Royal Free and University College Medical School
University College London

CANCER RESEARCH UK &
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The Lymphoma Trials Office
90 Tottenham Court Road
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19th May 2009

Ms Jenny Austin
Bedfordshire & Hertfordshire REC's
Hertfordshire REC
9th Floor
Terminus House
The High
Harlow, Essex
CM20 1XA

Dear Ms. Austin,

RE: A Phase ll Single Arm Study of the use of CODOX-M/IVAC with Rituximab (R-CODOX-M/IVAC) in the treatment of patients with Diffuse Large B-Cell Lymphoma (International Prognostic Index High or High – Intermediate Risk)

REC reference number: 05/Q0201/81
Amendment 7.0 – 19.05.2009

Please find enclosed, copies of the following:

Annex 2, notification of amendment 7.0, 19.05.2009
Protocol - Version 6.0, 13.05.2009 (tracked changes & untracked)
Patient Information Sheet - Versions 6.0, 13.05.2009 (tracked changes & untracked)
Consent Form - Versions 6.0, 13.05.2009 (tracked changes & untracked)
GP letter - Version 5.0, 13.05.2009 (tracked changes and untracked)
Letter of support from the Leukaemia Research Fund (LRF) 29.05.2008

A list of amendments made to the main protocol (pages shown as in tracked copy), are as follows:

- **Change of study title**

  The title of the study is being changed to 'Phase II Single Arm Study of the use of CODOX-M/IVAC with Rituximab (R-CODOX-M/IVAC) in the treatment of patients with Diffuse Large B-Cell Lymphoma (DLBCL) or Burkitt's Lymphoma (BL) of International Prognostic Index (IPI) High or High Intermediate Risk', to include Burkitt's lymphoma.

- **Inclusion of Burkitt's Lymphoma patients in to the trial (section 4.2 pg 16, section 3.1 pg 12)**

It is felt and supported by the LRF that patients with Burkitt's lymphoma (BL) should be allowed entry in to the main trial. This has been proposed for four main reasons:

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Firstly published data suggests excellent results have been reported using CODOX-M/IVAC. Patients have been successfully treated with this regimen in the NCRI 'badged' LY10 study ' A prospective clinicopathological study of dose modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogentic and immunophenotypic criteria'. This aimed to develop diagnostic criteria for Burkitt's lymphoma and to evaluate the efficacy of dose modified CODOX-M/IVAC.

Since the closure of this trial, no study exists for this group of patients, leaving a gap available for the inclusion of Burkitt's patients.

It provides an excellent opportunity to explore the role of Rituximab in treating patients with BL in the current R-CODOX-M/IVAC trial.

A final practical point to make is that this group of patients is notoriously difficult to diagnose on presentation, therefore it is likely that BL patients will be entered on to this study regardless of this change in the inclusion criteria. Currently an unreliable and subjective morphological criterion exists for these patients.

It would seem logical then to include BL patients for the reason that the CODOX-M/IVAC regimen has already proved successful in these patients and now the LY10 study has closed to recruitment a gap exists to evaluate the role of Rituximab in this regimen.

All relevant sections of the protocol have been changed to reflect the inclusion of this group of patients.

- **Change of contact details (section 1, pg 6)**
- **Change of primary outcome measure and endpoint to progression free survival (section 3.2 pg 12)**
- **More information given on non-haematological toxicity & dose modification (section 8.2 pgs 28 & 29)**
- **Statistical Consideration section was changed to reflect the change in endpoint and inclusion of Burkitt's lymphoma patients (section 13, pg 37)**
- **Change of section name from 'safety reporting' to 'pharmacovigilance' with more information given (section 15 pg 38)**

More comprehensive information has been added in response to advice received from the Pharmacovigilance Coordinator at the trials centre.

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- **Additional information in Appendix 5- Methotrexate Administration (pg 62)**

It has been recommended in line with the UKALL 12 protocol that Septrin be stopped one week prior to the administration of High Dose Methotrexate to avoid any potential drug interactions.

- **An extensive list of toxicities expected with the chemotherapy drugs, both general and specific (appendix 6, pg 74)**

- **Removal of appendices – PIS, Consent and GP letter**

Appendices (Patient Information Sheet), (Consent forms) and (GP Letter) have been removed from the main protocol. These documents are now each stand alone documents.

- **PIS, Consent and GP letter**

The inclusion of Burkitts Lymphoma patients has been added to the information in the PIS and GP letter. Title of the study on the consent form, PIS and GP letter has also been changed. The PIS has also been updated to include the advice given by Roche over the concern of patients developing Progressive Multifocal Leukoencephalopathy (PML) having been treated with Rituximab (PIS, pg 4). An additional patient consent form to this effect is also attached.

Please do not hesitate to contact me should you have any further queries.

Yours sincerely,

Toyin Adedayo
Clinical Trial Coordinator