



CLL Trials Newsletter

ADMIRE, ARCTIC, CLL207, COSMIC, CLL201, CHOP-OR, RIAItO, CLL210 and RESPeCT

May 2011

Trials open to recruitment

ADMIRE

CI: Professor Peter Hillmen

Does the Addition of Mitoxantrone Improve Response to FCR chemotherapy in patients with CLL: A randomised phase IIB trial of fludarabine, cyclophosphamide and rituximab (FCR) with or without mitoxantrone (M) in previously untreated CLL

Trial Design

- Phase II, multi-centre, randomised, controlled open-label, parallel group
- Principal objective is to compare the complete response (CR) rates as defined by IWCLL criteria in each treatment group
- 218 patient over 30 months (including the 12 month trial extension)
- Funded by Roche Products Limited – **rituximab provided free of charge**
- Sponsor: Leeds Teaching Hospitals NHS Trust

Current Status

- Opened to recruitment in June 2009
- **30** centres open to recruitment. 1 centre in set-up
- **126** patients recruited
- Congratulations and many thanks to the top 2 recruiting centres:
 - **East Kent Hospitals NHS Trust** (12 pts)
 - **University Hospital of Wales, Cardiff** (10 pts)

ARCTIC

CI: Professor Peter Hillmen

Attenuated dose Rituximab with ChemoTherapy In CLL: A randomised phase IIB trial in previously untreated patients with CLL to compare fludarabine, cyclophosphamide and rituximab (FCR) with FC, mitoxantrone (M) and low dose rituximab (FCM-miniR)

Trial Design

- Phase II, multi-centre, randomised, controlled open-label, parallel group
- Principal objective is to compare the complete response (CR) rates as defined by IWCLL criteria in each treatment group
- 206 patient over 18 months (currently applying for an 18 month trial extension)
- Funded by the Health Technology Assessment Programme (HTA)
- Sponsor: Leeds Teaching Hospitals NHS Trust

Current Status

- Opened to recruitment in November 2009
- **23** centres open to recruitment . 3 centres in set-up
- **83** patients recruited
- Congratulations and many thanks to the top 2 recruiting centres:
 - **Oxford Cancer and Haematology Centre** (12 pts)
 - **Birmingham Heartlands Hospital** (12 pts)

Recruitment Message ADMIRE and ARCTIC

Recruitment in both trials is currently under target. Please continue to screen **all** potential patients to help reach the recruitment targets. Please remember to complete monthly non-randomisation logs and return them to the CTRU.

Key Eligibility Criteria for ADMIRE and ARCTIC

- B-CLL with a characteristic immunophenotype
- Binet's Stage B, C or Progressive Stage A
- Requiring therapy by the IWCLL criteria
- No prior therapy for CLL
- WHO performance status of 0,1 or 2

Don't Forget

Escalation of Significant Protocol Deviations

Please ensure that any significant protocol or safety breaches e.g. over or under-dosing errors are notified to the CTRU on both the relevant CRF and as soon as the issue is identified by email or telephone to the Trial Coordinator.

Timing of Samples in Relation to Consent

Trial consent and BioBank consent forms must be signed by the patient before any samples are obtained and sent to the laboratories. If you have any queries about the timing of samples then please contact the Trial Coordinator for clarification.

Pharmacovigilance Reporting Procedures

All SAE's and SUSAR's must be recorded on the Serious Adverse Events form and Suspected Unexpected Serious Adverse Reaction form and faxed to CTRU within **24** hours.

CRF Completion

Please ensure CRFs are as complete as possible and that they are returned to the CTRU within 2 weeks. This will reduce the amount of data queries and ultimately ensure that the results of trial and future management of patients with CLL are based on robust and reliable data.

CT Scan Reports

Remember to return a copy with the CRFs at baseline and 3 months post treatment.

Protocol Versioning

Protocol V4.0 will not be made live due to an error in section 10.3. Please ensure V3.0 of the protocol and associated documents are used until approval is gained for V5.0.

Trials open to recruitment

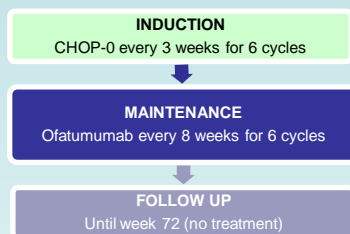
CHOP-OR

CI: Dr Anna Schuh

Single arm NCRI feasibility study of CHOP in combination with ofatumumab, in induction and maintenance for patients with newly diagnosed Richter's Syndrome

Trial Design

- Phase II, multi-centre, open-label, non-randomised feasibility study
- For patients with Richter's Syndrome
- Principal objective is the overall response rate to CHOP-O according to the Revised Response Criteria for Malignant Lymphoma
- 35 patients over 2 years
- Funded by GlaxoSmithKline – **ofatumumab provided free of charge**
- Sponsor: University of Oxford



Current Status

- Opened to recruitment 28th April 2011. No patients entered yet
- Being set up in 10 centres across the UK
- 3 initiation visits held and 2 further initiation visits scheduled

Key Eligibility Criteria

- Patients with B-CLL and newly diagnosed not previously treated and biopsy proven DLBCL Richter's transformation.
- ECOG Performance Status of 0, 1, 2 or 3.

RESPECT

CI: Adrian Bloor

Revlimid Early Stage Poor prognosis CLL Trial: A single arm phase II study to investigate the use of Lenalidomide in the treatment of patients with early stage CLL associated with poor prognostic factors

Trial Design

- Single arm, phase II trial, optimal 2-stage study design.
- Primary endpoint is MRD negative complete remission
- 40 patients over 2 years
- Funded by the Leukaemia Research Fund and Celgene – **lenalidomide provided free of charge.**
- Sponsor: The Christie NHS Foundation Trust

Current Status

- Opened to recruitment in May 2010
- 8 centres open to recruitment and 2 centres n set-up
- 8 patients screened and 1 patient enrolled

Key Eligibility Criteria

Previously untreated poor risk Binet stage A CLL. Defined by presence of ≥ 2 adverse risk factors:

- Unmutated IgV_H ($\geq 98\%$ germline homology)
- CD38 expression ($> 7\%$)
- Del 11q22 ($>20\%$)
- Del 17p13 ($>10\%$)

Trials in set-up

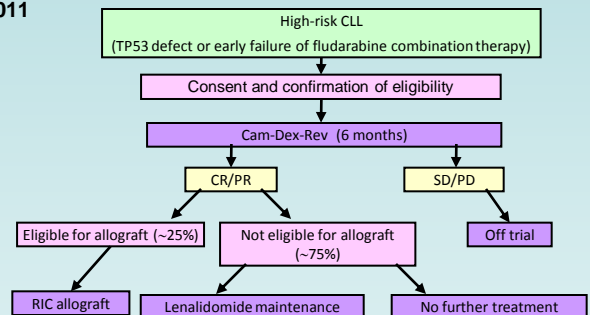
CLL210

CI: Professor Andrew Pettitt

A randomised phase II trial of alemtuzumab, dexamethasone and lenalidomide induction followed by lenalidomide maintenance or no further treatment for high risk CLL

Trial Design and Status

- Phase II, multi-centre, randomised
- Primary endpoints are the complete response rates after 6 months of induction therapy and the progression-free rate after 2 years of maintenance therapy
- 85 patients over 24 months
- Funded by Celgene – **lenalidomide provided free of charge**
- CTAAC endorsement received
- MHRA and ethics approval gained; expected to open to recruitment in **June 2011**



Key Eligibility Criteria

- CLL/SLL requiring therapy by IWCLL 2008 criteria
- TP53 deletion/mutation affecting at least 20% of CLL cells **or** resistant to fludarabine-containing combination therapy **or** relapse within 12 months of responding to fludarabine containing combination therapy
- No prior treatment with alemtuzumab, lenalidomide or high-dose glucocorticoids
- No more than 3 previous treatment episodes for CLL
- WHO performance status 0-2

COSMIC

CI: Professor Peter Hillmen

Combination FC plus Ofatumumab at Standard or Mega dose In CLL: A randomised, phase II trial in patients with relapsed CLL who are not refractory to fludarabine-based chemotherapy

Trial Design

- Phase II, multi-centre, randomised, controlled open-label, parallel group
- Principal objective is to assess the rate of Complete Response (CR or CR(i) by IWCLL criteria) following therapy with Standard Of-FC and Mega Of-FC
- 78 patients from 18 UK centres.
- Funded by GlaxoSmithKline - **ofatumumab will be supplied free of charge by GlaxoSmithKline**
- Sponsor: Leeds Teaching Hospitals NHS Trust

Current Status

- Endorsement by CTAAC/CRUK received
- Protocol almost complete and preparations for regulatory /ethical submissions underway
- Recruitment expected to commence in September 2011

Key Eligibility Criteria

- Previous treatment with at least one chemotherapeutic regime
- Life expectancy of at least 12 weeks
- Considered fit enough to receive fludarabine-based combinations
- No prior Ofatumumab

UK CLL Trials BioBank

CI: Professor Andrew Pettitt

Progress Update

To date we have stored over 7,200 vials of plasma, serum, saliva and mononuclear cells from blood and bone marrow. The trials that are closed to recruitment that we have material from are:

- CLL201
- CLL202
- CLL206
- CLL208

Those trials that are still open to recruitment that we collect samples from are:

- ARCTIC
- ADMIRE
- RESPeCT
- CHOP-OR

We will also be collecting samples from MABLE when open.

We have so far released samples for 2 projects; Dr Schuh in Oxford and Dr Oscier/ Cragg/ Strefford in Bournemouth/ Southampton. There are also 3 other requests for samples which have been submitted for review.

BioBank Issues

Consent

Please ensure that your patients are being consented to the correct version of the patient information sheet and consent form and that a copy of the consent form is sent with the baseline kit. The correct versions that should be used are:

- Patient Information Sheet v3.1 (April 2009)
- Consent Form v3.0 (December 2009)

Sample Faxes

Please remember to send the Sample Notification Fax to the UK CLL Trials Biobank when you are sending samples to the Biobank. This ensures that the Biobank know when samples should be arriving and it allows both the Biobank and CTRU to monitor sample compliance.

Sending Samples

Please ensure that samples are not sent to the Biobank on a Friday, or the day before a bank holiday. We need to process samples within 24 hours of being taken.

Questionnaire

To improve the procedures for users we sent a questionnaire out to all research nurses. We would be grateful if you could complete the questionnaire and return to the Biobank (only 16% returned).

Trials in set-up

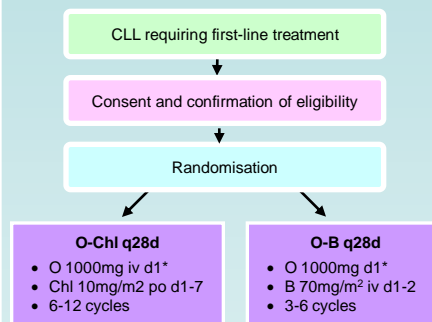
RIAltO

CI: Professor Andrew Pettitt

A Randomised Investigation of Alternative Ofatumumab-based regimens for less fit patients with CLL

Trial Design

- Phase III, multi-centre, randomised, open-label
- Principal trial objective is to compare O-Chl and O-B in patients considered not fit enough for R-FC with respect to progression free survival.
- 670 patients over 48 months
- Funded jointly by GlaxoSmithKline and Napp – **ofatumumab and bendamustine provided free of charge**



* The dose of ofatumumab in cycle 1 is 300mg on day 1 and 1000mg on day 8

Current Status

- Endorsement by CTAAC confirmed
- Protocol almost complete and preparations for regulatory submissions underway

Key Eligibility Criteria

- CLL requiring first-line treatment by 2008 IWCLL criteria
- Full dose R-FC inappropriate
- Able to tolerate chlorambucil at the dose used in the LRF CLL4 trial.

Trials in follow-up

CLL207

CI: Professor Peter Hillmen

Eradication of minimal residual disease (MRD) in patients with CLL with alemtuzumab: A phase II study

Trial Design

- Phase II, multi-centre, open label, single arm study
- Principal objective is to assess the efficacy and safety of subcutaneous alemtuzumab
- Funded by Bayer Schering Pharma / Genzyme Therapeutics – **alemtuzumab provided free of charge**
- Sponsor: Leeds Teaching Hospitals NHS Trust

Current Status

- Closed to recruitment January 2010
- 61 patients registered from 10 UK centres
- 47 patients treated with alemtuzumab
- 11 patients following 'Monitoring Investigation'
- 3 patients withdrew / ineligible

Follow Up

Data continues to be collected on an annual basis in order to follow patients for disease progression and overall survival. Please ensure you remember to return this valuable data ASAP.

Re-treatment

Please remember to notify CTRU ASAP of any patients receiving **re-treatment** with alemtuzumab.

Presentations and Publications

The initial results of the primary endpoint analysis were presented at the American Society of Haematology Meeting in December 2010, the British Society for Haematology Meeting in April 2011 and will be presented at the European Haematology Association Congress meeting in June 2011. A publication based on the results of the primary endpoint analysis will be produced during Summer 2011.

Trials in follow-up

CLL 201 FCM/FCM-R

CI: Professor Peter Hillmen

A randomised phase II trial of fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab in previously treated CLL

Please ensure that R&D approval for V4.0 of the protocol is in place and that data is returned ASAP.

Long Term Follow Up Data

We have extended the follow up period in order to collect overall survival and progression free survival data.

Publications

Full trial results are now available in the British Journal of Haematology: Hillmen P et al. A randomised phase II trial of fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab in previously treated CLL. *Br J Haematol.* 2011;152(5):570-578

Development of the CLL Trials Portfolio (1998 – 2011)

Patients fit for FCR

1998-2004

LRF CLL4 in untreated CLL

2005-2007

NCRI CLL201: FCM-R in relapsed CLL

2009+

NCRI ADMIRE Trial
FCR vs FCM-R in front line CLL

2010+

NCRI ARCTIC Trial
FCR vs FCM-miniR in front line CLL

Patients unfit for FCR

2007-2009

CLL208: Chlorambucil +R in untreated CLL

2009-2011

NCRI CLL7: Chlorambucil +/- ofatumumab

2011+

NCRI CLL9 (RIAltO): Chlorambucil +/- ofatumumab

Patients refractory to fludarabine/ p53 deleted

2003-2005

CLL202: Cam Flud in refractory CLL

2007-2009

NCRI CLL206: CamPred in 17p-CLL

2011+

NCRI CLL210: CamDexRev in refractory and 17p-CLL

Trial Contacts

ADMIRE and ARCTIC

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COSMIC

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CLL207

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CLL201

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RIAltO and CLL210

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CHOP-OR

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RESPECT

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UK CLL Trials BioBank

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To add Roche



The Leeds Teaching Hospitals NHS Trust

The Christie NHS Foundation Trust



The Royal Liverpool and Broadgreen University Hospitals NHS Trust