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

AUSTRALASIAN LEUKAEMIA AND LYMPHOMA GROUP

Trials Newsletter No 13

November 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.

PLEASE NOTE THE CORRECT FAX NUMBER AND ADDRESS OF THE ALLG TRIAL CENTRE

ALLG Trial Centre

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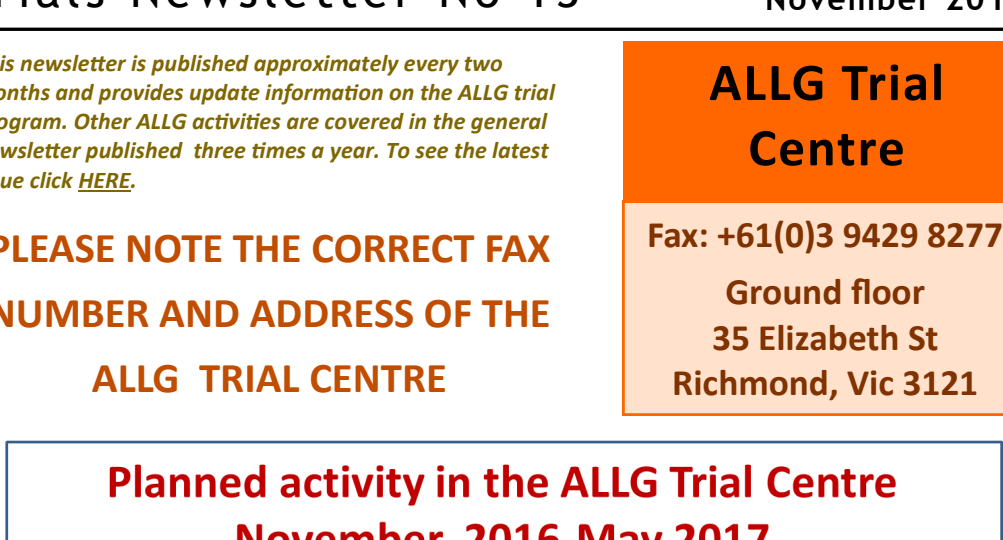

Milestones

- MM17 OPENED TO ACCRUAL 13/9/2016, FIRST PATIENT 28/9/2016 (Alfred)
- AMLM20 FIRST PATIENT 22/8/2016 (Royal Darwin)
- CML12 OPENED TO ACCRUAL 4/11/2016 (Royal Adelaide)
- MDS3 PUBLISHED JUNE 2016
- HD08 PUBLISHED SEPTEMBER 2016
- ALL3 PUBLISHED JUNE 2016
- MM13 PRESENTED JULY 2016
- MM20 FIRST HREC APPROVAL 17 NOVEMBER 2016 (Alfred)
- NHL21 ACCEPTED FOR PUBLICATION NOVEMBER 2016

Expressions of Interest

The ALLG Trial Centre is currently calling for the following new trial Expressions of Interests

TRIAL	PI	Contact	Period for EOI
HD10 Treatment optimization trial in the first-line treatment of advanced stage Hodgkin lymphoma; comparison of 6 cycles of escalated BEACOPP with 6 cycles of BrECADD	Mark Hertzberg	Kerina Princi	Open late December
MM19 A Phase 3 trial of thalidomide-dexamethasone consolidation versus thalidomide-dexamethasone-Ixazomib consolidation for transplant eligible multiple myeloma patients undergoing a single ASCT as part of front-line therapy	Andrew Spencer	Flora Yuen	Open until December 2016
MM20 A Multicentre Phase 3 Trial Comparing Elotuzumab -Cyclophosphamide-Thalidomide-Dexamethasone (E-CTD) with Cyclophosphamide-Thalidomide-Dexamethasone (CTD) for the Treatment of Relapsed and/or Refractory Multiple Myeloma (RRMM)	Andrew Spencer	Flora Yuen	Open until December 2016

More sites needed!

The following trials still have places for new sites to participate.

TRIAL	PI	CRA	Further information
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	Control/click HERE
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	Control/click HERE
AMLM20 A programme of development for older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome (AML LI-1)	Andrew Wei	Michelle Paul	Control/click HERE
CML12 A single arm phase II study to individualize dasatinib dosing based on trough levels and molecular response to maintain efficacy whilst minimising toxicity	David Yeung, Tim Hughes, Andrew Grigg	Michelle Paul	Control/click HERE
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	Robyn Hemmes	Control/click HERE

ALLG AT ASH, 3-6 DECEMBER SAN DIEGO

CONGRATULATIONS TO ALL ACCEPTED FOR PRESENTATION AT ASH:

AMLM12	ALLG	Andrew Wei for Ken Bradstock	oral
CML9	ALLG	David Yeung for Tim Hughes	oral
CLL6	ALLG	David Gottlieb	poster
MM13	international	ALLG Peter Mollee	oral
NHL25	international	ALLG Judith Trotman	oral

National Blood Cancer Registry

NATIONAL BLOOD CANCER REGISTRY (FORMERLY AMLM18)

CI: Andrew Wei

Project Coordinator: Shona Darby

Shona Darby returned to the ALLG in October 2016 in the new role of NBCR Project Coordinator. **Shona will manage all aspects of the registry with a focus on opening the project at as many ALLG sites as possible, streamlining data requests and working closely with the Registry Management committee.**

Shona previously worked at the ALLG in the role of Protocol Development Coordinator. She has broad experience in the Australian research environment including phase I to III clinical trials across various therapeutic areas such as oncology, haematology, diabetes, heart disease, dermatology, hepatitis and auto-immune disorders. Shona has experience in protocol development, ethics and trial set-up and management. She has a BSc (Parmacology & Biotechnology) and a Master of Medical Science in Drug Development. Please contact Shona with any queries regarding the Registry.

Welcome back to the ALLG Shona!

At present the Registry collects data only in AML and Uncommon Lymphoma. **Fields for ALL will open in December, and the registration eCRF is being updated to allow registration of all blood cancers. Programming is underway and we plan to go live to sites with this update by end of the year.** This will allow sites to register patients on the NBCR to submit samples from all blood cancer types to ALLG Biobank.

Trials news

Low grade NHL/CLL Disease Group

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

CLL5
CIs: Stephen Mulligan
CRA: Kerina Princi

The original intent of the CLL5 study was to follow all patients indefinitely, not only 12 months post treatment. **In October, the SDMC approved an amendment for this follow up.** The data is to be collected retrospectively from site files, (no mandated patient visits or interventions, are required). The close out (censor) date is 1/1/2016. Thank you to all sites for assistance.

NHL26
CIs: Judith Trotman
CRA: Suzanne Cake

NHL26 RePLY is a world-first study of PET-adapted therapy in relapsed FL, using R2 (rituximab plus lenalidomide) as consolidation therapy. Current accrual is 19 patients from 9 sites, and a total of 14 sites have been activated to participate in the trial.

The scientific and clinical merit of NHL26 is compelling and patients also have access to PET scans in a non-reimbursed environment.

A recent amendment allows registration of patients who have received chemotherapy, if the clinician thinks it appropriate, rather than the strict adherence to GELF criteria. This should make it easier to identify eligible patients.

We also strongly encourage cross-referral from non-participating sites, which also receives a separate cross-referral payment.

CLL6
CIs: David Gottlieb, Con Tam, Stephen Mulligan
CRA: Robyn Hemmes

A poster on the MRD analysis for this trial has been accepted at ASH - congratulations to all involved! Meanwhile the data collection continues for the interim analysis of the first 100 patients which will take place soon.

CLL7
CIs: Stephen Mulligan
CRA: Kerina Princi

This trial opened to accrual a year ago and is now available at 10 sites. To date 13 patients have been accrued from 6 sites. The trial is investigating an important gap in treatment options for older patients with co-morbidities. **We urge you to screen potentially eligible patients, and help improve the accrual rate.**

NHL16
CIs: John Seymour
CRA: Christine Vergara

The PRIMA extension study still needs your support until the end of the year!! The study ends on 31 December 2016.

As all CRFs are expected to be completed, monitored and received by Lysarc by February 2017 it is essential that outstanding items be completed as soon as possible. Most importantly, please ensure that LYSARC receive the CRF confirming consent to the extension. Eighteen countries and 795 patients are participating in the extension study.

The ALLG is proud to have been associated with this study, which has made a significant impact in the field, and has generated at least 18 publications and presentations to date.

NHLLOW5/TROG 99.03
CIs: Michael MacManus, John Seymour

In a world-first breakthrough for early stage low-grade lymphoma, the results of this trial show that patients live longer without a relapse with immuno-chemotherapy plus radiotherapy treatment rather than radiotherapy alone. The trial was a collaboration between TROG Cancer Research and the ALLG and the results were presented at American Society for Radiation Oncology (ASTRO) Annual Meeting in September.

Patients were randomised to one of two arms: radiotherapy alone or radiotherapy followed by six cycles of CVP or in the later part of the trial, Rituximab and CVP. The trial accrued 150 patients in Australia, New Zealand and Canada between 2000 and 2012. It was the first of its kind to be conducted.

Michael MacManus said, “No group anywhere in the world has ever managed to complete a trial comparing radiotherapy alone with radiotherapy and multi-agent chemotherapy or immuno-chemotherapy before.” Few trials groups can sustain a trial over the more than 15 years required to answer the question.

This trial is set to change the management of the disease worldwide. Congratulations to Michael MacManus and John Seymour and all participants for the superlative outcome.

Aggressive NHL/HL Disease Group

High grade NHL/HL Disease Group Chair: Mark Hertzberg

Co-Chair: Peter Mollee

HD10 Treatment optimization trial in the first-line treatment of advanced stage Hodgkin lymphoma; comparison of 6 cycles of escalated BEACOPP with 6 cycles of BrECADD New!
CI: Mark Hertzberg, Georgina Hodges
CRA: Kerina Princi

Standard therapy for the treatment of advanced HL involves 6 cycles of escalated BEACOPP chemotherapy. An alternative is BrECADD which omits the pneumonitis-associated Bleomycin. It also replaces vincristine with Brentuximab vedotin, chosen since it is more targeted, highly active as a single agent in relapsed HL, and has lower toxicity compared to conventional chemotherapy.

The HD10 trial aims to prove that the BrECADD is non-inferior to BEACOPP as first line treatment in advanced stage classical Hodgkin lymphoma. The lead international collaborative group is the German Hodgkin Lymphoma Study Group and the trial recently opened in Germany. The ongoing collaboration with Germany is a very important one for the ALLG lymphoma trial program.

The expected duration is 8.5 years from the beginning of recruitment to the final analysis of the study question. Approximately 100 Australian and New Zealand patients will be recruited over 15 sites. The trial has been approved by the SDMC. It is expected that site EOI and submission to HREC will start early next year.

The trial will be part of the Trials Enabling Program in collaboration with the Leukaemia Foundation.

NHL24
CI: Samar Issa
CRA: Kerina Princi

This trial closed to accrual in May and the international CIs are hoping to submit a late abstract to ASH. **Thank you to all sites who have submitted the DCFs.**

NHL29
CIs: Judith Trotman, Emma Verner
CRA: Christine Vergara

By the end of November, 20 out of a planned 21 sites will have been activated and currently there are 23 out of a target of 80 patients accrued. **Tissue is key in this trial. Any new patients ≥75 years having tissue biopsies for suspected DLBCL please ensure adequate diagnostic tissue is collected with at least 2-3 cores.**

NHL21
CI: Mark Hertzberg
CRA: Christine Vergara

Congratulations to Mark Hertzberg for the publication of this trial, which has been accepted in the journal Haematologica!

In the treatment of diffuse large B-cell lymphoma, a persistently positive PET scan typically carries a poor prognosis. This study sought to establish whether treatment intensification in such patients who are positive on interim PET scan after 4 cycles of R-CHOP -14 could improve outcomes.

The authors conclude that the results provide support for the further investigation of early selection of poor prognosis DLBCL patients, as identified by interim PET scanning, who might benefit from alternative therapeutic approaches to improve outcomes. The results also lend weight to the role of treatment intensification for those patients who are interim PET-positive Deauville score 4.

NHL25
CIs: Judith Trotman
CRA: Christine Vergara

All the data required for the final analysis have been submitted on time and we would like to thank all the sites for their efforts in meeting the challenging timelines. The first results of the study were discussed in a restricted committee due to the confidentiality required by the industry partner. An abstract has been submitted for the ASH meeting 2016. The analysis of the primary endpoint showed a statistically significant improvement in PFS for patients receiving REVLIMID®. However, the interim analysis of overall survival showed no benefit in the REVLIMID® arm.

Acute Leukaemia/MDS Disease Group

Acute Leukaemia/MDS Disease Group Chairs: Andrew Wei, Will Stevenson

ALL6
CI: Matthew Greenwood
CRA: Amanda Jager

A major amendment to the trial is currently being implemented to allow patients to consent to diagnostic samples & QOL prior to deciding whether to take part in the study. The aim is to prevent the need to re-biopsy patients and will also allow the patient more time to review the PICF and decide on participation. The revised protocol was sent out in early November and revised CRFS will be distributed in the near future.

AMLM17
CI: Andrew Wei
CRA: Christine Vergara

A new cohort consisting of Lenalidomide 25mg on D1-D21 & Romidepsin 12mg/m2 on D1, D8 and D15 has been opened and two patients from the Alfred have been enrolled. Two other sites, Queen Elizabeth and Gosford, will also re-open to recruitment. **The need now is for more sites to join in the phase I component of this trial for relapsed/refractory AML. Contact Christine if you are interested.**

AMLM20
CI: Andrew Wei
CRA: Michelle Paul

The first patient was registered in this trial on 22 August - congratulations to Royal Darwin Hospital. Four sites are now activated out of a total of 10 planned. **There is still capacity for more sites to participate in this trial in older patients with AML and high-risk MDS. If you are interested** contact Michelle.

MDS4
CI: Melita Kenealy
CRA: Tracey Gerber

Thank you to the all of the sites who completed data queries. New! Any sites with outstanding queries please forward the responses as soon as possible. **The data is currently being analysed and it is critical to the figures to have a complete dataset.**

ALL08 BLAM- A phase IIb study of Blinatumomab + Cytarabine (AraC) and Methotrexate in adult B-precursor Acute Lymphoblastic Leukaemia
CI: Shaun Fleming

Outcomes for ALL patients in the older age group remain poor despite modern treatment regimens. These patients suffer disproportionately from both treatment related toxicity and higher rates of disease relapse. **The new ALL08 BLAM study will be one of the first studies worldwide of the novel drug Blinatumomab in combination with chemotherapy for the up-front treatment of ALL.**

This is a single arm proof-of-concept study that will be carried out across Australian sites. It will include Blinatumomab with AraC and Methotrexate in B cycles of the Hyper-CVAD regimen. The treatment utilises a low-dose chemotherapy debulking phase to enhance the safety of Blinatumomab, reducing the risk of cytokine release syndrome.

New! The trial will accrue 30 patients aged 40-65 over 3 years, with a planned follow up of 2 years, and includes a suite of correlative studies. The protocol is still in development and EOI are expected to be sent out April 2017.

APML5 An ALLG proposal to assess oral ATO in the initial therapy of acute promyelocytic leukaemia
CI: Harry Iland
CRA: Amanda Lane

The ALLG APML4 study, published last year, showed that ATRA + arsenic trioxide (ATO) + idarubicin had the best outcome in high-risk patients (those with very high white cell counts). Experts in the USA and Canada now recommended this combination for the treatment of high-risk patients. A major drawback of ATO-based treatment is its requirement for daily 2-hour infusions extending over several months which have an impact on QOL.

The APML5 protocol will utilise an oral form of ATO, which will dramatically simplify treatment and reduce resource utilisation, and may also reduce toxicity. The protocol involves a detailed pharmacokinetic study to establish the oral product’s bioavailability. The first part of the study will involve 8 patients and establish the dose for the second part which will involve 20.

It is anticipated that the trial will open early in 2017 and will continue for approximately 5 years. The lead site (RPA) submitted to their HREC in early November and other sites who expressed interest will be added to the application towards the end of the year.

CML/Myeloproliferative Neoplasms Disease Group

CML/MPN Disease Group Chairs David Yeung

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

This trial has been chosen for an oral presentation at ASH. Congratulations to all involved! Thank you to all the sites who submitted data and data queries. We would greatly appreciate it if sites can continue to reconsent patients and submit follow up data expeditiously.

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
CRA: Michelle Paul

Michelle has recently taken over as the new CRA responsible for this trial. The first site (Royal Adelaide) was activated on 4 November and the trial is now open to accrual. Several other sites are due to be activated soon. **There are at present 13 sites and places are still remaining for two more sites to participate.**

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

All sites have now been activated for this trial and current accrual is 58. **Thank you to everyone who has contributed to the improvement in accrual.** The possibility of a cessation study as part of this protocol is currently being explored by the DGC. Watch this space!

BMT Disease Group

BMT Disease Group Chairs: Ian Lewis

BM06
CI: David Ritchie
CRA: Tracey Gerber

The next goal with this trial is to submit an abstract, so it is essential that missing data be completed as quickly as possible. Tracey will contact all sites with outstanding CRFs in the near future.

Myeloma Disease Group

Multiple Myeloma Disease Group Co-Chair: Peter Mollee
Co-Chair: Hang Quach

MM16
CI: Joy Ho
CRA: Suzanne Cake

This trial utilises Carfilzomib/dexamethasone until progression, to answer the important question of the utility of SFLC measurements in renal failure and the prediction of renal recovery, and the efficacy and tolerability of this regimen in patients with renal impairment. Accrual is currently 19 of a target of 40. Cohort 2 is open to at 5 sites: RPA, Calvary Mater Newcastle, The Alfred, Royal Adelaide and Princess Alexandra. **We encourage clinicians at other sites to refer your patients to these participating centres.**

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: Flora Yuen, Alfred Clinical Research Centre

Congratulations to the Alfred Hospital for being the first site to open to accrual on 13 September. The first patient was registered only 2 weeks later on 28 September, and since then 6 patients out of a target of 50 have been registered. Seven more sites will be activated in the near future. There is room for more sites to participate however it is limited, if interested please contact Flora.

MM14
CI: Andrew Spencer, Anna Kalff, Hang Quach
CRA: Nola Kennedy, Alfred Clinical Research Centre

In November 2016 the last registered patient completed cycle 10 of maintenance and provided the last correlative samples. The protocol has defined this point as the time for analysis. Each site will be sent the analysis CRF to confirm the survival date and status for all study participants. After that, patients may continue to get study drug., and according to the protocol, patients will be followed for 3 more years for safety, disease progression and survival.

MM15
CI: Andrew Spencer
CRA: Nola Kennedy, Alfred Clinical Research Centre

Some patients in this trial are still in maintenance phase. Please continue to submit up-to-date maintenance forms every 2 months to the EMN Data Centre in Torino. A conventions document has already been provided to give sites guidelines about data entry. Please contact Nola if you need a copy

MM20 A Multicentre Phase 3 Trial Comparing Elotuzumab-Cyclophosphamide-Thalidomide-Dexamethasone (E-CTD) with Cyclophosphamide-Thalidomide-Dexamethasone (CTD) for the Treatment of Relapsed and/or Refractory Multiple Myeloma (RRMM) New!
CI: Andrew Spencer
CRA: Flora Yuen, Alfred Clinical Research Centre

The standard treatment for relapsed/refractory patients is cyclophosphamide, thalidomide and dexamethasone. This treatment is affordable, well tolerated and has quite good outcomes. But despite the availability of novel agents, MM remains incurable accounting for 20% of all deaths from haematologic malignancy. The ALLG MM20 trial investigates the addition of a new immunomodulatory drug called elotuzumab. This is a potentially attractive option, particularly where there is limited access to high-cost alternatives.

Patients will be randomised to standard treatment + Elotuzumab or a current standard of care. The treatment period is 12 months with median follow-up of 2 years. The accrual target is 300 patients over three years, and the trial is planned to run at 24 sites throughout Australia. Expressions of interest are still open. If you are interested please contact Flora.

The trial was approved by HREC at the Alfred on 17 November and is expected to open to recruitment soon.

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!
CIs: Hang Quach (ALLG), Wee Joo Chng (Asian Myeloma Network)
CRA: Robyn Hemmes

All patients with MM are destined to relapse even with the best available approved agents. Median OS from diagnosis in the current era is around 5.4 years. **Given that myeloma remains an incurable disease, future improved OS is therefore reliant on the expansion of salvage options for patients with RRMM.** The idea of combining a proteasome inhibitor (PI) and an immunomodulatory drug such as thalidomide or lenalidomide is attractive in MM due to the efficacy which obviates the need for chemotherapy that is known lead to secondary cancers. The ALLG MM18 trial uses combination carfilzomib (a PI) and thalidomide, as opposed to lenalidomide, a more affordable regimen that is more applicable to the Asia-Pacific region.

In a new venture, the trial will be a collaboration between the ALLG and the Asian Myeloma Network (AMN), with a target of 50 patients from each group. Accrual is expected to take 2 years followed by a 1 year follow up period.

Fifteen sites will participate in Australia/NZ. Site selection is currently taking place, but there are 2-3 positions available. If your site is interested please contact Robyn Hemmes. We expect site activations to start around March 2017.

The ALLG Trials Newsletter is edited by Janey Stone and approved by Delaine Smith and Megan Sanders.
Questions or comments? E-mail us at info@allg.org.au