INCA

Protocol Summary

Short Title/acronym: INCA
Sponsor name & reference: University College London – 11/0475
Funder name & reference: Cancer Research UK - CR UK/A13920
Design: A multicentre, randomised, phase II trial

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: 132 (66 in each arm)
Planned number of sites: UK (25-50)

Inclusion Criteria:

- 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 registration 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

Exclusion Criteria

- 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 Gilberts 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 or normal
- 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

Translational Research: 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.

Costs to site: Cyclophosphamide, Gemcitabine, Prednisolone, Rituximab, Vincristine and G-CSF will be provided by site from hospital stocks. Sites must fund the cost of postage and packaging of the translational research samples.

Treatment summary

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 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

*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 reason 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.

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*

*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. The Inotuzumab ozogamicin should be infused within 1 hour at room temperature at a rate of 50 mL/hour.

Gem-R-CVP arm:

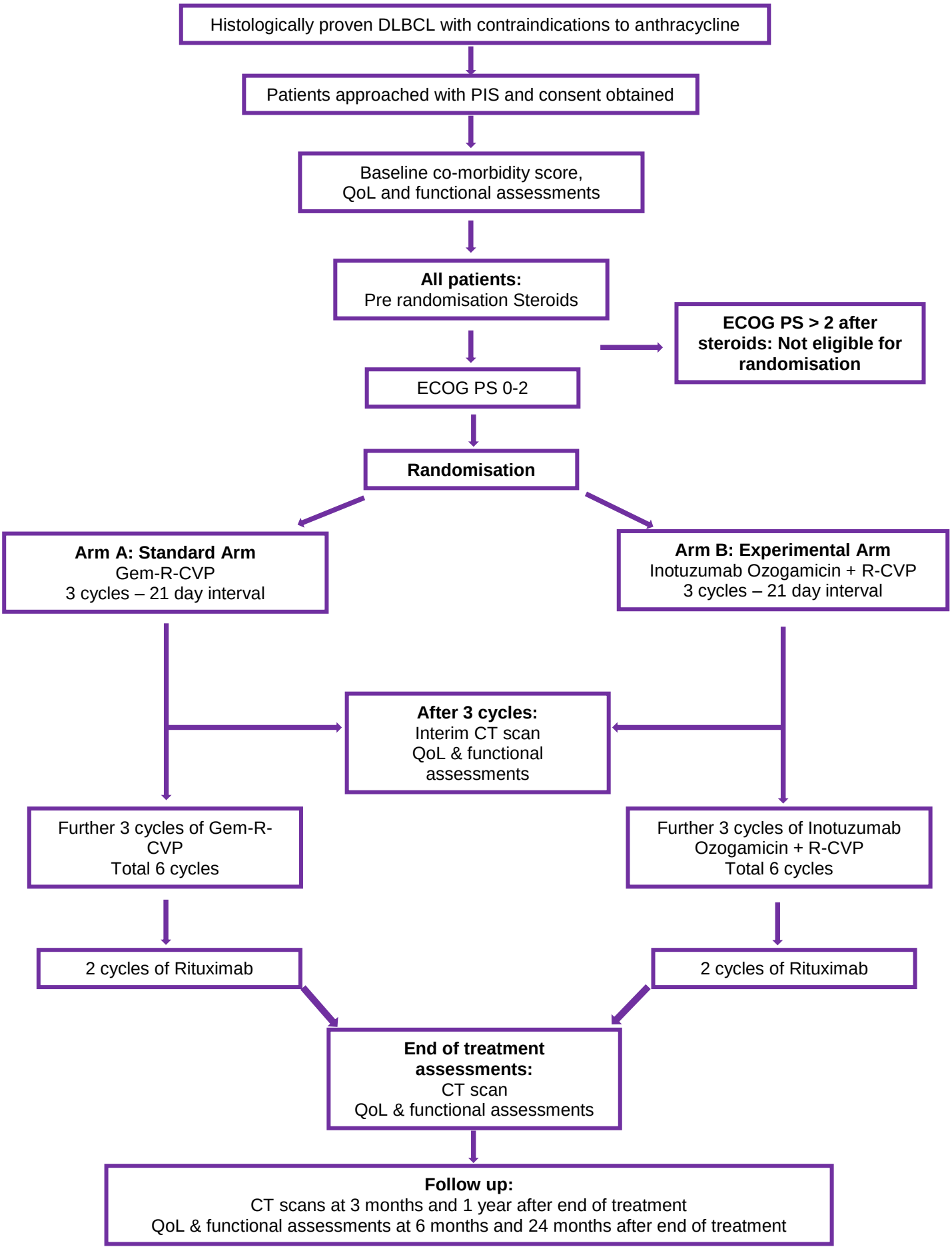
D1, D8 Gemcitabine Up to 1g/m^2 IV*
D1 Cyclophosphamide 750mg/m^2 IV
D1 Vincristine 1.4mg/m^2 (max 2mg) IV
D1-5 Prednisolone 100mg OD Oral**
D1 Rituximab 375mg/m^2 IV
D9-17 Primary GCSF prophylaxis

****Patients with ECOG 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.*

***Prednisolone should be given in the morning of day 2 and premed with paracetamol 1g (PO) and chlorpheniramine 4mg (PO) according to local policies.*

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 Rituximab 375mg/m^2 at 21-day intervals (i.e. 8 doses of Rituximab in total).


Histologically proven DLBCL with contraindications to anthracycline
Patients approached with PIS and consent obtained
Baseline co-morbidity score, QoL and functional assessments
All patients: Pre randomisation Steroids
ECOG PS > 2 after steroids: Not eligible for randomisation
ECOG PS 0-2
Randomisation
Arm A: Standard Arm
Gem-R-CVP
3 cycles – 21 day interval
Arm B: Experimental Arm
Inotuzumab Ozogamicin + R-CVP
3 cycles – 21 day interval
After 3 cycles:
Interim CT scan
QoL & functional assessments
Further 3 cycles of Gem-R-CVP
Total 6 cycles
Further 3 cycles of Inotuzumab Ozogamicin + R-CVP
Total 6 cycles
2 cycles of Rituximab
2 cycles of Rituximab
End of treatment assessments:
CT scan
QoL & functional assessments
Follow up:
CT scans at 3 months and 1 year after end of treatment
QoL & functional assessments at 6 months and 24 months after end of treatment