



**November 2003
investigators
meeting, Brisbane**



ANNUAL RESEARCH REPORT 2003

November 2003

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CHAIRMAN'S REPORT

This is my first report as chairman of the ALLG. At the AGM on May 9th, Ken Bradstock stepped down as chairman after steering the group since its formation over four years ago. The ALLG was formed through the amalgamation of the two co-operative groups involved in clinical trials in haematological malignancies, the Australasian Leukaemia Study Group (ALSG) and the Australian and New Zealand Lymphoma Group (ANZLG). On behalf of all the members I would like to acknowledge Ken's tremendous contribution as inaugural chairman. His wisdom and diplomacy will be sorely missed. I am sure Ken will remain an active member of the group and continue as a driving force of many clinical trials.

In his report at the last AGM, Ken pointed out how far the group had come in only four years, having established a unified trials group which enjoys widespread recognition nationally, internationally and among the pharmaceutical industry. This was accompanied by the establishment of a sound financial accounting and the creation of a stable administrative framework, with written working rules and an efficient central office. Public presentation has been substantially improved through the website and the annual Research Report. The groups activities have been both extended and deepened by the establishment of the Laboratory Science Committee, the Tissue Bank and the Safety and Data Monitoring Committee. At the same time the relationship with the pharmaceutical industry has matured and is now on a sound basis with the prospect of future close collaborations continuing.

Among the challenges facing the group is the need to maintain financial and intellectual independence in our relationship with the pharmaceutical industry and the importance of developing links with other national cancer trials groups to establish research infrastructure funding. The relationship with the Leukaemia Foundation of Australia is cordial, but needs to be cemented and further developed both for financial reasons and also to promote consumer representation and understanding of consumer needs within our group. Associated with this is the need to develop a mechanism for consumer representation on ALLG.

This has been another productive year with the group continuing to maintain clinical trials and laboratory studies encompassing the full range of haematological malignancies. During this year, the ALLG has been involved in 13 Phase II and 8 Phase III trials, 6 of these involving collaborations with other international groups. Currently 21 trials are open to accrual with a number of others under development.

Among studies that have been successfully completed this year include the ALLG's CML6 which reached its target accrual. The NHL10 MINT trial reached its international target accrual of 820 patients in October. Australia played a major role being second largest accruing country after Germany, and in population terms equal to Germany.

A number of trials are already being conducted in collaboration with international trials groups but stronger links with the international clinical research community should be forged to our mutual advantage. However, we must continue to encourage innovative local research projects and funding sources need to be established to enable this type of work to continue. It is important to improve the publication record of the ALLG and increase the number of research grants coming in for group activities.

The Safety and Data Monitoring Committee was formed under the chairmanship Phil Rowlings who has since had to step down temporarily for personal reasons. The acting chairman is Graham Young. The committee has met three times via teleconferencing. Operating rules and procedures have been established and all current trials have been reviewed. I would like to thank Phil, Graham and the other members for the work they have put in to this important committee of the group.

There are a number of financial and legal issues that the ALLG must resolve. Increasingly, studies supported by pharmaceutical companies require us to sign legally binding contracts. Another issue which has been considered but never resolved is indemnity insurance for ALLG clinical trials. These issues are under discussion by the executive.

The AMP Leukaemia and Lymphoma Tissue Bank is now firmly established under the direction of Paula Marilton and I would like to thank her for the hard work she has put into this important venture by the group. The Policy and Procedures Manual for the Tissue Bank has been written and is available in a dedicated area of the ALLG website as are a number of other documents relating to the Tissue Bank..

The Trial Centre, located at the Centre for Biostatistics and Clinical Trials at Peter MacCallum Cancer Centre, is developing long term plans around the concept of electronic registration and randomisation of patients via the website and electronic remote data entry. This would require substantial upgrading of software and databases and a grant application has been submitted by the Centre to the NHMRC in conjunction with the ALLG and TROG.

The ALLG website has proved an increasingly important resource over the last year, with the majority of members using it to obtain trial and meeting information and download documents. The website has been expanded this year with new areas developed for the Tissue Bank and Laboratory Science studies. The Executive and the SDMC now also have their own areas where documents required by the respective committee members can be posted.

There have been some changes at the Trial Centre. Consequent on Jane Matthews planned retirement, the ALLG has a new Bio-statistician, John Reynolds. John has a PhD in Statistics, with a minor in Genetics, from North Carolina State University. He was previously the Chief Biometrician in the Department of Natural Resources and Environment (Victoria) and has extensive experience as a statistical consultant in the food, veterinary and agricultural industries.). Janey Stone's hard work and enthusiasm for the group has been recognised by her appointment as the Executive Officer of the ALLG, in addition to her continuing role as a Trial Coordinator. Deborah Cruickshank has been appointed as the administrative officer, while Nancy Guzzo-Pernell and Juliana Di Iulio are the other two main Trial Coordinators. One trial, the MM6 trial, is being run from the Alfred Hospital with Nola Kennedy as the Trial Coordinator.

Finally I would like to thank the other members of the executive who stood down at the May meeting. John Seymour was the ALLG treasurer for the past four years and was instrumental in establishing order to our accounting systems. David Ma has been an active member of the executive and made contributions in a number of areas particularly in the areas of ethics and conflict of interest. This year has also seen the retirement of Jane Matthews from the ALLG. Jane has been the Bio-statistician for the ALLG and previously for both the ALSG and ANZLG since their inception. I would like to thank her for the tremendous work she has done for the groups over 20 years.

Max Wolf, Chairman, ALLG

ELECTED MEMBERS OF ALLG EXECUTIVE COMMITTEE IN 2003

CHAIRMAN

Dr. Max Wolf

Peter MacCallum Cancer Centre, Melbourne

VICE CHAIRMAN

Associate Professor Timothy Hughes

Royal Adelaide Hospital, Adelaide

SECRETARY

Dr John Moore

St Vincent's Hospital, Sydney

TREASURER

Associate Professor Jeffrey Szer

Royal Melbourne Hospital, Melbourne

Dr Chris Arthur

Professor Peter Browett

Dr. Paula Marlton

Dr Andrew Spencer

Royal North Shore Hospital, Sydney

University of Auckland, New Zealand

Princess Alexandra Hospital, Brisbane

Alfred Hospital, Melbourne

ALLG TRIAL CENTRE

TRIAL CENTRE BIOSTATISTICIAN

Dr. Jane Matthews (until Jul 2003) Statistical Centre, Peter MacCallum Cancer Centre, Melbourne

Dr John Reynolds (from Aug 2003) Statistical Centre, Peter MacCallum Cancer Centre, Melbourne

EXECUTIVE OFFICER

Ms Janey Stone

Peter MacCallum Cancer Centre, Melbourne

CLINICAL TRIAL CO-ORDINATORS

Ms Janey Stone

Dr Juliana di Iulio

Dr Nancy Guzzo-Pernell

Ms Sophie Katsabanis

Dr Kate Richards

Ms Nola Kennedy (Alfred Hospital)

ADMINISTRATIVE OFFICER

Ms Deborah Cruickshank

TRIAL CENTRE CONTACTS

Address: Statistical Centre, Peter MacCallum Cancer Centre, St Andrew's Place,
East Melbourne, Victoria, 3002

or

Locked Bag 1, A'Beckett St, Victoria, 8006

Telephone: 03-9656 1265 *or* 03-9656 1084 *or* 03-956 1380 (Administrative Officer)

Fax: 03-9656 1420

Email: Deborah.Cruickshank@petermac.org

Web site: www.petermac.org/allg/

ALLG TRIAL SUBCOMMITTEES

INTERMEDIATE AND HIGH GRADE NON-HODGKINS LYMPHOMA, HODGKINS DISEASE CHAIRS

Dr. Max Wolf
Professor Peter Browett
SUBCOMMITTEE

Dr David Christie
Dr Devinder Gill

CML, MYELOPROLIFERATIVE DISEASE, MYELOYDYSPLASIA CHAIRS

Associate Professor Timothy Hughes
Associate Professor Kerry Taylor
SUBCOMMITTEE

Dr Chris Arthur
Associate Professor Andrew Grigg

LOW GRADE NON-HODGKINS LYMPHOMA, MYELOMA, CHRONIC LYMPHOCYTIC LEUKAEMIA CHAIRS

Dr. John Seymour
Dr Andrew Spencer
SUBCOMMITTEE

Professor Doug Joshua
Dr Steve Mulligan

ACUTE LEUKAEMIA CHAIRS

Dr Chris Arthur
Associate Professor Ken Bradstock
SUBCOMMITTEE

Dr Ian Lewis
Dr John Seymour

BONE MARROW TRANSPLANTATION CHAIRS

Associate Professor Jeffery Szer
Dr John Moore

SUBCOMMITTEE

Associate Professor Ken Bradstock
Andrew Grigg

LABORATORY SCIENTIFIC COMMITTEE CHAIRS

Dr. Paula Marlton
Associate Professor Harry Iland

SUBCOMMITTEE

Laboratory Science Committee

SUPPORTIVE CARE CHAIRS

Dr Peter Bardy
Dr Monica Slavin
SUBCOMMITTEE

Dr Phillip Mondy
Dr John Moore

SAFETY AND DATA MANAGEMENT COMMITTEE REPORT

At the request of the ALLG Executive an independent Safety and Data Management Committee (SDMC) has been established to oversee safety and data management aspects of ALLG trials. This Committee is an advisory committee to the Executive.

The major responsibilities of the Committee are to independently review reports of toxicity from the Study Chairmen and to make appropriate recommendations. In addition, interim analysis data will be reviewed in the light of stopping rules based on statistical advice. It is envisaged that all future ALLG Trials will be reviewed by this committee to provide safety and data management advice.

The Committee has now met formally on 3 occasions and plans to meet on a regular basis prior to each ALLG Meeting to review each active trial under the auspices of the ALLG.

The current membership of the Committee is A/Prof Graham Young (Haematologist, Sydney) and 4 other voting members viz: Prof Ray Lowenthal (Haematologist and Oncologist, Hobart), Dr Martin Stockler (Oncologist and Clinical Trials Specialist, Sydney) Judy Simpson (Biostatistician, Sydney) and John Stubbs (Patient Advocate, Sydney), together with support from the Trial Centre - John Reynolds (ALLG Statistician), Janey Stone (Trial Centre Data Manager) and, Deborah Cruickshank (Administrative Officer). Data managers of individual trials attend the meetings while their trials are being reviewed.

All ALLG members are encouraged to approach this committee on appropriate matters of Safety and Data Management.

Graham Young, Chairman, SDMC

PUBLICATIONS AND PRESENTATIONS 2003

Publications 2003

1. Zucca E, Conconi A, Mughal TI, Sarris AH, Seymour JF, Vitolo U, Klasa R, Ozsahin M, Mead GM, Gianni MA, Cortelazzo S, Ferreri AJ, Ambrosetti A, Martelli M, Thieblemont C, Moreno HG, Pinotti G, Martinelli G, Mozzana R, Grisanti S, Provencio M, Balzarotti M, Laveder F, Oltean G, Callea V, Roy P, Cavalli F, Gospodarowicz MK. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. *Journal of Clinical Oncology*. 2003 Jan 1;21(1):20-7. (IF: 8.773)
2. Campbell JK, Matthews JP, Seymour JF, Wolf MM, Juneja SK. Optimum trephine length in the assessment of bone marrow involvement in patients with diffuse large cell lymphoma. *Annals of Oncology*. 2003 Feb;14(2):273-6.
3. Massimo Federico, Monica Bellei, Pauline Brice, Maura Brugiattelli, Arnon Nagler, Christian Gisselbrecht, Luciano Moretti, Philippe Colombat, Stefano Luminari, Francesco Fabbiano, Nicola Di Renzo, Anthony Goldstone, and Angelo Michele Carella for the EBMT/GISL/ANZLG/SFGM/GELA Intergroup HD01 Trial.
High-Dose Therapy and Autologous Stem-Cell Transplantation Versus Conventional Therapy for Patients With Advanced Hodgkin's Lymphoma Responding to Front-Line Therapy.
Journal of Clinical Oncology, Vol 21, No 12 (June 15), 2003: 2320-2325
4. A. Wirth, H.M. Prince, M. Wolf, J. M. Stone, J. P. Matthews, J. Gibson, C. MacCleod, J. Szer, A. Grigg, B. To, D. Roos, A.P. Schwarzer, S. Davis.
Optimal Timing to Reduce Morbidity of Involved Field Radiotherapy with Transplantation for Lymphomas; A Prospective Australasian Leukaemia and Lymphoma Group Study

Presentations/abstracts 2003

1. Andrew Spencer, Andrew Roberts, Michael Bailey, Horst Schran and Kevin Lynch on behalf of the Australasian Leukaemia and Lymphoma Group.
No evidence for an adverse interaction between zoledronic acid and thalidomide: preliminary safety analysis from the Australasian Leukaemia and Lymphoma Group (ALLG) MM6 trial.
ASH December 2003
2. Janey Stone, Jenny Beresford, Ken Bradstock.
Easily updated webpage design via an Access database: the Australasian Leukaemia and Lymphoma Group (ALLG) experience
Controlled Clinical Trials, Supplement, Vol 24, No 3S, 2003: 139S
3. Janey Stone, Max Wolf and Jane Matthews
Review of endpoint data at close-out of a 5-year randomised multi-centre Australasian Leukaemia and Lymphoma Group (ALLG) trial
Controlled Clinical Trials, Supplement, Vol 24, No 3S, 2003: 135S
4. DL White, VA Saunders, AB Lyons & TP Hughes.
The Value of Imatinib Sensitivity Studies as Predictors of Cytogenetic and Molecular Response in CML Patients.
HSANZ October 2003, Christchurch
5. K Taylor, S Branford, T Hughes, A Schwarzer, C Arthur, R Filshie, I Prosser, A Enno, A Mills, J Norman, S Wright, N Guzzo-Pernell, J Larsen, K Lynch, J Wellwood, R Rodwell, D Taylor, M Ellis, A Josephson for the Australasian Leukaemia and Lymphoma Group.
Imatinib produces substantial molecular remissions in interferon treated chronic phase (CP) chronic myeloid leukemia (CML) in longstanding bcr-abl positive cytogenetic remission (CCR)
HSANZ October 2003, Christchurch
6. J Seymour, A Grigg, J Matthews, K Taylor N Guzzo-Pernell, A Mills, K Lynch and T Hughes.
A prospective analysis of the consequences of Imatinib Mesylate inhibition of sensitive kinases other than BCR-ABL in patients with previously untreated early chronic phase CML.
ASH December 2003, San Diego
7. T Hughes, S Branford, J Matthews, J Seymour, K Taylor, N Guzzo-Pernell, A Harper, R Filshie, J Morton, C Arthur, A Schwarzer, M Hertzberg, Z Rudzki, M Copeman, K Lynch and A Grigg.
Trial of higher dose Imatinib with selective intensification in newly diagnosed CML patients in the chronic phase.
ASH December 2003, San Diego

TRIALS IN PROGRESS

Acute leukaemia

ALL3 **A phase II study of induction therapy using idarubicin and infusional high dose cytarabine for adult patients with de novo untreated acute lymphoblastic leukaemia**

Trial Chairman: Ken Bradstock/John Seymour

Main Trial Objectives: To assess the toxicity of combination chemotherapy with infusional high dose cytarabine and Idarubicin in previously untreated patients aged 20 to 55 years with precursor B ALL.

Trial Status: Open to accrual

Date study opened: 29 November 2001

Date 1st patient enrolled: 08 June 2002

| | | | |
|---|------|---|----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 25 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 11 |
| Number of participating sites: | 7 | Number of sites with patients entered: | 5 |
| Expected final accrual date: | 2004 | | |
| Date study closed to accrual: | | | |

Brief details of Serious/Unexpected Adverse Events experienced to date: 2 early deaths following induction therapy due to infectious complications

Summary of Results: not applicable

Publications: none to date

Comments: ongoing study. Data on molecular evaluation of residual disease critical to design of subsequent studies..

Acute leukaemia

AML11 **Non-myeloablative allogeneic stem cell transplantation (NMSCT) in adults with intermediate and adverse prognosis AML in first complete remission**

Trial Chairman: Andrew Grigg

Main Trial Objectives: To evaluate the kinetics of T cell and myeloid chimerism in patients with intermediate and poor prognosis AML in first CR receiving two different MNSCT conditioning regimens (FluCy and FluMel), and to relate chimerism to the incidence and severity of GVHD

Trial Status: Open to accrual

Date study opened: 9 March 2001

Date 1st patient enrolled: April 2001

| | | | |
|---|-----|---|----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 40 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 20 |
| Number of participating sites: | 7 | Number of sites with patients entered: | 5 |

Expected final accrual date: April 2004

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date: 1 patient relapsed D 98 despite gut GVHD refractory to ATG - deceased.

Summary of Results: 2 other relapses in evaluable patients post BMT.

Publications:

Comments: 2 patients relapsed prior to commencing conditioning.
1 patient not evaluable due to disease state
Sustained donor CD3 chimerism, rising donor myeloid chimerism observed.
14 patients in CR at 30/9/2003. Median of 402 days, range 36 - 994 days.
Two patients have developed grade II acute GVHD and one patient grade IV as above.
Five patients have had limited chronic GVHD.

Acute leukaemia

AML12 **A randomised trial of idarubicin dose escalation in consolidation therapy following intensive induction chemotherapy incorporating high dose cytarabine in patients with untreated adult acute myeloid leukaemia.**

Trial Chairman: Ken Bradstock, John Seymour

Main Trial Objectives: To determine whether intensified therapy with Idarubicin during consolidation therapy can improve leukemia-free survival in patients less than 60 years of age with newly diagnosed AML who have achieved a complete remission with ICE induction chemotherapy.

Trial Status: Open to accrual

Date study opened: May 2003

Date 1st patient enrolled: ?

| | | | |
|---|-----|---|-----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 325 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 9 |
| Number of participating sites: | 10 | Number of sites with patients entered: | 6 |

Expected final accrual date: May 2008

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date: None reported to date

Summary of Results: Not relevant

Publications: None

Comments: This trial is in the early stages of accrual..

Acute leukaemia

CMLALL1 **A phase II pilot study of Glivec (STI571) combined with induction chemotherapy in blast-phase chronic myeloid leukaemia and philadelphia chromosome-positive acute lymphoblastic leukaemia**

Trial Chairman: Ken Bradstock/Jason Lickliter

Main Trial Objectives: Investigate the safety and tolerability of Glivec in combination with induction chemotherapy for blast phase CML and Ph+ ALL

Trial Status: Open to accrual

Date study opened: 15 March 2002

Date 1st patient enrolled: March 2002

| | | | |
|---|-----|---|----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 30 |
| Current total accrual (international): | | Current total accrual (ALLG): | 16 |
| Number of participating sites: | 11 | Number of sites with patients entered: | 7 |

Expected final accrual date: Mid 2004

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date: A total of SAE reports have been recorded on 8 cases entered on the study. In 2 cases, the physician believed that the adverse may possibly have been attributable to Glivec or its interaction with chemotherapy. In 1 case, it was considered that Glivec may have prolonged neutropenia in a patient with chemotherapy-induced enterocolitis. In another patient with severe multi-organ failure, Glivec could not be ruled out as a contributing cause of death. Other SAE's appear unrelated, including: subdural haematoma, sepsis, pulmonary infiltrate, acute pulmonary haemorrhage secondary to fungal infection. A meeting of the trial safety committee on 8/7/03 concluded that the trial remain open. Two further evaluable patients are required to complete the first Glivec dose cohort of 8.

Summary of Results Not applicable

Publications: None to date

Comments: Study open to accrual in first Glivec dose schedule cohort..

Intermediate and high grade NHL/HD

HDNHL4 An ALLG/TROG prospective multicentre study of involved field RT with transplantation for HD and NHL

Trial Chairman: Andrew Wirth/Miles Prince

Main Trial Objectives: Determine in-field and distant failure rates when involved-field radiotherapy added to transplantation

Trial Status: Open to accrual

Date study opened: February 2003

Date 1st patient enrolled: 24 September 2003

| | | | |
|---|-----|---|-----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 100 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 1 |
| Number of participating sites: | 6 | Number of sites with patients entered: | 1 |

Expected final accrual date: unknown

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date: nil
Summary of Results

Publications:

Comments:

Intermediate and high grade NHL/HD

LY02

A prospective, non-randomised study of chemotherapy and radiotherapy for osteolymphoma

| | | | |
|--|--|---|----|
| Trial Chairman: | David Christie | | |
| Main Trial Objectives: | To optimise overall survival, determine prognostic factors, avoid pathological fractures and study natural history. | | |
| Trial Status: | Open to accrual | | |
| Date study opened: | December 1999 | | |
| Date 1st patient enrolled: | 15 September 2000 | | |
| Accrual target (international): | (support from IELSG being presently canvassed) | Accrual target (ALLG): | 70 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 18 |
| Number of participating sites: | 18 | Number of sites with patients entered: | 11 |
| Expected final accrual date: | 2010 | | |
| Date study closed to accrual: | | | |
| Brief details of Serious/Unexpected Adverse Events experienced to date: | Three Serious Adverse Events have been submitted, both are typical side effects of chemotherapy, no other significant toxicity. No further SAE's since the previous report | | |
| Summary of Results | n/a | | |
| Publications: | To be presented at the Australasian Orthopaedic Association Meeting October 2003. | | |
| Comments: | Conducted in collaboration with TROG and supported by AROLG IELSG-14 is also proceeding, which is a retrospective study of Primary Bone Lymphoma and when completed it will hopefully foster participation of the IELSG in LY2. Please consider participating by . | | |

Intermediate and high grade NHL/HD

LY04

A phase II study of idarubicin-based combined modality therapy in primary central nervous system lymphoma

Trial Chairman: John Seymour/Peter O'Brien

Main Trial Objectives: Phase 2 study of Idarubicin and Methotrexate combined with low-dose cerebral irradiation. Primary endpoint is overall survival.

Trial Status: Open to accrual

Date study opened: September 2001

Date 1st patient enrolled: December 2001

| | | | |
|---|----|---|----|
| Accrual target (international): | | Accrual target (ALLG) | 53 |
| Current total accrual (international): | | Current total accrual (ALLG): | 13 |
| Number of participating sites: | 13 | Number of sites with patients entered: | 8 |

Expected final accrual date: 2005

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date: SAE's x 15 in 9 patients
Acute toxicity analysis after the first 10 patients revealed Grade 4 neutropaenia rate of 40% relating to Idarubicin.

Summary of Results

Publications:

Comments: Filgrastim following Day 1 and Day 22 Idarubicin will be introduced as standard therapy following Tial Management Committee meeting 16/10/03. Dose reduction will be mandated following neutropaenic sepsis..

Intermediate and high grade NHL/HD

LY05

A phase II randomised study to assess the reponse of fludarabine in combination with cyclophosphamide vs fludarabine in combination with cyclophosphamide and Mabthera in patients with untreated mantle cell lymphoma

Trial Chairman: Simon Rule (UK) and John Seymour (ALLG)

Main Trial Objectives: This is a phase II randomised study to assess the response of fludarabine in combination with cyclophosphamide in patients with untreated mantle cell lymphoma. The randomisation is for the addition or not of Mabthera to this regimen. This is a UK wide study co-ordinated under the auspices of the National Cancer Research Network (NCRN) Lymphoma Clinical Studies Group (formally UKCCCR) and in Australia and New Zealand under the auspices of the Australasian Leukaemia and Lymphoma Group (ALLG). The primary end-point is response rate, with secondary end-points of time to progression, toxicity profile, and overall survival.

Trial Status: Open to accrual

Date study opened: August 2002 internationally

Date 1st patient enrolled: August 2002

| | | | |
|---|----|---|----|
| Accrual target (international): | 85 | Accrual target (ALLG): | 25 |
| Current total accrual (international): | 49 | Current total accrual (ALLG): | 0 |
| Number of participating sites: | 7 | Number of sites with patients entered: | 0 |

Expected final accrual date: end 2004

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date: None yet reported

Summary of Results

Publications: None.

Comments: All patients aged ≥ 18 years with previously untreated mantle-cell lymphoma (diagnosis confirmed on immunophenotypic and morphological criteria, although there will be central pathology review including FISH and molecular analyses) are eligible. The study drugs Fludarabine (IV) will be provided by Schering and Mabthera by Roche to approved sites. There is also a small per patient payment to ALLG sites. The excellent accrual to the study in the UK has lead to discussions regarding the potential expansion of accrual to allow formal comparison of response rates between treatment arms. A final decision is likely in early 2004..

Intermediate and high grade NHL/HD

LY06

A clinicopathological study in Burkitt's and Burkitt-like NHL

Trial Chairman: Max Wolf (ALLG)

Main Trial Objectives: Pathological

1. To describe BL and the related Burkitt-like lymphoma in terms of morphology, phenotype and cytogenetics, using, where possible, fresh tumour tissue.
2. To determine whether cytogenetic and molecular changes are associated with, or predictable from, the immunophenotype of the tumour cells or patient characteristics such as age, in particular to examine the relationship of t(14:18) to bcl2 expression.
3. To determine whether the presence of specific cytogenetic and molecular changes (in particular the presence of t(14:18) in addition to the t(8:14)) is associated with an adverse outcome (progression-free and overall survival) using this treatment.

Clinical

1. To assess the activity of CODOX-M/IVAC using a lower dose of methotrexate (compared to the UKLG LY06 Trial) of 3g/m² in a phase II study in adult sporadic BL and Burkitt-like lymphoma.
2. To further assess the activity of these regimens in patients with leukaemic BL and, by modifying chemotherapy doses, to include older patients often excluded from clinical trials.

Trial Status: Open to accrual

Date study opened: 30/4/2002 internationally

Date 1st patient enrolled: 30/4/2002

| | | | |
|---|-------|---|---|
| Accrual target (international): | 100 | Accrual target (ALLG): | |
| Current total accrual (international): | 49 | Current total accrual (ALLG): | 5 |
| Number of participating sites: | 6 | Number of sites with patients entered: | 4 |
| Expected final accrual date: | 2007? | | |
| Date study closed to accrual: | | | |

Brief details of Serious/Unexpected Adverse Events experienced to date: 10 SAEs (7 UK, 3 ALLG) reported, 7 definitely or probably related to treatment.

Summary of Results

Publications: Nil to date

Comments:

Intermediate and high grade NHL/HD

LY07

A phase II study of CHOP, with intrathecal methotrexate followed by radiotherapy in patients with primary testicular NHL

Trial Chairman: John Seymour (ALLG)

Main Trial Objectives: Efficacy and toxicity of treatment regimen including IT prophylaxis, full anthracycline-based chemo-immunotherapy and irradiation to the contralateral testis, based on the findings of the retrospective IELSG study which showed (1) poor outlook with abbreviated therapy even with localised disease (2) high CNS recurrence risk and (3) high risk of recurrence in the contralateral testis (J Clin Oncol in press).

Trial Status: Open to accrual

Date study opened: 1 Jan 2001 Internationally

Date 1st patient enrolled: 5 Feb 2001 Internationally

| | | | |
|---|----------------------|---|----------------------|
| Accrual target (international): | 50 | Accrual target (ALLG): | 5 |
| Current total accrual (international): | 26 | Current total accrual (ALLG): | 0 |
| Number of participating sites: | 20 (internationally) | Number of sites with patients entered: | 12 (internationally) |

Expected final accrual date: 2005

Date study closed to accrual: NA

Brief details of Serious/Unexpected Adverse Events experienced to date: Single case of pulmonary embolism (not treatment related).

Summary of Results

Publications: Nil to date

Comments: Roche International will provide Mabthera for ALLG sites to accrue. The aim would be to have one site in each major city open for accrual. Protocol revision requested by Peter MacCallum ethics committee and this will be submitted,.

Intermediate and high grade NHL/HD

NHL11

A phase II study of a modified "Hyper-CVAD" frontline therapy for patients with poor prognosis diffuse large B-cell and peripheral T-cell non-Hodgkin's lymphoma

Trial Chairman: John Seymour/Paula Marlton

Main Trial Objectives: Primary endpoint is complete remission rate (CR and CRU) using International Workshop criteria. Will compare this with anticipated rate (stratified for immunophenotype and IPI score). Also analyse 2-year PFS and OS as well as safety.

Trial Status: Open to accrual

Date study opened: July 2001

Date 1st patient enrolled: August 2001

| | | | |
|---|------|---|----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 70 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 30 |
| Number of participating sites: | 18 | Number of sites with patients entered: | 9 |
| Expected final accrual date: | 2006 | | |
| Date study closed to accrual: | N/A | | |

Brief details of Serious/Unexpected Adverse Events experienced to date: 62 SAE reports to date (1 G-CSF-related). 3 patients have ceased study treatment due to SAE's (1 septic death / 1 psoas abscess and septicemia / 1 neutropenic enterocolitis). 41 episodes of readmission for fever / infection (37 with neutropenia, 4 with normal counts). Unplanned readmissions occur with similar frequency after "A" and "B" cycles. 4 known instances of progressive disease (1 fatal during first cycle) and two cases of CNS recurrence. According to the stated early stopping rules for safety and lack of efficacy, the study remains open for accrual.

Summary of Results

Publications: None to date

Comments: Funding support for drugs and per-patient costs from Mayne Health, Amgen. Revised protocol circulated 10 May 2002. Further consideration for subsequent amendment in early 2003 to allow use of Peg-filgrastim and Mabthera, depending upon regulatory status..

Intermediate and high grade NHL/HD

NHL13

Randomized study of ICE plus Rituximab (R-ICE) vs DHAP plus Rituximab (R-DHAP) in previously treated patients with CD20 positive diffuse large B-cell lymphoma, eligible for transplantation followed by randomized maintenance treatment with Rituximab.

Trial Chairman: David Ma/Devinder Gill

Main Trial Objectives: Part I, induction therapy: To evaluate the efficacy and the safety of ICE plus rituximab (R-ICE) in comparison with DHAP plus rituximab (R-DHAP) in previously-treated patients with CD20-positive large B-cell lymphoma eligible for autologous transplantation.

Part II, maintenance therapy : To evaluate the efficacy and safety of Mabthera maintenance therapy after transplantation.

Trial Status: Open to accrual

Date study opened: August 2003

Date 1st patient enrolled:

| | | | |
|---|-----|---|----|
| Accrual target (international): | 400 | Accrual target (ALLG): | 60 |
| Current total accrual (international): | 1 | Current total accrual (ALLG): | 0 |
| Number of participating sites: | 0 | Number of sites with patients entered: | 0 |

Expected final accrual date: end 2008

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date: None

Summary of Results: None

Publications: None to date

Comments: None.

Laboratory Science Studies

LS01

PCR screening for CBF rearrangements in AML

Trial Chairman: Paula Marlton, Russell Saal

Main Trial Objectives:

1. To establish a rapid and robust RT-PCR assay incorporating suitably validated control genes for the purpose of identifying CBF rearrangements at diagnosis in AML.
2. To identify the incidence of cryptic CBF rearrangements (not identified by cytogenetics) and establish if prognostic significance differs from rearrangements detected cytogenetically.

Trial Status: Open to accrual

Date study opened: October 1999

Date 1st patient enrolled:

| | | | |
|---|--|---|-----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 100 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 70 |
| Number of participating sites: | Open to all centres participating in ALLG frontline leukaemia trials | Number of sites with patients entered: | |
| Expected final accrual date: | Study extended to include AMLM12 and other new AML trials | | |

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date:

Summary of Results 3 of the first 50 cases had a cryptic CBF rearrangement.

Publications: Russell Saal, Paula Marlton, Georgina Timson, Marcus Waugh, Francisca Springall, Karen Grimmett, Devinder Gill, and Harry Iland. A Rapid RT-PCR Screening Assay Incorporating Multiplexed Validated Control Genes for CBF Rearrangements at Diagnosis in AML. HS

Comments:

Laboratory Science Studies

LS02

Assessment of minimal residual disease in good prognosis AML by quantitative real time PCR

Trial Chairman: Paula Marlton

Main Trial Objectives:

1. To develop quantitative RT-PCR assays for the measurement of leukaemia specific fusion transcripts in AML associated with CBF rearrangements.
2. To monitor leukaemia levels in patients with CBF AML through treatment and remission using quantitative RT-PCR.
3. To correlate clinical progress with assay results to assess the clinical utility of the assays.

Trial Status: Closed to accrual

Date study opened: July 1998

Date 1st patient enrolled:

| | | | |
|---|--|---|----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 50 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 26 |
| Number of participating sites: | Open to all centres participating in ALLG frontline leukaemia trials | Number of sites with patients entered: | |
| Expected final accrual date: | December 2002 | | |

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date:

Summary of Results Clinical data retrieval for correlative analysis ongoing.

Publications:

Comments: The next phase of this work will be incorporated in the CBF AML clinical trial pending successful funding..

Laboratory Science Studies

LS07

CMLALL1 scientific study

Trial Chairman: Ken Bradstock/Jason Lickliter

Main Trial Objectives:

Trial Status: Open to accrual

Date study opened: 15 March 2002

Date 1st patient enrolled:

| | |
|---|---|
| Accrual target (international): | Accrual target 30 (ALLG) |
| Current total accrual (international): | Current total 5 |
| Number of participating sites: | accrual (ALLG): Number of sites with patients entered: |

**Expected final accrual
date:**

**Date study closed to
accrual:**

**Brief details of
Serious/Unexpected
Adverse Events
experienced to date:
Summary of Results**

Publications:

Comments: Samples on patients accrued to date are stored at -70 degrees at treating institutions. Arrangements for transport to the Queensland Institute of Medical Research for analysis have been finalized. Preliminary studies using the control Ph+ cell line K562 are underway..

Laboratory Science Studies

LS08

Laboratory Studies for MM6 - the effect of FGFR3 expression on the action of thalidomide.

Trial Chairman: Joy Ho (for laboratory evaluation of thalidomide/FGFR3 interaction)

Main Trial Objectives: To evaluate the effect of FGFR3 overexpression on the action of thalidomide. A significant number (15 - 25%) of myeloma tumours have t(4;14) translocation that potentially upregulates FGFR3 expression. Since thalidomide is known to inhibit basic FGF, we test the hypothesis that overexpression of one of its receptors, FGFR3 may modulate response to thalidomide.

Trial Status: Open to accrual

Date study opened: 26 Feb 02

Date 1st patient enrolled: 2 April 02

**Accrual target
(international):**

**Accrual target
(ALLG)** 224
evaluable
patients

**Current total accrual
(international):**

**Current total
accrual (ALLG):** 49 pre-
transplant
bone marrow
samples, 11
post-
transplant
samples

**Number of participating
sites:** 32

**Number of sites
with patients
entered:** 20

**Expected final accrual
date:**

**Date study closed to
accrual:**

**Brief details of
Serious/Unexpected
Adverse Events
experienced to date:
Summary of Results**

Of 49 pre-transplant samples, 42 have been flow-sorted, of which satisfactory RNA yield has been obtained from 38 samples. Eleven post-transplant samples have been received, 9 received 12 months post transplant as per protocol, and 2 were received at 8 months. Seven of the 11 post-transplant samples have been flow sorted, all of which provided good RNA yield. A total of 13 pre-transplant samples have completed expression analysis, of which 4 demonstrates increased FGFR3 expression by FGFR3:b-actin cDNA ratios by Taqman-based real-time RT-PCR. Analysis proceeding.

Publications:

Comments: This project will require continuing support from contributing centres for samples. It addresses an important question on the mechanism of the action of thalidomide..

Laboratory Science Studies

LS09

Profiling dynamics of EBV-specific cytotoxic T-cell response in Hodgkin's Disease and its implications for immunotherapy

Trial Chairman: Dr Rajiv Khanna: QIMR
Dr Paula Marlton: PAH
Dr John Seymour: Peter Mac
Dr David Joske: Sir Charles Gairdner
Dr Craig Underhill; Dr Kerrie Clarke: Border
Medical Oncology

Main Trial Objectives:

1. Ex-vivo profiling of EBV-specific CTL responses in the 3 patient categories
2. Phenotypic analysis of EBV latent and lytic antigen-specific CTL responses using MHC-peptide tetramer technology

Trial Status: Open to accrual

Date study opened: Nov 01

Date 1st patient enrolled: Nov 01

Accrual target (international):

Accrual target (ALLG) 20 newly diagnosed; 20 relapsed; 20 long term survivors

Current total accrual (international):

Current total accrual (ALLG): 18 newly diagnosed; 29 long term survivors; 3 relapsed

Number of participating sites: 4

Number of sites with patients entered: 4

Expected final accrual date: unknown

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date:
Publications:

Comments: Additional sites are encouraged to join to improve the accrual of relapsed patients. All categories will continue to accrue until the relapse target is met..

Laboratory Science Studies

LS10

Mitochondrial mutations in AML

Trial Chairman: Bryone Kuss

Main Trial Objectives: 1. To establish the frequency of mitochondrial mutations in acute myeloid leukaemia. 2. To examine the potential use of these mutations as a generic marker for the assessment of minimal residual disease. 3. To evaluate whether the assessment of MRD provides prognostic information as to treatment response and treatment outcome.

Trial Status: Open to accrual

Date study opened:

Date 1st patient enrolled:

**Accrual target
(international):**

**Accrual target
(ALLG)** patients
accrued to
AML7
study of the
ALLG

**Current total accrual
(international):
Number of participating
sites:**

**Current total
accrual (ALLG):
Number of sites
with patients
entered:**

**Expected final accrual
date:**

**Date study closed to
accrual:**

**Brief details of
Serious/Unexpected
Adverse Events
experienced to date:
Summary of Results**

The analysis of data from stored samples in our own institution is encouraging from the perspective of frequency of mutations and the sensitivity of the assays employed. A detailed update will be provided at the meeting.

Publications: one manuscript currently submitted

Comments: There are current difficulties with regard to obtaining ethics approval for patients who were initially enrolled in the AML7 study. At this time the ALLG did not have in place prospective approval for a scientific study on stored patient samples. This problem has been addressed and resolved in our own institution but needs to be addressed by each participating centre. This problem will be discussed at the Nov Scientific committee meeting..

Laboratory Science Studies

LS11

Laboratory Studies for MM6 – T cell Clones

| | | | |
|--|---|---|--|
| Trial Chairman: | Doug Joshua | | |
| Main Trial Objectives: | To study | | |
| | 1. the incidence of expanded T cell clones. | | |
| | 2. the prognostic significance of T cell Clones | | |
| | 3. changes in T cell clones with therapy | | |
| Trial Status: | Open to accrual | | |
| Date study opened: | 26 February 2002 | | |
| Date 1st patient enrolled: | 2 April 2002 | | |
| Accrual target (international): | | Accrual target (ALLG) | 224 evaluable patients |
| Current total accrual (international): | | Current total accrual (ALLG): | 44 pretransplant blood samples. 11 post transplant blood samples |
| Number of participating sites: | 32 | Number of sites with patients entered: | 20 |
| Expected final accrual date: | | | |
| Date study closed to accrual: | | | |
| Brief details of Serious/Unexpected Adverse Events experienced to date: | | | |
| Summary of Results | The TCR Vb repertoire was analysed to detect T cell expansions. A total of 55 peripheral blood samples have been received from 44 different patients. The incidence of T cell expansions was 52%. Five patients have been studied pre and past transplantation. Pretransplant T cell expansions were evident post transplant in 4/6 patients. Further follow up will produce more significant data. | | |
| Publications: | | | |
| Comments: | This project requires support from contributing centres. | | |

Low grade NHL/Myeloma/CLL

CLL2

International Phase III-Trial in B-cell CLL Intermediate-dose chlorambucil vs cladribine vs fludarabine

Trial Chairman: Stephen Mulligan (ALLG),
Gunnar Juliusson (Sweden)

Main Trial Objectives: Analysis of first-line therapy in B-CLL

Trial Status: Open to accrual

Date study opened: November 1998

Date 1st patient enrolled: ~January 1999

| | | | |
|---|---------------------|---|--|
| Accrual target (international): | 500 | Accrual target (ALLG): | 120 |
| Current total accrual (international): | Total: 159 patients | Current total accrual (ALLG): | 61 |
| Number of participating sites: | 17 | Number of sites with patients entered: | 17 (Australia) 19 (Sweden) 10 (Norway) 1 (Finland) 1 (Denmark) 1 (UK) Total 49 |

Expected final accrual date: end 2003?

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date: SAEs currently being assessed

Summary of Results

Publications: Nil to date

Comments:

Low grade NHL/Myeloma/CLL

German FCM

A 2x2 randomised study of FCM chemotherapy +/- concurrent Mabthera and +/- maintenance Mabthera for patients with a range of relapsed/refractory "low grade" lymphomas including mantle cell NHL

| | | |
|--|--|--|
| Trial Chairman: | Wolfgang Hiddeman (international), John Seymour (ALLG) | |
| Main Trial Objectives: | Response rates, PFS +/- Mabthera | |
| Trial Status: | Open to accrual | |
| Date study opened: | Q4 1998 internationally, August 2000 Australia | |
| Date 1st patient enrolled: | Q4 1998 internationally, August 2000 Australia | |
| Accrual target (international): | 200 | Accrual target (ALLG): 10 |
| Current total accrual (international): | 147 patients entered first randomisation as of October 2002, 130 entered second randomisation | Current total accrual (ALLG): 10 (4 Albury, 6 PMCI) |
| Number of participating sites: | 2 | Number of sites with patients entered: 2 |
| Expected final accrual date: | ? Early 2004 | |
| Date study closed to accrual: | First randomisation closed on the basis of superior response rate with FCM plus Mabthera based on interim analysis of October 2001. | |
| Brief details of Serious/Unexpected Adverse Events experienced to date: | No increased infectious episodes seen with the addition of Mabthera in primary treatment. Moderate increase in grade 3/4 Haematologic toxicity rate with concurrent Mabthera | |
| Summary of Results | Superior response rate overall for the addition of Mabthera (82% vs 61%) with higher CR rate (37% vs 14%). The favorable effect of the addition of Mabthera was consistent across histological subtypes, degree of prior therapy, and age. Statistically significant improvements in progression-free survival and overall survival. | |
| Publications: | Semin Oncol 30(Suppl. 2):16-20, 2003. Proceedings European Haematology Association June 2003. | |
| Comments: | First randomisation closed due to higher response rate with the Mabthera arm. All patients now enrolled receive FCM plus Mabthera. Second randomisation +/- Mabthera maintenance (weekly x 4 at 3 and 9 months) remains open. | |

Low grade NHL/Myeloma/CLL

LY03

A randomised trial of chlorambucil vs fludarabine as initial therapy of Waldenstrom's macroglobulinaemia and splenic lymphoma with villous lymphocytes

| | | | |
|--|---|---|----------------------------|
| Trial Chairman: | Steve Johnson (international) John Seymour (ALLG) | | |
| Main Trial Objectives: | Randomised comparison of chlorambucil 8mg/m ² /d x 10 d q 28d, versus fludarabine 25mg/m ² IV daily x 5, q 28d as the first systemic cytotoxic therapy for patients with Waldenstrom's macroglobulinemia, SLVL or lymphoplasmacytic NHL. Primary endpoint is response rate. | | |
| Trial Status: | Open to accrual | | |
| Date study opened: | June 2001 | | |
| Date 1st patient enrolled: | June 2001 | | |
| Accrual target (international): | 400 | Accrual target (ALLG): | 30 |
| Current total accrual (international): | 40 | Current total accrual (ALLG): | 1 |
| Number of participating sites: | 61 internationally, 7 ALLG | Number of sites with patients entered: | 20 internationally, 1 ALLG |
| Expected final accrual date: | 2008 | | |
| Date study closed to accrual: | | | |
| Brief details of Serious/Unexpected Adverse Events experienced to date: | Nil reported to date. | | |
| Summary of Results | Not yet performed | | |
| Publications: | None to date | | |
| Comments: | Still no active institutions with study approval in the following regions: Metropolitan Sydney, Adelaide, Perth, New Zealand. Fludarabine is supplied for study patients from Schering Australia with the likely availability of oral fludarabine in 2004.. | | |

Low grade NHL/Myeloma/CLL

MM6

A multicentre randomised phase III study of low-dose thalidomide, prednisolone and zoledronic acid versus prednisolone and zoledronic acid for post-asct maintenance therapy in patients with multiple myeloma.

| | | | |
|--|--|---|------------------------|
| Trial Chairman: | Andrew Spencer | | |
| Main Trial Objectives: | Evaluate role of low-dose thalidomide as maintenance following ASCT. | | |
| Trial Status: | Open to accrual | | |
| Date study opened: | 26 Feb 2002 | | |
| Date 1st patient enrolled: | 2 April 2002 | | |
| Accrual target (international): | n/a | Accrual target (ALLG): | 224 evaluable patients |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 102 |
| Number of participating sites: | 32 | Number of sites with patients entered: | 22 |
| Expected final accrual date: | Late 2004 | | |
| Date study closed to accrual: | | | |
| Brief details of Serious/Unexpected Adverse Events experienced to date: | 15 SAEs. Predominantly infective. No deaths. | | |
| Summary of Results | | | |
| Publications: | A Spencer, A Roberts, M Bailey, H Schran and K Lynch on behalf of the Australasian Leukaemia and Lymphoma Group. No evidence for an adverse interaction between zoledronic acid and thalidomide: preliminary safety analysis from Australasian Leukaemia and Lymphoma Group (ALLG) MM6 trial. ASH December 2003 | | |
| Comments: | Parallel laboratory/tissue banking and pharmacokinetic studies in progress.. | | |

Low grade NHL/Myeloma/CLL

MM7

A multicentre phase II study of the safety and efficacy of thalidomide post-allogeneic stem cell/bone marrow transplantation in multiple myeloma

Trial Chairman: John Gibson/Doug Joshua

Main Trial Objectives: to determine safety of thalidomide as post allotransplant consolidation and maintenance therapy

Trial Status: Open to accrual

Date study opened: 2002

Date 1st patient enrolled: 04 December 2002

| | | | |
|---|-----|---|----|
| Accrual target (international): | | Accrual target (ALLG) | 20 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 4 |
| Number of participating sites: | 4 | Number of sites with patients entered: | 3 |

Expected final accrual date:

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date: Independent data monitoring committee to be established

Summary of Results

Publications:

Comments:

Low grade NHL/Myeloma/CLL

NHLOW4 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)

Trial Chairman: Max Wolf

Main Trial Objectives: Randomised study of CHOP +/- Mabthera. The objectives are to determine the effect of addition of MabThera to CHOP in relapsed low-grade NHL on response and to determine the effect of maintenance MabThera on progression-free survival.

Trial Status: Open to accrual

Date study opened: 1 February 1999

Date 1st patient enrolled: 1 February 1999

| | | | |
|---|---------------|---|----|
| Accrual target (international): | 752 | Accrual target (ALLG): | 75 |
| Current total accrual (international): | 433 | Current total accrual (ALLG): | 64 |
| Number of participating sites: | 34 | Number of sites with patients entered: | 17 |
| Expected final accrual date: | December 2004 | | |
| Date study closed to accrual: | | | |

Brief details of Serious/Unexpected Adverse Events experienced to date: The Newsletter distributed in February 2003 details the adverse events. There do not appear to be any differences in adverse events between the two arms.

Summary of Results

Publications: nil yet

Comments:

Low grade NHL/Myeloma/CLL

NHLOW5

A randomised multicentre trial of involved field radiotherapy vs involved field radiotherapy plus chemotherapy for stage I-II low grade follicular lymphoma

| | | | |
|--|--|---|-----|
| Trial Chairman: | Michael MacManus/John Seymour | | |
| Main Trial Objectives: | Primary endpoint is progression-free survival with 87% power to detect improvement in 5-year PFS from 60 to 75%. Also powered to detect OS benefit of 15% at 10 years. Central molecular monitoring and second malignancy data collected incorporated. | | |
| Trial Status: | Open to accrual | | |
| Date study opened: | December 1999 | | |
| Date 1st patient enrolled: | December 1999 | | |
| Accrual target (international): | n/a | Accrual target (ALLG): | 200 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 42 |
| Number of participating sites: | 22 | Number of sites with patients entered: | 14 |
| Expected final accrual date: | end 2004 | | |
| Date study closed to accrual: | | | |
| Brief details of Serious/Unexpected Adverse Events experienced to date: | One case grade 3 neurosensory toxicity in chemo arm. | | |
| Summary of Results | | | |
| Publications: | | | |
| Comments: | Five patients from Princess Margaret in Toronto, the remainder Aust/NZ. | | |

Myeloproliferate disease/Myelodisplasia

CML4

Pilot study to determine the efficacy and safety of Glivec (STI571) alone and Glivec (STI571) plus Intron A in the early recovery phase post autologous blood or marrow transplant for advanced phase chronic myeloid leukaemia and Ph-positive acute lymphoblastic leukaemia

Trial Chairman: Tim Hughes/Chris Arthur

Main Trial Objectives: Primary: To assess the safety of Glivec introduced early in the recovery phase post autograft. Secondary: To assess haematological and cytogenetic response to Glivec post autograft; To assess safety and efficacy of combination therapy with alpha interferon and Glivec

Trial Status: Open to accrual

Date study opened: 07 January 2002

Date 1st patient enrolled: January 2002

Accrual target (international): n/a

Accrual target (ALLG) up to 48 evaluable patients

Current total accrual (international): n/a

Current total accrual (ALLG): 15

Number of participating sites: 10

Number of sites with patients entered: 5

Expected final accrual date: end 2004?

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date: SAEs suspected to be caused by Glivec: Haemorrhagic gastritis x1; abdominal pain, gall stones x1

Summary of Results

Publications: nil

Comments:

Myeloproliferate disease/Myelodisplasia

CML5

A phase II study of efficacy and safety of Glivec(r) in patients with chronic myeloid leukaemia and complete or near complete cytogenetic response to interferon-alpha therapy

| | | | |
|--|---|---|----|
| Trial Chairman: | Dr Kerry Taylor | | |
| Main Trial Objectives: | 1. To assess whether switching these patients to Glivec improves response when assessed at a molecular level. 2. To assess the safety of treatment with Glivec in such CML patients who have had prolonged stable complete or near complete response to IFN therapy | | |
| Trial Status: | Open to accrual | | |
| Date study opened: | 18 April 2002 | | |
| Date 1st patient enrolled: | April 2002 | | |
| Accrual target (international): | n/a | Accrual target (ALLG): | 30 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 25 |
| Number of participating sites: | 12 | Number of sites with patients entered: | 9 |
| Expected final accrual date: | end 2003? | | |
| Date study closed to accrual: | | | |
| Brief details of Serious/Unexpected Adverse Events experienced to date: | Herpes simplex unrelated to Glivec. | | |
| Summary of Results | The ALLG explored Imatinib in 22 longstanding IFN-treated CP patients in CCR or near CCR (<10% Ph+ve metaphases). Patients had been in CCR/near CCR for 30 months (6-117) and were 63 (22-176) months from diagnosis. IFN was stopped and Imatinib 400mg daily commenced. Patients were assessed for toxicity and efficacy with serial 3 monthly bone marrow cytogenetic and quantitative bcr-abl/bcr analyses on peripheral blood and marrow. No patients experienced significant toxicity with Imatinib being well tolerated. 15 patients (12- CCR, 3 – near CCR) are assessable following 9 months of Imatinib therapy: six patients have achieved molecular remission (peripheral blood bcr-abl/bcr analysis) while three patients have reduced levels and six patients stable levels on peripheral blood bcr-abl/bcr analyses since study commencement. This latter group tended to contain those who have already exhibited major molecular response on Interferon whereas patients who achieved molecular remission or significant reduction tended to be those who had not achieved such pre-trial responses. There was no significant difference between the median peripheral blood and bone marrow values at each assessment timepoint emphasizing suitability of peripheral blood for molecular monitoring. Crossover to Imatinib in long term IFN-treated patients is safe and can produce significant molecular remissions without toxicity. The efficacy in this setting supports studies investigating combined or sequential IFN-Imatinib approaches in chronic phase. | | |
| Publications: | 2003 HSANZ/ASH abstracts. | | |
| Comments: | Accrual continues. No significant toxicity. Encouraging early results. | | |

Myeloproliferate disease/Myelodisplasia

PT1

A Medical Research Council randomised trial to compare aspirin vs hydroxyurea/aspirin in intermediate risk primary thrombocythaemia, and hydroxyurea/aspirin vs anagrelide/aspirin in high risk primary thrombocythaemia

| | | |
|--|--|---|
| Trial Chairman: | Andrew Grigg | |
| Main Trial Objectives: | To define the natural history and optimal treatment of various risk groups of primary thrombocythaemia. | |
| Trial Status: | Open to accrual | |
| Date study opened: | June 1997 | |
| Date 1st patient enrolled: | 12 July 1997 (international), 4 August 1997 (Australia) | |
| Accrual target (international): | 600 patients in each of the 3 risk groups | Accrual target (ALLG) |
| Current total accrual (international): | low risk: 61 intermediate risk: 118 (2 excluded) high risk: 818 (11 excluded) | Current total accrual (ALLG): 30 |
| Number of participating sites: | 9 | Number of sites with patients entered: 6 |
| Expected final accrual date: | 2004 perhaps for the low and intermediate risk groups | |
| Date study closed to accrual: | | |
| Brief details of Serious/Unexpected Adverse Events experienced to date: | see below | |
| Summary of Results | Preliminary analysis of the high risk group suggests an adverse early outcome (more vaso-occlusive events and myelofibrosis) in the anagrelide arm, prompting the principal investigators to recommend cessation of anagrelide in these patients | |
| Publications: | | |
| Comments: | The trial still accruing patients in the low and intermediate risk groups; the high risk is closed to accrual . | |

TRIALS CLOSED TO ACCRUAL IN 2003

Bone Marrow Transplantation

BM01 **Mini allograft study in chronic myeloid leukaemia and myeloma**

Trial Chairman: Tim Hughes/Peter Bardy

Main Trial Objectives: To assess the timing and characteristics of donor engraftment inpatients receiving T-cell depleted peripheral blood stem cell allografts after non-myeloablative conditioning therapy

Trial Status: Open to accrual

Date study opened: January 1999

Date 1st patient enrolled: 18 August 1999

| | | | |
|---|-----|---|----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 40 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 42 |
| Number of participating sites: | 7 | Number of sites with patients entered: | 5 |

Expected final accrual date:

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date: The last protocol modification was aimed at addressing an unacceptably high rate of failed T-cell engraftment. Two patients have been transplanted using the active protocol

Summary of Results: Analysis currently underway.

Publications:

Comments: Trial amended in December 2000 to include NHL and CLL patients and in January 2002 to see the addition of Mycophenolate to immunosuppression regimen. The later amendment has been accepted at RMH campus where accrual continues. Resubmission at Royal Adelaide is anticipated in last quarter of 2002. Six patient slots are available to complete accrual..

Bone Marrow Transplantation

BM02

Pamidronate post allogeneic bone marrow transplantation

Trial Chairman: Andrew Grigg

Main Trial Objectives: To assess whether pamidronate prevents loss of bone density after allogeneic BMT

Trial Status: Closed to accrual

Date study opened: March 1999

Date 1st patient enrolled: March 1999

| | | | |
|---|-----|---|-----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 120 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 120 |
| Number of participating sites: | 5 | Number of sites with patients entered: | 5 |

Expected final accrual date:

Date study closed to accrual: September 2002. Last patient reached one year F/U 09/03

Brief details of Serious/Unexpected Adverse Events experienced to date: None

Summary of Results: Not yet available

Publications:

Comments: Primary endpoint is reduction in bone loss at 1 year. Analysis underway pending financial support for stats. analysis. Awaiting CRF forwarding from sites..

Intermediate and high grade NHL/HD

NHL10 Intergroup trial of first line treatment for patients with diffuse large-cell non-Hodgkin's lymphoma with a CHOP-like chemotherapy regimen with or without the anti-CD20 antibody rituximab (IDEC-CSB8)

Trial Chairman: David Ma/Devinder Gill

Main Trial Objectives: To evaluate the efficacy and tolerability of addition of CD20 antibody to standard combination chemotherapy in untreated patients with intermediate grade NHL with low IPI.

Trial Status: Open to accrual

Date study opened: 8 February 2001

Date 1st patient enrolled: 8 February 2001

| | | | |
|---|-----|---|----|
| Accrual target (international): | 820 | Accrual target (ALLG): | 80 |
| Current total accrual (international): | 820 | Current total accrual (ALLG): | 84 |
| Number of participating sites: | 31 | Number of sites with patients entered: | 24 |

Expected final accrual date: Oct 2003

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date: Up until May 03 there were 268 SAE's in 173 patients of which 9 were life threatening. Five patients died. Further details are not available.

Summary of Results: First safety analysis due Nov 03.

Publications: None to date

Comments:

Laboratory Science Studies

LS06

FLT3 mutations in APL

Trial Chairman: Harry Iland

Main Trial Objectives: To determine the frequency and significance of FLT3 mutations, including internal tandem duplications (ITD) and point mutations, in patients treated on the APLM3 trial

Trial Status: Closed to accrual

Date study opened: January 2001

Date 1st patient enrolled:

Accrual target (international):

Accrual target (ALLG): Patients registered on the APLM3 trial

Current total accrual (international):

Number of participating sites: Laboratory studies based in the Kanematsu Laboratories, Royal Prince Alfred Hospital

Current total accrual (ALLG):
Number of sites with patients entered:

Expected final accrual date: October 2002

Date study closed to accrual:

Brief details of Serious/Unexpected Adverse Events experienced to date:
Summary of Results

Detection of FLT3 internal tandem duplications and point mutations involving codons 835 and 836 has been successfully achieved. Analysis of the effect (if any) of these mutations on response to therapy, relapse rate and survival will be performed once accrual has been completed and followup data are sufficiently mature. Our data suggest that FLT3 ITD are very frequent in APL patients (approximately 36%), and a strong correlation between ITD and bcr3 breakpoints has been identified. A further 8% of patients have mutations in and around codons 835/836 of FLT3.

Publications:

Comments:

Low grade NHL/Myeloma/CLL

CLL3 **Randomized study of Fludarabine and Cyclophosphamide with or without Genasense (Bcl-2 antisense oligonucleotide) in patients with relapsed or refractory chronic lymphocytic leukemia**

Trial Chairman: John Seymour (ALLG)

Main Trial Objectives: To compare the proportion of patients with relapsed or refractory CLL (prior treatment including fludarabine) randomized to treatment with fludarabine plus cyclophosphamide (Flu/Cy) vs. Flu/Cy combined with Genasense (Bcl-2 antisense oligonucleotide) who achieve a complete response (CR) or nodular partial response (n-PR)

Trial Status: Closed to accrual

Date study opened: Unknown

Date 1st patient enrolled: Unknown

Accrual target 200

(international):

Current total accrual Unknown

(international):

Number of participating Unknown internationally. 14

sites: ALLG sites participated

Accrual target 30

(ALLG)

Current total accrual (ALLG):

Number of sites with patients entered:

Expected final accrual date:

Date study closed to accrual: July 2003

Brief details of Serious/Unexpected Adverse Events experienced to date: None reported

Summary of Results

Publications: None.

Comments: Accrual closed, follow-up of treated patients continuing, final analysis of response rates expected in Q1 2004..

Myeloproliferate disease/Myelodisplasia

CML6

A phase II study in adult patients with newly-diagnosed chronic myeloid leukaemia of initial intensified Glivec therapy and sequential therapy for non-responders

Trial Chairman: Tim Hughes/Andrew Grigg

Main Trial Objectives: To assess overall rates and duration of CCR and MR achieved using a schedule of intensive, escalated and combination therapy with Glivec, in association with Figrastim support, in adults with newly diagnosed chronic phase CML over a 2 year period

Trial Status: Closed to accrual

Date study opened: October 2002

Date 1st patient enrolled: October 2002

| | | | |
|---|-----------------|---|-----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 100 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 103 |
| Number of participating sites: | 19 | Number of sites with patients entered: | 19 |
| Expected final accrual date: | 01 October 2003 | | |
| Date study closed to accrual: | | | |

Brief details of Serious/Unexpected Adverse Events experienced to date:

- SAE is suspected to be caused by Glivec
- Menorrhagia x1
- Anaemia x7
- Febrile neutropenia x1
- headaches and nausea x3
- peripheral oedema x1
- fatigue x1
- diarrhoea x3
- acute pancreatitis x2
- Thrombocytopenia x1
- cholecystitis x1
- acute renal failure x1

Summary of Results

Publications: ASH abstract and oral presentation

Comments: Sites must be able to collect, process and delivery samples for molecular monitoring to the IMVS every 2 months to allow complete data collection and real time monitoring.

TRIALS WITH ANALYSIS TO BE PRESENTED IN 2003

Acute leukaemia

AML M8 **A phase 2 study of mitozantrone and intermediate dose cytarabine in fit patients over 60 years of age with de novo acute myeloid leukemia**

Trial Chairman: Andrew Grigg

Main Trial Objectives: To evaluate complete response rate, remission duration and overall survival in patients over 60 years with de novo AML treated with intermediate dose cytarabine and mitozantrone

Trial Status: Undergoing analysis

Date study opened: Nov 1995

Date 1st patient enrolled: 15 July 1996

| | | | |
|---|-----|---|----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 45 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 45 |
| Number of participating sites: | 14 | Number of sites with patients entered: | 14 |

Expected final accrual date:

Date study closed to accrual: 5 May 2000

Brief details of Serious/Unexpected Adverse Events experienced to date: There were 4 instances of grade 4 toxicity, all in induction: 3 haematological, 1 cardiac. Besides alopecia, the grade 3 toxicities were limited to cutaneous (3 instances), N&V (4), Diarrhoea (2) and stomatitis (3) and occurred in both Induction and consolidation.

Summary of Results Final analysis virtually completing - awaiting decision on eligibility of a couple of patients

Publications:

Comments:

Bone Marrow Transplantation

BM03

MabThera post autograft for mantle cell lymphoma

Trial Chairman: Andrew Grigg

Main Trial Objectives: To assess the tolerability of MabThera post autograft; molecular analysis as a secondary end-point

Trial Status: Closed to accrual

Date study opened: May 1999

Date 1st patient enrolled: June 1999

| | | | |
|---|-----|---|----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 12 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 13 |
| Number of participating sites: | 8 | Number of sites with patients entered: | 5 |

Expected final accrual date:

Date study closed to accrual: 31st October 2001

Brief details of Serious/Unexpected Adverse Events experienced to date: Following a detailed Australian and international review of all SAE's, performed July 2001, consensus was that no SAE's were attributable to mabthera.

Summary of Results: Pending last patient completing 2 year assessments. Presented at HSANZ meeting in Christchurch.

Publications:

Comments: Final patient completing two year assessment late September enabling analysis to be completed..

Intermediate and high grade NHL/HD

HDNHL1 **A phase II study of comprehensive irradiation with peripheral blood progenitor cell transplantation in Hodgkin's disease and non-Hodgkin's lymphoma**

Trial Chairman: Andrew Wirth

Main Trial Objectives: To evaluate the toxicity and efficacy of pre- and post-autograft radiotherapy to sites of bulk disease in relapsed lymphoma patients

Trial Status: Undergoing analysis

Date study opened: March 1997

Date 1st patient enrolled: 1997

| | | | |
|---|-----|---|----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 31 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 30 |
| Number of participating sites: | 5 | Number of sites with patients entered: | 5 |

Expected final accrual date:

Date study closed to accrual: 17 December 1999

Brief details of Serious/Unexpected Adverse Events experienced to date: During pre-transplant RT: 2 patients with grade 3 haematological toxicity, no grade 4. During/after post-transplant RT: 4 patients with grade 3 haematological toxicity, no grade 4

Summary of Results

Publications:

Comments: Manuscript currently in preparation. Follow-up study now open.

Intermediate and high grade NHL/HD

HDNHL3 Phase II study of DICE chemotherapy in patients with lymphoma

Trial Chairman: Miles Prince

Main Trial Objectives: Toxicities, Response Rates, PFS, OS

Trial Status: Undergoing analysis

Date study opened: July 1997

Date 1st patient enrolled: 17 July 1997

| | | | |
|---|-----|---|----|
| Accrual target (international): | n/a | Accrual target (ALLG): | 40 |
| Current total accrual (international): | n/a | Current total accrual (ALLG): | 40 |
| Number of participating sites: | 5 | Number of sites with patients entered: | 5 |

Expected final accrual date: 2003

Date study closed to accrual: 26 April 2000

Brief details of Serious/Unexpected Adverse Events experienced to date: Grade III/IV hematological and non-hematological toxicity rates were 78% and 33%, respectively, and were not significantly higher for the ³ 55 age cohort.

Summary of Results O-DICE is effective, suitable as a salvage regimen, well tolerated in poor prognosis and older patients, and can be delivered in an outpatient setting.

For the entire cohort, ³ 55y, <55yr, the estimated 2yr overall survival (OS) was 54%, 45% and 66%, respectively. For the entire cohort, ³ 55y, <55yr the estimated 2yr progression-free survival (PFS) was 29%, 18% and 44%, respectively.

Publications: Final draft manuscript due for submission end November

Comments:

Intermediate and high grade NHL/HD

NHL08

Trial to evaluate early high dose therapy (HDCT) and autologous bone marrow transplantation (ABMT) as part of planned initial therapy for poor risk intermediate grade non Hodgkin's lymphoma

Trial Chairman: Joe McKendrick

Main Trial Objectives: To compare elective auto transplantation in first remission with standard chemotherapy in patients with poor prognosis intermediate grade NHL.

Trial Status: Undergoing analysis

Date study opened: January 1992

Date 1st patient enrolled: 4 December 1992 (ALLG)

| | | | |
|---|-----|---|----|
| Accrual target (international): | 500 | Accrual target (ALLG): | |
| Current total accrual (international): | 456 | Current total accrual (ALLG): | 48 |
| Number of participating sites: | 11 | Number of sites with patients entered: | 11 |

Expected final accrual date:

Date study closed to accrual: 31 October 2001

Brief details of Serious/Unexpected Adverse Events experienced to date: Nil.
Summary of Results

Publications:

Comments:

Laboratory Science Studies

LS05

Quantitative RT-PCR for PML-RARa in APL

| | |
|--|--|
| Trial Chairman: | Harry Iland |
| Main Trial Objectives: | To establish quantitative real-time RT-PCR using DNAzyme technology for PML-RARa rearrangements in patients enrolled in the APML3 trial. Variables to be examined include the number of transcripts at diagnosis and at each phase of treatment, the rate of decline of transcripts during initial induction/consolidation, and the value of rising levels in predicting relapse. |
| Trial Status: | Closed to accrual |
| Date study opened: | 2001 |
| Date 1st patient enrolled: | |
| Accrual target (international): | Accrual target (ALLG) patients enrolled in APML3 |
| Current total accrual (international): | Current total accrual (ALLG): |
| Number of participating sites: | Samples from all patients enrolled in the APML3 trial. The laboratory work is performed at Johnson & Johnson Research Laboratories through a collaboration with Dr Alison Todd and Tanya Applegate. Number of sites with patients entered: |
| Expected final accrual date: | October 2002 |
| Date study closed to accrual: | 24 June 1905 |
| Brief details of Serious/Unexpected Adverse Events experienced to date: | |
| Summary of Results | Preliminary data suggest that single round quantitative RT-PCR is at least as sensitive as nested non-quantitative analysis, and rising levels precede haematological and cytogenetic relapse. |
| Publications: | Applegate TL, Iland HJ, Mokany E and Todd AV: Diagnosis and molecular monitoring of acute promyelocytic leukemia using DzyNA RT -PCR to quantify PML/RARa fusion transcripts. Clin Chem 48:1338-1343, 2002. Applegate TL, Iland HJ, Mokany E and Todd AV: Mol |
| Comments: | Quantitation of PML-RARa transcripts with bcr1, bcr2 and bcr3 breakpoints has been successfully achieved. Studies are currently in progress to determine if there is any relationship between PML-RARa transcript levels and (i) PML breakpoint; (ii) the presence or absence of FLT3 mutations (internal tandem duplications and codon 835/836 mutations). |

NATIONAL AND INTERNATIONAL COLLABORATIONS

National collaborations 2003

Trans-Tasman Radiation Oncology Group

International collaborations 2003

Medical Research Council - MRC (UK)

European Organisation for Research and Treatment of Cancer - EORTC (Belgium)

Mabthera International Trial (MINT) Study Group – coordinated by the German High Grade NHL Study Group (Germany)

Groupe d'Etude des Lymphomes de l'Adulte – GELA (France)

National Cancer Research Institute – NCRI (UK)

Nordic group (coordinators of the International Phase III-Trial in B-cell CLL) (based in Sweden)

International Extranodal Study Group (Switzerland)

Central and Southern Lymphoma Group (UK)

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