

HAEMATOLOGY ONCOLOGY RESEARCH TEAM

WELCOME!

MARCH 11 ISSUE 7

Welcome to the seventh edition of the Haematology Oncology research team newsletter! In this edition we will continue to update you on the latest haematology and lymphoma trial news.

FOCUS ON: NEW AGENTS IN NHL AND MYELOMA

STUDIES...OPEN

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HODGKIN LYMPHOMA

- **PAIReD:** Reduced intensity transplantation using the BEAM-Alemtuzumab protocol for primary refractory/relapsed refractory Hodgkin's disease.
- **ReACH:** Reduced intensity sibling allogeneic transplantation for relapsed, chemosensitive, PET positive Hodgkin lymphoma.
- **RATHL:** PET-adapted dose-escalation of therapy in advanced stage HL.
- **AETHERA:** Randomisation of SGN-35 versus best supportive care post autograft in relapsed Hodgkin Lymphoma

MANTLE CELL LYMPHOMA

- **SPRINT:** Randomised phase 3 comparing Lenalidomide to 'dealers choice' chemotherapy.
- **CD19:** As with follicular NHL.
- **MinoAllo:** Low intensity allo transplant in remission 1 of mantle cell lymphoma

DLBCL

- **14 Vs 21 PET sub study:** prognostic value of early PET after 2 cycles of R-CHOP.
- **ORRCHARD:** Rituximab-DHAP Vs. Ofatumumab-DHAP in relapsed disease.
- **CD19:** Phase I study of adoptive transfer of autologous T Cells with pre-conditioning chemotherapy and IV IL2 in CD19 positive malignancy.

FOLLICULAR LYMPHOMA

- **FORT:** Randomisation of high Vs. low dose radiotherapy for any radiotherapy indication in FL.
- **CD19:** Phase I study of adoptive transfer of autologous T Cells with pre-conditioning chemotherapy and IV IL2 in CD19 positive malignancy.
- **PACIFICO:** Randomisation of R-CVP versus R-FC first line in patients over the age of 60.
- **GAUDI Extension:** GA101+CHOP in untreated FL

T-CELL LYMPHOMA

- **GemBex:** Gemcitabine and Bexarotene in cutaneous T-cell lymphoma.
- **T-cell project:** Database registration for all T-cell NHL.
- **CHOP-Campath:** Phase 2 dose escalation study to find the MTD of Campath in conjunction with CHOP.
- **Belief:** Belinostat in relapsed/refractory disease
- **J&J:** phase 1 HDACi in any relapsed NHL, especially focused on CTCL



STUDIES IN PLANNING

WEBSITE

For more information on any of our trials in setup or currently recruiting please [click here](#) to visit our website

- **MAC:** Transplant of umbilical cord blood in haematological diseases using myeloablative conditioning.
- **RIC:** Transplant of umbilical cord blood in haematological diseases using reduced intensity conditioning.
- **ReModel B:** R-CHOP plus bortezomib in newly diagnosed DLBCL
- **DLBCL Len:** Lenalidomide in relapsed DLBCL ineligible for transplant
- **SGN-35/CHOP:** combining this novel ADC with CHOP for untreated systemic ALCL

STUDIES...OPEN

AML / MDS

- **AML16:** NCRN study for older AML/high risk MDS.
- **AML17:** NCRN study for adults with AML/high risk MDS.
- **AML 18:** NCRN study for adults with AML/high risk MDS.
- **MDS Registry Study:** European registry for newly diagnosed MDS with low or INT-1 Risk.
- **MDS 005:** Lenalidomide vs placebo in transfusion-dependent anaemia due to IPSS Low or Int-1 risk MDS without deletion 5q[31].
- **Clavella:** Elacytarabine vs investigators choice in late stage AML.

ALL

- **UKALL2003:** UK national randomised trial for children and young adults with ALL.

MYELOMA

- **Myeloma X:** Determine the role of a 2nd autologous transplant after high-dose chemotherapy.
- **Myeloma XI:** Thalidomide, Lenalidomide and Bortezomib combinations with maintenance Lenalidomide.
- **KW2478-INT-001:** Phase 2/3 study of KW-2478 with Bortezomib in relapsed/refractory myeloma.
- **Panorama:** HDAC inhibitor with bortezomib and dexamethasone.
- **MUKone:** Starting dose of bendamustine in combination with thalidomide and dexamethasone.
- **Reveal:** Velcade combination chemotherapy in AL amyloidosis.
- **Castlemans:** CNTO plus best supportive care in Castleman's disease.

TRANSPLANT

- **Ricaza:** Adjunctive azacitidine in patients undergoing RIC allogeneic transplant for AML / MDS.
- **CMV impact:** Immunoprophylactic Adoptive Cellular Therapy Study.
- **PAIReD:** Reduced intensity transplant for primary refractory/relapsed refractory Hodgkin's.
- **ReACH:** Reduced intensity sibling allogeneic transplant for relapsed, chemosensitive, PET positive Hodgkin Lymphoma.
- **MinoAllo:** Low intensity allo transplant in mantle cell lymphoma.

CML

- **Spirit 2:** Comparison of imatinib and dasatinib in newly-diagnosed chronic phase CML.

CLL

- **Admire:** NCRN comparative study of FCR vs FCR plus mitoxantrone in untreated CLL.
- **Mable:** A Phase IIIb study of Rituximab with bendamustine or Chlorambucil.
- **CLL009:** Safety and efficacy of Lenalidomide dose regimens in relapsed/refractory B-Cell CLL.
- **Respect:** Use of Lenalidomide in early stage CLL with poor prognostic factors.
- **PICLLe:** Olaparib in CLL with an 11q deletion or ATM mutation and relapsed/refractory patients



**WE NEED
YOUR
HELP!**

As a tertiary referral centre we specialise in clinical trials that may not be available anywhere else in your catchment area. We ask you to review all your patients who may be eligible for our studies. We are relying on outside referrals to recruit to these studies, so please get in touch.

If you would like any more information about any of our studies, contact details for the research team are available on page 8.



FOCUS ON... NEW AGENTS IN NHL

Phase I/II studies with new agents form approximately half of the lymphoma research team's trial portfolio. Small molecules and monoclonal antibodies are the main classes under investigation.

LENALIDOMIDE

Lenalidomide (REVLIMID® Celgene Corp., NJ, USA) is a member of a class of compounds known as immunomodulators. Derived from thalidomide, which already has proven efficacy in multiple myeloma, it has multiple mechanisms of action including:

- Direct anti-tumor effect
- Inhibition of the microenvironmental support for tumor cells
- Anti-angiogenesis/osteoclastogenesis
- Immunomodulatory effects (probably via IL2-receptor and TNF α)

It is a well tolerated oral agent with an ORR of ~50% in phase I/II studies in relapsed mantle cell NHL. Studies in relapsed DLBCL will begin later this year.

RO5072759 (aka GA101)

RO5072759 (Roche, France) is a 3rd generation anti-CD20 monoclonal which has demonstrated substantially greater potency *in vitro* than rituximab. RO5072759 is a humanized and glycoengineered monoclonal antibody, derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics:

- High affinity binding to CD20 type II epitope
- Increased anti-body dependent cellular cytotoxicity (ADCC) by natural killer (NK) cells and monocytes.
- Low complement dependent cytotoxicity (CDC) activity related to the recognition of the CD20 type II epitope and the lack of CD20 localisation into lipid rafts after binding of the monoclonal antibody to CD20.
- Increased direct cell death induction related to an elbow hinge amino exchange of the Fab region and the recognition of CD20 type II epitope.

Given the significantly greater ADCC and direct cell death induction, it is possible that RO5072759 may have greater efficacy than rituximab (Mabthera®), particularly in the 80-85% of patients who are carriers of the Fc γ RIIIa low-affinity receptor polymorphism and, as a consequence of lower CDC activity, RO5072759 may produce fewer and milder infusion-related reactions.

Studies in follicular lymphoma and CLL are underway, with one in DLBCL proposed.

FOCUS ON... STUDIES WITH NEW AGENTS

Every issue we will be focusing on a specific study or disease area in order to increase recruitment. Please see our 'focus on pages' this month featuring studies which will be suitable for your mantle cell lymphoma or myeloma patients.

SPRINT

A phase 2 multicentre, randomised, open-label study of lenalidomide versus investigators choice chemotherapy in relapsed or refractory mantle cell lymphoma.

Primary Objective: To determine the tumour response of lenalidomide monotherapy or single agent of investigator's choice in patients with mantle cell lymphoma (MCL) who have relapsed after or are refractory to at least 1 and up to 3 prior chemotherapy regimens

Secondary Objectives

- To evaluate the safety, time to progression, progression-free survival and overall survival of lenalidomide monotherapy or single agent of investigator's choice

Inclusion Criteria:

- Patients with histologically proven mantle cell non-Hodgkin's lymphoma [MCL]
- Patients who have progressed or relapsed after or are refractory to at least one, and up to three prior chemotherapy regimens, and who have documented progressive disease
- Must have had at least one prior combination chemotherapy regimen with an alkylating agent, and comprising either an anthracycline and/or cytarabine and/or fludarabine (with or without rituximab)
- Prior stem cell transplant is allowed

Exclusion Criteria:

- Transformed lymphoma
- Prior use of lenalidomide
- Prior radiotherapy within 4 weeks prior to randomization
- Patients who are candidates for autologous or allogeneic transplantation at the time of inclusion into the study

GAUDI EXTENSION

An open-label, multi-centre, randomised, phase Ib study to investigate the safety and efficacy of RO5072759 given in combination with CHOP chemotherapy in patients with untreated follicular non-Hodgkin's lymphoma.

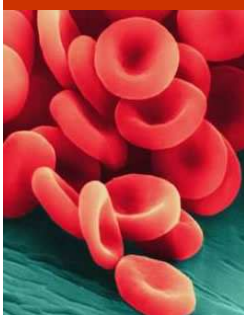
Objective: To investigate the safety of RO5072759 given in combination with CHOP, in patients with untreated CD20+ B-cell follicular lymphoma

Study Design

- Eligible patients will receive a maximum of 8 Cycles of RO5072759 + CHOP given 3 weekly
- Subjects achieving PR/CR will proceed to maintenance therapy with RO5072759

Inclusion Criteria:

- CD20+ B-cell follicular lymphoma with no prior systemic therapy
- Biopsy or re-biopsy of lymph nodes within 5 months prior to treatment is required
- At least one bi-dimensionally measurable lesion on CT
- Age >18 years.
- ECOG performance status of 0-2



FOCUS ON... MYELOMA

NEWLY DIAGNOSED:

Myeloma XI
(page 5)

1ST—3RD RELAPSE (NOT VELCADE REFRACTORY):

KW2478-INT

(page 5)

Panorama

(page 6)

ANY LINE OF RELAPSE:

MUK one

(page 7)

MYELOMA XI

Randomised comparisons in myeloma patients of all ages of thalidomide, Lenalidomide and bortezomib combinations, and maintenance lenalidomide.

Primary Objectives:

Intensive: To compare a thalidomide-containing regimen (CTD) with a lenalidomide-containing regimen (RCD), as induction treatment prior to HDT.

Non-intensive: To compare an attenuated thalidomide-containing regimen (CTDa) with an attenuated lenalidomide-containing regimen (RCDa).

Inclusion Criteria:

- Aged 18 or greater.
- Newly diagnosed as having symptomatic or non-secretory multiple myeloma.

Exclusion Criteria:

- Solitary plasmacytoma of bone or extramedullary plasmacytoma
- Previous or concurrent active malignancies, except surgically-removed basal cell carcinoma of the skin or other in situ carcinomas.
- Previous treatment for myeloma *except*: local radiotherapy to relieve bone pain or spinal cord compression; prior bisphosphonate treatment; corticosteroids within the last 3 months.
- Allergy to compounds containing boron or mannitol
- Grade 2 of greater peripheral neuropathy, or acute renal failure

KW2478-INT

An open-label, dose escalation, multicenter phase 1/2 study of KW-2478 in combination with Bortezomib in subjects with relapsed and/or refractory multiple myeloma

Primary Objective: Establish safety, tolerability and RP2D of KW-2478 in combination with bortezomib .

Inclusion Criteria:

- Myeloma confirmed by clonal bone marrow plasma cells > 10%, M-protein in serum or urine (except in non-secretory myeloma) and evidence of end-organ damage attributed to underlying plasma cell proliferative disorder
- Between 1—3 prior regimens for MM which they did not respond or from which they have relapsed
- Life expectancy of ≥ 3 months
- Must not have progressed while receiving any prior Bortezomib alone or in combination (if applicable)

Exclusion Criteria:

- Non-secretory or bi-clonal MM
- Hypersensitivity to boron or mannitol
- Prior treatment with any Hsp90 inhibitors or a previous allograft transplant



FOCUS ON... MYELOMA

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(page 5)

1ST—3RD RELAPSE (NOT VELCADE REFRACTORY):

Panorama and
KW2478-INT
(page 6)

ANY LINE OF RELAPSE:

MUK one
(page 7)

PANORAMA

A multicenter, randomised, double-blind, placebo controlled phase III study of panobinostat in combination with Bortezomib and dexamethasone in patients with relapsed multiple myeloma

Primary Objective: To compare progression-free and overall survival

Inclusion Criteria:

- Multiple myeloma confirmed by monoclonal immunoglobulin on electrophoresis, bone marrow plasma cells $\geq 10\%$ or biopsy proven plasmacytoma and related organ or tissue impairment
- 1 to 3 prior lines of therapy and requiring treatment for:
 - ◊ relapsed
 - ◊ relapsed to at least one prior line and refractory to another (by not reaching a MR or progressing under therapy)
- Either serum M-protein $\geq 1\text{g/dl}$ and/or urine M-protein $\geq 200\text{mg/24h}$

Exclusion Criteria:

- Progression under all prior lines of antimyeloma therapy
- Refractory to prior Bortezomib
- Allogeneic SCT recipient presenting with GvHD
- Intolerance to Bortezomib or dexamethasone or components of these
- Prior treatment with DAC inhibitors

MUK ONE

An open label, multi-centre, randomised, parallel group phase II selection trial to identify the optimal starting dose of Bendamustine (60 vs 100 mg/m²) when given in combination with thalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma.

Primary Objective: To determine the optimal dosing regimen when Bendamustine is combined with thalidomide and dexamethasone in relapsed/refractory myeloma.

Inclusion Criteria:

- Males and females aged ≥ 18 years, ECOG 0—3 and life expectancy of least 3 months.
- Histologically confirmed multiple myeloma with measurable disease parameters requiring therapy for relapsed or refractory disease (first relapse or later)

Exclusion Criteria:

- Non secretory MM.
- Relapsed on previous Bendamustine therapy.
- Laboratory values for platelets, ANC, serum bilirubin, ALT/AST, creatinine clearance within the ranges specified in the protocol, within 14 days before enrolment.
- Grade ≥ 2 peripheral neuropathy within 14 days before enrolment.
- Seropositive for HIV, or active hepatitis A, B or C infection.
- Concurrent or previous malignancies (< 12 months post end of treatment).
- Uncontrolled or severe cardiovascular disease within 6 months of enrolment.



**ARE YOU
GCP
TRAINED?**

If not, please see below for details on how to book on to a course at The Christie

TRIAL NEWS

ORCHARD

This important study in relapsed DLBCL is recruiting well with 6 subjects enrolled here at The Christie. As it is a Northwest Exemplar study, the focus is on the Network to keep up this excellent early start. Please discuss all relapsed/refractory DLBCL with the lymphoma research team.

TOP RECRUITERS FOR MUK ONE!

As the first site in the Myeloma UK Early Phase Clinical Trial Network to gain R&D approval for the MUK one study we have continued our success by recruiting the first 4 patients and being the current top recruiter.

TEAM NEWS



THERAPY ACCELERATION PROGRAM

Congratulations to the Leukaemia and Lymphoma team at The Christie who have been selected to be part of the Therapy Acceleration Program (TAP) with the Leukaemia and Lymphoma Society.

The aim of the TAP is to remove existing barriers to leukaemia, lymphoma and myeloma therapy and drug development and to fast track clinical trials. The Leukaemia and Lymphoma Society will provide funding to projects that have the potential to change the standard of care of patients with blood cancer.

For further information please [click here](#) to go to the Leukaemia and Lymphoma Society website.

GCP TRAINING

IS YOUR GCP TRAINING UP TO DATE?

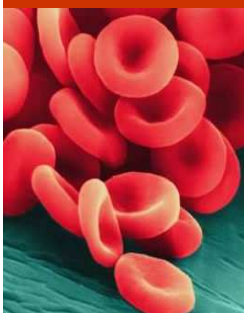
If you are working in clinical trials, it is essential that you complete GCP training every 2 years. For dates and to book on please contact Richard Firmstone in R&D on 0161 918 7572 or email Richard.Firmstone@christie.nhs.uk.

Introduction sessions (full day)

Wednesday 1st June; Friday 12th August; Thursday 3rd November

Update sessions (half day—morning or afternoon)

Thursday 11th August; Wednesday 2nd November



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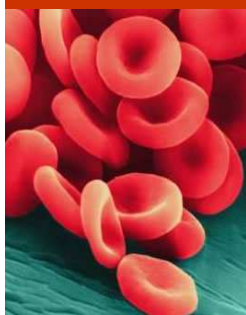
**NEXT
ISSUE**
June 10

In our next issue
we will be
focusing on...

T-cell lymphoma
& MDS

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