2nd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 13-14, 2021

Starhotels Majestic

Scientific board:
Marco Ladetto (Alessandria)
Umberto Vitolo (Candiolo-TO)

Impact of Lugano conferences on the lymphoma research

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Lymphoma research aim

- Better understanding of the disease
- Better outcome of the patients
- Practice change

Evolution of lymphoma understanding and treatment from 1-ICML (1981)

- What has changed since then?

The Lugano Workshops

- **1990** Prognostic models in DLCL
- **1993** Classification of GI-NHL
- **1996** REAL classification validation
- **1999** DLBCL molecular biomarkers
- **2002** Primary CNS Lymphoma
- **2005** Peripheral T-cell lymphomas
- **2008** NHL in developing countries
- **2011** Staging and response criteria
- **2013** Tailored treatment in DLBCL
- **2015** Follicular Lymphoma
- **2017** Endpoints in NHL clinical trials
- **2019** Liquid biopsy in lymphoma

What we knew before 1-ICML (1981)

- HD: Infectious disease? Neoplastic?

  Long term remissions with MOPP

- NHL: Six classifications

  First long-term remissions (cures?) for advanced diffuse histiocytic lymphoma with C-MOPP and CHOP

De Vita et al.: The Lancet 1975; 1:248-250
Jones et.al: Cancer 1979; 43:417-425

ON SOME

MORBID APPEARANCES

OF

THE ABSORBENT GLANDS

AND

SPLEEN.

BY DR. HODGKIN.

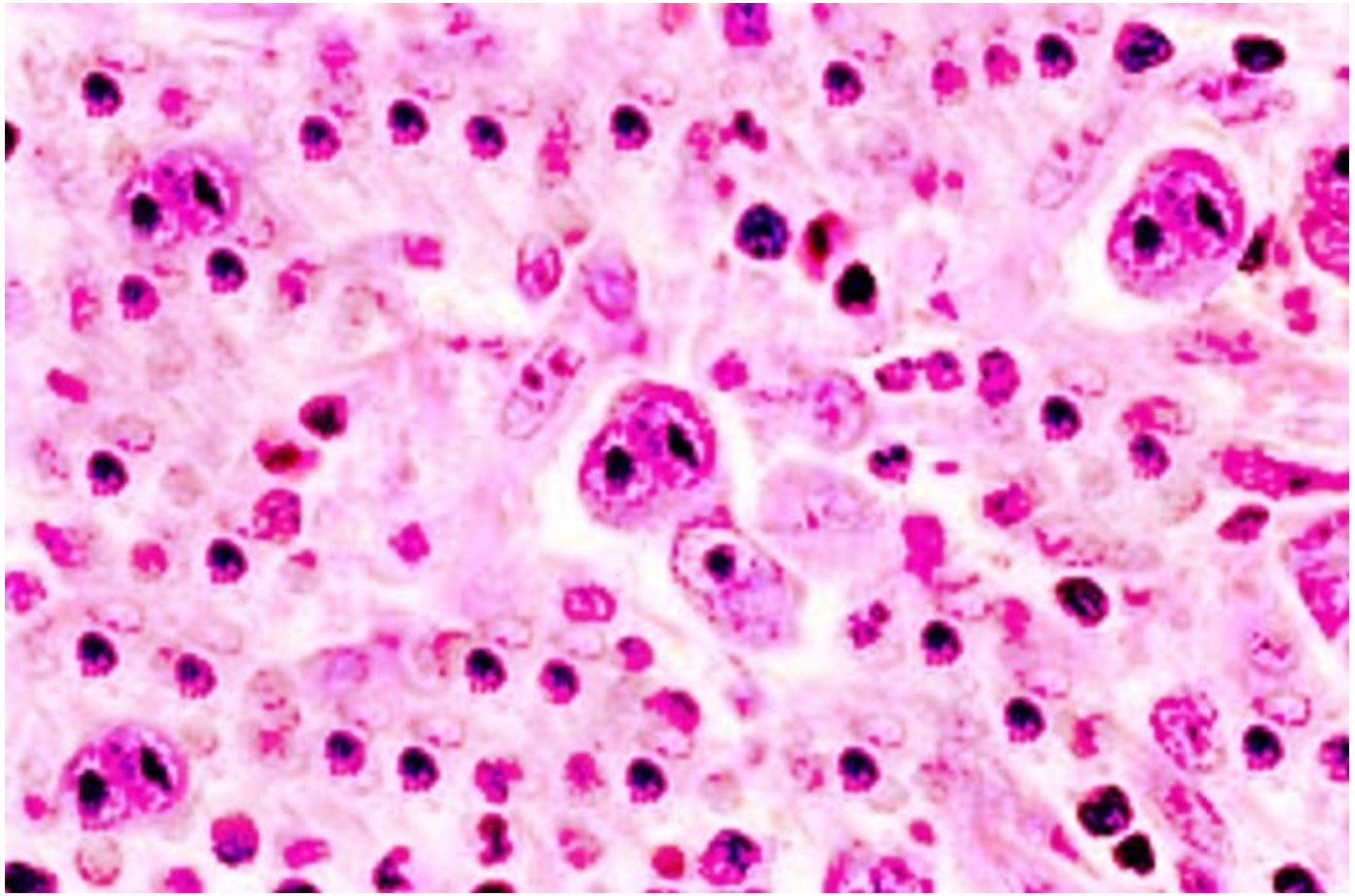
PRESENTED

BY DR. R. LEE.

READ JANUARY 10TH AND 24TH, 1832.

THE morbid alterations of structure which I am about to describe are probably familiar to many practical morbid anatomists, since they can scarcely have failed to have fallen under their observation in the course of cadaveric inspection. They have not, as far as I am aware, been made the subject of special attention, on which account I am induced to bring forward a few cases in which they have occurred to myself, trusting that I shall at least escape severe or general censure, even though a sentence or two should be produced from some existing work, couched in such concise but expressive language, as to render needless the longer details with which I shall trespass on the time of my hearers.

Reed Sternberg Cells



Aggarwal P and Limaiem F. 2021 PMID: 31194473

The mystery of HD/HL

- Still at 5-ICML, in 1993
  « Is Hodgkin's disease an infectious disease?»

  Diehl. Abstract 20. Ann. Oncol. Suppl.2, 1994:105-111

- Hodgkin's disease becomes Hodgkin's lymphoma with the WHO classification in 2001

  Stein. Hodgkin lymphomas: Introduction. In WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 3° edition, IARC Press, Lyon 2001

The mystery of HD/HL (II)

Cell of origin: «Could be a lymphocyte»

- 1-ICML (1981):

  Kaplan, Abstr. 2

- 2-ICML (1984): “The bulk of current evidence favours (…) the interdigitating reticulum cell”

  Berard, Abstr. 72

- 4-ICML (1990): «These findings support the notion that these cells are lymphocytic in origin, and that EBV is involved inthe pathogenesis of a significant number of cases of Hodgkin’s disease»

  Stein, Abstr. 01

The mystery of HD/HL (III)

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 10962–10966, November 1994
Medical Sciences

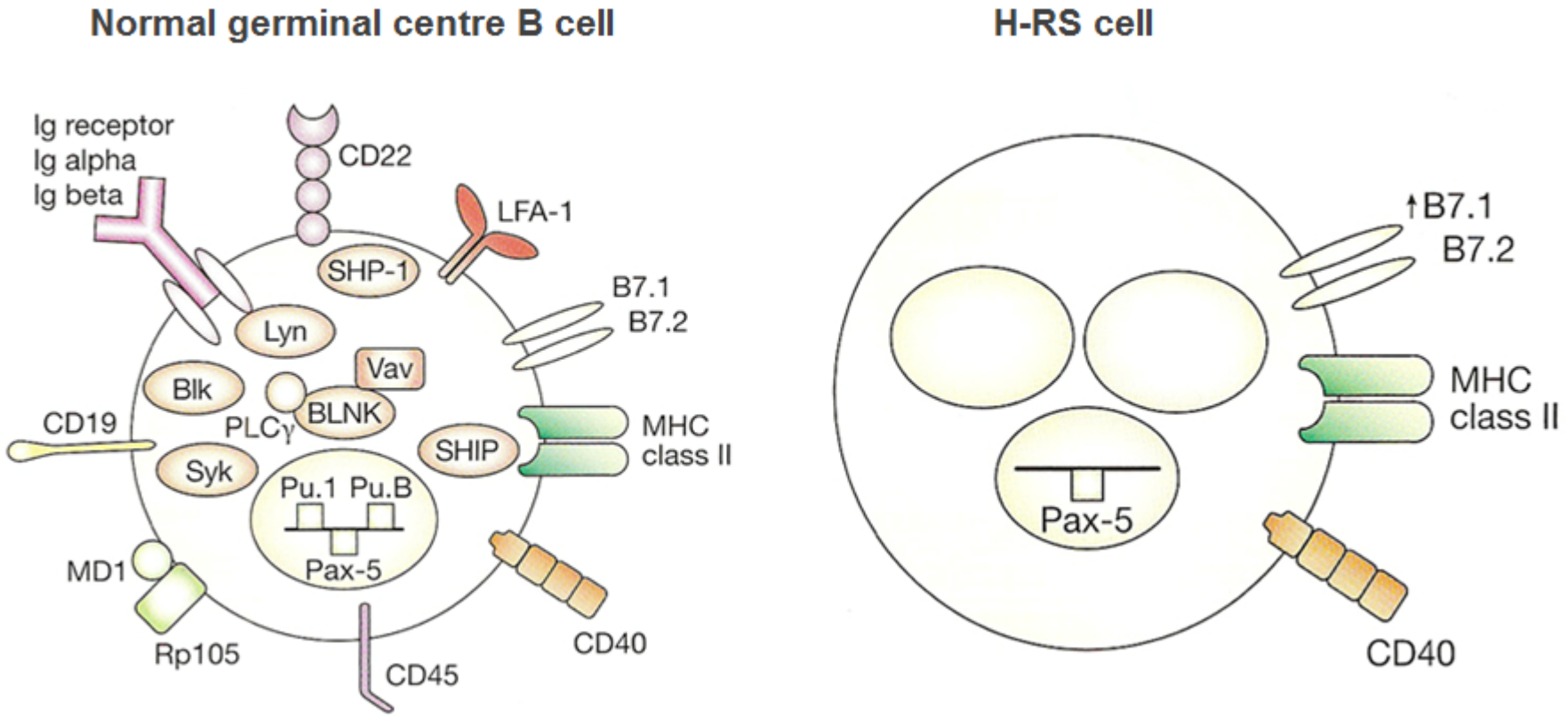
Hodgkin disease: Hodgkin and Reed–Sternberg cells picked from histological sections show clonal immunoglobulin gene rearrangements and appear to be derived from B cells at various stages of development

RALF KÜPPERS*†, KLAUS RAJEWSKY*, MIN ZHAO‡, GÜNTHER SIMONS‡, RALF LAUMANN*, ROBERT FISCHER‡, AND MARTIN-LEO HANSMANN‡

*Institute for Genetics, and ‡Department of Pathology, University of Cologne, 50931 Cologne, Germany

Contributed by Klaus Rajewsky, July 20, 1994

The lost B-cell indentity of H-RS cells



How do H-RS cells survive?
Through stimulation of NFkB pathway?

Thomas et al. Lancet Oncology, 2004

HL: Long-term toxicity

Already at 1-ICML (1981)

- different speakers underlined an alarming increase of secondary malignancies

  De Vita: Abstr. 1; Kaplan: Abstr. 2

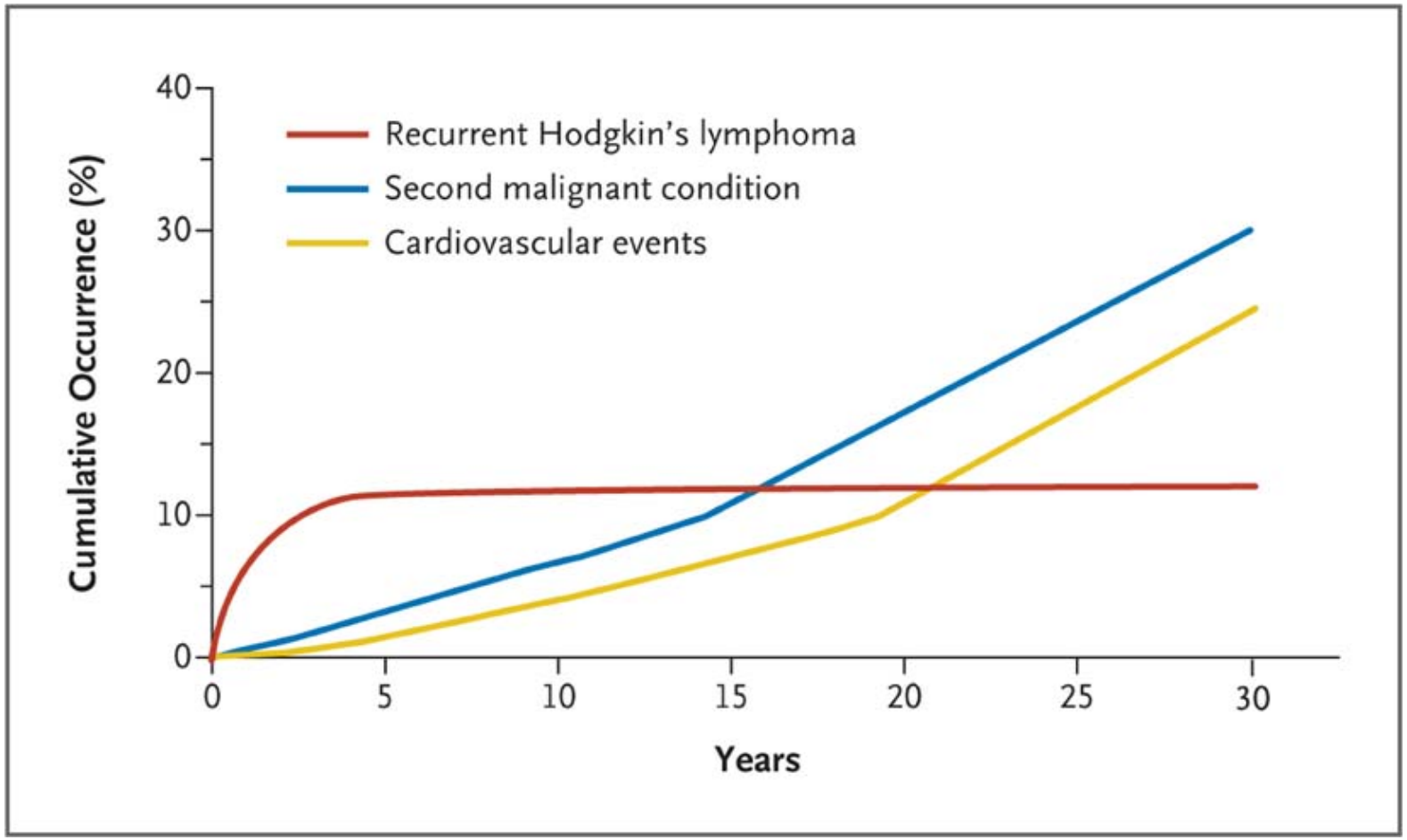
  Bonadonna: Abstr. 4; Young: Abstr. 25

- Several speakers proposed the “children model”

  - no laparotomy
  - limited radiotherapy
  - less toxic chemotherapy

  Abstracts 13-17

Risk of recurrent HL, second cancer and cardiovascular events after radio-chemotherapy



Armitage. NEJM; 2010;363:653-662

Hodgkin Lymphoma Treatment

Overall goals of treatment

- Cure of the lymphoma

- Minimization of late toxicity
  - Gonadal
  - Cardiovascular
  - Neoplastic – secondary malignancies

Role of PET

- To predict outcome
- To define response
- to drive treatment

ICML Workshops preceded a new staging classification

- A workshop was held at the 11th ICML in Lugano, Switzerland, in June 2011, that included leading hematologists, oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine physicians, representing major international lymphoma clinical trials groups and cancer centers.
- Clinical and imaging subcommittees presented their conclusions at the 12th ICML, leading to revised criteria for staging and response evaluation.
- As a result, FDG-PET/CT was formally incorporated into standard staging for FDG-avid lymphomas.

The Lugano Classification, 2014

VOLUME 32 · NUMBER 27 · SEPTEMBER 20 2014

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister

See accompanying article on page 3048

Lymphoma classifications in 1981

Pieter Bruegel the Elder. The Great Tower of Babel (oil on wood panel, c. 1563)

TABLE 1. Six Classifications of Non-Hodgkin's Lymphomas As Used in the NCI-Sponsored Study

British National Lymphoma Investigation

Follicular lymphoma	
Follicle cells, predominantly small	A
Follicle cells, mixed small and large	B
Follicle cells, predominantly large	C
Diffuse lymphoma	
Lymphocytic, well differentiated (Small round lymphocyte)	D
Lymphocytic, intermediately differentiated (Small follicle lymphocyte)	E
Lymphocytic, poorly differentiated (Lymphoblast)	
(a) Non-Burkitt	F
(b) Burkitt's tumors	G
(c) Convoluted cell mediastinal lymphoma	H
Lymphocytic/mixed small lymphoid and large cell (mixed follicle cells)	I
Undifferentiated large cell (Large Lymphoid Cell)	J
Histiocytic cell (Mononuclear Phagocytic Cell)	K
Plasma cell (Extramedullary Plasma Cell)	L
Malignant lymphoma, unclassified	M
Plasmacytoid differentiation	N
Sclerosis, banded	O
Sclerosis, fine	P

Rappaport

Nodular	
Lymphocytic, well differentiated	A
Lymphocytic, poorly differentiated	B
Mixed, lymphocytic and histiocytic	C
Histiocytic	D
Diffuse	
Lymphocytic, well differentiated without plasmacytoid features	E
Lymphocytic, well differentiated with plasmacytoid features	F
Lymphocytic, poorly differentiated without plasmacytoid features	G
Lymphocytic, poorly differentiated with plasmacytoid features	H
Lymphoblastic, convoluted	I
Lymphoblastic, non-convoluted	J
Mixed, lymphocytic and histiocytic	K
Histiocytic without sclerosis	L
Histiocytic with sclerosis	M
Burkitt's tumor	N
Undifferentiated	O
Malignant lymphoma, unclassified	P
Composite lymphoma	Q

Dorfman

Follicular (or follicular & diffuse)	
Small lymphoid	A
Mixed, small and large lymphoid	B
Large lymphoid	C
Diffuse	
Small lymphocytic, without plasmacytoid differentiation	D
Small lymphocytic, with plasmacytoid differentiation	E
Atypical small lymphoid	F
Lymphoblastic, convoluted	G
Lymphoblastic, nonconvoluted	H
Large lymphoid, without plasmacytoid differentiation	I
Large lymphoid, with plasmacytoid differentiation	J
Mixed small and large lymphoid	K
Histiocytic	L
Burkitt's lymphoma	M
Lymphoepithelioid cellular (Lennert's Lymphoma)	N
Mycosis fungoides	O
Undifferentiated	P
Lymphoma associated with sclerosis	Q
Malignant lymphoma, unclassified	R
Composite lymphoma	S

Lukes and Collins

Undefined cell type	A
T-cell type, small lymphocytic	B
T-cell type, Sezary-mycosis fungoides (Cerebriform)	C
T-cell type, convoluted lymphocytic	D
T-cell type, immunoblastic sarcoma (T Cell)	E
B-cell type, small lymphocytic	F
B-cell type, plasmacytoid lymphocytic	G
Follicular center cell, small cleaved	H
Follicular center cell, large cleaved	I
Follicular center cell, small non-cleaved	J
Follicular center cell, large non-cleaved	K
Immunoblastic sarcoma (B-Cell)	L
Subtypes of follicular center cell lymphomas	
1. Follicular	M
2. Follicular and diffuse	N
3. Diffuse	O
4. Sclerotic with follicles	P
5. Sclerotic without follicles	Q
Histiocytic	R
Malignant lymphoma, unclassified	S

Kiel

Low grade malignancy	
Lymphocytic, chronic lymphocytic leukemia	A
Lymphocytic, other	B
Lymphoplasmacytoid	C
Centrocytic	D
Centroblastic-centrocytic, follicular, without sclerosis	E
Centroblastic-centrocytic, follicular, with sclerosis	F
Centroblastic-centrocytic, follicular and diffuse, without sclerosis	G
Centroblastic-centrocytic, follicular and diffuse, with sclerosis	H
Centroblastic-centrocytic, diffuse	I
Low grade malignant lymphoma, unclassified	J
High grade malignancy	
Centroblastic	K
Lymphoblastic, Burkitt's type	L
Lymphoblastic, convoluted cell type	M
Lymphoblastic, other (Unclassified)	N
Immunoblastic	O
High grade malignant lymphoma, unclassified	P
Malignant lymphoma, unclassified (Unable to specify "high grade" or "low grade")	Q
Composite lymphoma	R

WHO

Nodular lymphosarcoma, prolymphocytic	A
Nodular lymphosarcoma, prolymphocytic-lymphoblastic	B
Diffuse lymphosarcoma, lymphocytic	C
Diffuse lymphosarcoma, lymphoplasmacytic	D
Diffuse lymphosarcoma, prolymphocytic	E
Diffuse lymphosarcoma, prolymphocytic-lymphoblastic	F
Diffuse lymphosarcoma, lymphoblastic	G
Diffuse lymphosarcoma, immunoblastic	H
Diffuse lymphosarcoma, Burkitt's tumor	I
Mycosis fungoides	J
Plasmacytoma	K
Reticulosarcoma	L
Malignant lymphoma, unclassified	M
Composite lymphoma	N

NCI-Sponsored Study of NHL Classifications

Summary and Description of Working Formulation for Clinical Usage

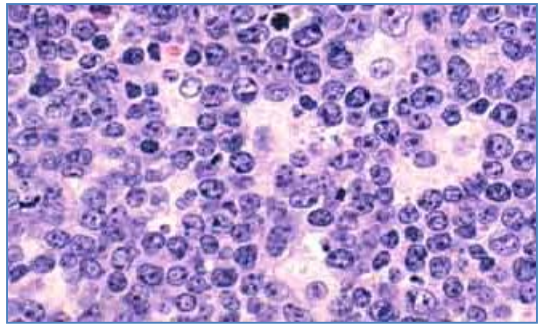
- International multi-institutional study of 1175 NHLs
- Histologic slides and clinical records were examined from previously untreated patients diagnosed between 1971 and 1975 at four institutions.
- The formulation is not proposed as a new classification but as a translation among the various systems to facilitate comparison of therapeutic trials.

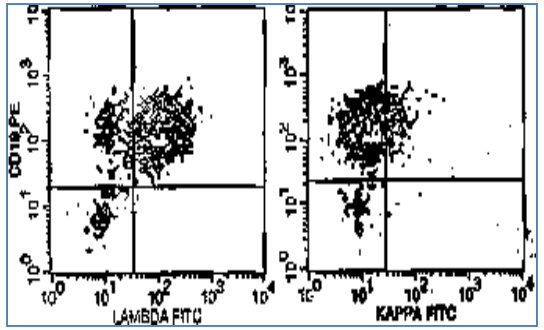
Cancer 1982, 49:2112-2135
Berard: Abstr. 3, ICML-1

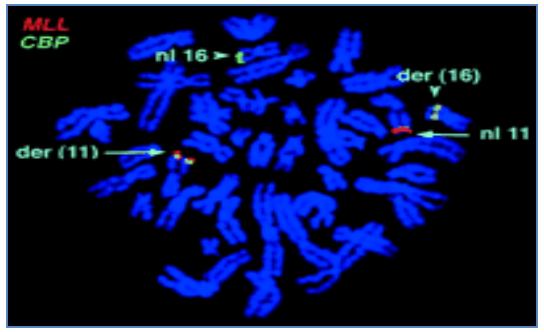
Lymphoma classifications

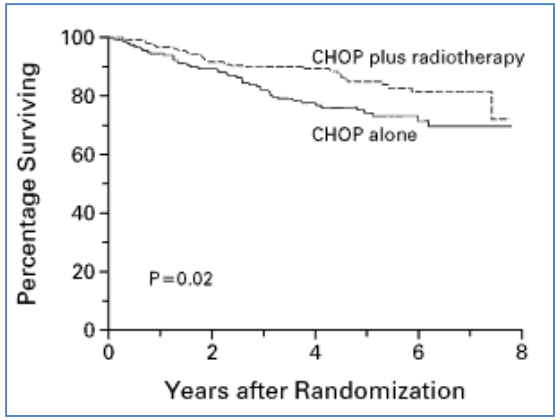
- Rappaport classification (US, first proposal in 1956 used until the late 1970's)
- BNLI classification (UK, 1974)
- Kiel classification (Europe,1974, revised in 1988)
- Lukes and Collins classification (US, 1975)
- NCI Working Formulation (1982)
- REAL - Revised European-American Lymphoma classification (1994)
- New WHO classification (2001, revised in 2008, updated in 2016)

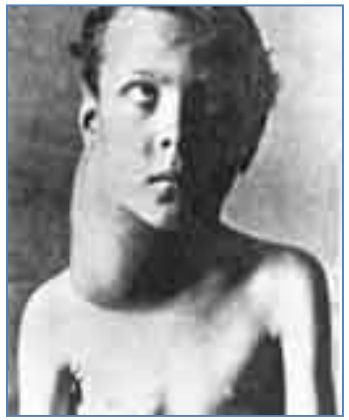
A new paradigm in the REAL Classification











A number of distinct disease entities defined by specific morphologic, phenotypic, genetic and clinical features

The Lugano Workshops

- **1996, Validation of the REAL Classification**
  - The REAL classification was not easily accepted - especially by US clinicians- and it was evident that the clinical significance of the new lymphoma entities and the practical utility and clinical relevance of the new classification needed to be tested

The NHL Classification Project

RAPID COMMUNICATION

A Clinical Evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin's Lymphoma

By The Non-Hodgkin's Lymphoma Classification Project

The recognition of several new types of non-Hodgkin's lymphoma (NHL) in recent years has led to proposals for changing lymphoma classifications, including a new proposal put forth by the International Lymphoma Study Group (ILSG). However, the clinical significance of the new entities and the practical utility of this new proposal have not been studied. Therefore, we performed a clinical evaluation of the ILSG classification. A cohort of 1,403 cases of NHL was organized at nine study sites around the world and consisted of consecutive patients seen between 1988 and 1990 who were previously untreated. A detailed protocol for histologic and clinical analysis was followed at each site, and immunologic characterization as to T- or B-cell phenotype was required. Five expert hematopathologists visited the sites and each classified each case using the ILSG classification. A consensus diagnosis was also reached in each case, and each expert rereviewed a 20% random sample of the cases. Clinical correlations and survival analyses were then performed. A diagnosis of NHL was confirmed in 1,378 (98.2%) of the cases. The most common lymphoma types were diffuse large B-cell lymphoma (31%) and follicular lymphoma (22%), whereas the new entities comprised 21% of the cases. Diagnostic accuracy was at least 85% for most of the major lymphoma types, and reproducibility of the diagnosis was 85%. Immunophenotyping improved the diagnostic accuracy by 10% to 45% for a number of the major types. The clinical features of the new entities were distinctive. Both the histologic types and the patient characteristics as defined by the International Prognostic Index predicted for patient survival. In conclusion we found that the ILSG classification can be readily applied and identifies clinically distinctive types of NHL. However, for clinical application, prognostic factors as defined by the International Prognostic Index must be combined with the histologic diagnosis for appropriate clinical decisions.

Blood,Vol 89, No 11 (June 1), 1997: pp 3909-3918

The Lugano Workshops

- **1990** Prognostic Models in DLCL

  - Many institutions treating a large number of NHL patients have developed in the late 1980s a variety of prognostic models to identify patients requiring a more intensive therapy.

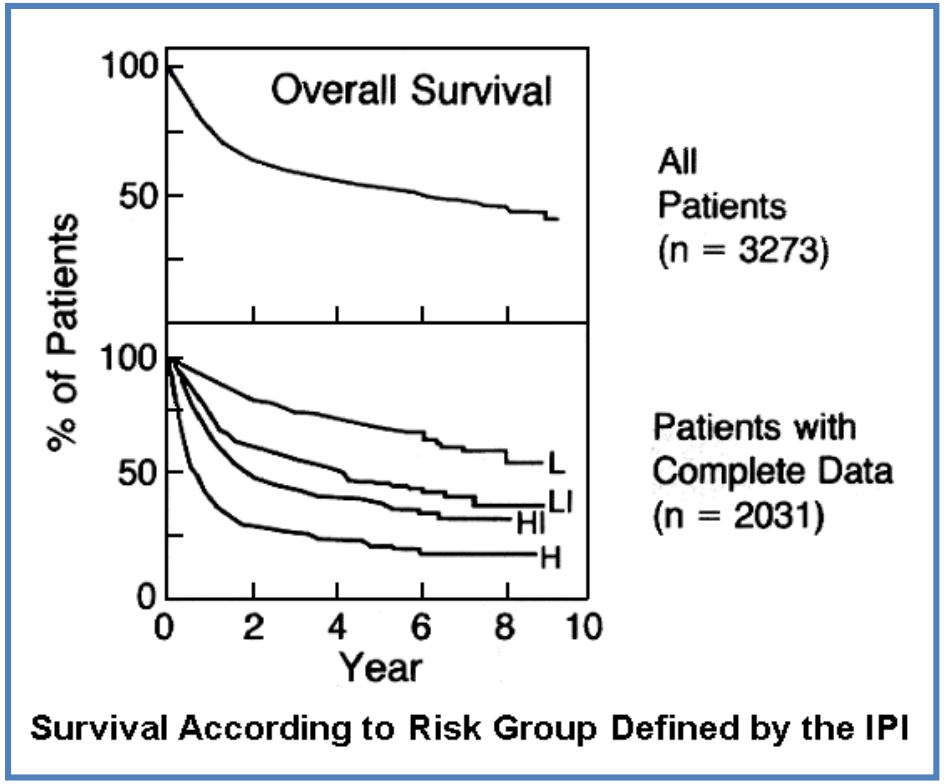
  - No consensus on a standard model for predicting outcome in aggressive lymphoma on the basis of clinical presentation features.

The International Prognostic Index

A Predictive Model for Aggressive Non-Hodgkin's Lymphoma

The International Non-Hodgkin's Lymphoma Prognostic Factors Project

The NEW ENGLAND JOURNAL of MEDICINE
1993;329:987-994



Survival According to Risk Group Defined by the IPI

The Lugano Workshops

- **1999,** Molecular Identification of Biological Diagnostic and Prognostic Markers in NHL

  - In the late 1990s molecular and analytical advances made it practical to quantitate the expression of thousands of genes in parallel using DNA microarrays. The « lymphochip » was designed to study the lymphoma gene expression…

NHL Gene Expression Profiling Projects

NATURE MEDICINE • VOLUME 8 • NUMBER 1 • JANUARY 2002

Diffuse large B-cell lymphoma outcome prediction by gene-expression profiling and supervised machine learning

Margaret A. Shipp[1], Ken N. Ross[2], Pablo Tamayo[2], Andrew P. Weng[3], Jeffery L. Kutok[3], Ricardo C.T. Aguiar[1], Michelle Gaasenbeek[2], Michael Angelo[2], Michael Reich[2], Geraldine S. Pinkus[3], Tane S. Ray[6], Margaret A. Koval[1], Kim W. Last[4], Andrew Norton[5], T. Andrew Lister[4], Jill Mesirov[2], Donna S. Neuberg[1], Eric S. Lander[2,7], Jon C. Aster[3] & Todd R. Golub[1,2]

The New England Journal of Medicine

VOLUME 346 JUNE 20, 2002 NUMBER 25

THE USE OF MOLECULAR PROFILING TO PREDICT SURVIVAL AFTER CHEMOTHERAPY FOR DIFFUSE LARGE-B-CELL LYMPHOMA

Andreas Rosenwald, M.D., George Wright, Ph.D., Wing C. Chan, M.D., Joseph M. Connors, M.D., Elias Campo, M.D., Richard I. Fisher, M.D., Randy D. Gascoyne, M.D., H. Konrad Muller-Hermelink, M.D., Erlend B. Smeland, M.D., Ph.D., and Louis M. Staudt, M.D., Ph.D., for the Lymphoma/Leukemia Molecular Profiling Project

12-ICML, Workshop on June 18th, 2013

"Identification of diffuse large B-cell lymphoma subtypes: a way towards tailored treatment"

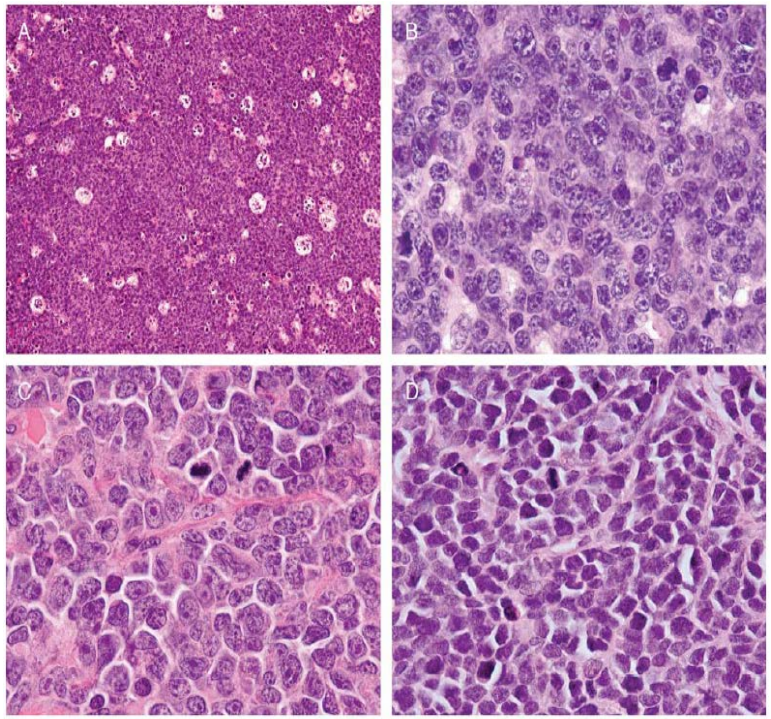
M. Shipp reporting the workshop

DLBCL categories

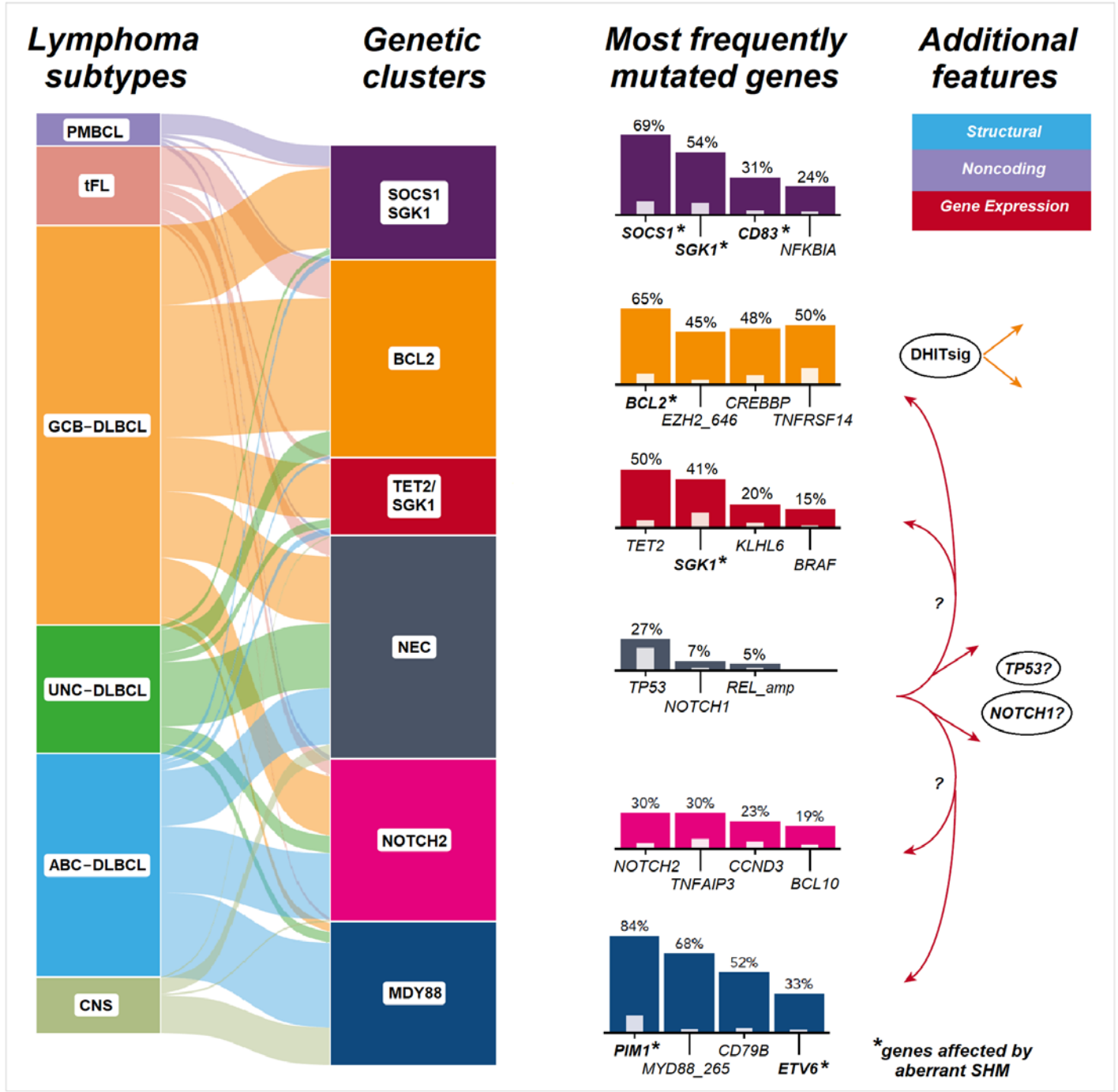
- DLBCL with characteristic morphologic, immunohistochemical or molecular features
- DLBCL, not otherwise specified
- DLBCL specified by site
- DLBCL associated with EBV o HHV8 infection
- B-cell lymphomas, unclassifiable (with features intermediate between DLBCL and BL or between DLBCL and classical HL)

Double hit B-cell lymphomas

- Recurrent translocations with *MYC*/8q24 breakpoints
- *BCL2 or BCL6* and *MYC* involvement
- No unifying morphological features
- Aggressive behaviour, often chemorefractory

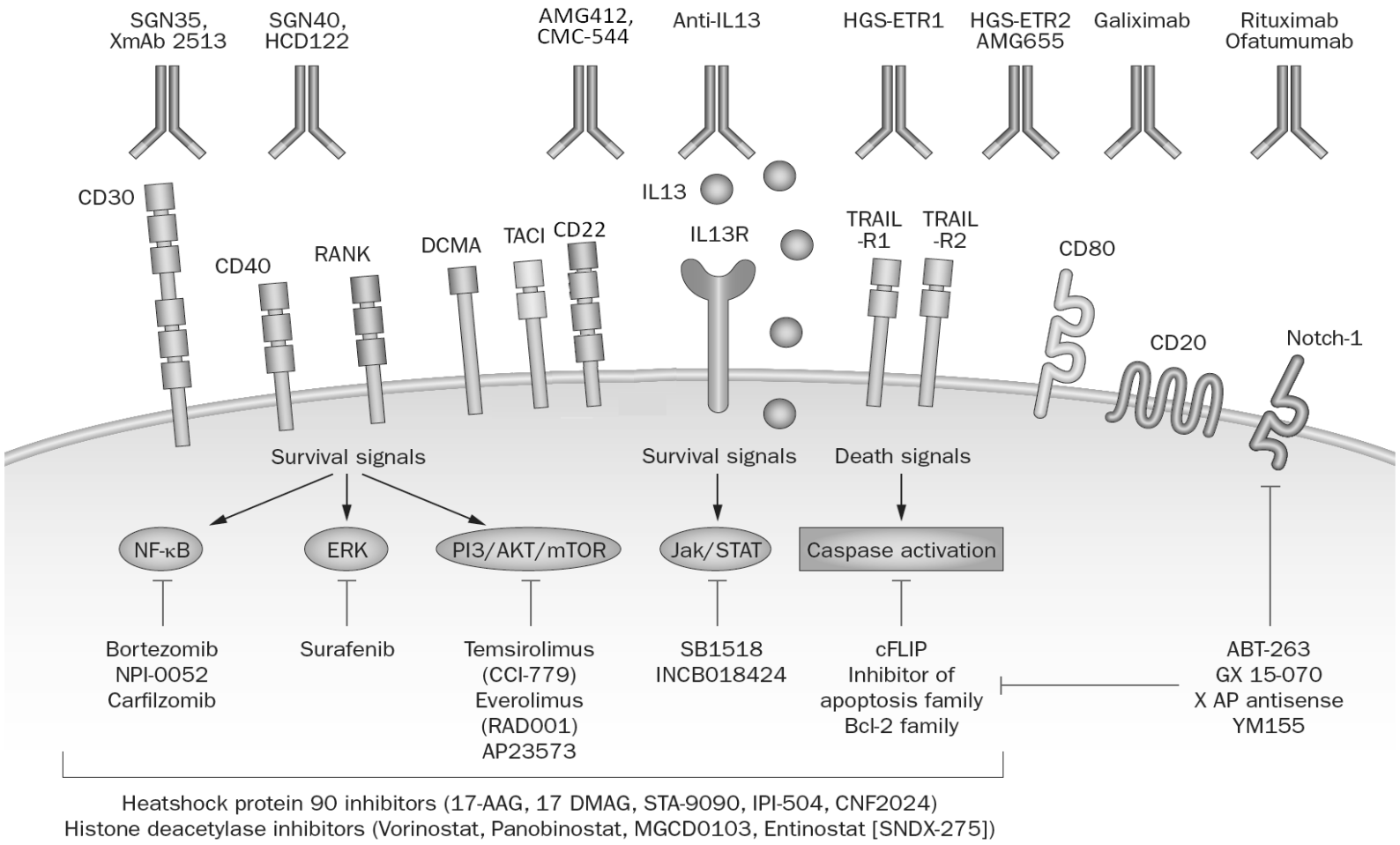


Aukema et al. Blood 2011; 117:2319-2332



Morin & Scott. *Blood*, 2020

Targeted therapy for lymphoma



Modified from: Younes, *Nat. Rev. Clin. Oncol*. 8, 85–96 (2011)

The Lugano Workshops

Published OnlineFirst March 13, 2018; DOI: 10.1158/1078-0432.CCR-17-3021

Perspective

Clinical Cancer Research

Report of the 14th International Conference on Malignant Lymphoma (ICML) Closed Workshop on Future Design of Clinical Trials in Lymphomas

Anastasios Stathis[1], Alexia Iasonos[2], John F. Seymour[3], Catherine Thieblemont[4], Vincent Ribrag[5], Emanuele Zucca[1,6,7], and Anas Younes[2]

The Lugano Workshops

- **1993,** Classification and Staging of GI-NHL

  - Peter Isaacson presented preliminary data on antibiotic therapy in MALT lymphoma and proposed a GI-NHL histological classification based on criteria that will be largely incorporated in the REAL classification

The Lugano Staging System

Annals of Oncology 5: 397–400, 1994.

Special article

Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma

A. Rohatiner on behalf of: F. d'Amore, B. Coiffier, D. Crowther, M. Gospodarowicz, P. Isaacson, T. A. Lister, A. Norton, P. Salem, M. Shipp & R. Somers

Key words: non-Hodgkin's lymphoma, gastro-intestinal lymphoma, staging, hystology

Isaacson's proposal for a GI-NHL classification

B-cell

MALT type

IPSID

DLCL (including those arising at MALT sites)

Mantle cell (Lymphomatous polyposis)

Burkitt's

Other types corresponding to nodal equivalents

T-cell

Enteropathy associated T-cell lymphoma (EATCL)

Other types not associated with enteropathy

Rohatiner, Ann Oncol 1994

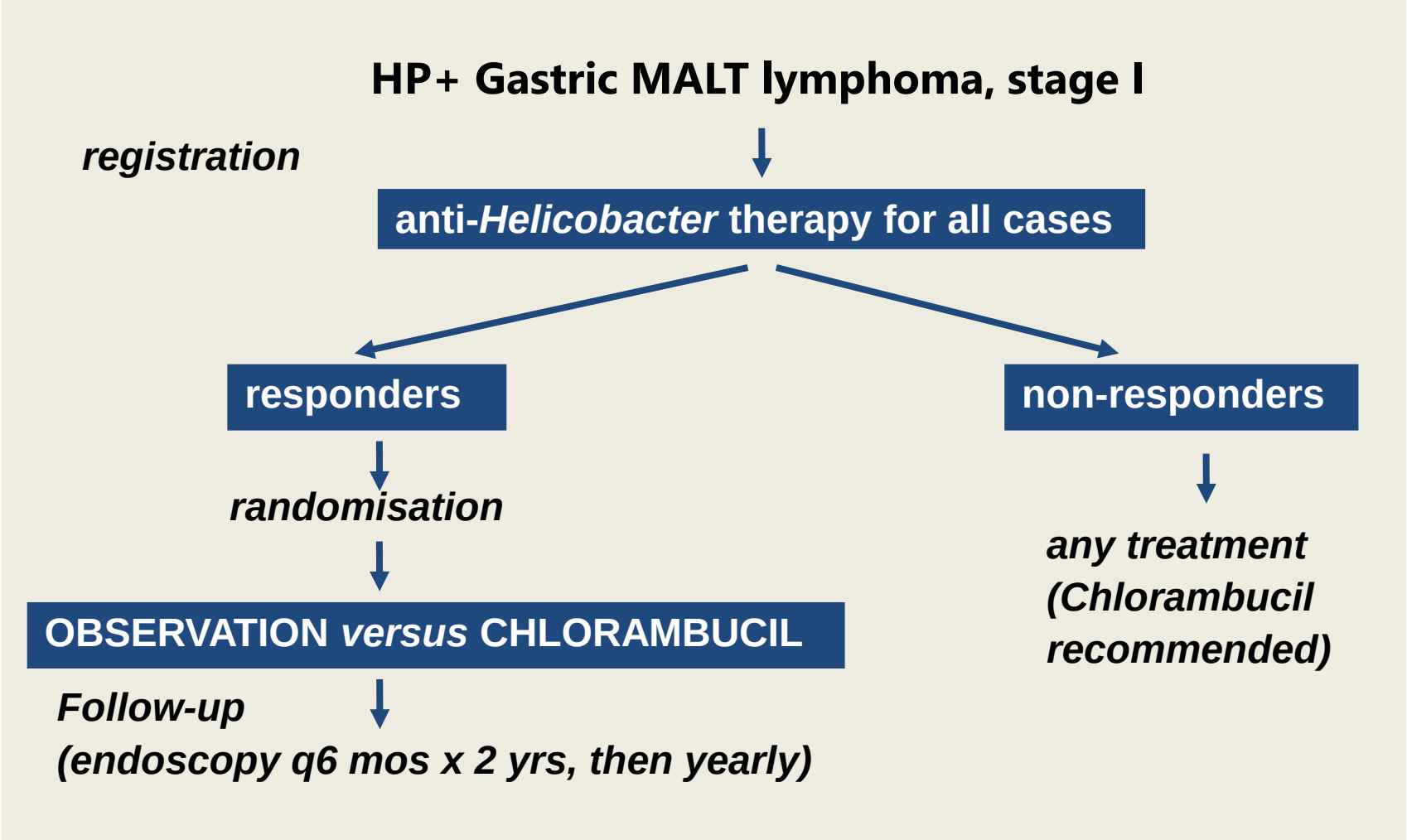
Modified Blackledge staging system for GI-NHL

“The Lugano System for primary GI Lymphoma”

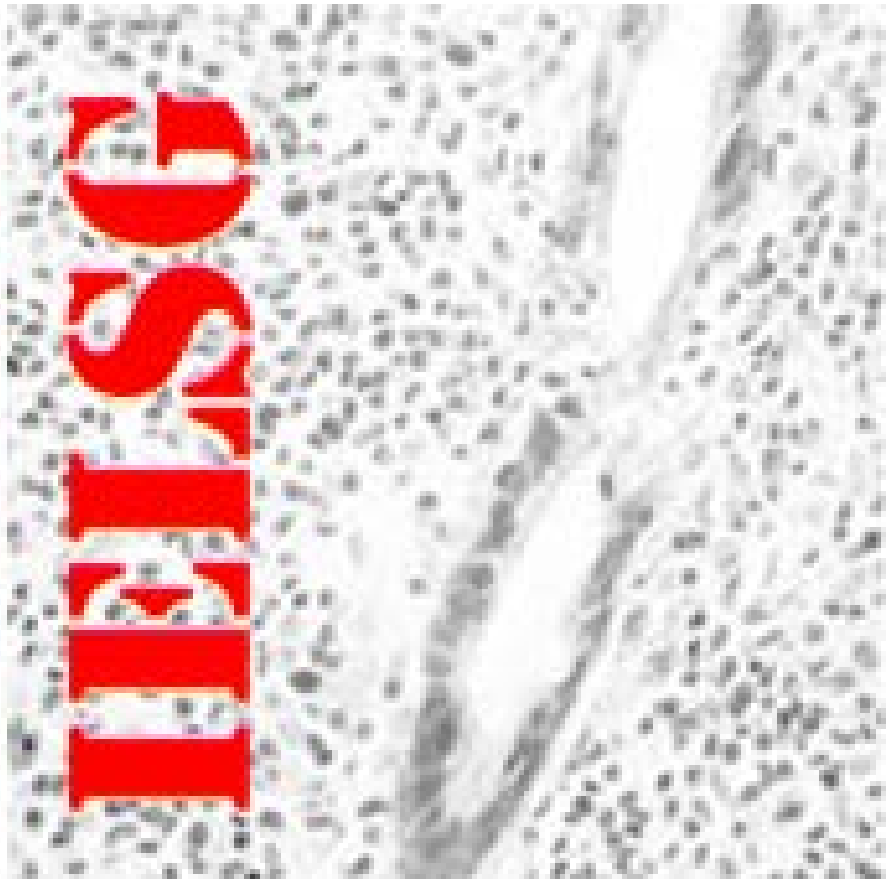
- stage I = confined to GI tract
  single primary or multiple, non-contiguous
- Stage II = extending into abdomen
  - II_1 = local nodal involvement
  - II_2 = distant nodal involvement
- Stage IIE = penetration of serosa to involve adjacent organs or tissues
- Stage IV = disseminated extranodal involvement,
  or, concomitant supra-diafragmatic nodal involvement

Rohatiner, Ann Oncol 1994

The LY03 intergroup study

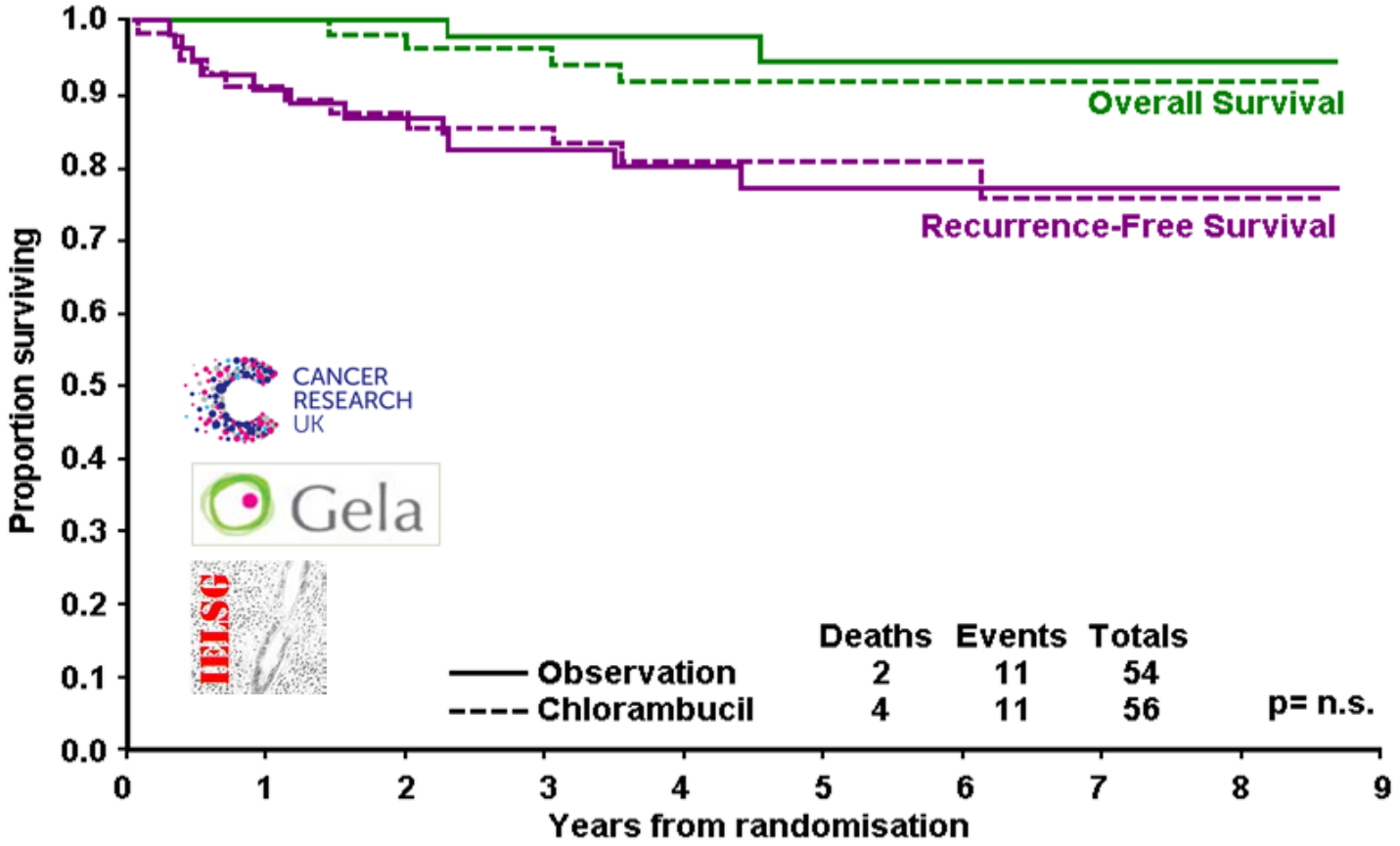


International Extranodal Lymphoma Study Group



LYO3/IELSG3 Trial of gastric MALToma

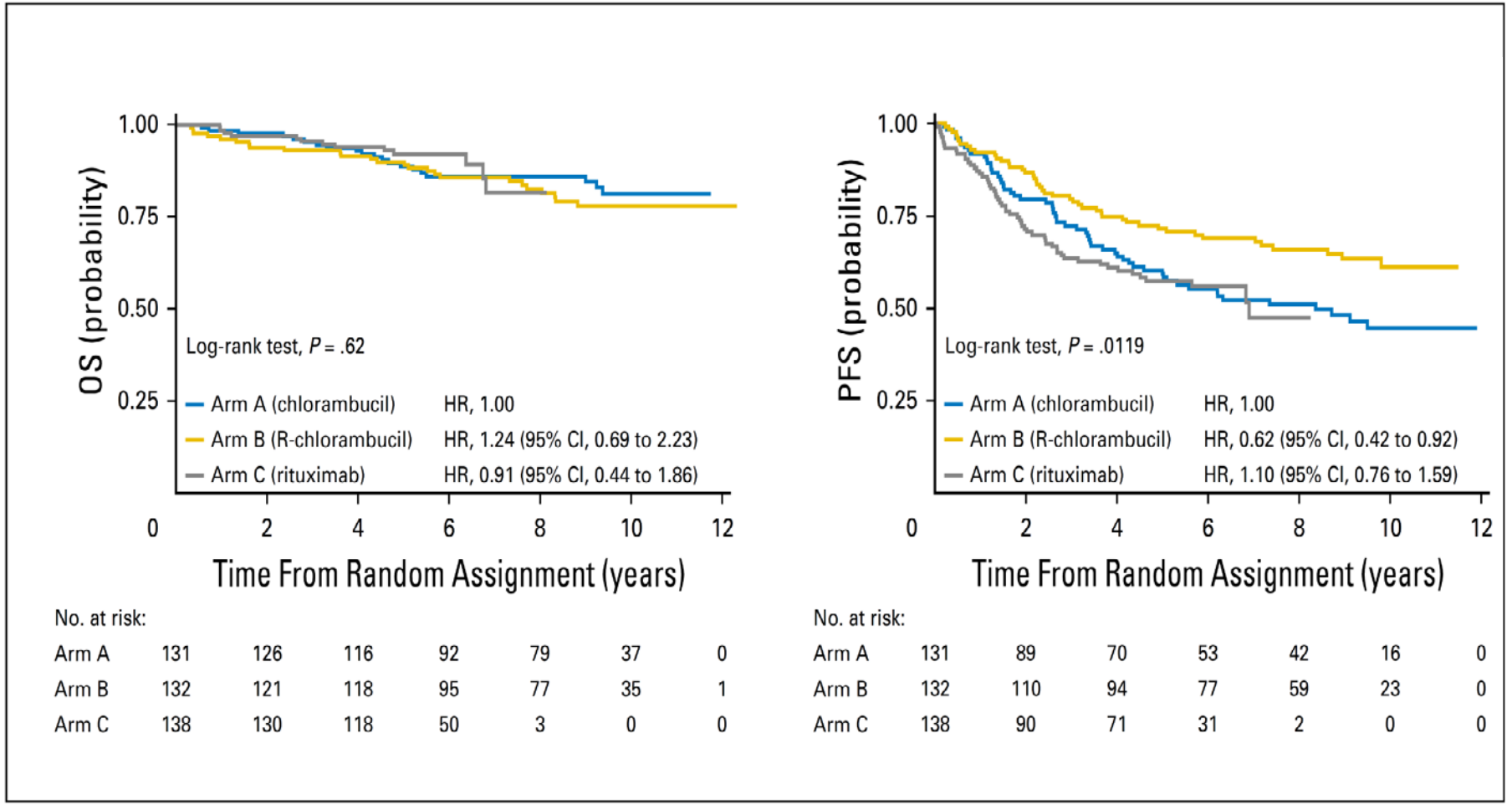
Chlorambucil vs. observation after H. pylori eradication



LY03 results first presented at 9-ICML
Abstract no. 74

B. Hancock, et al. Br J Haematol, 2009

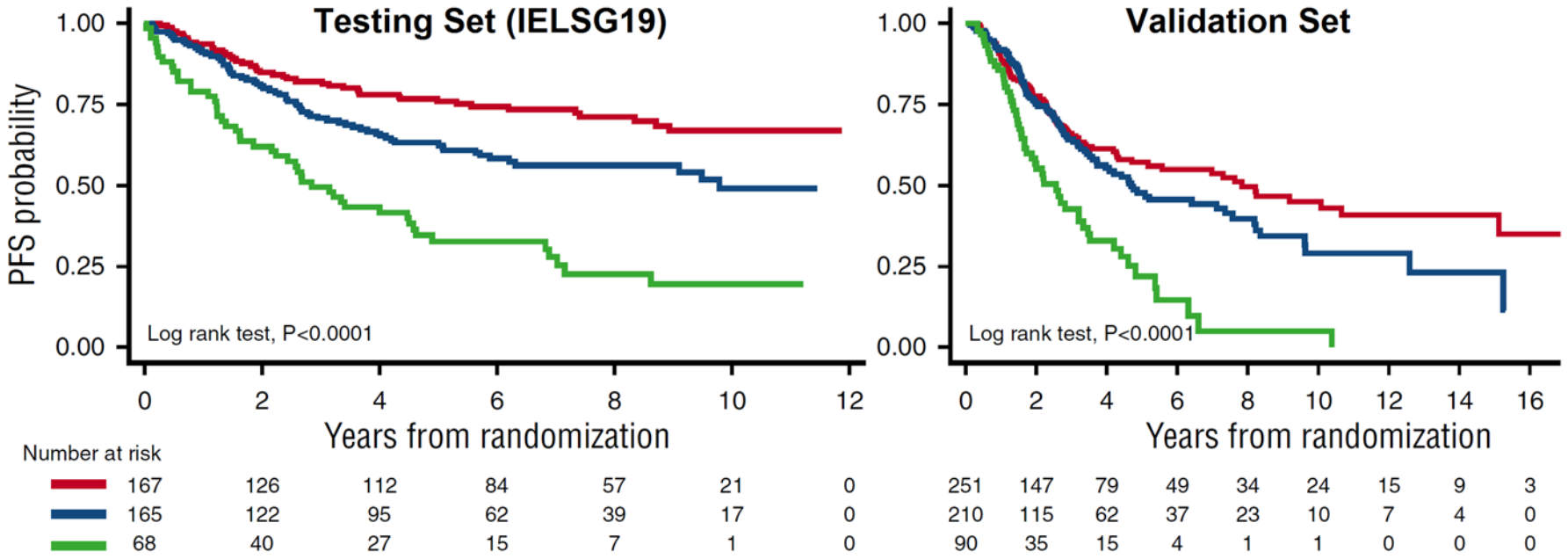
IELSG19 randomized trial



Zucca E, et al. JCO 2017; 35:1905-12

The MALT- IPI

MALT-IPI Risk Factors
Stage III-IV
Age>70 years
LDH >UNL



Thieblemont C, et al. Blood 2017;130:1409-17

The Lugano Workshops

- **2002,** Primary CNS Lymphoma

  - Under the sponsorship of the IELSG, a multidisciplinary symposium on PCNSL was held. One important objective of the meeting was the establishment of an international collaborative group to conduct laboratory investigations and multidisciplinary studies.

The IPCG

VOLUME 23 · NUMBER 22 · AUGUST 1 2005

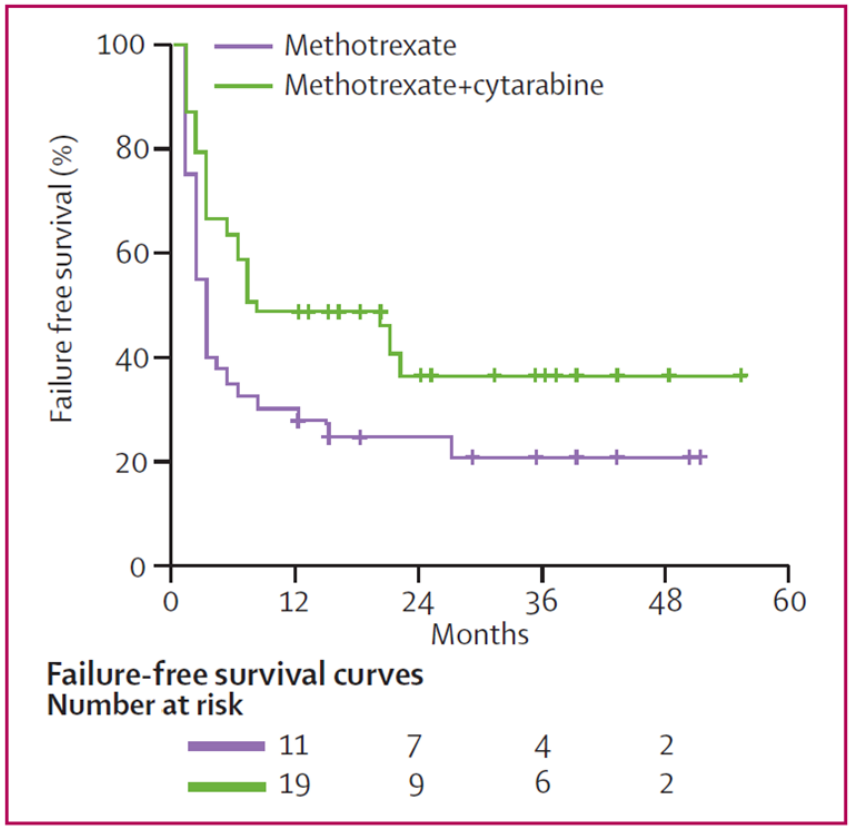
JOURNAL OF CLINICAL ONCOLOGY

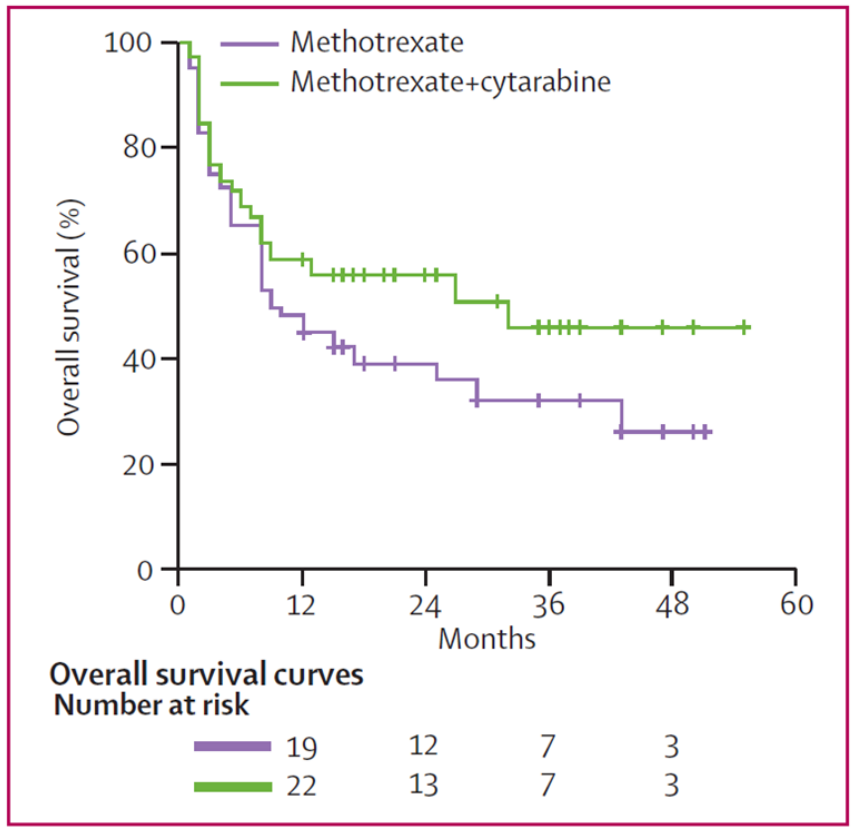
ORIGINAL REPORT

Report of an International Workshop to Standardize Baseline Evaluation and Response Criteria for Primary CNS Lymphoma

Lauren E. Abrey, Tracy T. Batchelor, Andrés J.M. Ferreri, Mary Gospodarowicz, Elisa J. Pulczynski, Emanuele Zucca, Justine R. Smith, Agnieszka Korfel, Carole Soussain, Lisa M. DeAngelis, Edward A. Neuwelt, Brian Patrick O'Neill, Eckhard Thiel, Tamara Shenkier, Fransesc Graus, Martin van den Bent, John F. Seymour, Philip Poortmans, James O. Armitage, and Franco Cavalli

HD Ara-C plus MTX: the new standard

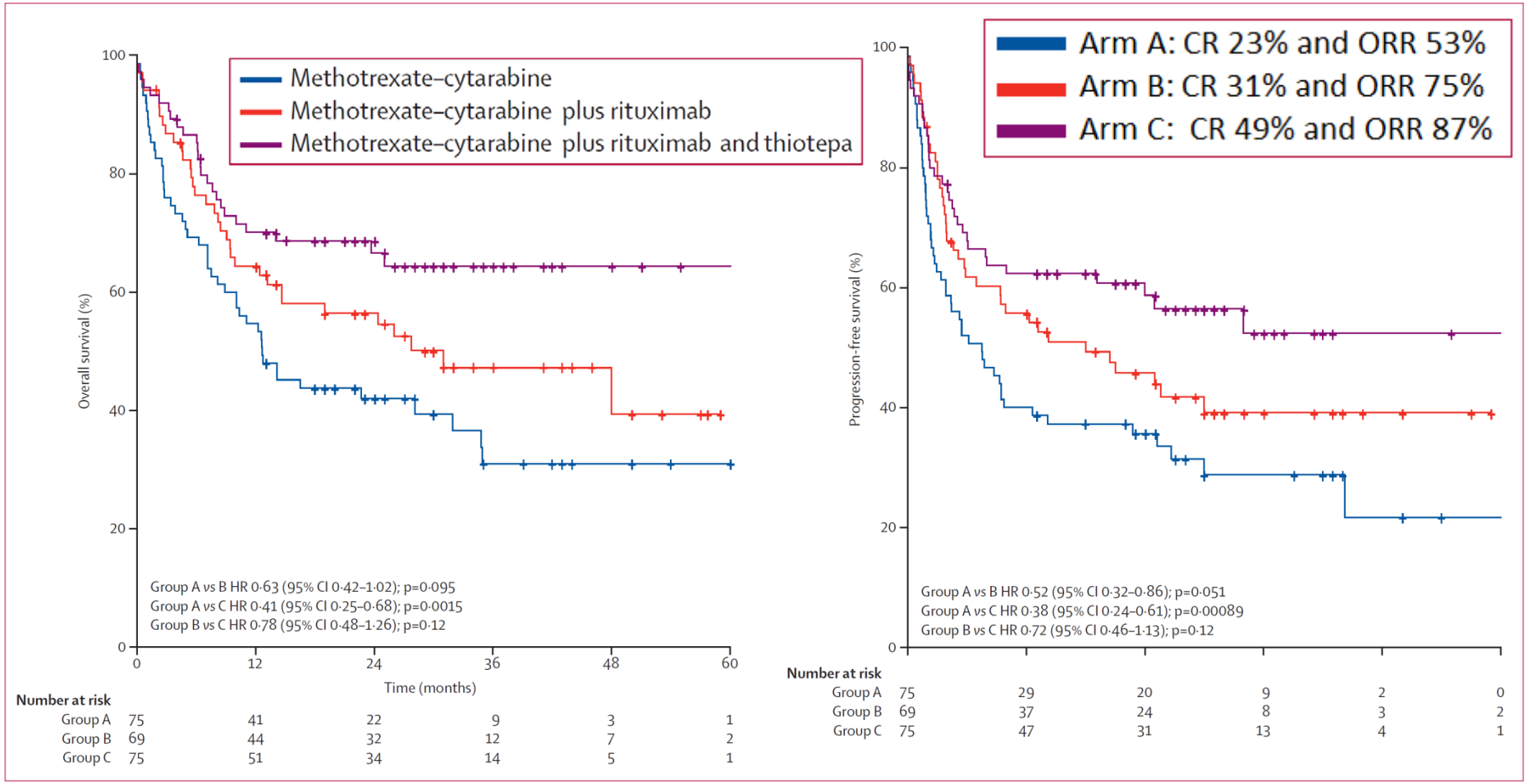




	HD MTX alone	HD Ara-C plus HD MTX	
CR	18% (95% CI 6–30)	46% (95% CI 31–61)	p=0·006
ORR	40% (95% CI 25–55)	69% (95% CI 55–83)	p=0·009

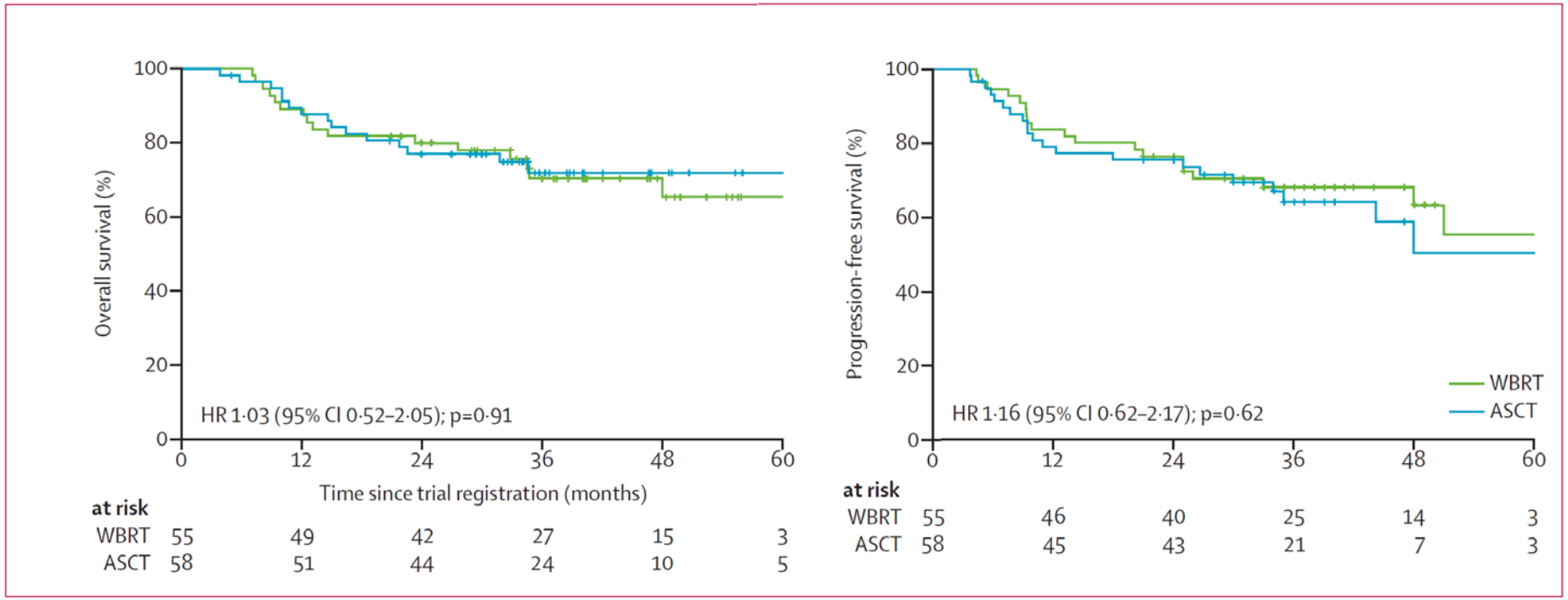
Ferreri et al, Lancet 2009

Improving the standard



Ferreri et al, Lancet Hematol 2016

WBRT or stem cell transplant?

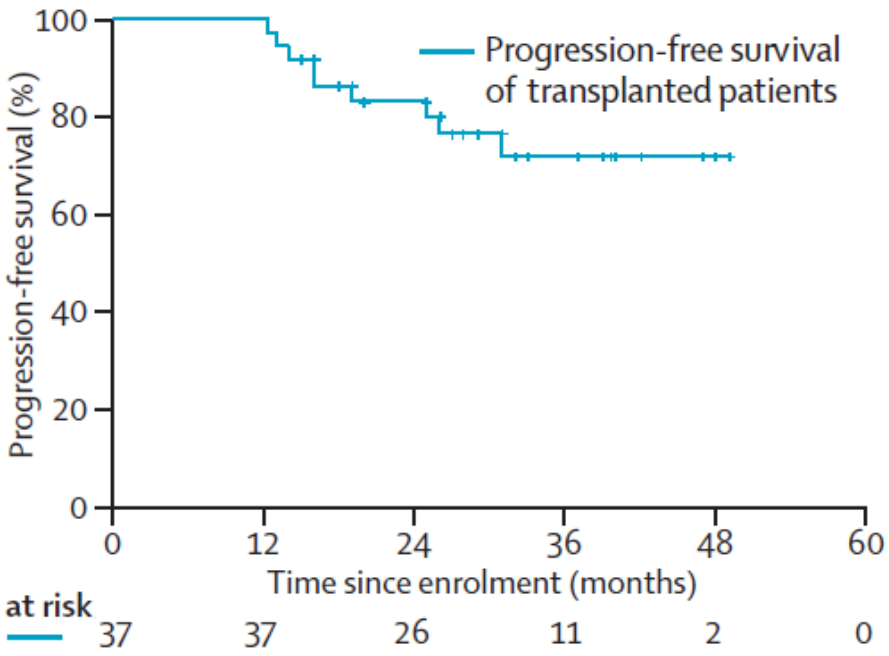


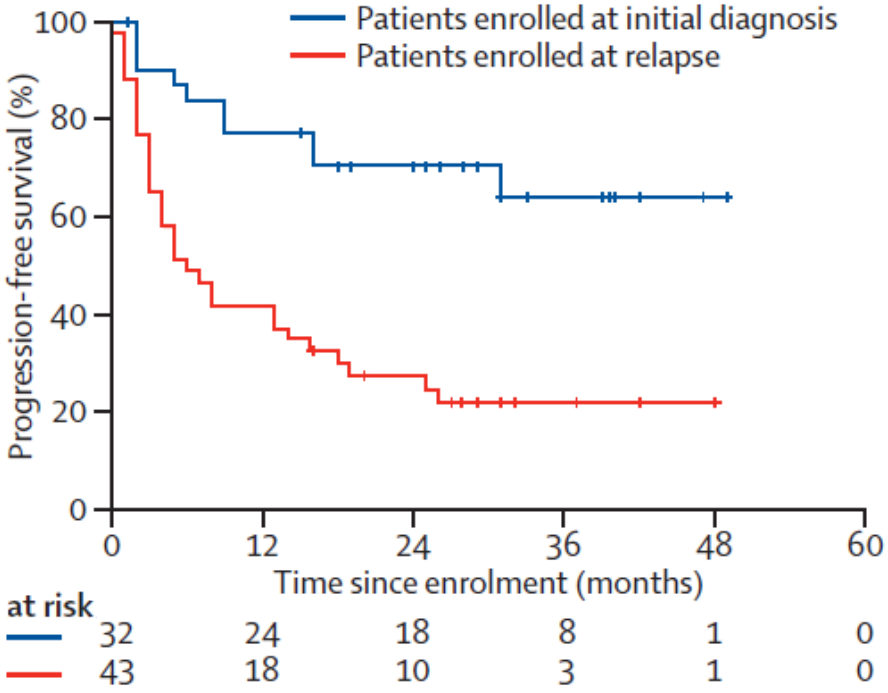
Overall and progression-free survival curves of randomly assigned patients (per-protocol populations)

Ferreri et al, Lancet Hematol 2017

IELSG42 Trial (MARIETTA)

MATRix-RICE followed by ASCT in DLBCL with secondary CNS involvement





Ferreri et al, Lancet Hematol 2021

9-ICML Workshop on PTCL

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Clinicopathologic Characteristics of Angioimmunoblastic T-Cell Lymphoma: Analysis of the International Peripheral T-Cell Lymphoma Project

Massimo Federico, Thomas Rudiger, Monica Bellei, Bharat N. Nathwani, Stefano Luminari, Bertrand Coiffier, Nancy L. Harris, Elaine S. Jaffe, Stefano A. Pileri, Kerry J. Savage, Dennis D. Weisenburger, James O. Armitage, Nicholas Mounier, and Julie M. Vose

15-ICML Workshop on Liquid biopsy

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Check for updates

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COMMENTARY

The development of liquid biopsy for research and clinical practice in lymphomas: Report of the 15-ICML workshop on ctDNA

Davide Rossi[1,2] | David M. Kurtz[3] | Mark Roschewski[4] | Franco Cavalli[1] | Emanuele Zucca[1,2] | Wyndham H. Wilson[4]

Hematol Oncol. 2020 Feb;38(1):34-37. doi: 10.1002/hon.2704.

The Lugano Conference has witnessed 40 years of continuous progress in the understanding and treatment of lymphomas, often directly contributing to major breakthroughs... I am sure this successful story will continue