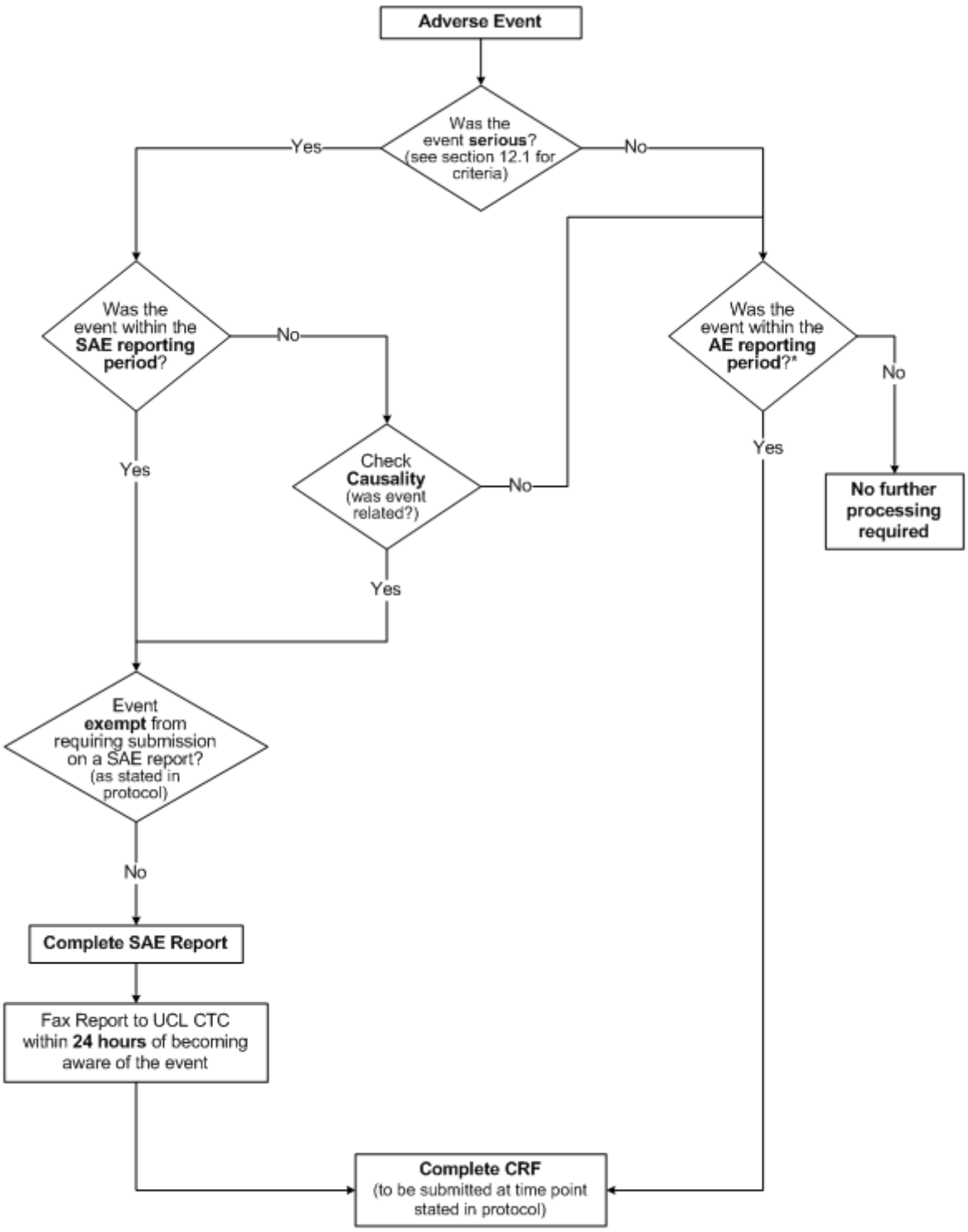
Completed SAE Reports must be faxed within 24 hours of becoming aware of the event to UCL CTC

Fax: +44 (0)20 7679 9861

SAE Follow-Up Reports

All SAEs must be followed-up until resolution and until there are no further queries. Sites must ensure any new and relevant information is provided promptly. If the event term changes or a new event is added, the causality must be re-assessed by an investigator. If the event is not being reported within 24 hours to UCL CTC, the circumstances that led to this must be detailed in the SAE/SAR Report to avoid unnecessary queries.

Adverse Event Reporting Flowchart



*This applies if AE and SAE reporting periods differs.

SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the RSI (the current IB for inotuzumab ozogamicin and SPC for gemcitabine).

The CI, or their delegate (e.g. a clinical member of the TMG), may be contacted to review the SAE and to perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

UCL CTC will submit all SAE Reports concerning patients who have received Inotuzumab Ozogamicin to Pfizer Limited according to the timelines outlined in the agreement between UCL and Pfizer Limited.

12.3 SUSARs

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the MHRA within the required timelines.

Wherever possible evaluations of causal relationship by both the site and the Sponsor's clinical reviewer will be reported.

Informing Sites of SUSARs

UCL CTC will inform all PIs of any SUSARs that occur on the trial. PIs will receive a quarterly line listing which must be processed according to local requirements.

UCL CTC will forward reports received from Pfizer Limited regarding SUSARs that have occurred on other trials using Inotuzumab Ozogamicin to all PI's. These must be processed according to local requirements and filed with the applicable IB.

12.4 Safety Monitoring

UCL CTC will provide safety information to the Trial Management Group (TMG) and the Independent Data Monitoring Committee (IDMC) on a periodic basis for review.

Trial safety data will be monitored to identify:

- new adverse reactions to the trial treatment regimen or individual trial treatments;
- a higher incidence in rare adverse events than is stated in the IB/SPC for a trial treatment;
- trial related events that are not considered related to the trial treatment regimen.

If UCL CTC identifies or suspects any issues concerning patient safety at any point during the trial, the CI or TMG will be consulted for their opinion and if necessary the issue will be referred to the IDMC.

12.5 Pregnancy

If a female trial patient or the female partner of a male trial patient becomes pregnant at any point during the trial, the site must submit a trial specific Pregnancy Report to UCL CTC by fax within **24 hours** of learning of its occurrence.

The site must request consent from a pregnant trial patient or female partner of a male patient to report information regarding a pregnancy using:

- For female patients: the trial specific Pregnancy Monitoring Information Sheet and Informed Consent Form for trial patients.

- For female partners of male patients: the trial specific Pregnancy Monitoring Information Sheet and Informed Consent Form for partners of study patients

If consent is not given, the notification that a pregnancy has occurred will be retained by UCL CTC however no further action will be taken on the information detailed in the report.

All pregnancies must be reported by faxing a completed Pregnancy Report within 24 hours of becoming aware of the pregnancy to UCL CTC
Fax: +44 (0)20 7679 9861

Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed-up until an outcome is determined. Follow-up Pregnancy Reports must be submitted to UCL CTC by fax within **24 hours** of learning of the outcome. Reports must include an evaluation of the possible relationship of each trial treatment to the pregnancy outcome.

SAEs during pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. Refer to section 12.2.2 (Reporting of Serious Adverse Events (SAEs)) for details.

Pregnancy Report processing at UCL CTC

UCL CTC will submit a report to the MHRA and the REC if the pregnancy outcome meets the definition of a SUSAR. Refer to section 12.3 (SUSARs) for details.

UCL CTC will submit all Pregnancy Reports concerning exposure to Inotuzumab Ozogamicin to Pfizer Limited according to the timelines outlined in the agreement between UCL and Pfizer Limited.

12.6 Development Safety Update Reports (DSURs)

Safety data obtained from the trial will be included in DSURs that UCL CTC will submit to the MHRA and the REC.

UCL CTC will provide Pfizer Limited with DSURs that include information regarding Inotuzumab Ozogamicin.

13 INCIDENT REPORTING AND SERIOUS BREACHES

13.1 Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. An incident report may be requested and will be provided, but an equivalent document (e.g. Trust Incident form) is acceptable where already completed.

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

13.2 Serious Breaches

A "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, UCL CTC will inform the MHRA and REC within 7 calendar days of becoming aware of the breach.

UK sites must have written procedures for notifying the sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches).

14 TRIAL MONITORING AND OVERSIGHT

UK participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

UCL CTC will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

14.1 On-Site Monitoring

The degree of on-site monitoring will be proportionate to the objective, purpose, phase, design, size, complexity, endpoints and risks associated with the trial.

Details of monitoring activities will be included in the trial monitoring plan which will be provided to Sites. The monitoring plan will be under review throughout the trial and updates provided as necessary.

Sites will be sent a letter in advance confirming when a routine monitoring visit is scheduled to take place. The letter will include a list of the documents to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Monitoring Follow Up

Following a monitoring visit, the Trial Monitor/Trial Coordinator will provide a follow up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

14.2 Central Monitoring

Sites will be requested to submit screening logs and staff delegation logs to UCL CTC at the frequency detailed in the trial monitoring plan or on request and these will be checked for consistency and completeness. Also refer to sections 4.2.2 (Required documentation) and 6.1 (Screening log).

Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Checks of the criteria listed on the randomisation form will be undertaken by an appropriately trained UCL CTC staff member prior to randomisation. Also refer to section 7.1 (Randomisation).

Details relating to the informed consent process will be collected on the randomisation form and are subject to review by CTC as part of patient eligibility.

Copies of completed drug accountability logs must be returned to UCL CTC for all trial patients. Sites will be required to submit logs in accordance with the trial monitoring plan.

Data received at UCL CTC will be subject to review in accordance with section 11.4 (Data Queries).

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File and Pharmacy Site File at the frequency detailed in the trial monitoring plan. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Patients will be flagged with the Health and Social Care Information Centre to enable long-term follow-up of these patients.

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk (e.g. evidence of an overdose having been administered, indication that stopping rules for an IMP were not observed following an adverse reaction, etc.), the matter will be raised urgently with site staff and escalated as appropriate (refer to section 13 (Incident Reporting and Serious Breaches) and 14.3 ('For cause' on-site monitoring) for further details).

14.3 'For Cause' On-Site Monitoring

Additional on-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit and confirming when it will take place. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. Refer to section 13 (Incident Reporting and Serious Breaches) for details.

14.4 Oversight Committees

14.4.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and INCA trial staff from UCL CTC (see page 1). The TMG will be responsible for overseeing the trial. The group will meet regularly approximately twice a year or as necessary and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Haematological Oncology Clinical Studies Group.

The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA. All PIs will be kept informed of substantial amendments through their nominated responsible individual and are responsible for their prompt implementation.

Members of the TMG will be required to sign a TMG charter outlining their duties and responsibilities.

14.4.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funders and Sponsor.

Members of the TSC will be required to sign a TSC charter outlining their duties and responsibilities.

14.4.3 Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held annually to review interim analyses or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

Members of the IDMC will be required to sign an IDMC charter outlining their duties and responsibilities.

14.4.4 Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with section 12.0 (Pharmacovigilance).

15 WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, collection of biological samples, follow-up and data collection.

15.1 Discontinuation of Trial Treatment

A patient may be withdrawn from trial treatment whenever such treatment is no longer in the patient's best interests, but the reasons for doing so must be recorded in the patient's notes and on the relevant Case Report Form(s). Reasons for discontinuing treatment may include:

- Disease progression whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Patient decision not to continue with trial treatment
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the site investigator's opinion
- Non-compliance with the trial treatment and/or procedures
- If a female patient becomes pregnant or male/female fails to use adequate birth control (for patients of childbearing potential)

In these cases patients will remain within the trial for the purposes of follow-up and data analysis according to the treatment option to which they have been allocated unless they explicitly withdraw consent.

If a patient expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. If the patient gives a reason for their withdrawal, this should be recorded.

15.2 Future Data Collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected, with the exception of essential safety data, and recorded on the relevant CRF. In this event data due up to the date of withdrawal must be submitted but no further data, other than essential safety data sent to UCL CTC. The patient will also be removed from flagging with the Health and Social Care Information Centre.

15.3 Losses to Follow-Up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for follow-up via GP. Details of participating trial sites can be obtained from the UCL CTC trial team who must be informed of the transfer of care and follow up arrangements. If it is not possible to transfer to a participating site, the registering site remains responsible for submission of forms.

If a patient is lost to follow-up at a site every effort should be made to contact the patient's GP to obtain information on the patient's status.

Patients lost to follow up will be tracked by UCL CTC via the Health and Social Care Information Centre.

16 TRIAL CLOSURE

16.1 End of Trial

For regulatory purposes the end of the trial will occur when all patients have completed at least two years of follow-up post-treatment at which point the 'declaration of end of trial' form will be submitted to the MHRA and Ethics Committee, as required.

Following this, UCL CTC will advise sites on the procedure for closing the trial at the site.

16.2 Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained securely for a minimum of 5 years after the end of the trial, and in accordance with national legislation..

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3 Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 14.4.2 Trial Steering Committee (TSC) and 14.4.3 Independent Data Monitoring Committee (IDMC)). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

16.4 Withdrawal from Trial Participation by a Site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for any patients recruited into the trial at that site and other responsibilities continue as per the CTSA.

17 STATISTICS

17.1 Sample Size Calculation

The study is designed as a randomised phase II trial and aims to show an increase in the 2 year progression free survival (PFS) rate of 15% in the IO-R-CVP arm.

A total of 61 PFS events (progressions or deaths) are required to detect a hazard ratio of 0.62, which equates to a 15% improvement in 2-year PFS of IO-R-CVP compared with Gem-R-CVP (50% to 65%) with a 15% one sided alpha level and 80% power.

132 patients (66 in each arm) will be recruited over a period of 3 years and it is anticipated that a further 1 year follow-up will be required to observe the 61 events needed.

The sample size was calculated using NQuery.

Patients will be replaced if they are withdrawn from the study prior to receiving any IMP or if found to be ineligible due to a misdiagnosis.

17.2 Population for Analysis

All patients will be included in the primary analysis, progression free survival. In the analysis of response we will consider all patients who received at least one cycle of treatment as well the group who completed at least 3 cycles.

17.3 Analysis of the Primary Endpoint

The primary endpoint is progression free survival rate and will be analysed using Kaplan-Meier survival analysis and Cox regression (or restricted mean survival time (RMST) if the assumption of proportionality is violated). PFS time will be measured from date of randomisation until progression or death. Patients who are alive without progression will be censored at the date last seen.

A subgroup analysis of PFS will be carried out for different levels of the Co-morbidity score (Cumulative Illness Rating Scale (CIRS)), IPI, LVEF and ADL/IADL.

17.4 Analysis of Secondary Endpoints

17.4.1 Efficacy (secondary)

- Kaplan–Meier methods will be used to analyse overall survival. Survival times will be calculated from the date of randomisation until death. Patients who are alive will be censored at the date last seen.
- Rates of response at the end of treatment, according to the revised International Working Group response criteria for non-Hodgkin's lymphoma (Cheson criteria [17]) will be compared (see Appendix 2 for details).
- Compliance to treatment (number of cycles, dose delays and reductions) will be compared.

- The impact of the steroids and subsequent treatment on performance status and functionality.

- Toxicity will be closely monitored (see below) and the numbers of grade 3 and 4 events (according to CTCAE v 4.03) compared between the arms.

17.4.2 Health related Quality of Life and functional assessments

- Co-morbidity score: Cumulative Illness Rating Scale (CIRS)
- Quality of life questionnaire: EORTC QLQ-C30
- Functionality assessments: ADL and IADL

QOL and functionality will be analysed using methods for repeated measures, such as mixed modelling.

Descriptive statistics will be used to investigate the Co-morbidities seen at baseline.

17.5 Interim Analyses

There will be no formal interim analyses, however the independent data monitoring committee will see the unblinded results at least once a year to monitor the safety and efficacy endpoints.

As Inotuzumab Ozogamicin is an unlicensed drug we will be monitoring the toxicities in this arm very closely. The table below outlines the number of events we would need to observe before requiring a TMG safety review or to consider stopping the trial**.**

The number of events needed to consider stopping recruitment early is such that the exact lower 95% CI (one-sided) exceeds 15% i.e. the true rate is likely to exceed these limits.

Number of Patients (N)	Number of treatment related deaths needed for TMG safety review (more than 15% of N)	Number of treatment related deaths needed to consider stopping
10	2	4
15	3	6
20	4	7
25	4	8
30	5	9
35	6	10

18 ETHICAL AND REGULATORY CONSIDERATIONS

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with all relevant guidance, laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928
- Human Rights Act 1998
- Data Protection Act 1998
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Human Tissue Act (Scotland) 2006
- Medicines Act 1968
- Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice
- the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

18.1 Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the NRES Committee Yorkshire and the Humber-Leeds East Research Ethics Committee (REC) and Health Research Authority (HRA) approval for conduct in the UK.

UCL CTC will submit Annual Progress Reports to the REC, commencing one year from the date of ethical approval for the trial.

18.2 Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA.

18.3 Site Approvals

The Lead Comprehensive Local Research Network (CLRN) Trent has given NHS permission following global governance checks. Local governance checks will be undertaken by local CLRNs associated with individual trial sites.

Evidence of approval from the Trust R&D for a trial site must be provided to UCL CTC. Sites will only be activated when all necessary local permissions for the trial have been obtained.

18.4 Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approval(s), as appropriate, for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments promptly.

18.5 Patient Confidentiality & Data Protection

Patient identifiable data, including their initials, date of birth and NHS number will be required for the randomisation process and will be provided to UCL CTC.. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.

19 SPONSORSHIP AND INDEMNITY

19.1 Sponsor Details

Sponsor Name:	University College London
Address:	Joint Research Office Gower Street London WC1E 6BT
Contact:	Director of Research Support
Tel:	020 3447 9995/2178 (unit admin)
Fax:	0207 3447 9937

19.2 Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

20 FUNDING

Pfizer Limited is supporting the central coordination of the trial through UCL CTC.

Pfizer Limited will be supplying Inotuzumab Ozogamicin free of charge to sites for this trial.

CR UK is providing endorsement for the trial through the Clinical Trials Awards and Advisory Committee, CTAAC.

21 PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. The TMG will form the basis of the writing committee and advise on the nature of publications. If there are named authors, these should include the Chief Investigator(s), Trial Coordinator(s), and Statistician(s) involved in the trial. Contributing site investigators in this trial will also be acknowledged. Data from all sites will be analysed together and published as soon as possible. Participating sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data is owned by the Sponsor. However, drug companies who have provided funding towards the trial will be permitted to see the draft manuscripts and make comments at least 45 days prior to submission for publication. The Clinicaltrials.gov number and CR UK funding reference number allocated to this trial will be quoted in any publications resulting from this trial.

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APPENDIX 1: ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine transaminase
ALP	Alkaline Phosphatase
AR	Adverse Reaction
AST	Aspartate aminotransferase
B-HCG	β-human chorionic gonadotropin
BSA	Body Surface Area
CCC	Country Coordinating Centre
CI	Chief Investigator
CIRS	Cumulative illness rating score
CLS	Country Lead Site
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CSF	Cerebrospinal fluid
CT	Computerised Tomography
CTA	Clinical Trial Authorisation*)*
CTAAC	Clinical Trials Award and Advisory Committee
CTCAE	Common Terminology Criteria for Adverse Events
CTSA	Clinical Trial Site Agreement
DLBCL	Diffuse Large B Cell Lymphoma
DNA	Deoxyribonucleic acid
DSHNHL	Deutsche Studiengruppe Hochmaligne Non-Hodgkin-Lymphome
DSUR	Development Safety Update Report
EBV	Epstein Barr Virus
EGFR	Estimated Glomerular Filtration Rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylene Diamine Tetra Acetate
EEA	European Economic Area
EMA	European Medicines Agency
EORTC	The European Organisation for Research and Treatment of Cancer
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
G	Gram
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GEM	Gemcitabine
GFR	Glomerular Filtration Rate
HMDS	Haematological Malignancy Diagnostic Service
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IADL	Instrumental Activities of Daily Living
IB	Investigator's Brochure
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
INO	Inotuzumab ozogamicin
ISF	Investigator Site File
IV	Intravenous

LCRN	Local Clinical Research Network
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LVEF	Left Ventricular Ejection Fraction
MCG	Microgram
MG	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
ml	Millilitre
NCRI	National Cancer Research Institute
NIHR	National Institute for Health Research
NIMP	Non Investigational Medicinal Product
NHL	Non Hodgkins Lymphoma
NHS	National Health Service
NHS IC	National Health Service Information Centre
od	Once Daily
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PI	Principal Investigator
po	By mouth
PR	Partial Response
PSF	Pharmacy Site File
QOL	Quality of Life
REC	Research Ethics Committee
RQ-PCR	Real-time quantitative polymerase chain reaction
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL CTC	CR UK and UCL Cancer Trials Centre
WBC	White Blood Cells
WHO	World Health Organisation

APPENDIX 2: REVISED CHESON CRITERIA FOR RESPONSE ASSESSMENT

Response rates will be classified using revised response criteria for malignant lymphoma published by International Harmonization Project on Lymphoma [17].

The designation of **Complete Response (CR)** requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in
patient outcome.

Complete Response unconfirmed (CRu):
The use of the above definition for CR and that below for PR **eliminates** the category of CRu. **i.e. a response of CRu will not be permitted.**

Partial Response (PR):
The designation of PR requires all of the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase should be observed in the size of other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6. No new sites of disease should be observed.

7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.

Stable Disease (SD):
Stable disease (SD) is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfil those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (after CR)/Progressive Disease (after PR, SD):
Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤1.0 x≤1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use, response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

Summary table:

Response	Definition	Nodal masses	Spleen/Liver	Bone Marrow
CR	Disappearance of all evidence of disease	**(a)** FDG- avid or PET positive prior to therapy; mass of any size permitted if PET negative. **(b)** Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immuno-histochemistry should be negative
PR	Regression of measurable disease and no new sites of disease	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes **(a)** FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site **(b)** Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	**(a)** FDG-avid or PET positive prior to therapy; PET Positive at prior sites of disease and no new sites on CT or PET **(b)** Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapse or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [18F] fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

APPENDIX 3: ECOG PERFORMANCE STATUS SCALE

ECOG PERFORMANCE STATUS [29]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	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
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX 4: INTERNATIONAL PROGNOSTIC INDEX [30]

One point is scored for each of the following variables.

- Age >60 years
- Serum LDH >upper limit of normal
- Performance status 2-4
- Ann Arbor Stage III-IV
- >1 extranodal site of disease

Score 0-1 = low risk
Score 2 = low-intermediate risk
Score 3 = high-intermediate risk
Score 4-5 = high risk

APPENDIX 5: PROTOCOL VERSION HISTORY

Protocol:		Amendments:		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
1.0	13th July 2012	n/a	n/a	n/a
1.1	4th September 2012	n/a		Vital sign monitoring added to:- Section 5.1 – Pre registration evaluation Section 8.2 – Assessments during treatment Table 1 – Schedule of assessments Added >2.5 times normal level of AST/ALT and ALP as an exclusion criteria in: Section 5.3.1 (exclusion criteria) Added ALP measurement to AST/ALT Section 7.3.3 – Dose modifications Bilirubin levels amended in section 7.3.3 to match exclusion criteria in:- Section 5.3.1 – Inclusion and Exclusion criteria for registration Removed reference to the use of a patient diary and documenting the return of oral prednisolone in: Section 4.0 – Informed consent Section 6.1 – Registration Section 8.2 – Assessments during treatment

2.0		17.0		Updated to latest CTC protocol template 4.1 23Apr13
			Section 6.1 – Pre-registration evaluation	Diagnostic biopsy can be done any point prior to registration. ECG must now include QTcF interval CT scan of the neck should be done but for those cases it has been omitted, it does not need to be repeated as long as a full clinical examination has been performed (ideally to include an ultrasound/MRI) Bone marrow trephine biopsy can now be performed after steroid pre phase has started in cases of urgent clinical need Optional – A PET-CT can now be done for staging as long as the CT component of the PET-CT is contrast enhanced BCSH guidance on CNS prophylaxis in NHL should be followed. High risk – serum LDH >ULN and more than 1 extranodal localisation or involvement of testicular, breast and paraspinal sites. CNS directed therapy may be added if, in the opinion of the PI, there is significant risk of CNS involvement Prothrombin time added to biochemistry tests
			Section 6.3 – Patient eligibility	Superficial bladder cancer added to inclusion criteria for no active malignant disease Exclusion criteria – Attributable to lymphoma removed for serum bilirubin greater than upper limit of normal. Haemolysis added. Exclusion criteria – Attributable to lymphoma removed for ALT and/or AST and ALP greater than 2.5 times the upper limit of normal Serological evidence for Hepatitis B or C amended in exclusion criteria 2 new exclusion criteria added – Patients with history of Venoocclusive Disease (VOD) and Sinusoidal Obstructive Syndrome (SOS) and Patients with screening of QTcF interval >470msec

			Section 6.3.3 – Contraceptive advice	Contraceptive advice changed – single barrier method only needed within the trial
			Section 6.3.4 – Long term infertility	Recommendation added for sites to speak to patients about egg preservation prior to trial entry
			Section 8.2 – Summary treatment schedule	Break between steroid pre-phase and randomised treatment changed to no break and steroid pre phase changed to a maximum of 14 days Recommendation of when G-CSF should be stopped added to the protocol Details of pre-medications to be given to patients on the IO-R-CVP arm added to the protocol (paracetamol 1g (PO) and chorpheniramine 4mg (PO)
			Section 8.3 – trial treatment details	BSA should be recalculated now in case of weight variation of 10% Dose banding is now allowed in the trial Clarification that diluted IO must be covered (with an amber bag or covered with foil) Clarification that IO infusion should be 1 hour Clarification that administration of gemcitabine should be given according to local guidelines and policies
			Section 8.4 – Dose modifications	Dose modification section re-formatted and additional sections added
			Section 8.6 – Concomitant medication	Details of medications to be avoided for patients on the IO-R-CVP arm
			Section 8.9 – Other trial treatments/ interventions	Clarification on the definition of high risk of CNS involvement and treatment of CNS disease changed
			Section 9.2 – Assessments during treatment	FBC and serum biochemistry can be done up to 3 days before treatment. ECG with QTcF should be done before starting each cycle of IO-R-CVP Prothrombin time added to biochemistry tests Clarification that CT scan before 4 cycle must be contrast enhanced

			Section 9.3 – Assessments on completion of trial treatment	β2 microglobulin removed from assessments during treatment and follow up BM biopsy only needs to be done now if BM was initially involved and the CT shows CR or Cru Prothrombin time added to biochemistry tests Clarification that CT scan should be contrast enhanced Optional: A PET-CT can be used to determine response as long as the CT component of the PET-CT in contrast enhanced.
			Section 9.4 – Assessments during follow-up	Removed the requirement to perform AE and toxicity assessments during follow up Clarification that CT scan should be contrast enhanced
			Various sections	Administrative changes throughout the protocol after review from CPAS
2.1	11th August 2014	N/A – non-substantial amendment	Section 1,1 (Summary of trial design) and 3 (Trial design)	Clarification that the maximum dose of Vincristine is 2mg so that it is in line with the treatment section of the protocol and summary of drug arrangements
			6.1 (pre-registration evaluations) and 9.2 (assessments during treatment)	Clarification that an average of 3 ECG's should be conducted at baseline and prior to each cycle of I-O in order to calculate the QTcF interval (as indicated in the dose modification section of the protocol)
			8.4 (dose modification)	Clarification that if bilirubin is >2.5x ULN dose reduce Vincristine by 50% as per the SPC and manufacturers guidance MHRA and REC will be notified of the above mentioned changes when the next substantial amendment is submitted.
3.0	15th October 2014		1.1 Summary of Trial Design	Information updated in line with rest of protocol changes
			1.2 Trial Schema	Updated in line with rest of protocol changes
			3.0 Trial Design (and treatment arms)	Clarification that all patients will receive steroids and that patients will be treated with a lower dose of Gemcitabine depending on the ECOG PS

			6.1 (Pre-randomisation evaluation)	All assessments need to be done with the specified time frame before randomisation as registration step has been removed from the trial. Clarification what needs to be done if contrast is contraindicated or CT scan outside the 35 day window Assessments which need to be done after patient has received some steroids made clearer
			6.3.1 (Inclusion and Exclusion criteria for randomisation)	A concurrent (synchronous) diagnosis of low grade lymphoma is allowed and has been moved to the inclusion criteria so clearer ECOG performance status 0-2 added to inclusion criteria as needs to be done before randomisation ECOG performance status 3-4 added to exclusion criteria before randomisation
			7.0 (Randomisation procedures) 8.2 (Trial treatment)	Registration stage removed from protocol as patient's are now registered and randomised at the same time All patients will receive steroids before randomised treatment so pre-phase section removed from protocol. Clarification on when steroids don't need to be given and also when randomised treatment should start New dosing schedule for patients receiving Gemcitabine added
			8.3 (Trial treatment details) 8.4 (Dose modifications)	New dosing schedule for patients receiving Gemcitabine added Dose reduction schema amended in line with new lower dose of Gemcitabine
			9.2 (Assessments during treatment, on completion of trial treatment (9.3) and follow up (9.4)) Table 1 – Schedule of Assessments	Clarification what needs to be done if contrast is contraindicated or CT scan outside the 35 day window Amended in line with rest of protocol – pre-registration assessments removed, updated CT information added
			12.1 Definitions of Adverse Events	SUSAR term updated in line with current CTC protocol template

			12.2.2 Serious Adverse Events (SAEs)	SAE processing at UCL CTC paragraph updated in line with current CTC protocol template
			14.2 Central Monitoring	Informed consent log no longer used in the trial as information collected on randomisation form. Paragraph relating to this log removed
			17.1 (Sample size calculation)	Sample size reduced to 132 patients (66 patients per arm) and recruitment period increased to 3 years
4.0	16th November 2015	31	1.1 Summary of Trial Design	Updated in line with rest of protocol
			Throughout protocol	'significant cardiac comorbidities' replaced with 'significant comorbidities' as 'diabetes', 'hypertension' are acceptable comorbidities according to eligibility criteria
			6.1 Pre-randomisation evaluation	Translational research section updated detailing which samples are optional within the trial
			6.3.1 Inclusion and Exclusion criteria for randomisation	Patients with a previous diagnosis of low grade lymphoma which hasn't been treated with systemic therapy are now eligible for the trial Clarification added whether patients with history of malignant disease may be eligible for the trial
			Table 1, Schedule of Assessments	Sample information updated in line with rest of the protocol
			9.3 Assessments on completion of trial	Clarification that bone marrow biopsy at the end of treatment is optional if the end of treatment PET-CT scan is clear

5.0	22nd December 2016	Substantial	Various	Updated to latest CTC protocol template 7.0 25Jul2016. Various sections moved, new information added to the following sections:- 4.1.1 Selection of Principal Investigator and other investigators at site; 4.2.1 Site Initiation; 6.2 Patient Eligibility; 6.3 Pregnancy and birth control; 6.3.4 Contraceptive Advice; 6.3.5 Action to be taken in the event of a Pregnancy; 8.5 Management of Overdoses, Trial Treatment error or Occupational Exposure; 11.4 Data Queries; 15.1 Discontinuation of Trial Treatment
			1.1 Summary of Trial Design	Anticipated duration of recruitment changed to 4 years as recruitment period extended for a further year
			1.2 Trial schema	1 year changed to 24 months as per rest of protocol
			3.0 Trial Design	Clarification that the Inotuzumab Ozogamicin is light sensitive and must be protected from light during preparation and administration of the infusion using a UV protective covering. Infusion time should be 1 hour at room temperature

			6.1 Pre-randomisation evaluation	Now in Section 9.0 Assessments – clarification that QTcF interval should be done as per rest of protocol not QTc
			8.3 Trial treatment details	Clarification that the Inotuzumab Ozogamicin is light sensitive and must be protected from light during preparation and administration of the infusion using a UV protective covering. Infusion time should be 1 hour at room temperature. Expiry time of Inotuzumab Ozogamicin changed to 4 hours as per new information received from Pfizer
			9.2 Assessments during Treatment	Clarification that QTcF interval should be done as per rest of protocol not QTc
			Table 1 Schedule of Assessments	Clarification that QTcF interval should be done as per rest of protocol not QTc
			12.2.2 Serious Adverse Events	Pfizer have never been sent SAE quarterly line listings so this has been deleted
			17.1 Sample Size Calculation	Patients will be replaced if found to be ineligible due to a misdiagnosis
			17.3 Analysis of the Primary Endpoint	Additional information relating to the analysis of the primary end point has been added to the protocol
			Various	Minor administrative changes throughout the protocol