Improving the treatment and the lives of patients with blood cancers through clinical trial research

AUSTRALASIAN LEUKAEMIA AND LYMPHOMA GROUP

Trials Newsletter No 11

February 2016

This newsletter is published approximately every two months and provides update information on the ALLG trial program. Other ALLG activities are covered in the general newsletter published three times a year. To see the latest issue click HERE.

ALLG Trial Centre

Fax: +61(0)3 9429 8277
35 Elizabeth St
Richmond, Vic 3121

CML9—at nine years! 2007-2016

Although imatinib altered the course of CML from a fatal disease to a chronically manageable condition, outcomes are heterogeneous. The CML9 TIDEL-II study was designed to maximise outcomes in CML through the optimised use of imatinib, and the newly available second generation TKI nilotinib. Conceived following the successes of the CML6 (TIDEL-I) study, CML9 patients followed a schema of imatinib dose escalation for failure to achieve adequate trough levels, or for failure to achieve time dependent molecular targets. Patients were switched to the more potent nilotinib for persistent toxicity or failure to achieve targets. **CML9 treatment goals were thought to be ambitious at the time, but have since been adopted by the European Leukaemia Network and the National Comprehensive Cancer Network in their treatment guidelines.**

The excellent outcomes in terms of molecular response and survival were reported in Blood in 2015. A number of correlative study products are also coming to fruition. **Importantly, it also demonstrated that excellent clinical research continues to be performed through collaborative trials in Australasia.**

LPLV for CML9 is scheduled in April 2016; we hope to deliver the final analysis to the membership by the October ALLG meeting. The PIs would like to take this opportunity to once again thank all investigators, trial coordinators and the ALLG for their support in this successful undertaking.

David Yeung

Milestones

- AMLM17 COHORT B RE-OPENED 6 NOVEMBER 2015
- NHL29 FIRST PATIENT (CONCORD) 7 NOVEMBER 2015
- CML12 APPROVED BY SDMC 22 DECEMBER 2015
- CLL7 FIRST PATIENT (BORDER MEDICAL ONCOLOGY) 11 DECEMBER 2015

Expressions of Interest

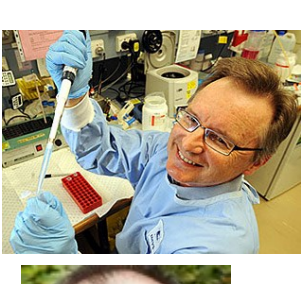
The ALLG Trial Centre is currently calling for Expressions of Interest for trial participation. Please contact us as follows:

TRIAL	PI	Contact person	Period for EOI
MM17 A multicentre single arm study of carfilzomib-thalidomide-dexamethasone (CarTD) for newly diagnosed transplant-eligible multiple myeloma (MM) patients refractory to initial bortezomib-based induction therapy	Andrew Spencer	Nola Kennedy	EOI open (approx. 15 places)
CLL07 An Australasian, phase II, multicentre, randomised, study investigating efficacy and safety for dose reduced fludarabine, cyclophosphamide and iv obinutuzumab (G-FC3) vs oral chlorambucil and iv obinutuzumab (G-Clb) in previously untreated, comorbid (CIRS score ≥6), elderly (≥65 years old) patients with CLL	Stephen Mulligan, Xavier Badoux, Con Tam	Kerina Princi	EOI closed (places remaining - contact Kerina)
AMLM21 A phase Ib/II clinical evaluation of Ponatinib in combination with 5-azacitidine in patients failing prior therapy for FLT3-ITD positive acute myeloid leukaemia	Andrew Wei	Amanda Lane	EOI closed (two places remaining—contact Amanda)
MM18 Single arm, multicentre study of Carfilzomib in combination with Thalidomide and Dexamethasone (CaTD) in patients with relapsed and/or refractory multiple myeloma (RRMM)	Hang Quach	Andrew Budniak	EOI open, deadline 5 February

Trials news

CML/Myeloproliferative Neoplasms Disease Group

CML/MPN Disease Group Chair Con Tam



Co-Chairs: Tim Hughes David Yeung

CML9
CIs: Tim Hughes, Andrew Grigg, David Yeung
CRA: Tracey Gerber

This is one of the most important trials ever undertaken by the ALLG. Conducted at 27 sites the trial accrued 210 patients between November 2007 and March 2011. The trial has already generated a number of publications. See the lead story for more information.

Thank you to sites who have submitted the amendment to HREC. All patients must be reconsented on the new consent form. Sites who have not progressed reconsenting of patients should continue to submit data up to 5 year mark for all patients.

Work on the upcoming analysis of survival, an important secondary endpoint, has begun. The plan is to submit to ASH, which requires the statistical analysis to occur in May, meaning data must be collected well before then. All outstanding patient data up to the 5 year mark must be sent in as soon as available.

The CRFs have changed over the last year. To ensure all sites are completing the essential CRFs, the ALLG will run interactive web-based training and information sessions which will include how to complete these forms with the correct information. Please also send in data clarification requests as quickly as possible.

CML12 A single arm phase II study to individualize dasatinib dosing based on trough levels and molecular response to maintain efficacy whilst minimising toxicity New!
CIs: David Yeung, Tim Hughes, Andrew Grigg

The design of the CML12 DIRECT study is based on the premise that therapeutic drug monitoring (TDM) and subsequent dose adapted dasatinib will preserve efficacy and yet minimise toxicity, especially pulmonary effusions. Based on evidence from previous studies , the CML12 study postulates that interventions should be aimed at patients over 60 years of age. The trial was approved by the SDMC on 22 December 2015 and will soon move to the ALLG Trial Centre for set-up. EOI are expected around April.

CML11 eCRF!
CIs: Tim Hughes, David Yeung, Andrew Grigg
CRA: Kerina Princi

A total of 27 patients (out of a target of 100) have been accrued to this trial. Registration of patients remains paper based, but all remaining data collection is via eCRF. Like any new system there have been a few teething problems but overall the transition has been as smooth as can be expected.

Ongoing monitoring indicates that interferon at low doses is well tolerated. **Enrolment in this study is behind schedule. We welcome expression of interest from new sites, and urge continuing engagement from currently open sites.** CML11, which is oriented to younger patients, will continue to accrue alongside CML12, which will target patients over 60.

Aggressive NHL/HL Disease Group

High grade NHL/HL Disease Group Chair: Mark Hertzberg

Co-Chair: Peter Mollee

NHL29 IRiC study. A Phase II Study of Ibrutinib, Rituximab and mini-CHOP therapy in very elderly patients with newly diagnosed DLBCL eCRF!
CI: Judith Trotman, Emma Verner
CRA: Christine Vergara

Three sites have now been activated for this trial, with three more activations scheduled for early February. All Australian sites (total 20) are planned to be activated by the end of Q2. The trial has now accrued two patients of a target of 80.

One important aspect of this trial is the aim to capture every patient ≥75 with newly diagnosed DLBCL so as to provide a true denominator of the patient population presenting at participating sites. For this reason it is essential that sites regularly update the patient screening logs. All presenting patients, whether or not consented for the study should be listed in the log.

More information is available in the NHL29 Trial Newsletter distributed in November and on the ALLG website or contact Christine.

NHL25
CI: Judith Trotman
CRA: Christine Vergara

The final analysis of the NHL25 REMARC study is now expected in July 2016 with a database lock on 30 June. Timelines for the analysis have been brought forward with the occurrence of the events, and the possibility of presenting the results of the study at the ASH meeting in December 2016.

The process of data cleaning based on a cutoff of 31 December 2015 is currently underway. **All CRFs and scans should be submitted, queries resolved and trial samples sent in soon as possible. Monitoring visits, conducted in Australia by INC, will be very intense for the next few months.** For further information contact Christine.

NHL21
CI: Mark Hertzberg
CRA: Christine Vergara

In the treatment of DLBCL, a number of studies have demonstrated that PET scanning performed after 2-4 cycles of therapy is predictive of outcome. However, a diversity of methodologies has led to wide variations in both negative and positive predictive values. Few studies have prospectively evaluated a change of treatment strategy guided by interim PET responses.

The NHL21 study investigated an early treatment intensification for patients who remain PET-positive after 4 cycles of R-CHOP-14. The trial accrued 162 patients from 20 sites in the period 2009 – 2013. **Following analysis last year, the results received an oral presentation in the Best of Asia/Pacific session at ASH in December, generating significant international interest.**

The main outcome was that PET+ patients who received dose intensification achieved significant improvement in 2 year FFS. To read the abstract presented control/click HERE.

HD4 BEACOPP (4 cycles escalated + 4 cycles baseline) versus ABVD (8 cycles) in stage III & IV Hodgkin's lymphoma
CI: Max Wolf
Contact: Janey Stone

This trial was sponsored internationally by the EORTC, with the ALLG contributing 15 patients between 2005 and 2008. **The manuscript has just been accepted for publication in JCO.** The international CI Patrice Carde wrote to all participants:

"Bravo to all present and past participants in the HD4 saga for their success. It confirms that fair work and persisting effort go through, sometimes. It is first the success of a collaborative effort between very different cooperative groups, linked into a common scientific task and through a solid and courageous data center. Let us tell you how proud we are of you and satisfied that our data will be publicized at the best possible level.

Bravo and thank you."

Patrice Carde, Nicolas Mounier, Catherine Fortpied
EORTC
on behlaf of all authors

Acute Leukaemia/MDS Disease Group

Acute Leukaemia/ MDS Disease Group Chair: Andrew Wei

NATIONAL BLOOD CANCER REGISTRY (FORMERLY AMLM18) eCRF!
CI: Andrew Wei
CRA: Amanda Jager

The AMLM18 Registry has now been renamed the National Blood Cancer Registry. All participating sites should have received the amendment to carry out this change. Thank you to RMH for progressing the amendment as lead HREC! With the amended protocol the electronic data entry for eCRF is available. Contact Amanda for the demonstration to ensure your site is ready!

AMLM16
CI: Andrew Wei
CRA: Andrew Budniak

To date 57 of a target of 99 patients have been registered in this trial. Nineteen sites have been activated with two more soon to open. With recruitment now having passed the halfway mark, the CI Andrew Wei thanked everyone for their support in the recent AMLM16 Trial Newsletter. **"With the positive results from the PKC412 (midostaurin) trial in FLT3 AML, AMLM16 study has become an even more important study, with several AML opinion leaders in the US and Europe commenting to me that this study will change practice if positive."**

Given how important the correlative samples for this study are, Andrew Budniak will send reminders at the appropriate times.

ALL6
CI: Matthew Greenwood
CRA: Amanda Jager

A confidential analysis is planned for this study mid-year to assess if a smaller accrual will be acceptable. Please send in all outstanding data and responses to queries to assist the analysis process. There will also be a protocol amendment to address outstanding issues.

AMLM20
CI: Andrew Wei
CRA: Amanda Jager

After many delays, the investigational drug for this trial, Ganetespib, has arrived in Australia. Places remaining in this arm are limited, so please fast track governance processes. Plans to open additional arms are underway.

AMLM21
CI: Andrew Wei
CRA: Amanda Lane

Eight sites have been selected for participation in the study with two additional sites available. The Alfred is the first site expected to be activated, having submitted to HREC prior to Christmas last year. Currently Amanda is building the eCRF and writing the study materials. **As this is a phase I study, sites will need to prepare appropriately to submit data in real time, to allow dose cohort decisions to be made.**

MDS4
CI: Melita Keneally
CRA: Marlyse Debrincat

This study is scheduled to close in March 2016. Please ensure that you answer any outstanding data queries and submit CRFs to the trial centre as soon as possible in preparation for upcoming final analysis.

AMLM12
CI: Ken Bradstock
CRA: Marlyse Debrincat

This study accrued 445 patients between 2003 and 2010 from 23 sites, and was the largest AML trial the ALLG has ever conducted. The Palifermin component was published in 2014. The main trial analysis took place last year and the manuscript is now in preparation with a view to publishing later this year. Please contact Marlyse with any queries.

Low grade NHL/CLL Disease Group

NHL/CLL Disease Group Chairs: Stephen Mulligan, Judith Trotman

CLL7 eCRF!
CIs: Stephen Mulligan, Xavier Badoux, Con Tam
CRA: Kerina Princi

This trial, the very first ALLG trial to commence its operations fully with the new eCRF, opened to accrual on 22 September using the Marvin digital system. Four sites have now been activated and two patients registered.

CLL5
CIs: Stephen Mulligan
CRA: Kerina Princi

While the first analysis of this trial is complete, in order to create a high impact publication, the patients need to be followed for more than 12 months. Thus an extended follow up on disease and vital status is planned, which will require protocol and PICF amendments. There will be 1-3 short CRFs for each patient.

CLL6
CIs: Stephen Mulligan
CRA: Andrew Budniak

This trial is now only 10 patients away from the 100th patient Interim Analysis. Thank you to sites for kindly prioritising the processing and submission of Response CRFs. If there are any remaining, please submit these as soon as you can.

Supportive Care Group

Supportive Care Chair: Rob Weinkove

Co-Chair: Zoe McQuilten

SC04
CI: Penny Schofield

The objectives of the REMIND phase II study (SC04) were to assess the clinical feasibility and acceptability of a telehealth-mediated nurse-led intervention aiming to increase oral therapy adherence amongst CML patients. The trial recruited 18 patients in 12 months of accrual from 4 sites, a much lower rate than anticipated. It became apparent that the major barrier was the low number of available eligible patients.

The trial closed to accrual on 19/3/2015 and a manuscript has been submitted for publication. **Outcomes of the phase I and phase II REMIND studies will provide valuable background information to support a funding application for a larger scale telehealth-mediated nurse-led intervention study .** The aim is to include a more diverse population (included CML patients) prescribed with oral chemotherapy treatment will be targeted.

BMT Disease Group

BMT Disease Group Chair: Ian Lewis

BM07
CI: Andrew Grigg
CRA: Bereha Khodr

The final statistical report will be prepared in Q1 2016 with any publications to follow later in the year. Sites will be notified when they can archive this trial. Thank you to all sites for answering data queries over the last 6 months.

Myeloma Disease Group

Multiple Myeloma Disease Group Chair: Peter Mollee

Co-Chair: Hang Quach

MM16
CI: Joy Ho
CRA: Suzy Cake

The first 10 pts have been recruited to this study. Therefore recruitment was put on hold as planned until the TMC and SDMC review the existing data prior to the recruitment of the next 26-30 pts. Sites will be notified of the time when recruitment can continue, expected to be late February. **The TMC will consider whether the dose of carfilzomib should be increased from 27mg/m2 to 56mg/m2 based on the toxicity seen in the 10 patients during the first 4 cycles.** Note that as one patient withdrew consent prior to receiving treatment, an 11th pqtient was registered before the recruitment freeze.

MM17 A multicentre single arm study of carfilzomib-thalidomide-dexamethasone (CarTD) for newly diagnosed transplant-eligible multiple myeloma (MM) patients refractory to initial bortezomib-based induction therapy New!
CI: Andrew Spencer
CRA: Nola Kennedy, Alfred Clinical Research Centre

EOI for this trial were sent out in January. The trial will be run from the Alfred Hospital. As each of the 5 staging points require specimens to be sent to the laboratory at the Alfred for the MRD test (flow cytometry), **sites expressing interest must have the capacity to send specimens overnight by Express Post.**

Fifteen sites engaged in transplanting MM are needed. If you have not participated in ALLG MM trials in the past, but are interested in this trial, please contact Nola.

MM18 Single arm, multicentre study of Carfilzomib in combination with Thalidomide and Dexamethasone (CaTD) in patients with relapsed and/or refractory multiple myeloma (RRMM) New!
CI: Hang Quach
CRA: Andrew Budniak

Approximately 2000 people are diagnosed with MM in Australia each year. Eventual relapse occurs in all patients after treatment due to the development of drug-resistance. Given that MM remains an incurable disease, new treatment options for patients with relapsed MM are needed.

Carfilzomib is a new drug that belongs to the same family as bortezomib, which is widely used for the treatment of MM, and has been shown to have fewer side effects. Carfilzomib has been shown to be effective in several trials. This phase II trial investigates the effectiveness and safety of carfilzomib in combination with thalidomide and dexamethasone for patients who have relapsed after prior treatment.

EOI for this trial were sent out in January, with up to 15 sites planned .

This newsletter was edited by Janey Stone and approved by Delaine Smith and Megan Sanders.

Questions or comments? E-mail us at info@allg.org.au