# IELSG-15 Study

**A Retrospective International Study of Primary Lymphoma of the Breast**

## Principal Investigators
- **Gail Ryan**
  - Peter MacCallum Cancer Institute
  - Melbourne, Australia
- **Giovanni Martinelli**
  - Istituto Europeo di Oncologia
  - Milano, Italia

## Other Investigators
- **Julie Vose**
  - University of Nebraska Medical Center
  - Omaha, Nebraska, U.S.A.
- **Barbara Pro**
  - M.D. Anderson Cancer Center
  - Houston, Texas, U.S.A.
- **John Seymour**
  - Peter MacCallum Cancer Institute
  - Melbourne, Australia

## Statistician
- **Richard Fisher**
  - Peter MacCallum Cancer Institute
  - Melbourne, Australia

## Pathologist
- **Giancarlo Pruneri**
  - Istituto Europeo di Oncologia
  - Milano, Italia

## Data Managers
**Europe / UK:**
- **Katia de Luzio**
  - Data Manager, Divisione di Ematologia Clinica
  - Istituto Europeo di Oncologia
  - via Ripamonti 435
  - 20141 Milano, Italia

**All other countries:**
- **Kate Reed**
  - Data Manager, Statistical Centre
  - Peter MacCallum Cancer Institute
  - Locked Bag 1, A’Beckett Street
  - Melbourne, Victoria, Australia, 8006

## Institutions Involved
- All IELSG-affiliated institutions

## Date of Protocol
- 26 November, 2001
CONTENTS

1 OBJECTIVES
2 BACKGROUND
3 SELECTION CRITERIA
4 DATA TO BE COLLECTED
5 ENDPOINTS
  5.1 ENDPOINT DEFINITIONS
  5.2 TIME-TO-EVENT VARIABLES
6 STATISTICAL CONSIDERATIONS
  6.1 POWER CALCULATIONS
  6.2 ANALYSES
7 SCHEDULE
8 STUDY MANAGEMENT
  8.1 CASE RECORD FORMS
  8.2 PATHOLOGY REVIEW
  8.3 CONFIDENTIALITY
9 PUBLICATION OF RESULTS
10 REFERENCES
1 OBJECTIVES

By
• retrospectively collecting data on all primary breast lymphomas treated in each participating institution and
• setting up a data base which includes patient characteristics, diagnostic and treatment modalities, relapse-free survival and overall survival

To
1. document treatment outcomes
2. identify any significant prognostic factors
3. review patterns of failure
4. make management recommendations based on the study results that can be evaluated in a prospective fashion

The study aims to answer questions of interest that have not been adequately addressed by series reported in the literature to date, specifically
• What features, if any, of primary breast lymphoma suggest that it should be treated differently to lymphomas of the same histology and stage presenting at other sites?
• If such features are identified, should a change in management be recommended to address these, e.g. is there a role for CNS prophylaxis or prophylactic irradiation of the uninvolved breast?

2 BACKGROUND

Primary lymphoma of the breast (PBL) is a rare clinico-pathological entity that accounts for 0.04-0.05% of all breast malignancies and less that 1% of all non-Hodgkin’s lymphomas. It comprises only 2% of localized extranodal presentations of lymphomas. Around 300 cases only have been identified in the literature, with most series consisting of less than ten patients. Almost all tumours are of B-cell lineage, with intermediate or high grade histology predominant, although follicular and MALT lymphomas have been described.

The largest individual series with clinical followup has been reported by Giardini et al. Thirty-five patients presenting with Stage I or II PBL were identified over a 30 year period. The commonest histology was diffuse large cell lymphoma (17 patients) with only 7 patients having low-grade histology. A variety of single and combined modality treatments were used. With a mean followup of 45 months, 17 patients had died of their disease, with an overall 5 year survival of 43%. Stage and histology were significant prognostic factors. Au et al. described a similar experience with their series of 14 cases over the period 1974 – 1996. With a median followup of 60 months, only five patients were still alive, one with relapsed disease. A number of CNS relapses were seen. Ha et al. analysed 23 patients with PBL treated between 1982 and 1994. He found a better survival in his group, despite similar patterns of histology and treatment, with a 5 year overall survival of 74% and relapse-free survival of 73% (65% and 70% respectively for patients with diffuse large cell lymphoma). Stage and International Prognostic Index were found to be statistically significant prognostic factors. A study of 19 patients by DeBlasio et al. showed a 66% survival at 4 years. Domchek at al. have identified a similar prognosis in their series containing 23 patients with PBL treated since 1988. With relatively short followup (median 28 months), 6 of 10 intermediate grade and 1 of 5 high grade patients treated with chemotherapy +/ radiotherapy remain in remission; 8 of 9 patients with low grade histology are alive at a median followup time of 46 months. They concluded that the outcome was dependent on histology and paralleled the outcome in other sites.

The reported series present a considerable divergence of results and conclusions. The majority consider this to be an unfavourable site of presentation, with significantly poorer prognosis than other early stage lymphomas, but this is not uniform. The rarity of the disease, variable treatment modalities and paucity of literature make it difficult to make valid conclusions about the epidemiology of the condition, most appropriate management, prognosis, and special features of this presentation compared with other sites of lymphoma presentation.
3 SELECTION CRITERIA

A patient will be included in this study if all of the following criteria are satisfied:

1. Histologically-proven non-Hodgkin’s lymphoma of the breast
2. Primary site one or both breasts with or without regional lymph nodal involvement
3. Presentation to the participating institution from January, 1980, onwards

A patient will be excluded if:

Presentation with recurrent or progressive lymphoma

Note that:

• Patients with either unilateral or bilateral presentation will be eligible. The staging of extranodal lymphoma presenting with involvement of both of a pair of organs remains controversial; but for the purposes of this study, patients with synchronous bilateral presentation are still eligible if there is no evidence of spread beyond the regional lymph nodes. These patients will be coded as Stage IV disease but will be considered to have one extranodal site for purposes of the International Prognostic Index.

• Patients presenting with either systemic disease with breast involvement or with recurrent lymphoma in the breast following earlier treatment of systemic disease are excluded

• All types of treatment will be eligible
4 DATA TO BE COLLECTED

Eligible patients will be identified through the contributing institution’s computerised medical record database using the appropriate ICD code

Data to be collected include:

- Epidemiological data
- Clinical characteristics
- Diagnostic modalities and their adequacy
- Biochemical parameters
- Histological diagnosis

- Type of surgery
- Radiotherapy dose, fractionation and fields
- Chemotherapy dose, agents used, number of cycles (systemic and intrathecal)

- Response
- Site of relapse
- Therapy of relapse
- Progression-free survival, disease-free survival, overall survival

- Central histological, immunophenotypic, and molecular review where feasible
5 ENDPOINTS

This retrospective study will be able to make a significant contribution to the literature on this rare lymphoma. The study will provide an overview of treatment practice and outcomes, and will examine the specific questions of interest detailed in the Objectives section. It is likely that results will suggest changes to current management practices that can be incorporated into a prospective study following on from this retrospective study.

5.1 Endpoint Definitions

Response
Response will be assessed one month after completion of planned initial therapy. Most patients will have achieved a complete response (CR) at that time. It is likely that the rare patient who has not achieved CR at that stage would undergo second line therapy and may subsequently achieve CR. The patient should, however, still be attributed the response category applicable at the planned assessment point. Details of subsequent therapy should be recorded.

A clinically residual mass in the breast at the end of treatment which is negative on functional imaging should be recorded as CR. If functional imaging has not been performed in this situation, but there is no evidence of subsequent progression in the breast, the response should be recorded as CR. If there is subsequent progression in the breast, then the response category should be recorded as PR or SD as per World Health Organisation criteria for response.¹

Complete response – CR – complete disappearance of all disease clinically and on imaging lasting at least four weeks
Partial response – PR – reduction of at least 50% in the size of the tumour for at least 4 weeks
Stable disease – SD – less than 50% reduction or less than 25% increase in the size of the tumour
Progressive disease – PD - increase of 25% or more in the size of the tumour

Relapse or progression
Dates and sites of first and second relapse/progression will be recorded.

Death
Date and cause of death should be documented. Relapse-free and overall survival will be estimated.

5.2 Time-to-event variables

All time will be measured from the start date of treatment for the primary breast lymphoma.

<table>
<thead>
<tr>
<th>Type</th>
<th>Patient subset</th>
<th>From*</th>
<th>To</th>
<th>Censored by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to locoregional</td>
<td>All patients</td>
<td>Treatment start date</td>
<td>Locoregional relapse</td>
<td>Close-out date</td>
</tr>
<tr>
<td>relapse</td>
<td></td>
<td></td>
<td></td>
<td>Loss to followup</td>
</tr>
<tr>
<td>Time to any relapse</td>
<td>All patients</td>
<td>Treatment start date</td>
<td>Relapse at any site</td>
<td>Close-out date</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Loss to followup</td>
</tr>
<tr>
<td>Relapse-free survival</td>
<td>All patients</td>
<td>Treatment start date</td>
<td>Relapse or death</td>
<td>Close-out date</td>
</tr>
<tr>
<td>Overall survival</td>
<td>All patients</td>
<td>Treatment start date</td>
<td>Death (any cause)</td>
<td>Close-out date</td>
</tr>
</tbody>
</table>

Potential follow-up time

The potential follow-up time for each patient will be the time from treatment start to the close-out date (see Section 6.2) for patients who have died or are still being followed up, and will be to the last date of follow-up for patients lost to follow-up. A minimum of one year’s follow-up will be required for inclusion in the primary analyses.
6  STATISTICAL CONSIDERATIONS

6.1  Power calculations

It is expected that about 300 patients, treated at contributing centres since 1980, will be entered into the study. The RFS rate and OS rate at 10 years are estimated to be about 50% and 60%, respectively. These figures would enable both the RFS and OS rates at 5 and 10 years to be estimated with standard errors of about 3.0% and 3.3%, respectively. Also, a difference in 10-year RFS rates of 20% (e.g. 60% vs 40%) between stages I and II could be detected with a probability (power) of about 90%.

6.2  Analyses

Statistical analysis will be performed by the study statistician, Dr. Richard Fisher, of the Peter MacCallum Cancer Institute.

The patient population used for the main analysis of the study will be those patients who received at least part of their initial treatment at the participating institution, and who enter the study at least one year prior to the close-out date. Survival times etc will be measured from the date of treatment start, unless treatment started prior to presentation at the participating institution, in which case the times will be measured from the date of presentation. This is done to avoid bias.

A close-out date for analysis will be determined from the earliest date of last follow-up from patients still alive and not lost to follow-up. All follow-up beyond this date will be ignored for the purposes of analysis in order to reduce bias. Patients who are still alive at the close-out date will have their time-to-event (time to relapse, relapse-free and overall survival duration) censored at that date and patients lost to follow-up before the close-out date will have their time-to-event censored at the date they were last known to be alive.

Time-to-event curves – time to relapse, relapse-free survival (RFS) and overall survival (OS) – will be estimated using the Kaplan-Meier method.

All prognostic factors are currently speculative. Those prognostic factors examined will include age, stage, bilaterality and histology (diffuse large cell). Comparisons of prognostic factor subgroups with respect to RFS, OS and time to relapse will be made using the logrank test. Assessment of continuous variables and of several variables simultaneously will be carried out using Cox regression. The cumulative incidences of local relapse (breast), distant relapse and death without prior relapse will be analysed in a competing risks analysis.

Interpretation of results

This being a retrospective study, accuracy and completeness of the data will not be ideal and there will be factors influencing outcome which will not be able to be controlled for in analyses. Hence, conclusions will only be suggestive and not definitive.
7 SCHEDULE

PHASE 1.
Collection of all the primary breast lymphoma cases treated in each Institution from 1980
Transfer of data onto Case Record Forms (CRFs)

PHASE 2.
CRFs and pathological material sent to IELSG Trials Coordination Centre by individual contributing sites

PHASE 3.
CRFs forwarded to data entry centres (Milano for Europe/UK, Melbourne for all other countries)
Pathological material forwarded to Milano
Transfer of collected data onto local data bases

PHASE 4.
Databases merged for analysis
Central analysis of data - Melbourne
Central histology review (according to REAL classification) - Milan
-immunophenotypic and molecular analysis where possible
-pathological review data included in database

PHASE 5.
Presentation and publication of data
Recommendations for future studies
8 STUDY MANAGEMENT

8.1 Case report forms

Data collected on each patient should be recorded on the approved CRF. CRFs may be completed by the site investigator or data manager. The site investigator is responsible for ensuring that all blank data spaces on each form are completed. A copy of the completed CRF should be retained by the site investigator for reference, and the original paper copy sent to IELSG headquarters:

Ms. Cristina Morinini
Trials Coordination Centre
International Extranodal Lymphoma Study Group
Istituto Oncologico della Svizzera Italiana
Ospedale San Giovanni
CH-6500 Bellinzona
Switzerland
Phone ++41 91 820 90 40 - 820 91 11
Fax ++41 91 820 91 82
E-mail <ielsg@ticino.com>

CRFs may be sent in batches rather than individually.

8.2 Pathology review

Central Pathology review is an important aspect of this study. The study Pathologist is Dr. Giancarlo Pruneri, of the Istituto Europeo di Oncologia, Milano. A variety of classification systems and pathological techniques have been in use during the study period, and reclassification of cases under the REAL/WHO system using standardized testing procedures is highly desirable. However, it is recognised that it may not be possible to obtain or transport original pathological material for review in all cases.

Instructions for Pathology Review

1. **Mandatory** - copy of the full original pathology report to be sent with the CRF

2. **Desirable** - representative paraffin block (preferred) OR fifteen unstained paraffin sections suitable for immunostaining OR full set of H&E and immunostained sections including controls pathology reports pertaining to any subsequent recurrences

Immunostaining with the following antigens is recommended:

- CD3, CD5, CD10, CD20, CD23, CD43, cyclin D1, bcl-2, bcl-6, Ki-67 for "small cell" B-lymphomas
- CD3, CD10, CD20, Ki-67 for diffuse large B-cell lymphomas
- CD3, CD5, CD10, CD20, CD34, CD79a, TdT, Ki-67, for Burkitt, Burkitt-like, and ALL
- CD3, CD4, CD5, CD30, CD56, TIA-1, granyme B, perforin for T-cell lymphomas
- CD3, CD5, CD15, CD20, CD30, p80/ALK and fascin for HD/ALCL

IgH gene and TCR receptor rearrangement analyses may be required for small biopsies where assessment of monoclonality is difficult on histology / immunostaining.

Analysis of bcl-2 (PCR) and bcl-1 gene translocation (PCR and FISH on paraffin section) will be performed by the central review laboratory for difficult cases (CD10 and bcl-2 negative follicular lymphomas, mantle cell lymphoma unreactive for CD5 due to overfixation).

The central laboratory is also interested in analyzing t(11;18) translocation in marginal zone lymphoma (RT-PCR or FISH).

All pathological material should be forwarded to IELSG headquarters (as above) for submission to the Pathology reviewer. The central reviewer may request additional material if necessary.
8.3 Confidentiality

Patient privacy and confidentiality will be respected. All information provided will be confined to the personnel involved in conducting the study. No identification of individual patients will be made in any presentation or publication.

9 PUBLICATION OF RESULTS

It is intended that a manuscript will be prepared for submission in an appropriate journal.

- Authorship on publications and presentations will comprise the study personnel who have made a significant contribution to the scientific content of the study and have reviewed and approved the manuscript.
- The principal investigator will be the first author on publications reporting the main aims of the study.

Presentations and publications will not be made without the knowledge and consent of all authors.
10 REFERENCES


8. Shipp M. Personal communication.