

NCRI Lymphoma Clinical Studies Group.

The Lymphoma Clinical Studies Group has had another busy and successful year. Highlights of the year were:

- Successful launch of new diffuse large B-cell lymphoma study, R-CHOP 14 vs 21.
- Continued good accrual to studies in Hodgkin's disease (PET and Stanford V) and Follicular lymphoma (Watch and Wait).
- Successful completion of recruitment for MCD vs FMD in follicular lymphoma, LY10 in Burkitt lymphoma.
- Reporting of results from EORTC 20981 at ASH showing a survival benefit in recurrent follicular lymphoma with maintenance Rituximab.
- Reporting the results of LY10 at ASCO
- Full publication of the results of LY09 and the 60+ trials.
- Funding of TRICC applications for molecular studies in diffuse large B-cell lymphoma and Hodgkin lymphoma.
- Central histopathology review of all cases entering clinical trials.
- CTAAC funding/approval for new studies in follicular lymphoma (PRIMA), Cutaneous T-cell lymphoma (GemBex), PET scanning in the R-CHOP 14 vs 21 study, RGCVP in elderly patients with diffuse large B-cell lymphoma, and Primary Mediastinal Lymphoma.
- LRF funding for the R-CODOX-M study in high risk diffuse large B-cell lymphoma
- Implementation of the EU clinical trials directive in the lymphoma trials office.
- Sub-groups are working well, with a steady stream of new proposals being brought forward. During 2006 10 new trials are projected to open, with a further 5 already planned for 2007.
- Good international collaboration, with many studies running in several countries.
- Overall level of accrual to trials maintained at 7.4% of incidence cases.

The Group also experienced a number of difficulties during the year:

- Continued problems with regulatory approvals, in particular sponsorship through University College London, especially for international studies, resulting in the significant delay of at least 4 key studies (PRIMA, Watch and Wait, CORAL, BEACOPP).
- Delayed re-opening of the mantle cell lymphoma study caused by misinformation from MHRA.
- Difficulties in determining the funding route for PET studies, whether from DoH subvention, CTAAC or by local commissioning arrangements. The absence of central DoH R&D guidance on this has been a major impediment to starting the trial.
- Long trial set-up times due to the need for multiple new agreements, specifically site agreements, drug supply agreements.
- Recruitment across NCRN continues to be heterogeneous, with some major centres opting out of trials. There is scope for much better recruitment in some areas.

Despite these difficulties, the Group is working well, with active trials in recruitment and sub-groups which continue to generate new trials ideas at a steady pace. The completed trials are being reported at major international meetings and in high impact Journals. Survival rates in recurrent follicular lymphoma will rise directly as a

result of studies conducted by this group if the results of the EORTC 20981 study are matched in routine practice by the use of maintenance therapy with Rituximab. The LY09 study will reduce the burden of toxicity from treatment for advanced Hodgkin's disease if the finding that ABVD is as effective as more complex multi-drug regimens leads to its adoption as standard therapy in the UK. The molecular definition of Burkitt lymphoma has been effectively revised as a result of the LY10 study, and this illustrates the strength of the central pathology review, including morphology, sophisticated immunophenotyping and molecular analyses, which is in place for the lymphoma trials portfolio.

The Group had a Progress Review by the NCRN on the 8th March 2005. The key strengths of the Group and issues which the Group needed to address, as identified by the Review Panel, are attached as an appendix.

Membership

An advertisement for new members in early 2006 produced a fair response and three new members joined the group as a result.

Annual Meeting

The Group serves as an effective focal point for the clinical community treating lymphoma in the UK, and the annual meeting is well attended by clinicians who enter patients on studies but who do not wish to take part in the study group or its sub-groups, as well as by the investigators.

Portfolio and accrual

International collaboration is a priority. Nine of the 22 trials currently open or in set-up are international studies, most conducted in collaboration with other groups such as EORTC, the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) or the International Lymphoma Study Group (IELSG). We are in discussion with the German Hodgkin lymphoma study group regarding the design of the next trial in advanced Hodgkin's disease.

The Group has excellent support from the patient representatives who are active and vocal. There are close relations with the Lymphoma Association, the principal patient support organisation in the UK, and this is something we will seek to build upon. We plan to discuss with NCRN how best to harness the interest and enthusiasm of the Lymphoma Association, specifically to raise awareness of trials among those newly diagnosed with lymphoma and to increase their input to the trials design process where possible.

The severe slowing of the regulatory processes seen during 2004/5 has to some extent been reversed and the trials which had been delayed are starting now, but set-up times are still very long. Only two trials were opened during 2004/5. This is in large part due to the difficulties of setting up sponsorship arrangements with University College London, which hosts the Lymphoma Trials Office and is thus responsible for sponsorship for most of the portfolio. The CORAL study has been held up for over two years by the sponsorship questions at UCL. The UK contribution to the important PRIMA study will be very limited because of these difficulties, and we will struggle to contribute 5% of the total patients before closure. This is not simply a problem for this trial, but serves to diminish the standing of the UK as a place where this work can be done, and undermines our ability to influence future collaborative trials.

As trials are designed for more specific sub-types of lymphoma it becomes more and more important to conduct them on an International basis. At present the UK is failing to match the speed of movement of our European collaborators and is rapidly

losing credibility as a result. The two critical problems here are the delays in sponsorship agreements at UCL and the delays caused by R&D departments in NHS Trusts. It is essential that the Department of Health develops a more effective means of organising R&D approvals in Trusts, something which to date has suffered from a lack of central guidance. The result is that every Trust has its own process, requiring different paperwork and individual scrutiny of trial agreements. This is enormously wasteful both for the NHS and for the research community, and requires correction as a matter of urgency.

Another area where the lack of strategic thinking in the Department of Health is manifest is in the investigation of the role of PET scanning in lymphoma. We have a trial approved by CTAAC to study the impact of PET scanning in diffuse large B-cell lymphoma, something for which there is a closing window of opportunity before these tests are implemented on an ad hoc basis with little reliable evidence. To date it has not been possible to identify how the costs of the scans will be met, since the commissioning of PET scans has not yet been rolled out nationally and we have been given negative replies by the administrators of the subvention fund. Despite direct interactions with the National Cancer Director, the Portfolio Manager for Department of Health Cancer Research and the finance manager for NHS R&D stretching over more than a year there is still no resolution as to how the costs of PET scans in this trial can be supported by the NHS.

Accrual was 7.4% of incidence cases.

Strategic plans for the next year:

The planned expansion of the portfolio will continue, and the group will seek to increase its activity particularly in T-cell lymphoma where to date there have been few prospective studies. A new study in advanced Hodgkin's disease will be planned, if possible with international collaboration.

An area of emphasis over the next year will be the development of better resources for correlative science and tumour banking from patients included in the trials. Tissue microarrays are already being planned, and the feasibility of banking of fresh frozen material in larger centres will be explored.

There is a significant number of members scheduled to rotate off the main group during the coming year, who have already been members for 5 years since the establishment of the group. Three of the five sub-group Chairs will be replaced in anticipation of this. Several of these are among the most active investigators, and we will seek approval to retain 2 or 3 of those currently involved in running trials on the main group in order to avoid a sudden loss of expertise.

Lymphoma Cancer Group Portfolio

* denotes an international study

Acronym	Title	PI(s)	Status
AILD	A phase II study of Fludarabine and cyclophosphamide with thalidomide maintenance in angioimmunoblastic T-cell lymphoma.	Dr Claudius Rudin	In set-up
BNLI 60+	A phase III trial comparing CHOP to PMItCEBO with or without G-CSF in patients aged 60 plus with aggressive non-Hodgkin's lymphoma.	Prof David Cunningham	Closed (1)

BNLI MCD vs FMD BNLI RCT	MCD vs FMD in follicular NHL	Dr Andy Haynes	Closed For submission to ASH
BNLI Stanford V	Protocol for a randomised phase III study of the Stanford V regimen, compared with ABVD for the treatment of advanced Hodgkin's disease	Prof Peter Hoskin	Open N=345
CHOP-Alemtuzumab	A phase II study of combination chemotherapy with alemtuzumab in peripheral T-cell lymphoma	Dr Rod Johnson	In set-up
CORAL *	Randomised study of ICE + Rituximab (R-ICE) versus DHAP + Rituximab (R-DHAP) in previously treated patients with CD20 positive diffuse large B-cell Non-Hodgkins lymphoma, eligible for high dose chemotherapy followed by randomised maintenance treatment with Rituximab	Prof David Linch	in Set-up
EATL study	A phase II study of intensified treatment for enteropathy-associated T-cell lymphoma	Dr Ann Lennard	In set-up
EBMT-LYM1 *	Randomised Study of Rituximab (MabThera) in Patients with Relapsed or Resistant Follicular Lymphoma Prior to High Dose Therapy as in Vivo Purging and to Maintain Remission Following High Dose Therapy	Prof AH Goldstone Dr Ruth Pettengell	Closed 2006
EORTC 20981 *	Chimeric anti-CD20 monoclonal antibody (Mabthera*) in remission induction and maintenance treatment of relapsed follicular non-Hodgkin's lymphoma : a phase III randomised clinical trial - Intergroup Collaborative Study (EORTC 20981) Including Amendment 4 (28.6.2000)	Prof Anton Hagenbeek Dr Robert Marcus	Closed (2)
EORTC PUVA/Targetin*	A randomised, open-label phase III trial to evaluate the efficacy and safety of Bexarotene (Targetin™) capsules combined with PUVA, compared to PUVA treatment alone in patients with mycosis fungoides	Dr Sean Whittaker	Open
Escalated BEACOPP (EORTC 20012) BEACOPP *	(4 cycles escalated + 4 cycles baseline) versus ABVD (8 cycles) in stage III & IV Hodgkin's Lymphoma – EORTC 20012	Prof Barry Hancock	Suspended
FORT	A phase III randomised controlled trial of low dose palliative radiotherapy for follicular lymphoma	Prof Peter Hoskin	Open N=6
GemBex	A Phase II study of Gemcitabine and Bexarotene (GemBex) in the treatment of cutaneous T-cell	Prof Tim Illidge	Open

	lymphoma		
IELSG10 *	A phase II study of CHOP, Rituximab, intrathecal methotrexate followed by radiotherapy in patients with primary testicular Non-Hodgkin's Lymphoma	Dr Dominic Culligan	In set-up
IELSG19/MALT *	Trial Multicentre randomised trial of Chlorambucil versus Chlorambucil plus Rituximab in extranodal marginal zone B-cell Lymphoma of Mucosa associated lymphoid tissue (MALT Lymphoma)	Prof Peter Johnson	Suspended
Intestinal t-cell trial	A phase II evaluation of high dose chemotherapy and autologous bone marrow transplantation for intestinal T cell lymphomas.	Dr Anne Lennard	in Set-up
LY T BNLI/LRF	Phase II Open Label Study of Thalidomide in Patients with Relapsed or Refractory Diffuse Large B-Cell Non-Hodgkins Lymphoma. MREC /02/2/4	Dr Chris Hatton	Closed 2006
LY02	A Randomised Trial to Evaluate Early High Dose Therapy and Autologous Bone Marrow Transplantation as Part of Planned Initial Therapy for Poor Risk Intermediate/High Grade Non-Hodgkin's Lymphoma	Prof David Linch	Closed 2003
LY07	A Multicentre Randomised Trial of Short Neo-Adjuvant Chemotherapy (VAPEC-B) plus Involved Field Radiotherapy (MIT) versus Mantle Radiotherapy	Prof John Radford	Closed (3)
LY09 *	A Randomised Trial of Therapy in Advanced Hodgkin's Disease	Prof Peter Johnson	Closed (4)
LY10 *	A clinicopathological study in Burkitt's and Burkitt-like non-Hodgkin's Lymphoma.	Dr Andrew Jack Dr Ben Mead	Closed (5)
NCRI Mantle Cell Lymphoma Trial	Phase II randomised study of fludarabine/ cyclophosphamide combinaton with or without Rituximab in patients with untreated mantle cell lymphoma	Dr Simon Rule	Closed. Phase III study in set-up.
NHL Good Risk	Phase III trial comparing CHOP to PMitCEBO in good risk stage II-IV patients with histologically aggressive non-Hodgkin's lymphoma		Closed 2004
PET after 2 cycles in NHL	after 2 cycles in NHL Blinded evaluation of prognostic value of FDG-PET after 2 cycles of chemotherapy in Diffuse Large B-cell Non-Hodgkin's Lymphom	Dr George Mikhaeel	in Set-up
PET Trial in Hodgkin's Disease	A randomised Phase III trial to determine the role of FDG-PET Imaging in Clinical Stages IA/IIA Hodgkin's Disease.	Prof John Radford	Open N=166

PK 2005 02	Pharmacogenetics and metabolism of cyclophosphamide in paediatric non-Hodgkin's Lymphoma.	Dr Gareth Veal	Open
PRIMA *	A multicentre phase III open-label randomized study in patients with advanced follicular lymphoma evaluating the benefit of maintenance therapy with rituximab after induction of response with chemotherapy plus rituximab in comparison with no maintenance therapy	Prof Andrew Lister Prof Gilles Salles	Open
R-CHOP 14 vs 21	A phase III multicentre randomised clinical trial comparing rituximab with CHOP given every 14 days and rituximab with CHOP given every 21 days for the treatment of patients with newly diagnosed diffuse large B cell non-Hodgkin's lymphoma	Prof David Cunningham	Open N=297
RGCVP	A phase II multicentre clinical trial of Rituximab, CVP and Gemcitabine for the treatment of patients with newly diagnosed diffuse large B-cell lymphoma considered unsuitable for R-CHOP chemotherapy	Dr Paul Fields	in Set-up
R-CODOX-M/IVAC	A 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 (age-adjusted international prognostic index high or high-intermediate risk)	Dr Andrew McMillan	in Set-up
SHIELD Study *	A phase II study, VEPEMB, in patients with Hodgkin's lymphoma aged > 60 years. (VEPEMB : Vinblastine, Endoxana (Cyclophosphamide), Procarbazine, Prednisolone, Etoposide, Mitozantrone, Bleomycin)	Prof Steve Proctor	Open N=32
SP1984	Cytotoxic T Cell therapy for EBV associated tumours	Prof Dorothy Crawford	Closed 2005
Waldenstrom's study *	Randomised trial of Chlorambucil vs Fludarabine as initial therapy of Waldenström's macroglobulinaemia & splenic lymphoma with villous lymphocytes	Dr Steve A Johnson	Open
Watch and Wait *	An intergroup randomised trial of rituximab vs a watch and wait strategy in patients with advanced stage, asymptomatic non-bulky follicular lymphoma (grades 1, 2 and 3)	Dr Kirit Ardeshtna	Open N=100

Publications / Presentations of trials that have closed:

1. Burton C, Linch D, Hoskin P, Milligan D, Dyer MJ, Hancock B, Mouncey P, Smith P, Qian W, MacLennan K, Jack A, Webb A, Cunningham D.

A phase III trial comparing CHOP to PMitCEBO with or without G-CSF in patients aged 60 plus with aggressive non-Hodgkin's lymphoma.

Br J Cancer. 2006 Mar 27;94(6):806-13.

2. Marinus H.J. Van Oers, Martine Van Glabbeke, Ivana Teodorovic, Cynthia Rozewicz, Richard Klasa, Robert E. Marcus, Max Wolf, Eva Kimby, Anton Hagenbeek.

Chimeric Anti-CD20 Monoclonal Antibody (Rituximab;Mabthera) in Remission Induction and Maintenance Treatment of Relapsed /Resistant Follicular Non-Hodgkin's Lymphoma: Final Analysis of a Phase III Randomized Intergroup Clinical Trial.

Blood, Volume 106, issue 11, November 16, 2005.

3. Radford JA, Cowan RA, Ryder WDJ, Johnson RJ, Banerjee SS, Deakin DP, Wilkinson PM, James RD, Crowther D.

Four weeks of VAPEC-B chemotherapy before involved field radiotherapy minimises the relapse rate in early stage, low risk Hodgkin's disease and is not associated with an excess of second of second malignancy.

Ann Oncol. 2002, 13, 25a.

4. P.W.M. Johnson, J.A. Radford , M.H. Cullen, M.R. Sydes, J. Walewski, A.S. Jack, K.A. MacLennan, S.P. Stenning, S. Clawson, P. Smith, D. Ryder, B.W. Hancock.

Comparison of ABVD and Alternating or Hybrid multi-drug regimens for the treatment of advanced Hodgkin's Lymphoma: Results of the UK Lymphoma Group LY09 Trial.

Journal of Clinical Oncology, 2005. 23:9208-9218.

5. J. Walewski, G. Mead, A. Jack, S. Barrans, J. Radford, S. Clawson, S. P. Stenning, W. Qian. Defining Burkitt's lymphoma (BL) with cytogenetics: LY10, a prospective clinicopathological study of dose-reduced (dr) CODOX-M/IVAC in patients with 100% Ki-67 staining B-cell non-Hodgkin's lymphoma (NHL).

2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S: 7557

Professor Peter Johnson, Chair

Appendix 1: Key strengths and issues from the Progress Review, March 2005

Strengths:

- The Group had made tremendous strides within the last 5-10 years and have developed a broad, ambitious, state-of-the-art, but not cutting-edge portfolio, which addresses relevant questions
- Success with funding submissions
- The Group enjoys a good international reputation

The Lymphoma Group needs to consider:

- Appointing an expert in transplantation to the main Group
- Whether or not to have a separate phase II Subgroup
- Clarifying the future strategy of the Group
- Meeting with the Director of NCRT to consider how best to support the collection and storage of tissue
- Extending working with pharmaceutical companies
- How a portfolio coordinator can best support the Group and its Subgroups