Lymphoma Disease Management

Overview and Principles of Therapy

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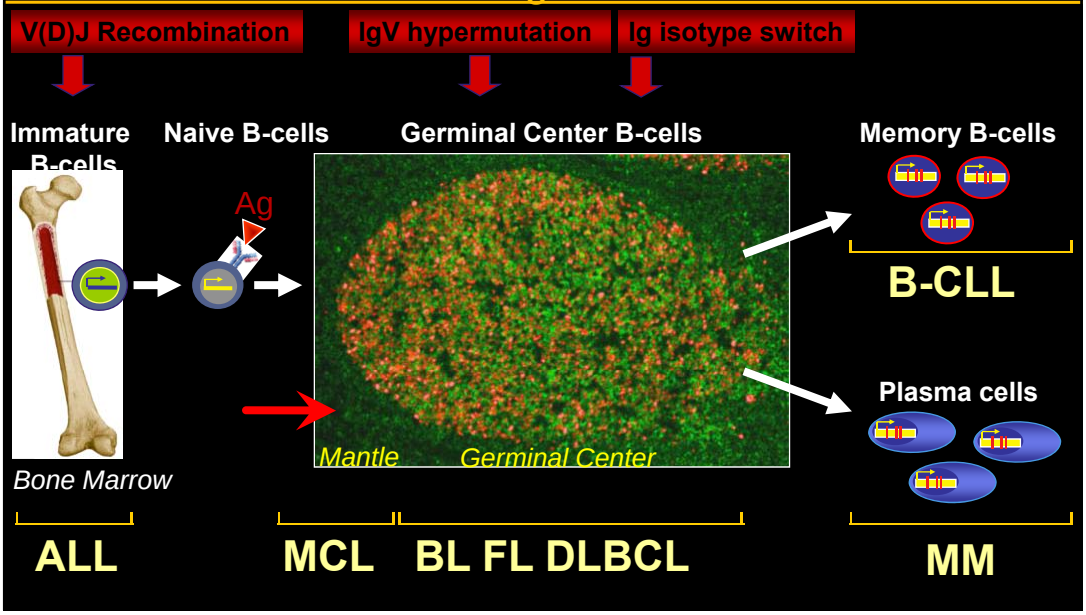
Lymphoma Overview and Principles of Therapy

- Non-Hodgkin's Lymphoma
  - Epidemiology
  - Classification/Staging
  - Indolent Lymphoma
  - Aggressive Lymphoma
- Hodgkin's Disease – Not Today
- New Approaches to Therapy – Not Today

The Ontogeny of Lymphoid Neoplasm's is Complex and Heterogeneous

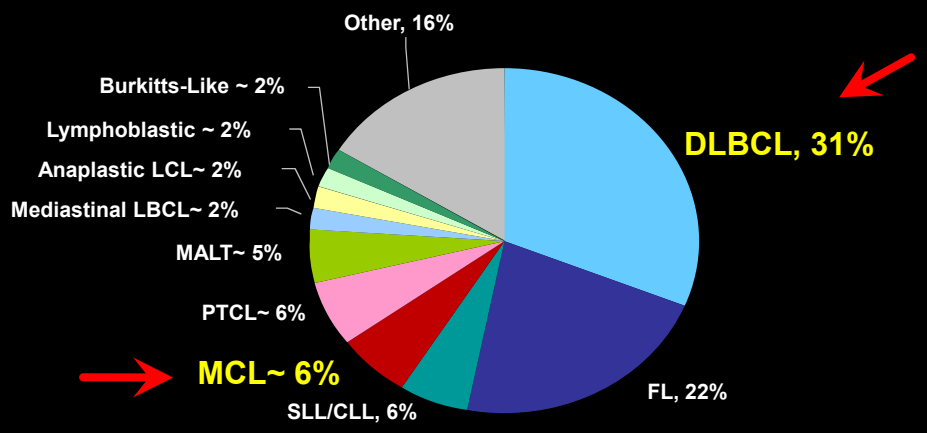


What is Lymphoma?

- **Non-Hodgkin's Lymphoma**
  - Typically presents with a clonal expansion of lymphocytes in lymph nodes
  - Different lymphomas arise from B, T, and NK cells
  - 85% of all lymphomas in the US are derived from B cells
  - Estimated 55,000 new cases
  - Indolent lymphomas account for approximately 40% of new diagnoses
  - Aggressive lymphomas account for 60% of presentations
- **Hodgkin's Disease**
  - Lymph nodes are involved with the characteristic Reed-Sternberg cells
  - Evidence suggest origin from a post germinal center B cell
  - Estimated 7,500 new cases
  - Peak of incidence in the 3rd and 4th decades of life
  - Vast majority of patients can be cured with current therapy

REAL Classification of NHL Subtypes

Most Lymphomas Are Relatively Rare



Armitage JO, Weisenburger DD. *J Clin Oncol*. 1998;16:2780-2795.

WHO/REAL Classification of Lymphoma

Characteristics of the 13 Most Common Entities

Subtype	Frequency (%)	Immunophenotype	Molecular Lesions
DLCL	31	CD20+	BCL2, BCL6, CMYC
FL	22	CD20+, CD10+, CD5-	BCL2
SLL/CLL	6	CD20 weak, CD5+, CD23+	+12, del(13q)
MCL	6	CD20+, CD5+, CD23-	CYCLIN D1
PTCL	6	CD20-, CD3+	Variable
MZL (MALT)	5	CD20+, CD5-, CD23-	BCL10, +3, +18
Mediastinal LCL	2	CD20+	Variable
ALCL	2	CD20-, CD3+, CD30+, CD15-, EMA+	ALK
LL (T/B)	2	T cell CD3+, B cell CD19+	Variable, TCL1-3
Burkitt-like	2	CD20+, CD10-, CD5-	CMYC, BCL2
MZL (Nodal)	1	CD20+, CD10-, CD23-, CD5-	+3, +18
SLL, PL	1	CD20+, clg+, CD5-, CD23-	PAX-5
BL	<1	CD20+, CD10+, CD5-	CMYC
TOTAL	88		

Categorizing the non-Hodgkin's Lymphomas

Aggressive Lymphoma

- Diffuse large B-cell NHL
- Peripheral T-cell NHL
- Burkitts lymphoma
- Lymphoblastic lymphoma
- Mantle cell lymphoma

- Approach with Curative Intent
- PBSCT Can Salvage Relapse
- Fatal if not Cured

Indolent Lymphoma

- Chronic lymphocytic leukemia (CLL)
- Small lymphocytic lymphoma (SLL)
- Follicular lymphoma
- Marginal Zone lymphoma
  - Nodal
  - Extranodal (MALTS)
  - Primary splenic

- Typically Incurable
- Possible Cure for Stage 1A Disease (RT or Chemo-RT)
- Chronic Disease Manageable
- Monoclonal antibodies changing natural history

Clinical Prognostic Factors Tell Only Part of the Story

International Prognostic Index (IPI)

Factor	Adverse
Age	>60 years
PS	≥2
LDH	>Normal
Extranodal sites	≥2
Stage	III-IV

Risk Group	Number of Factors Present	5-year DFS (%)	5-year OS (%)
Low	0-1	70	73
Low/Intermediate	2	50	51
High/Intermediate	3	49	43
High	4-5	40	26

Age-Adjusted

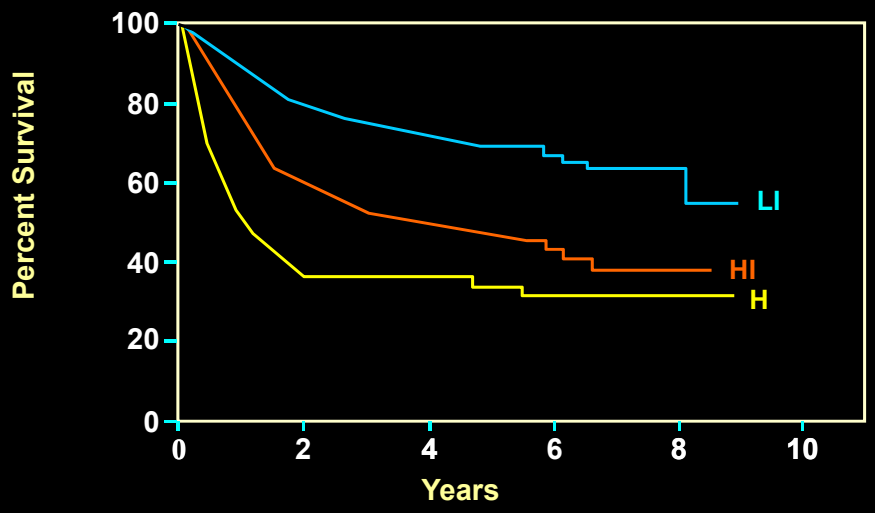
Factor	Adverse
PS	≥2
LDH	>Normal
Stage	III-IV

Age-Adjusted

Risk Group	Number of Factors Present	5-year OS Age>60 (%)	5-year OS Age≤60 (%)
Low	0	56	83
Low/Intermediate	1	44	69
High/Intermediate	2	37	46
High	3	21	32

The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med*. 1993;329:987-994.

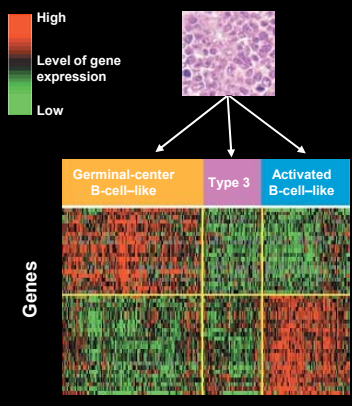
International Prognostic Index Predicts Overall Survival – What is Biological Basis?

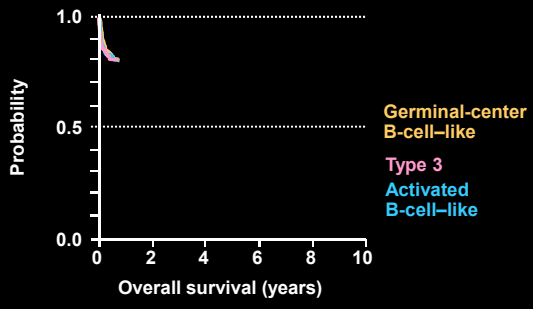


N Engl J Med.1993;329:987.

Prognostic Subgroups in *de novo* DLBCL Based on Ontogeny

DNA microarray analysis can be used to predict survival after chemotherapy





Rosenwald A et al. *N Engl J Med.* 2002;346:1937-1947.

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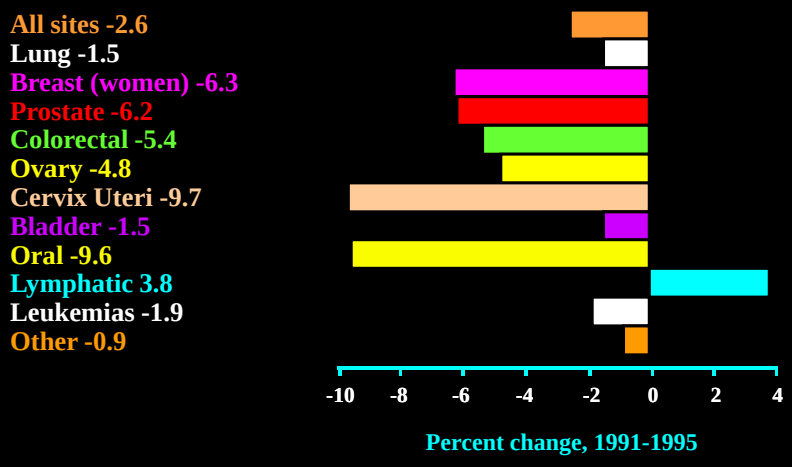
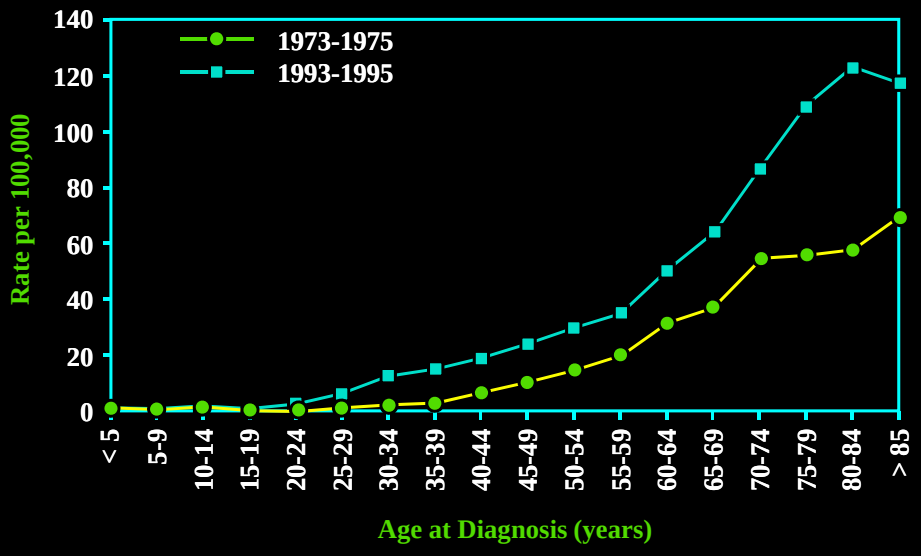
Trends in Cancer Mortality, 1991-1995

U.S. Cancer Mortality, All Ages



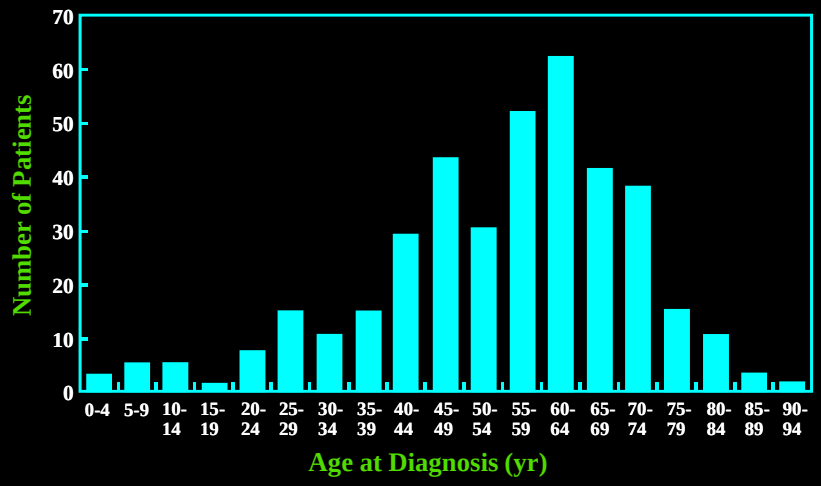
Non-Hodgkin's Lymphoma: SEER Incidence by Age

1973-1975 vs 1993-1995; All Races, Male



Age Distribution of Malignant Lymphoma

All Histologic Diagnoses



Data from the Royal Marsden Hospital 1962-1972.

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WORLD HEALTH ORGANIZATION (WHO) T-CELL LYMPHOMA CLASSIFICATION

A Whole Different Lecture

Precursor T/NK Neoplasms

Precursor T lymphoblastic leukemia/lymphoma

Blastic NK lymphoma

Peripheral T/NK Neoplasms

Predominantly leukemic/disseminated

- **T-cell prolymphocytic leukemia**
- **T-cell large granular lymphocytic**
- **NK/T-cell leukemia/lymphoma**
- **Adult T-cell leukemia/lymphoma**

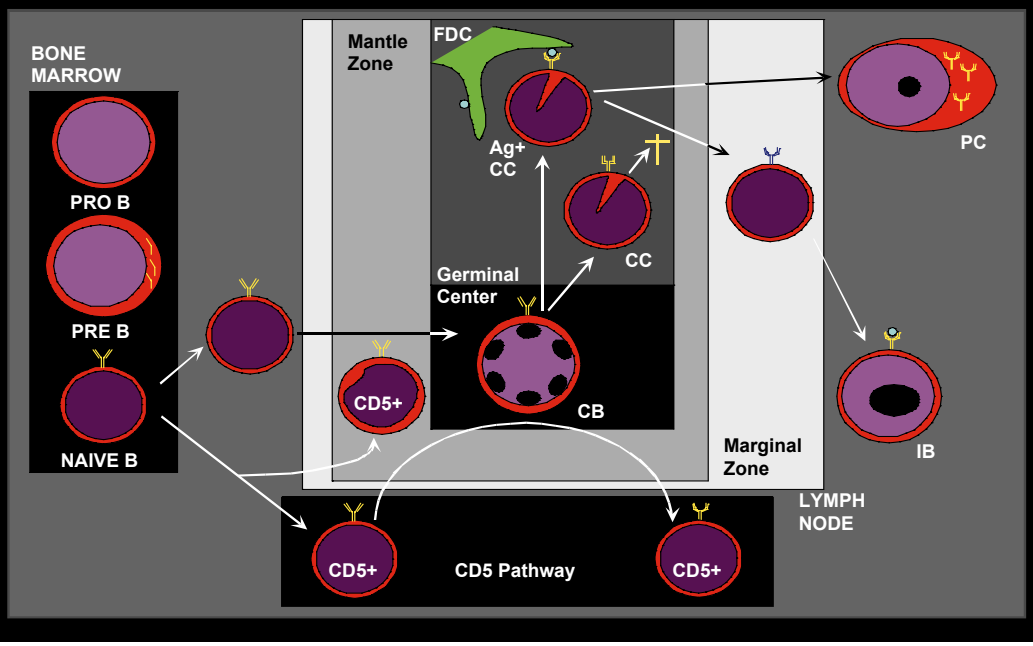
Predominantly nodal

- **Angioimmunoblastic T-cell lymphoma**
- **Anaplastic large cell lymphoma**
- **Peripheral T-cell lymphoma (Unspecified)**

Predominantly Extranodal

- **Mycosis Fungoides (CTCL)**
- **Sezary syndrome**
- **Primary cutaneous CD30+ disorders**
- **Anaplastic large cell lymphoma**
- **Lymphomatoid papulosis**
- **Subcutaneous panniculitis T-cell**
- **NK/T-cell lymphoma-nasal**
- **Enteropathy-type intestinal lymphoma**
- **Hepatosplenic T-cell lymphoma (γ,δ)**
- **Extranodal peripheral T/NK-cell lymphoma (Unspecified)**

B Cell Development



Clinical Staging of Lymphoma

Modified Ann Arbor Staging

- Clinical Stages
  - I: Single lymph node group
  - II: Multiple lymph node groups on one side of the diaphragm
  - III: Lymph nodes on both sides of the diaphragm
  - IV: Extra-nodal disease
- Modifiers
  - B: fevers, night sweats, weight loss
  - A: Absence of B symptoms
  - X: Mass > 10 cm or 1/3 thoracic diameter
  - E: Extra-nodal extension of disease

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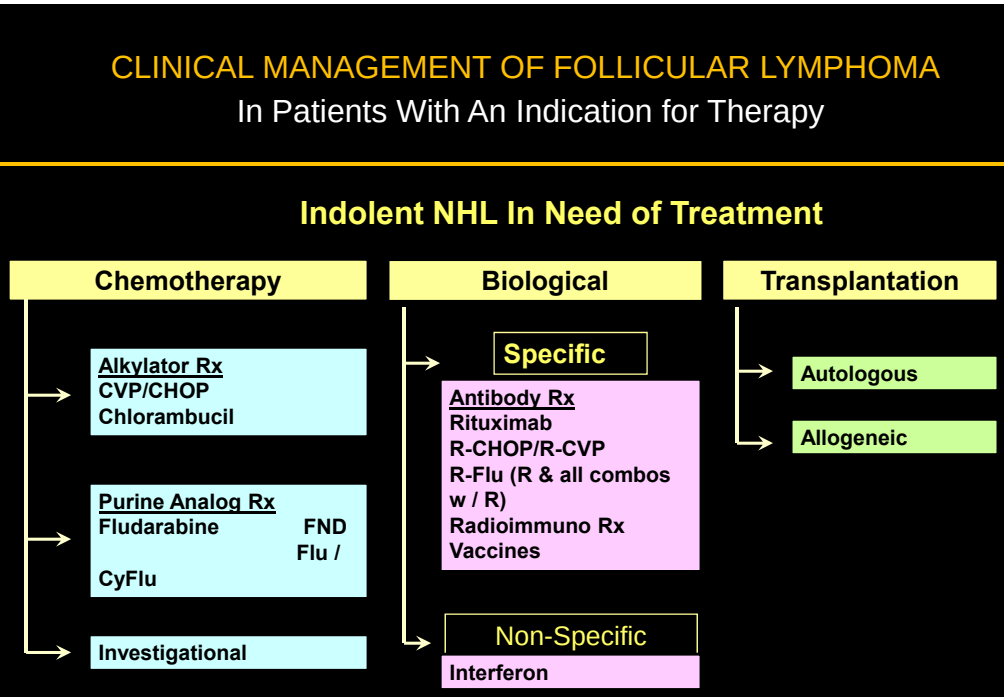
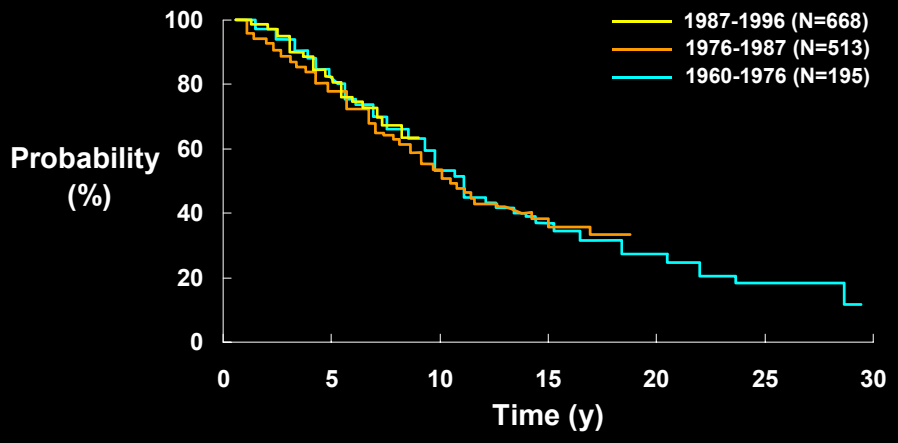
CLINICAL MANAGEMENT OF FOLLICULAR LYMPHOMA

In Patients With An Indication for Therapy



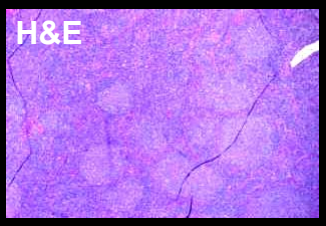
Indolent B-Cell Lymphoma

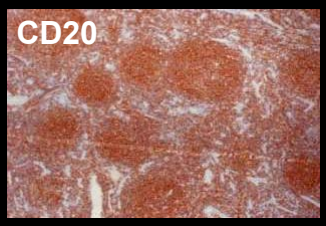
Survival by Era



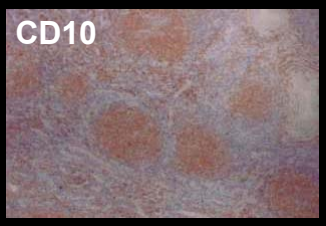
Courtesy of Sandra J. Horning, MD.

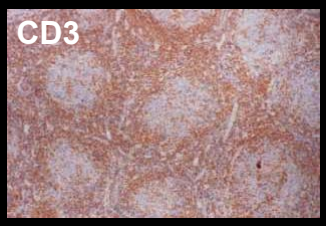
Follicular Lymphoma





CD 10+, CD 19+, CD 20+, CD 22+, LCA+, κ/λ clonal excess

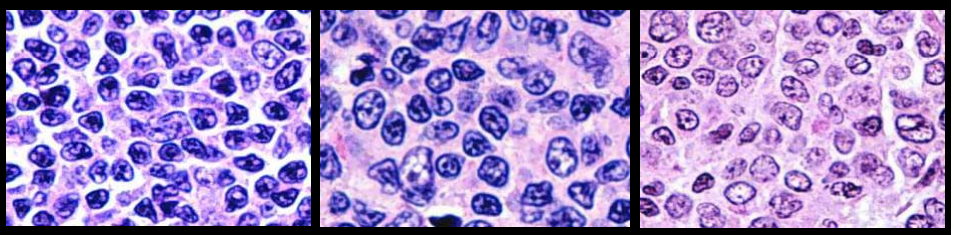




CD 3 -, CD 5 -, CD 15 -, CD 30 -

FL: Reproducibility of Grading

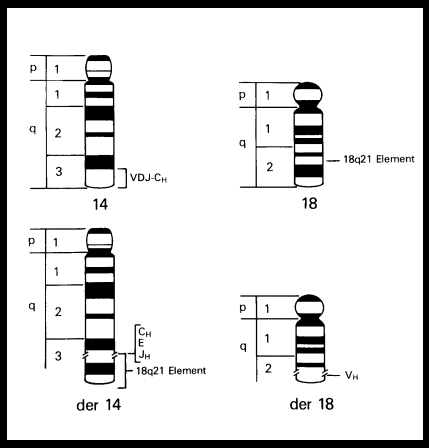
Berard Criteria



	Grade 1 Small Cleaved	Grade 2 Mixed	Grade 3 Large Cell
Large Cells Per High Power Field	<5	5-15	>15
Expert Concordance	72%	61%	60%

Follicular Lymphoma

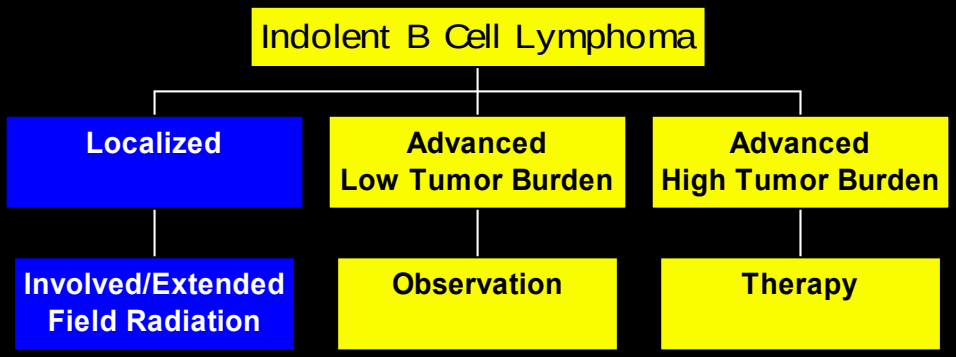
- Molecular
  - t(14;18) translocation
  - BCL2 is overexpressed
  - BCL2 is anti-apoptotic
- Clinical
  - Equal number of men and women
  - Uncommon in Blacks and Asians
  - Transformation is common
  - Spontaneous regress occurs in ~30% of cases
- Pathology
  - subtypes: Grades 1, 2, 3



Follicular Lymphoma
Histological Transformation (HT)

- Actuarial risk of HT is 25% to 60% at 8 years
- HT results from genetic alteration of a single cell
  - P53 mutation (~50%), translocations of c-myc (~15%) and BCL6 (~10%)
- Prognosis following HT is generally poor

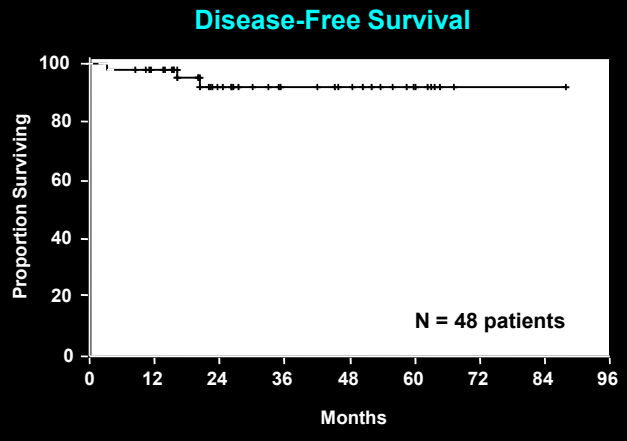
Indolent B Cell Lymphoma
Clinical Management



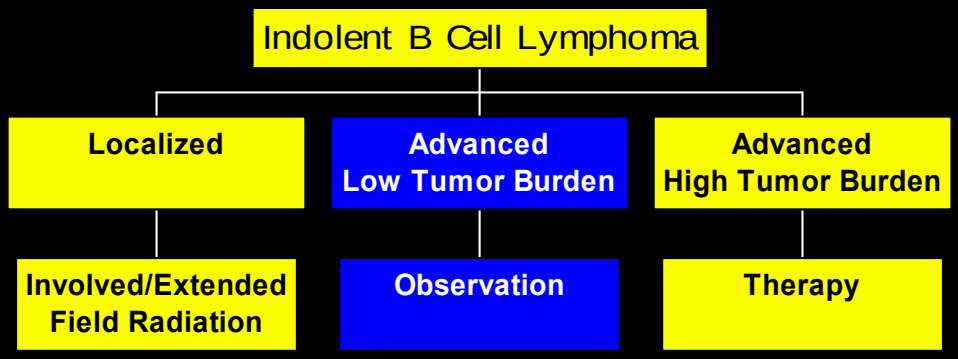
Gastric MALT Lymphoma
A *curable* low grade lymphoma

- Strong association with *Heliobacter pylori* infection
  - In 10%-50% of cases, treatment of the infection will result in regression of the lymphoma
  - Remissions may take up to 6 months
- Most patients who fail to respond to antibiotics can be *cured* with radiation therapy

Gastric MALT Lymphoma
A *curable* low grade lymphoma



Indolent B Cell Lymphoma
Clinical Management



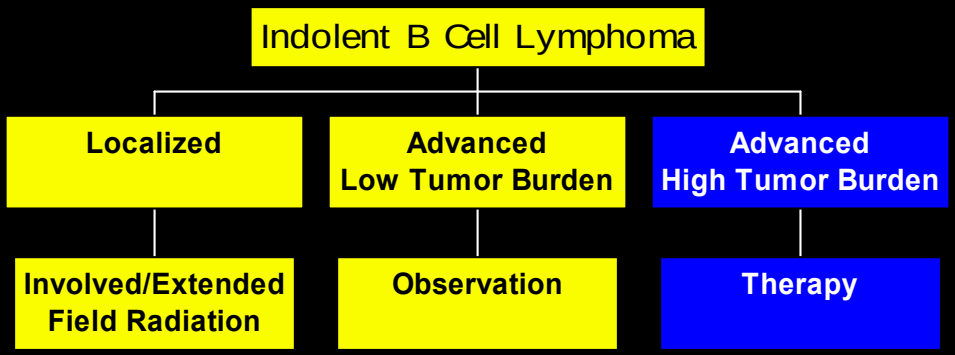
Indolent B Cell Lymphoma: Advanced Stage
Principles of Therapy

- Not curable with conventional therapy
- Presents in older patients who may have significant co-morbid conditions complicating therapeutic options
- Observation is appropriate if there are no indications for therapy
- Response duration is generally shorter with each course of therapy
- Enrollment on clinical trials is recommended if feasible

Indolent B Cell Lymphoma: Advanced Stage
Observation in Absence of an Indication for Treatment

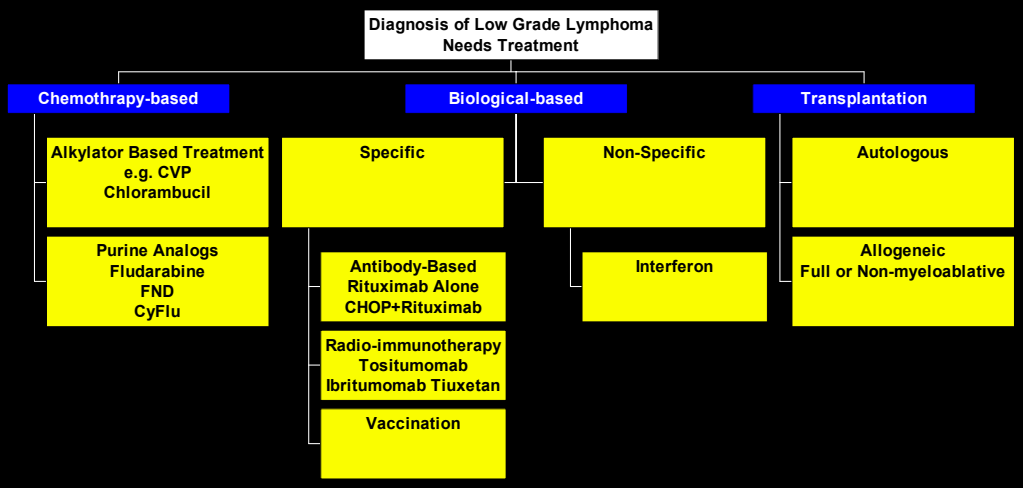
- Both prospective randomized and retrospective studies have:
  - No survival disadvantage
  - 3 year median progression to treatment
  - Same rate of histological transformation

Indolent B Cell Lymphoma
Clinical Management

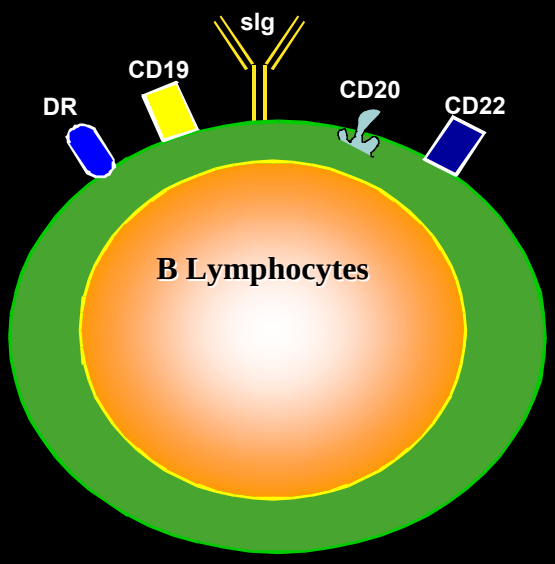


Indolent B Cell Lymphoma: Advanced Stage

Clinical Management with Indication for Therapy

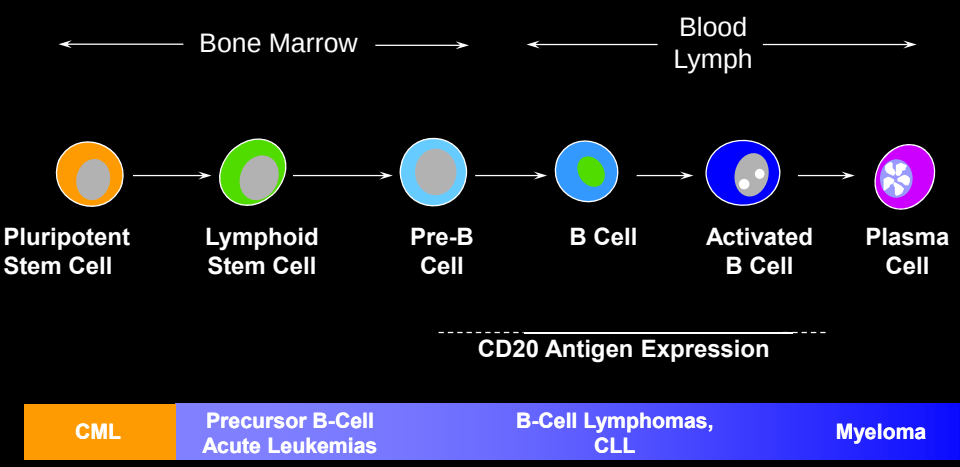


TARGETS ON B-CELLS

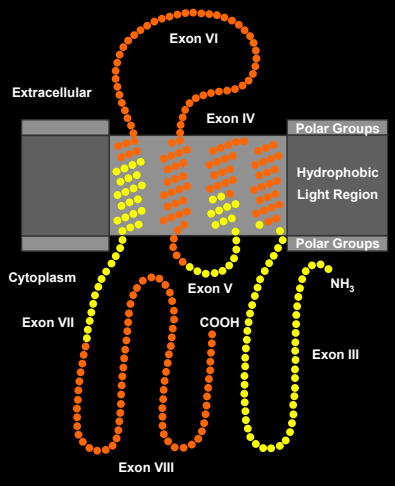


- Surface proteins can be targeted with:
  - Active immunotherapy
    - Vaccines
  - Passive immunotherapy
    - Unmodified MAbs
    - Conjugated MAbs
      - Radioisotopes
      - Drugs
      - Toxins
  - Peptides selected for binding
  - Small molecules

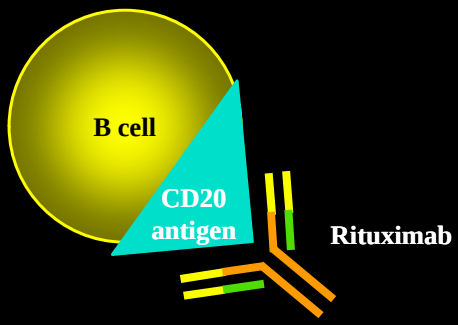
B-Cell Life Cycle
CD20 Tumor Specificity



B1 (CD20) Antigen



Mason et al. *Am J Pathol.* 1990;136:1215.

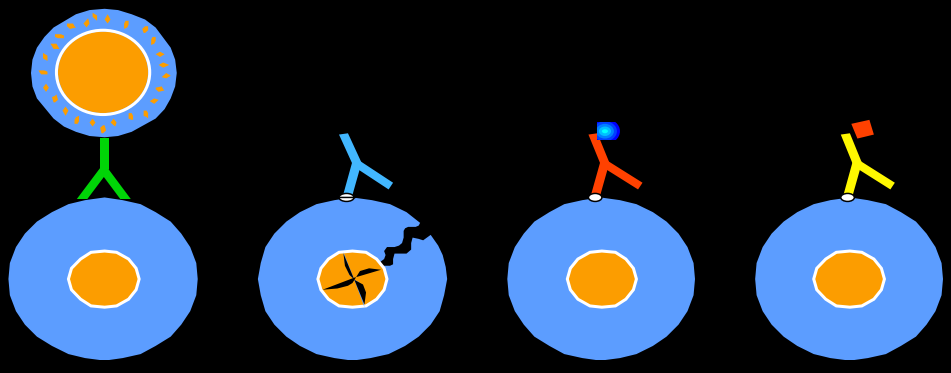


- Rituximab
  - Engineered derivative of IDEC-2B8
  - Murine antigen binding domain
  - Human κ constant region
  - Human Igγ1 constant region
  - Induces apoptosis

- CD20 antigen
  - Hydrophobic, 35 kD phosphoprotein
  - Expressed only on B lineage cells
  - Important for cell cycle initiation and differentiation
  - Does not shed or rapidly modulate off cell surface

- Effect of chimerism
  - $t_{1/2}$ = 76 h after 1st dose
  - $t_{1/2}$ = 206 h after 4th dose
  - Activates complement
  - Induces antibody dependent cell-mediated cytotoxicity

Cytotoxic Mechanisms of Monoclonal Antibodies

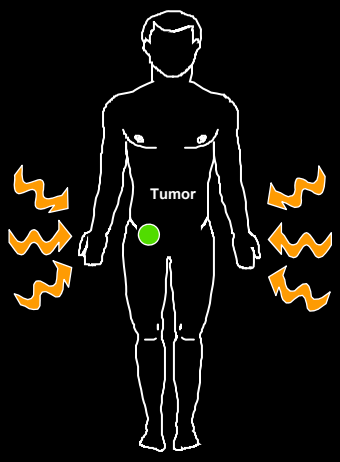


RITUXIMAB CLINICAL TRIAL SUMMARY
LOW GRADE LYMPHOMA

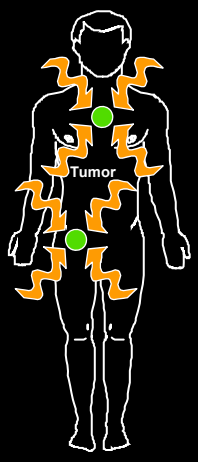
Trial Phase (Author)	N	Patient Population	Regimen	RR	RD Months	TTP (median) Months
Pivotal, Phase III (McLauglin et. al)	166	Low grade NHL, relapsed/refractory	Rituximab 375 mg/m^2 x 4	ORR 48% CR 6% PR 42%	11.2	13+
Rituximab/CHOP-Phase II (Czuczman et. al)	40	Low grade NHL, new dx or relapsed/ refractory	Rituximab 375 mg/m^2 x 6 CHOP x 6	ORR 95% CR 55% PR 40%	39.1+	41.1

RR	Response Rate	RD	Response Duration
ORR	Overall Response Rate	TTP	Time to tumor progression
CR	Complete reponse		
PR	Partial Response		

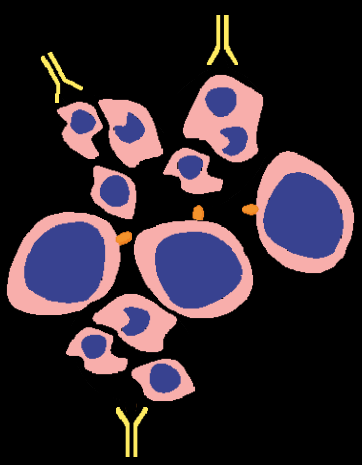
External Beam Irradiation



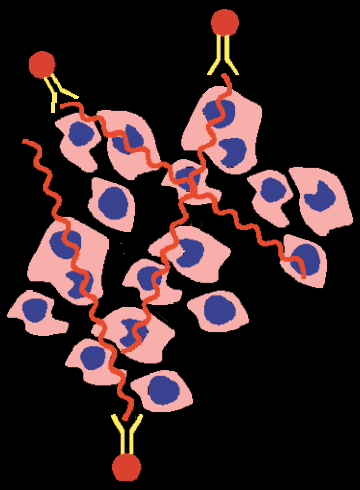
Radioimmunotherapy



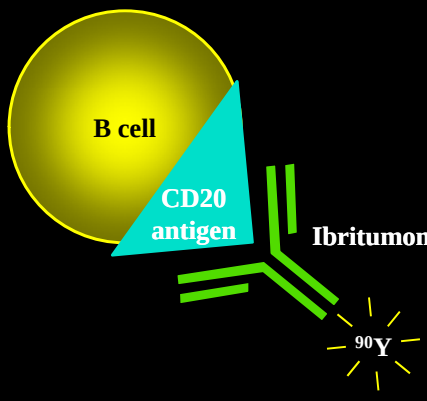
Crossfire Enhances Antibody Action



Naked Antibody



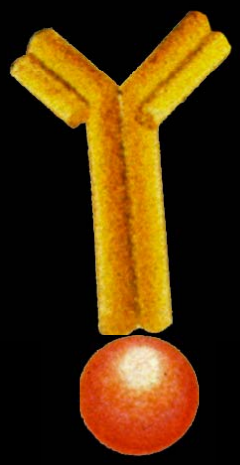
Radiolabeled Antibody



- Ibritumomab tiuxetan
  - Murine IDEC-2B8 (parent of rituximab)
  - MX-DTPA conjugated to antibody forming strong urea-type bond
  - Stable retention of ^{90}Y
- Yttrium-90
  - $t_{1/2}$ = 64 hours
  - Outpatient administration
  - Beta emission
    X_{90} = 5 mm

Iodine I 131 Tositumomab
Mechanism Of Action

- Iodine I 131 tositumomab
  - murine $IgG2_a$ anti-CD20 MAb
  - B-cell specific
  - triggers apoptosis
  - antibody-dependent cellular cytotoxicity
- Iodine-131 radioisotope
  - beta emission
    - ❋ short pathlength "crossfire" effect (~1mm)
  - gamma emission
    - ❋ allows individual dosimetry
- Iodine I 131 tositumomab
  - targeted radiotherapy

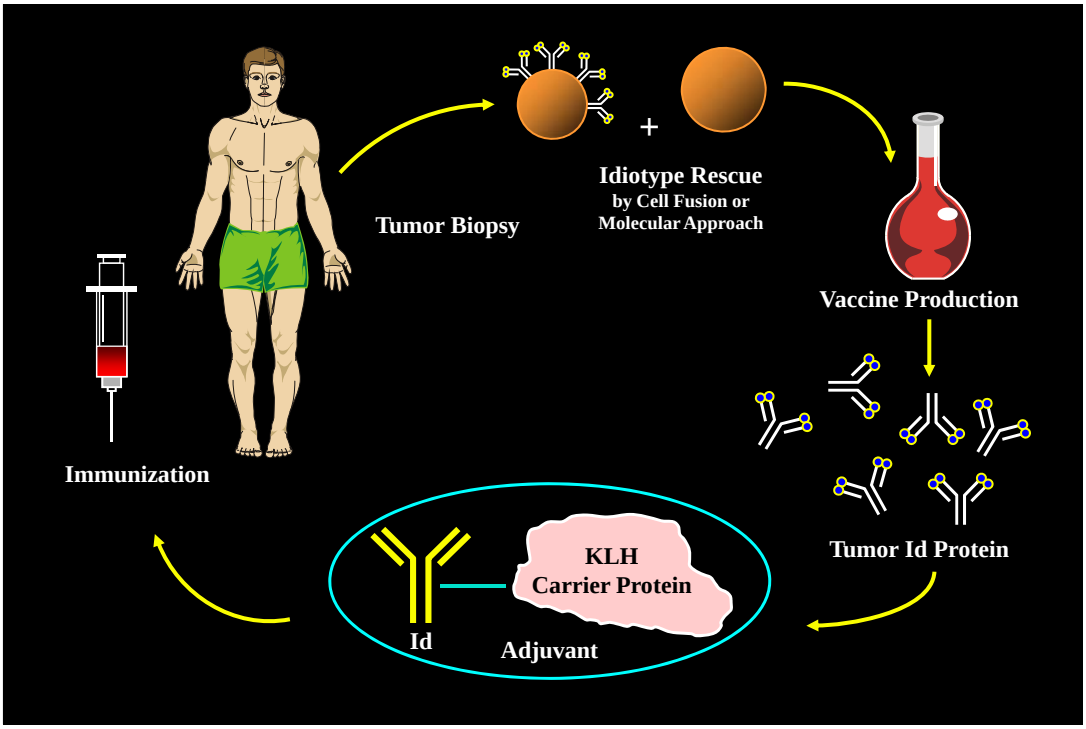


RITUXIMAB v ^{90}Y-2B8: RESPONSE TO THERAPY
INTERIM ANALYSIS (n=90)

Histology	Rituximab N (%)	Ibritumomab N (%)	p-value*
ORR	20 (43.5)	35 (79.5)	0.001
95% CI	28.1-58.9%	64.2-89.7%	
CR	3 (7%)	9 (21)	0.057
PR	17 (37%)	26 (59%)	

***Calculated from Cochran-Mantel-Haenszel test over histology type (A/Follicular/Transformed)**

Witzig, *et al.,* Blood, 94 (Supplement 1), Abstract 2805



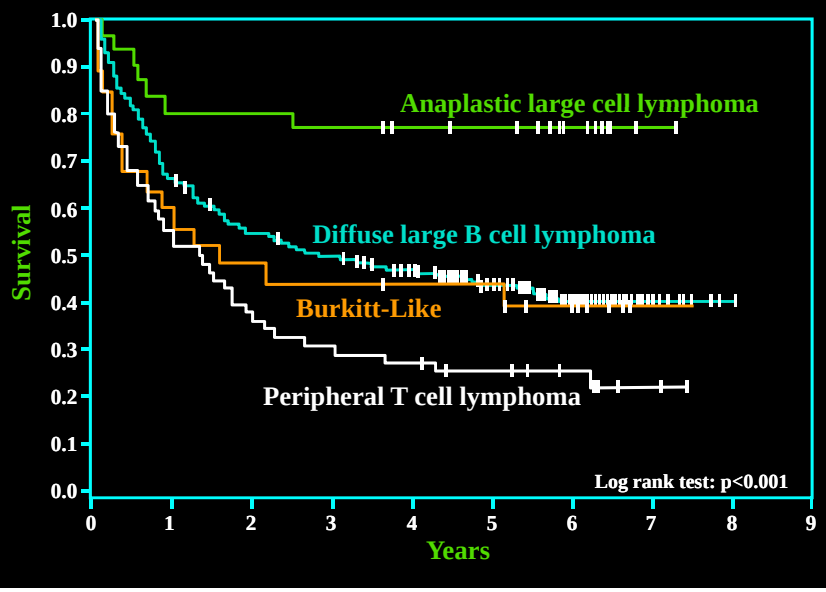
Indolent Lymphoma
Continuing Challenges

- Define the optimal use of antibody-based therapy
  - First line
  - In combination with chemotherapy
  - Sequentially with chemotherapy
- Refine the use of high dose therapy to provide maximal benefit
- Develop new targeted therapy based on molecular mechanisms of lymphomagenesis

Lymphoma Overview and Principles of Therapy

- Non-Hodgkin's Lymphoma
  - Epidemiology
  - Classification/Staging
  - Indolent Lymphoma
  - Aggressive Lymphoma
- Hodgkin's Disease
- New Approaches to Therapy

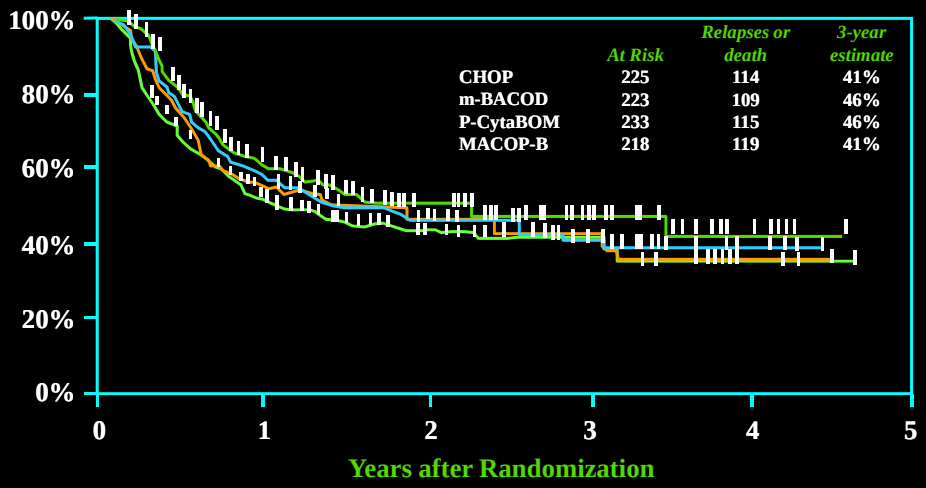
Overall Survival: Large Cell Histologies



Three Generations of Chemotherapy for NHL: Apparent Improvement in Outcome

First Generation	Second Generation	Third Generation
DFS: 35-45%	DFS: 50-70%	DFS: 60-75%
BACOP	ProMACE-MOPP	MACOP-B
MOPP	M-BACOD	ProMACE-CytaBOM
COPA-Bleo	COP-BLAM	ProMACE-MOPP 1/8
CAP-BOP		COP-BLAM III
COMLA		
COPA		
CHOP		

National High Priority Lymphoma Study:
Time to Treatment Failure by Randomized Treatment Arm



Fisher et al. *N Engl J Med.* 1993;328:1002.

International Prognostic Index

Prognostic Indicators (APLES)
• Age > 60 years
• Performance status > 1
• LDH > 1 x normal
• Extranodal sites > 1
• Stage III or IV

• Risk Category	Factors
• Low	0 or 1
• Low-intermediate	2
• High-intermediate	3
• High	4 or 5

Hiddemann. *E. J Cancer*. 1995; Jagannath et al. *J Clin Oncol*. 1986; Danieu et al. *Cancer Res*. 1986; Swan et al. *J Clin Oncol* 1989; Coiffier et al. *J Clin Oncol*. 1991; Shipp et al. *N Engl J Med*. 1993.

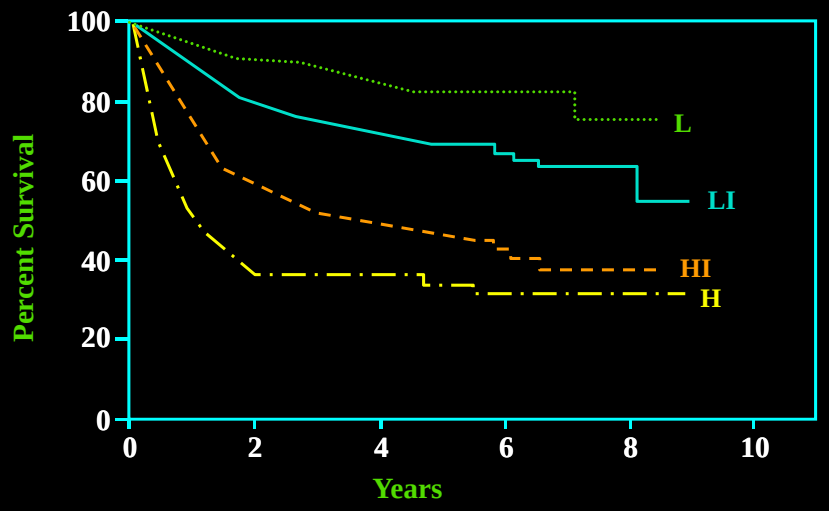
International Prognostic Index
Age-Adjusted (aaIPI)

Prognostic Indicators (PLS)
• Performance status > 1
• LDH > 1 x normal
• Stage III or IV

• Risk Category	Factors
• Low	0
• Low-intermediate	1
• High-intermediate	2
• High	3

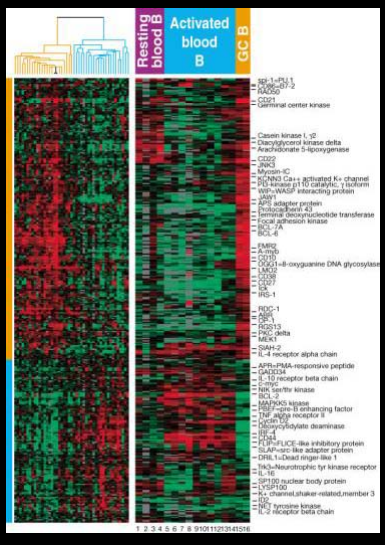
Shipp et al. *N Engl J Med*. 1993.

International Prognostic Index
Age-Adjusted Overall Survival

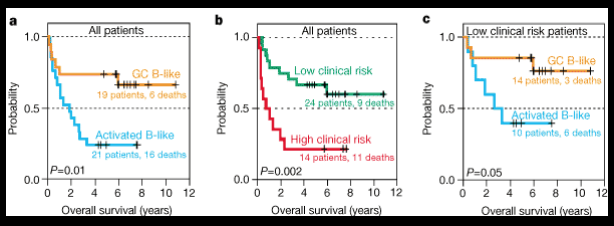


*N Engl J Med.*1993;329:987.

Diffuse Large B Cell Lymphoma
Distinct Forms Revealed by Expression Arrays

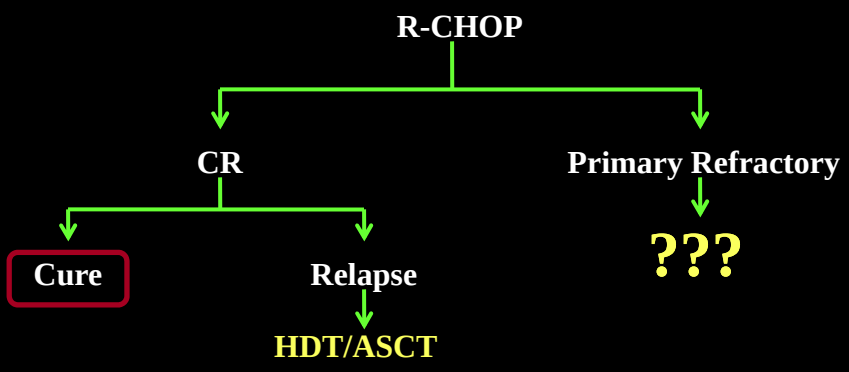


- Lymphochip expression array data segregates diffuse large B cell lymphoma into two molecular entities:
  - Germinal center phenotype
  - Activated B cell phenotype
- Molecular subtype is independent of International Prognostic Index risk group



Alizadeh *et al*. *Nature* **403**:503-511 (2000)

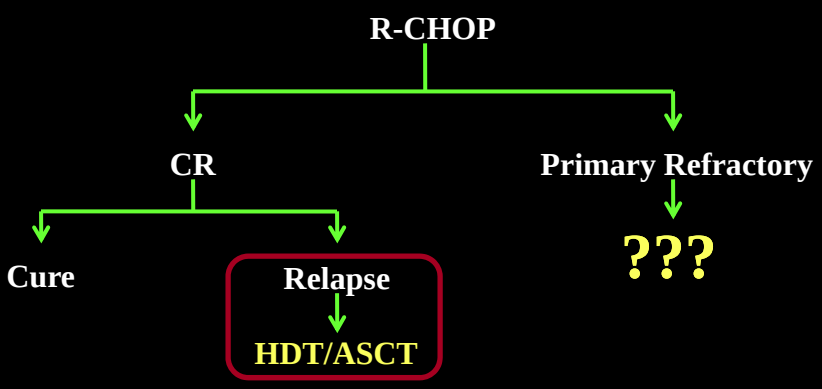
Management of Aggressive NHL



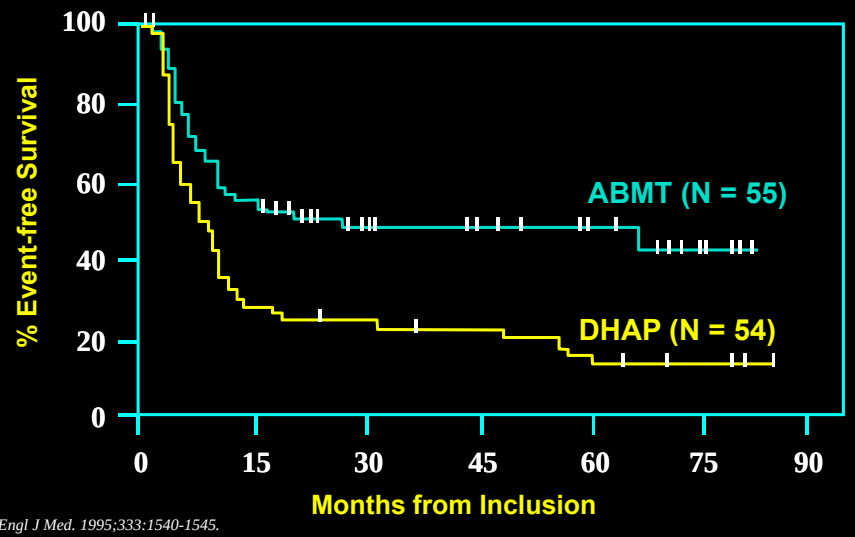
Aggressive Lymphoma

Second-line Therapy

Management of Aggressive NHL



Parma Trial: Event-free Survival



Philip et al. *N Engl J Med. 1995;333:1540-1545.*

Second Line Therapy for Aggressive NHL

- Ideal second line therapy
  - Provides effective reduction in tumor size
  - Results in minimal non-hematologic toxicity
  - Effectively mobilizes stem cells into the peripheral blood

Therapy for Aggressive NHL
Summary

- R-CHOP remains the standard, albiet with suboptimal results, for refractory
- Passive Immunotherapy in aggressive NHL has changed the landscape
- High dose therapy with ASCT is superior to chemotherapy for relapsed and refractory aggressive lymphoma
- A better response to second line therapy correlates with a superior outcome post ASCT
- Based on intention to treat, about 30% of patients are benefited by second-line therapy with high dose chemotherapy consolidation

Therapy for Aggressive NHL
Summary

- Patients with primary refractory disease, both induction failures and those achieving only a PR to first line therapy can benefit from ASCT
- Second-line age-adjusted international prognostic index (saaIPI) predicts survival
- Not all patients with relapsed and refractory aggressive NHL are potentially curable with this approach, particularly:
  - relapsed saaIPI IV
  - refractory saaIPI III/IV

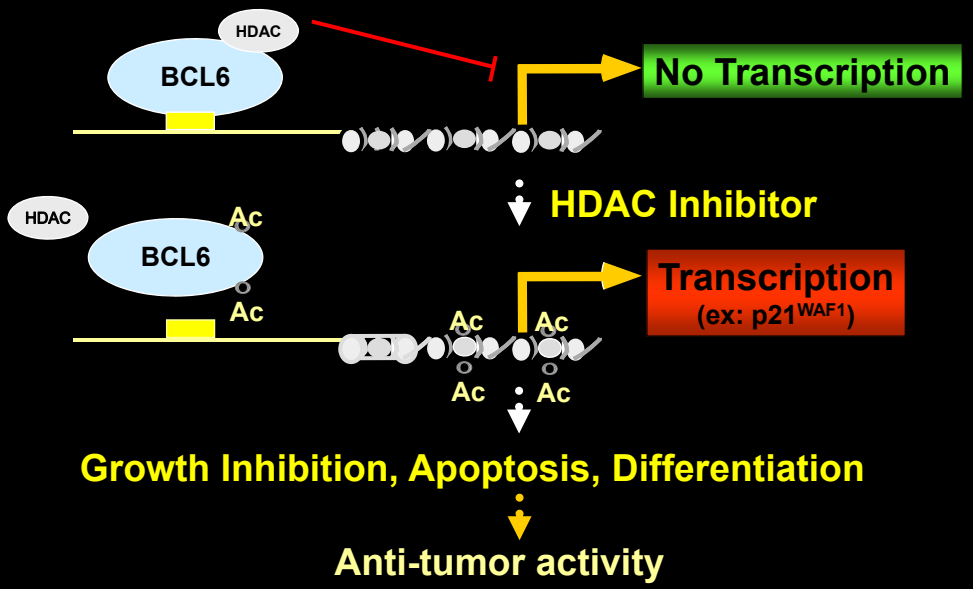
Second-line Therapy of NHL
Avenues for New Directions

- Improved cytoreduction (RICE)
- Improved HDT (TBI-Ifos-Etop)
  - Non-myeloablative alloBMT
- Post remission therapy
  - Cellular therapy
  - Post remission chemotherapy (after transduction of stem cells with drug resistance genes)
- Novel targeted therapy

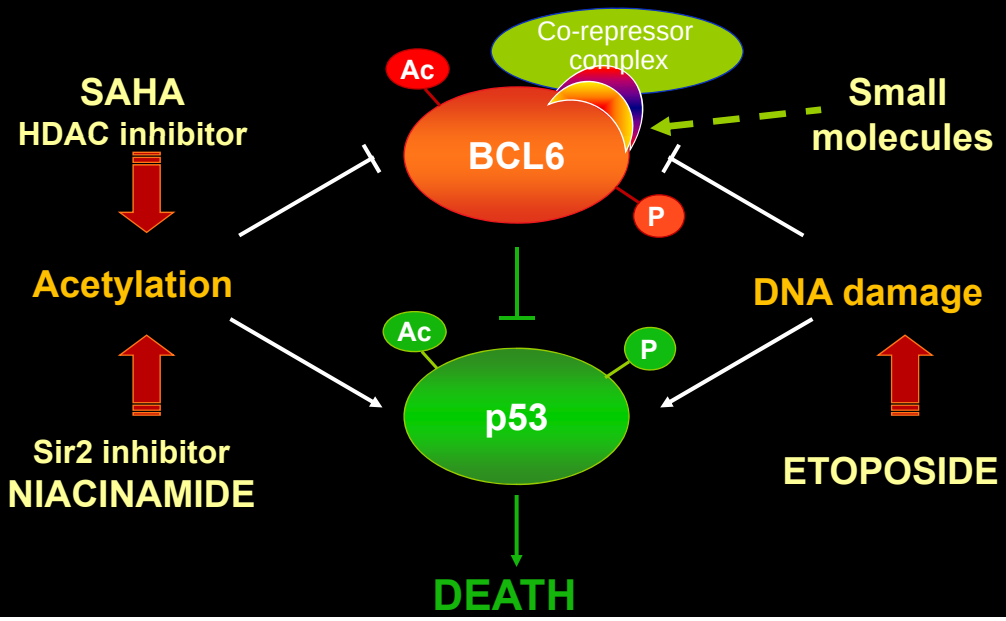
The Future of Cancer Therapy

Targeting the Molecular Pathways

TARGETING BCL-6 IN LYMPHOMA



The BCL6:p53 Network: A Rational Target



Thank You