

Lymphoma: An Update

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National Cancer

MAX. HEIGHT CLEARANCE

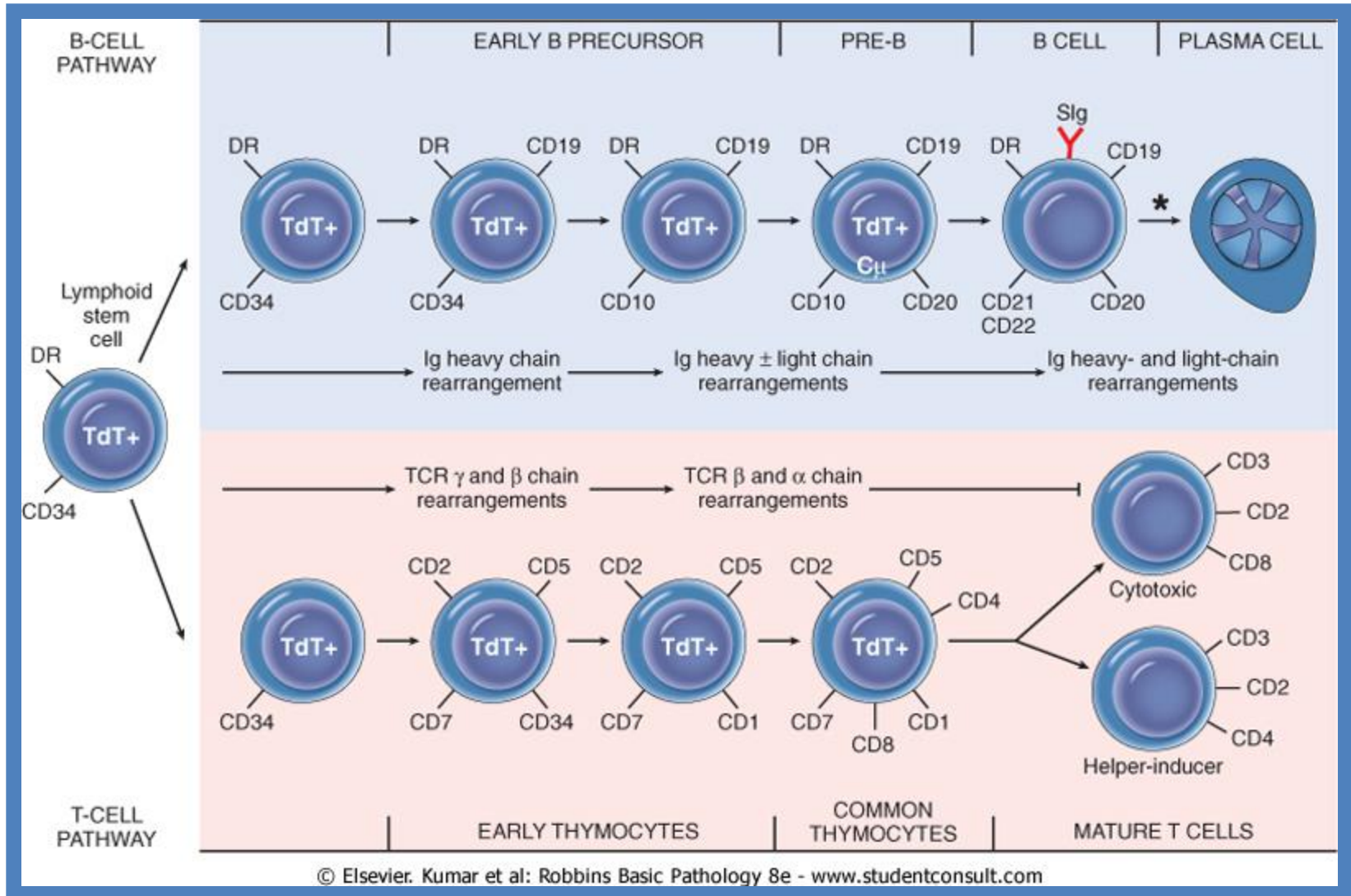
Major Developments in Lymphoma

- Major advances in our understanding of the biology, leading to a universally adopted WHO classification system
- Prognostic models incorporating molecular markers to guide therapy
- New chemotherapy regimens based on mathematical models: dose-density and dose-intensity
- Incorporation of immunotherapy has altered our therapeutic paradigms for B-cell disorders
- Development of targeted agents: radioimmunoconjugates, antisense oligonucleotide, bortezomib, etc

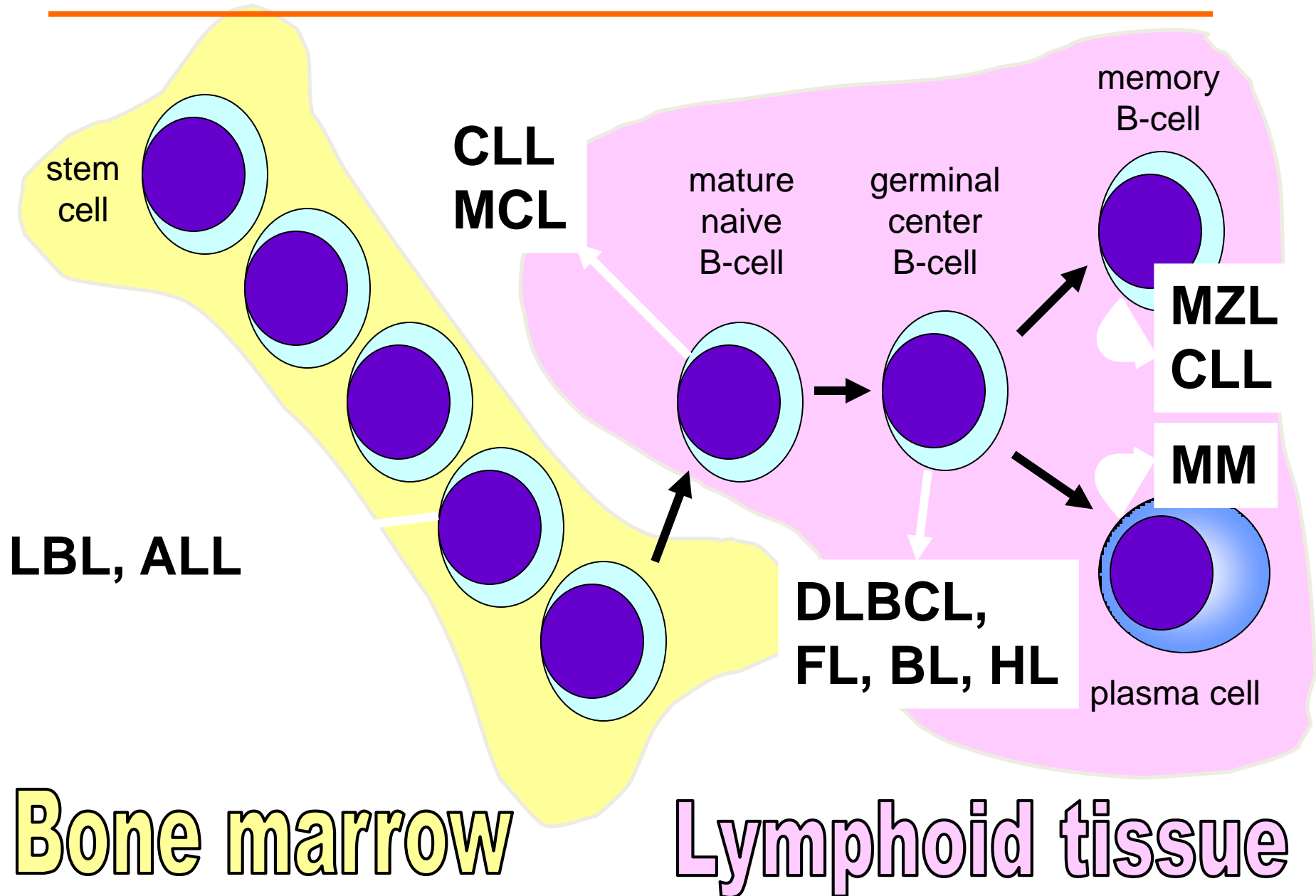
Lymphoma - Background

- Heterogeneous group of conditions
- Marked changes in lymphoma classification over time
- Older classification:
 - Working formulation
 - Luke-Collins
- Current WHO/REAL classification was first published only in the late 1990s

Background



B-Cell Development



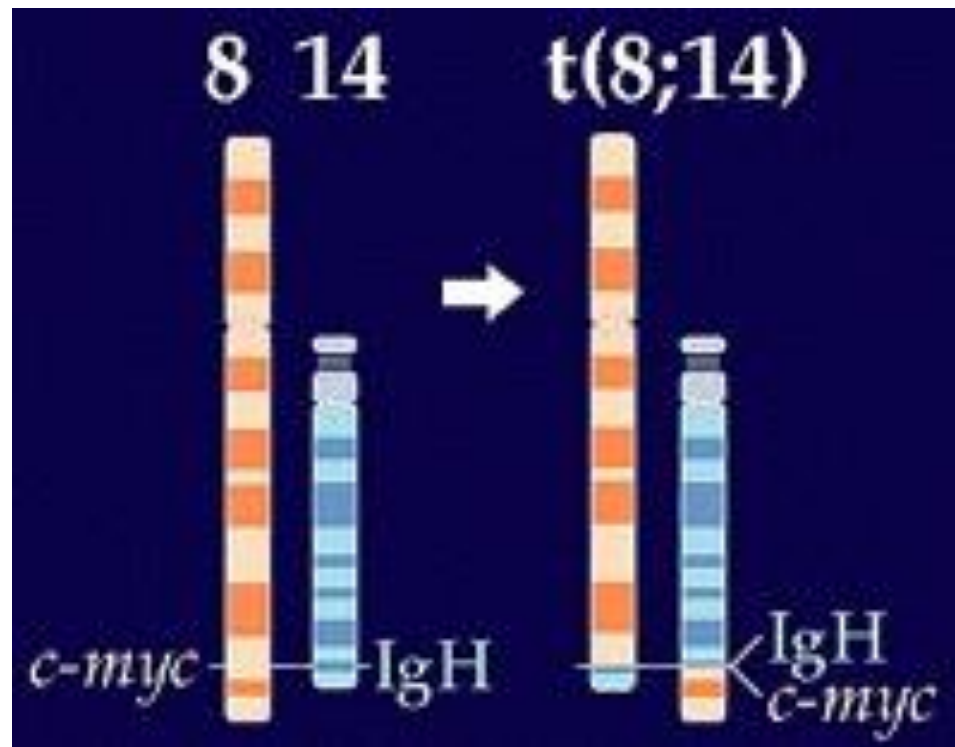
Genetic Aberrations

- Disease of proliferation:
 - Up-regulation of oncogenes involved in proliferation
 - c-myc, cyclin-D1
- Disease of accumulation
 - Up regulation of genes involved in apoptosis
 - e.g. BCL-2
- Translocation is a Hallmark of Haematological malignancies

Lymphoma Concepts

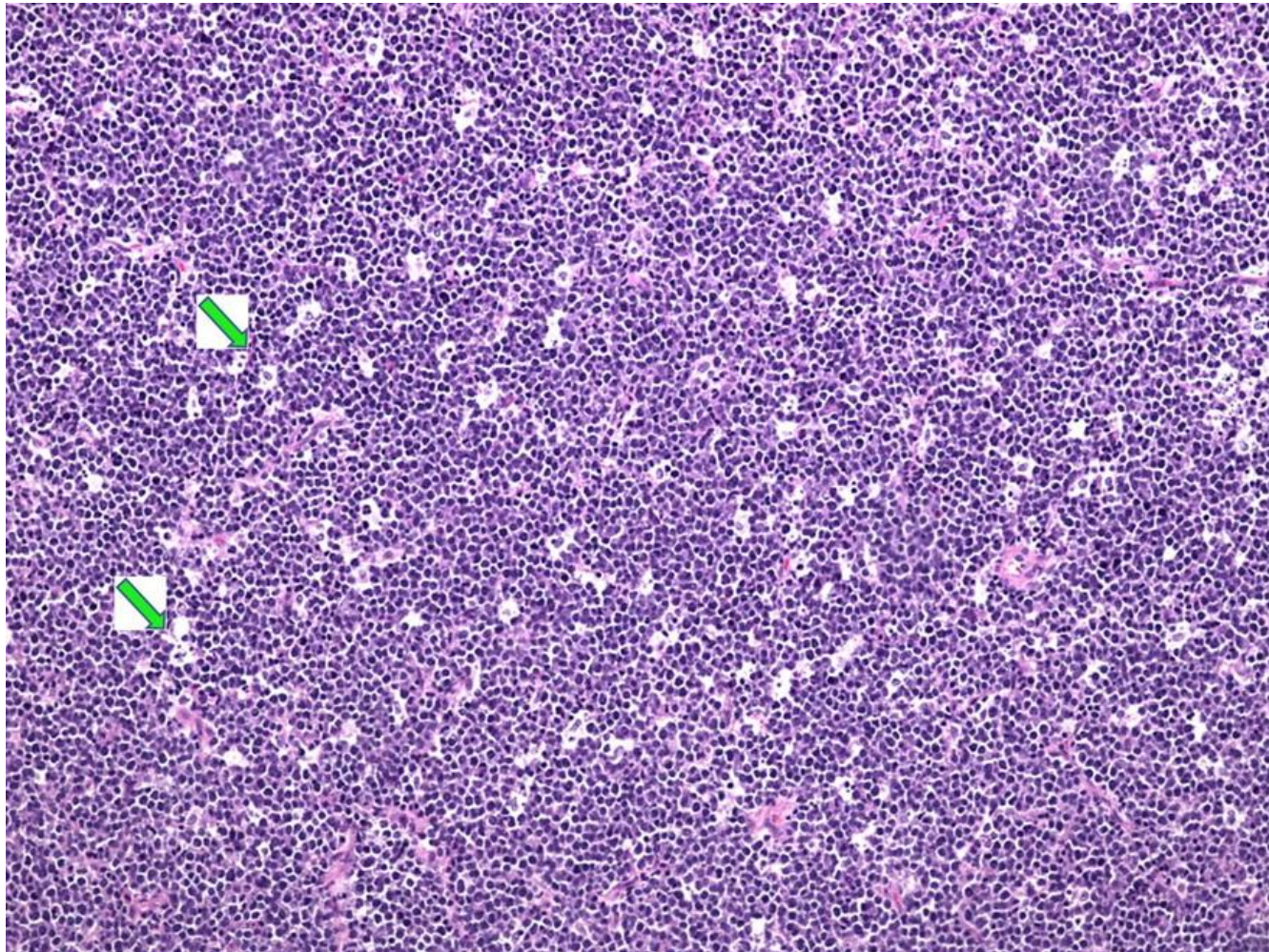
- Neoplastic counterparts of normal B or T cells in various stages of activation
- Each specific type of lymphoma is “driven” by a distinct molecular abnormality
- The clinical illness which ensues may be predicted by the “Biology” and characteristics of the specific lymphoid cell which predominates

Burkitt's Lymphoma

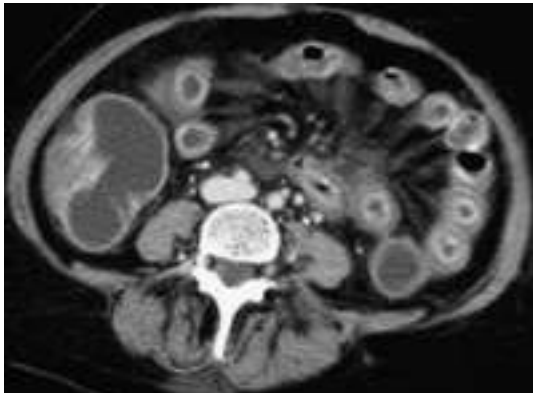
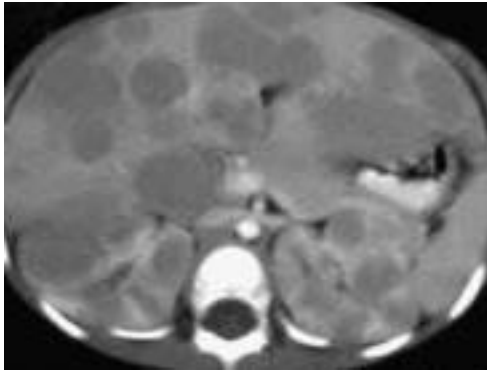


Over-expression of *c-myc*

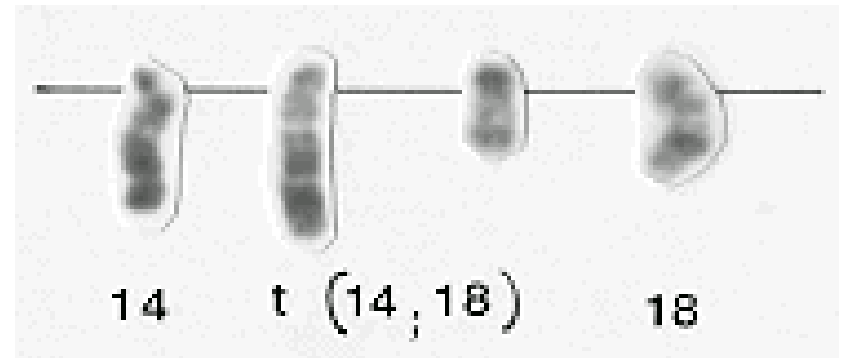
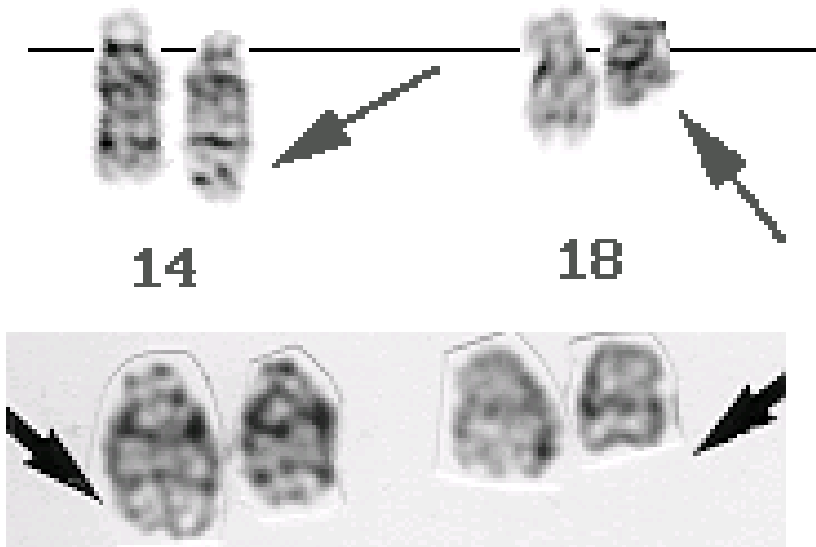
Burkitt's Lymphoma: Starry Sky



Clinical Behavior: Aggressive



Follicular Lymphoma



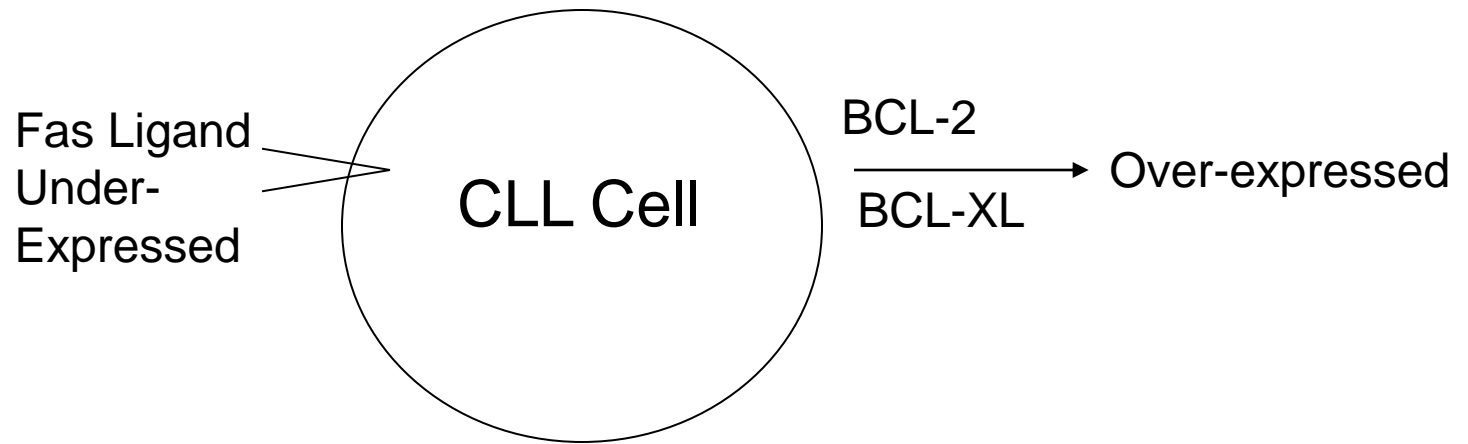
↑ Bcl2 essentially block apoptosis

Small Lymphocytic Lymphoma

Mechanism of Disease

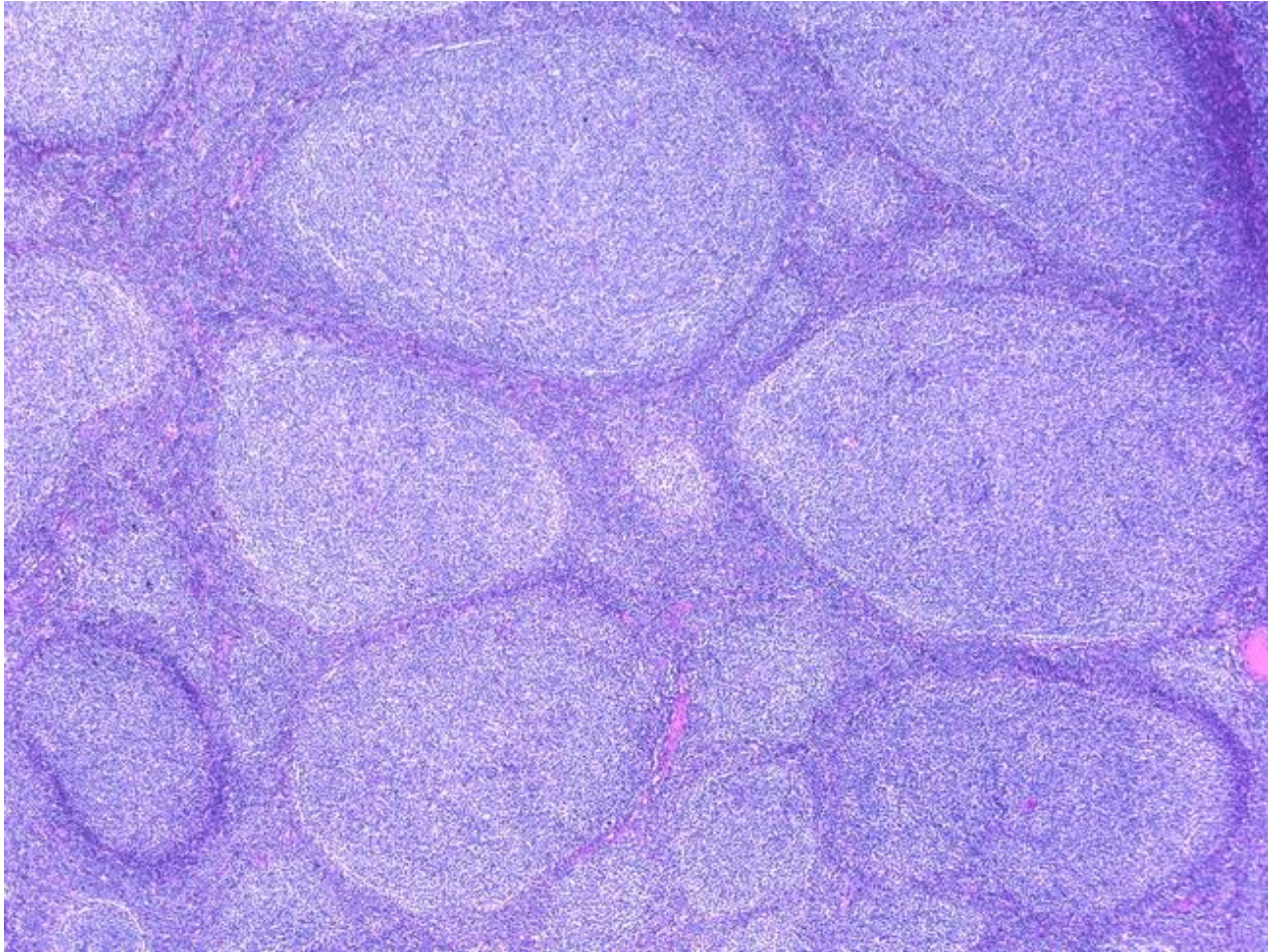


Failure of Apoptosis

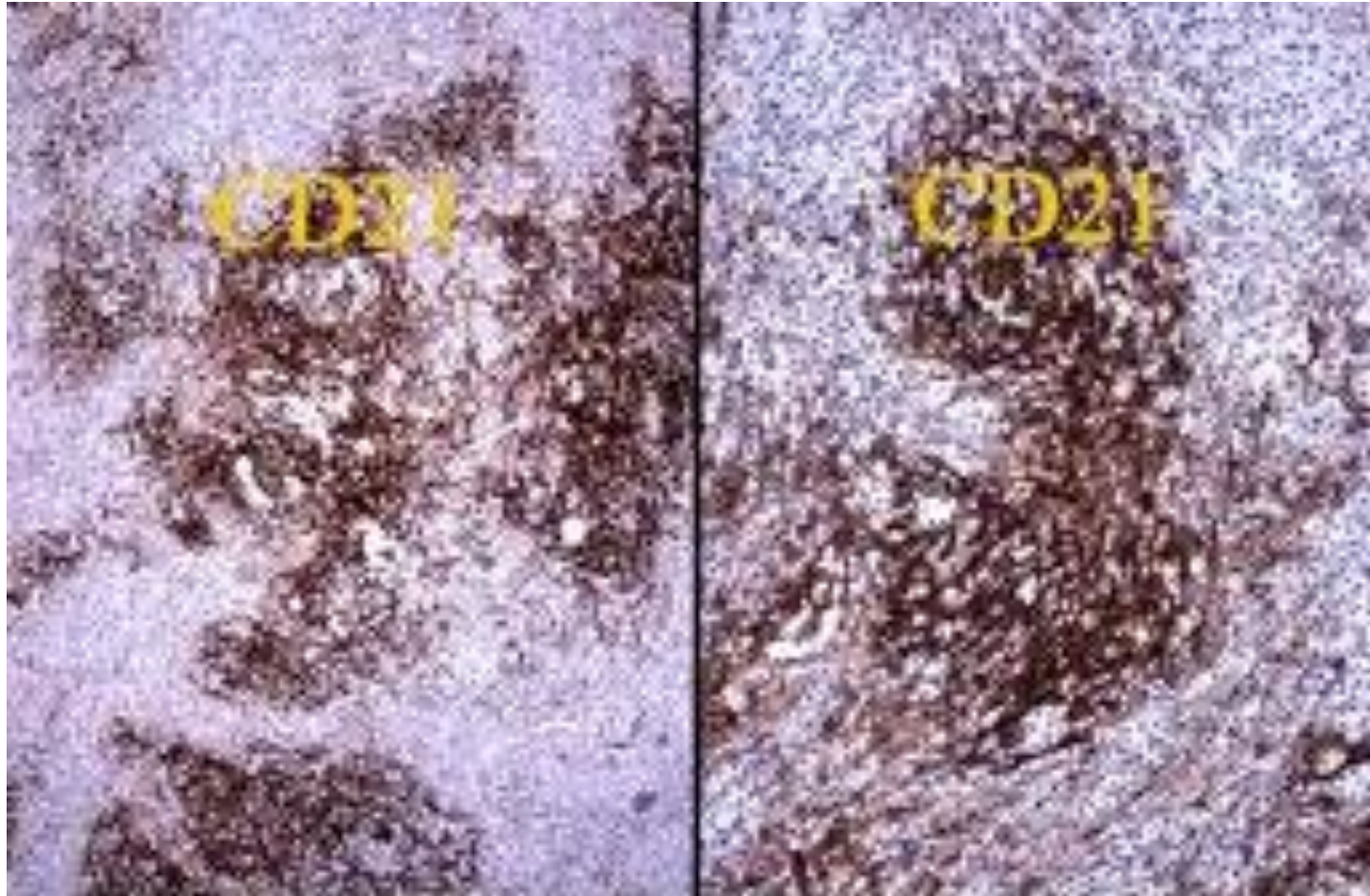


DISEASE OF ACCUMULATION

Morphology

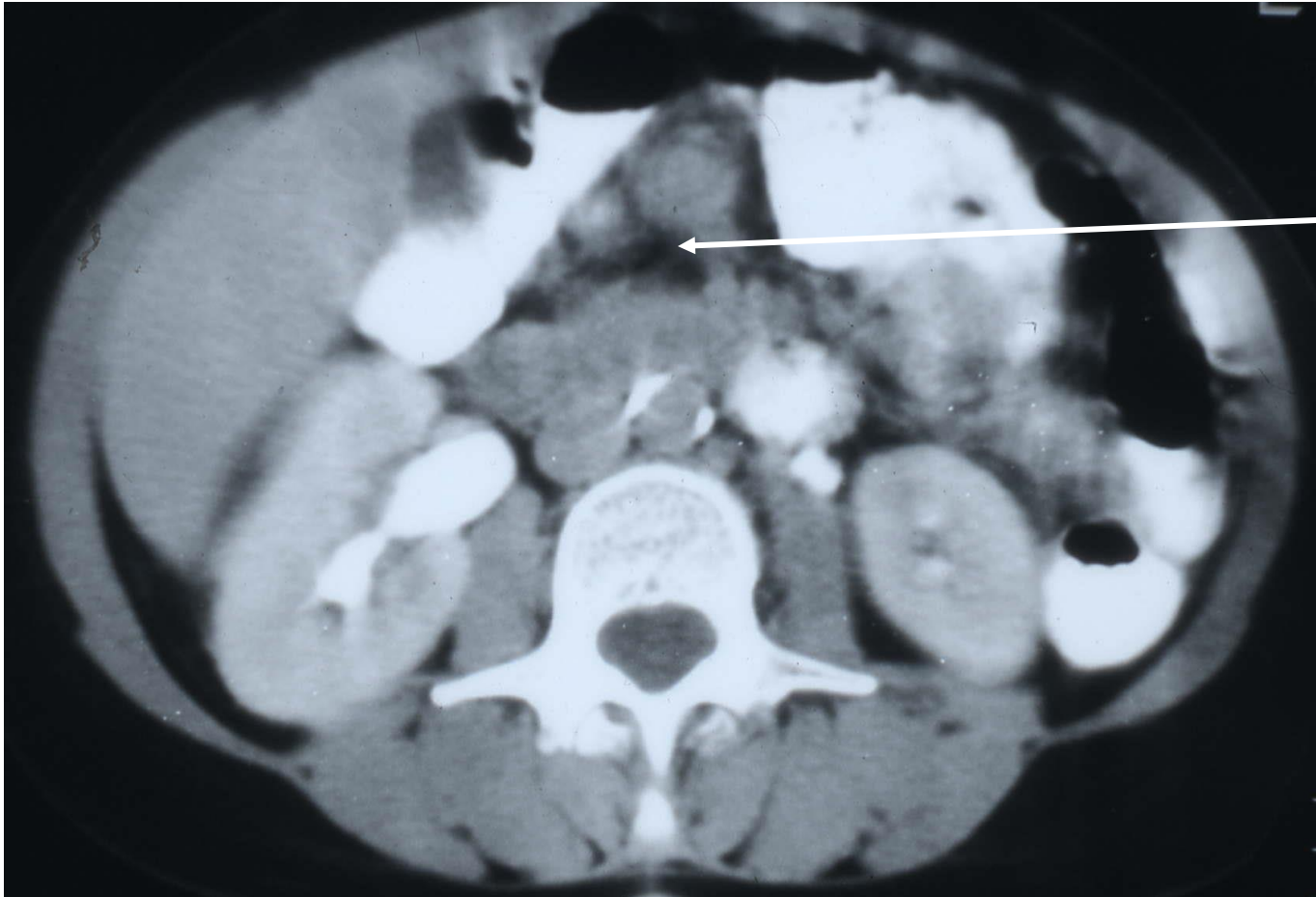


Follicular Lymphoma: Immunostains



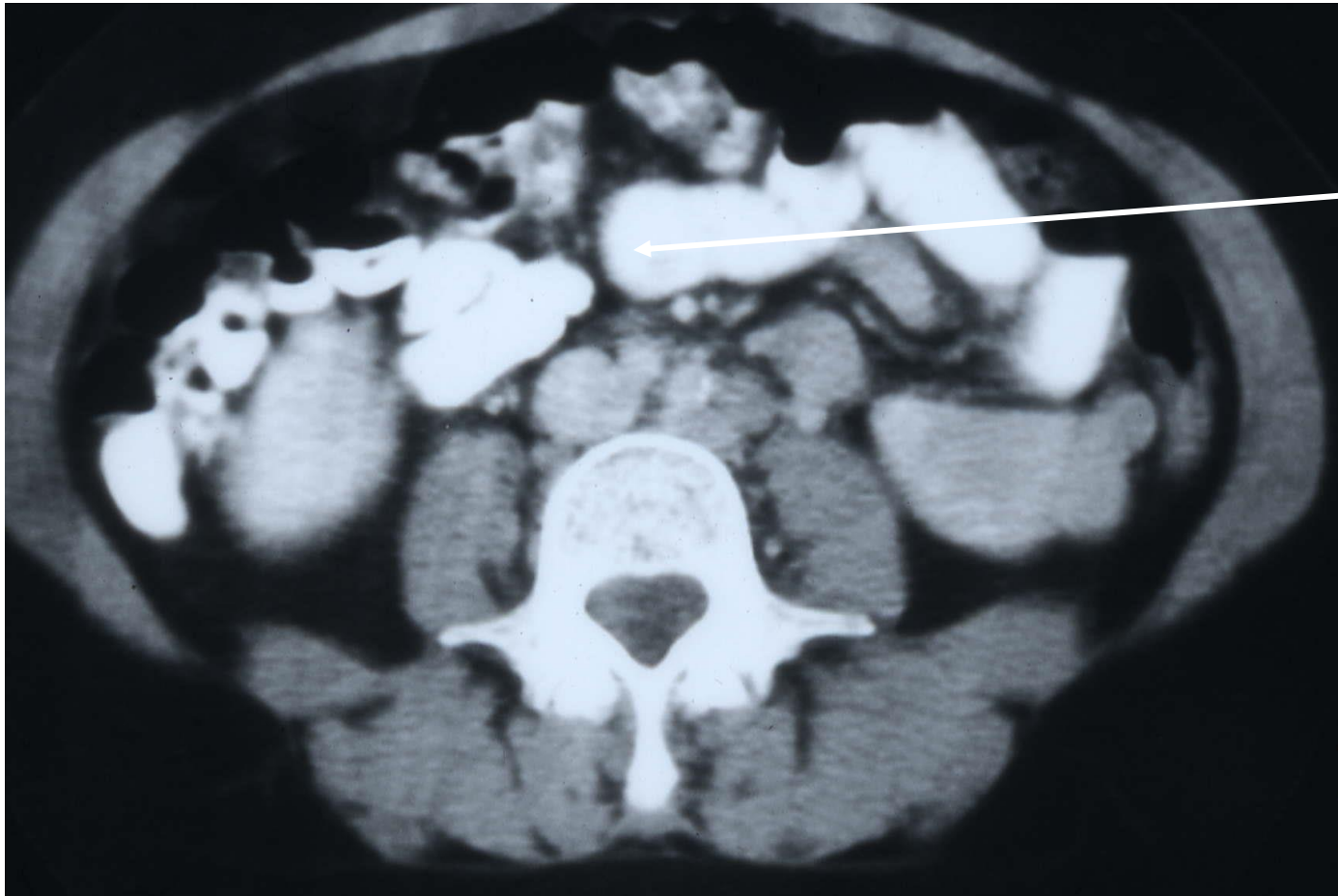
Follicular, grade 1

March, 1989



Follicular, grade 1

June, 1990



Morphology



Histiocyte

Small Cells

Intermediate Cells

Large Cells



Small round
(Lymphocyte)



Small cleaved
(Centrocyte)



Plasmacytoid small lymph
(Immunocyte)



Monocytoid small lymph
(Monocytoid lymph)



Lymphoblast
(Convolut Lymphoblast)



Small non-cleaved
(Burkitt's lymphoblast)



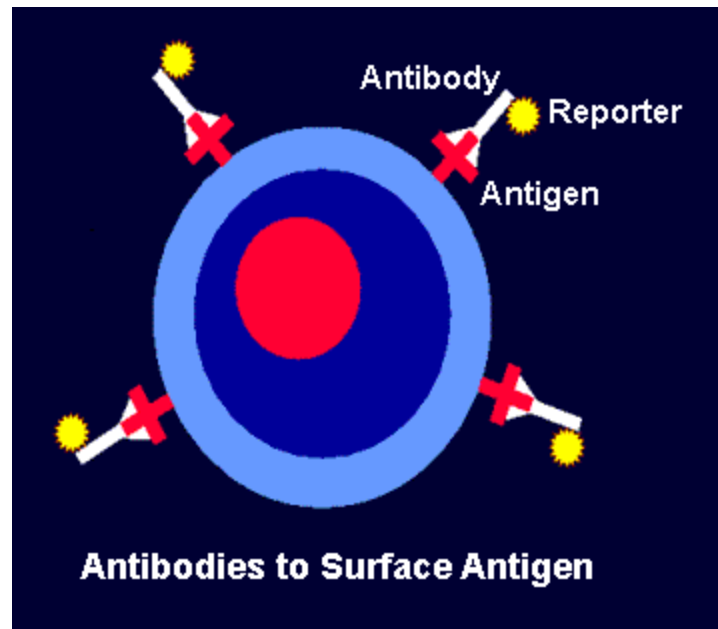
Large non-cleaved
(Centroblast)



Immunoblast
(Immunoblast)

Immunophenotyping

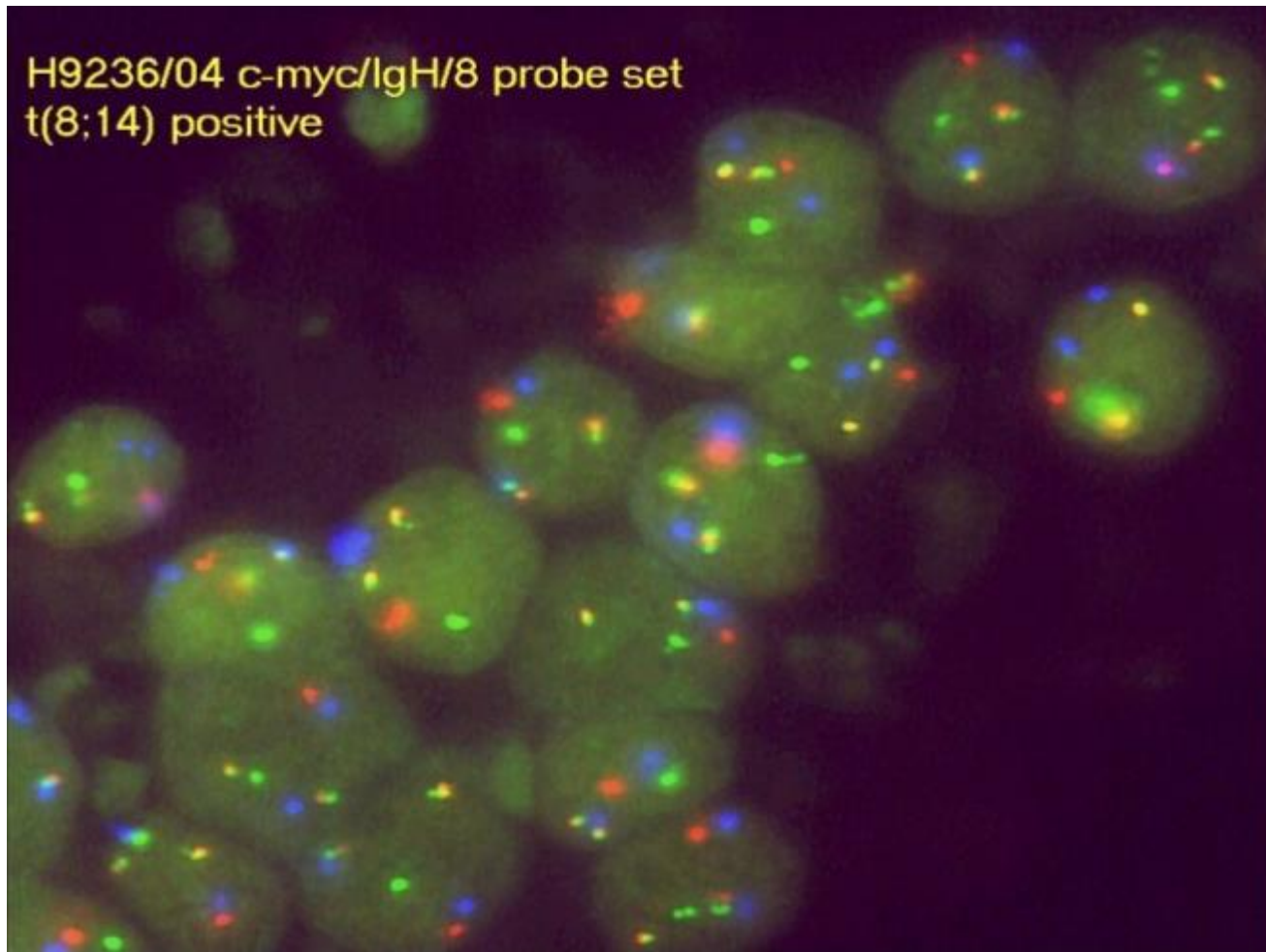
- **IMMUNOPHENOTYPING** refers to the technique of identifying molecules that are associated with lymphoma cells and that help to characterize them



Immunophenotypic Markers for Malignant Lymphocytes

Type of Lymphocyte	Surface Immunoglobulin	CD5	CD19	CD20	CD10	CD11c	CD22	CD23	CD43	CD103
CLL/SLL	+	+	+	+	—	—	—	+	+	—
MCL	++	+	+	+	±	—	+	—	+	—
HCL	++	—	+	+	—	+	+	—	—	+
LPL	++	—	+	+	—	—	+	—	—	—
SML	++	—	+	+	—	—	+	—	—	—
FCL	++	—	+	+	+	—	+	—	—	—

Fluorescence In Situ Hybridisation (*FISH*)



WHO CLASSIFICATION

- Morphology
- Immunophenotype
- Genetic Aberration
- Clinical Behaviour

Lymphoma Classification (based on 2001 WHO)

- B-cell neoplasms
 - Precursor B-cell neoplasms (2 types)
 - Mature B-cell neoplasms (19)
 - B-cell proliferations of uncertain malignant potential (2)
- T-cell & NK-cell neoplasms
 - Precursor T-cell neoplasms (3)
 - Mature T-cell and NK-cell neoplasms (14)
 - T-cell proliferation of uncertain malignant potential (1)
- Hodgkin lymphoma
 - Classical Hodgkin lymphomas (4)
 - Nodular lymphocyte predominant Hodgkin lymphoma

A Quick Working Classification of Lymphoma

Category		Survival of untreated patients	Curability	To treat or not to treat
Non-Hodgkin lymphoma	Indolent	Years	Generally not curable	Generally defer Rx if asymptomatic
	Aggressive	Months	Curable in some	Treat
	Very aggressive	Weeks	Curable in some	Treat
Hodgkin lymphoma	All types	Variable – months to years	Curable in most	Treat

Risk Factors

- Immunodeficiency
 - autoimmune disease
 - organ transplant
- Exposure to chemicals
 - pesticides, fertilizers, or solvents
- Infections
 - Epstein-Barr Virus
 - Human T-lymphotropic virus type 1
 - HIV
 - Hepatitis C
 - H-pylori

Risk of Non-Hodgkin's Lymphoma

Disorder	No. of studies	Pooled relative risk
Systemic lupus erythematosus	11	2.69 (1.68-4.30)
Multiple sclerosis	10	0.96 (0.48-1.92)
Sjögren syndrome	8	6.56 (3.10-13.9)
Primary	8	4.75 (1.79-12.6)
Secondary	8	9.57 (2.90-31.6)
Scleroderma	7	0.69 (0.20-2.40)
Immune thrombocytopenia	5	2.13 (0.47-9.73)
Myasthenia gravis	6	1.45 (0.31-6.82)
Polymyositis/dermatomyositis	5	ND

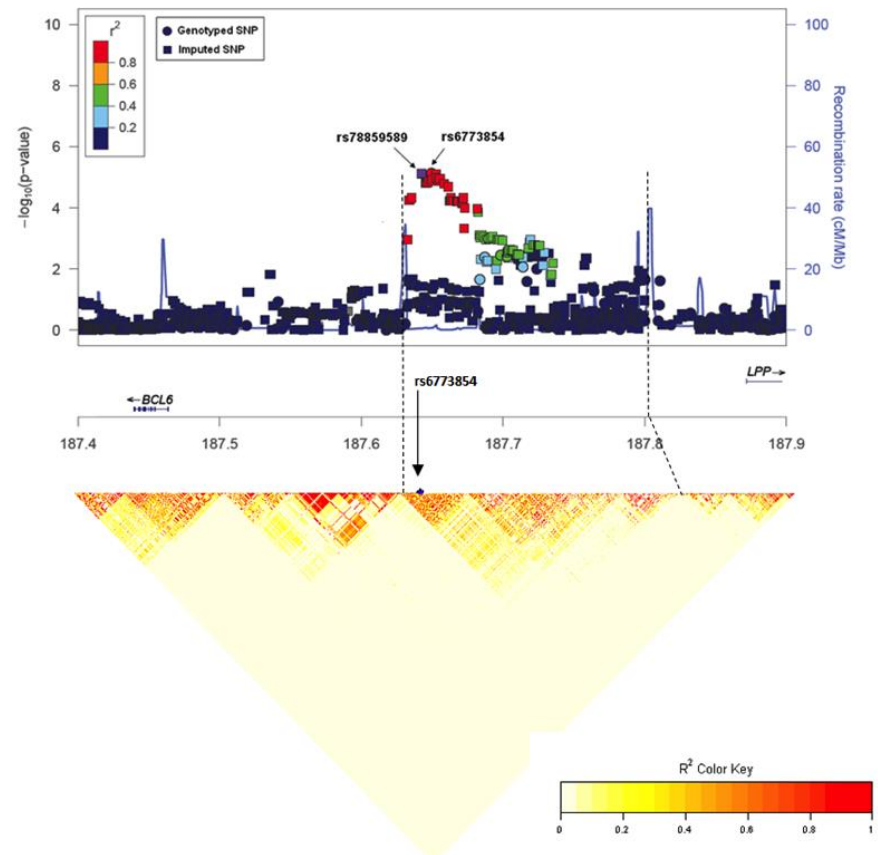
HBV Prevalence by Sex and Age: Lymphoma patients vs. General Population

	Lymphoma		Control		<i>p</i>
	n	% HBV +	n	% HBV +	
Sex					
Male	332	8.1	2356	4.9	≤0.025
Female	224	13.4	2342	3.6	≤ 0.001
Age, yr					
14-39	104	7.7	2544	3.3	≤0.025
40-49	95	11.6	1140	5.5	≤ 0.025
50-59	123	13	629	4.9	≤ 0.001
60-69	122	11.5	385	4.1	≤ 0.01
Total	556	10.3	4698	4.1	≤ 0.001

Lim ST et al. Eur J Haematol 2008

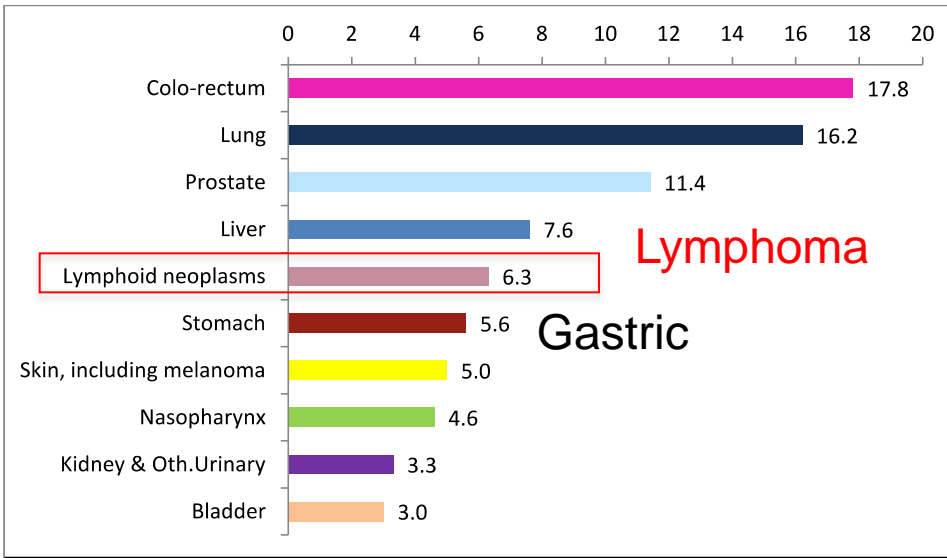
Epidemiology: Genetic Risk factors

- GWAS of 253 Chinese cases with B-NHLs and 1500 healthy controls recruited in Singapore and further validation in 3 independent samples of Han Chinese
 - Currently working on a fine mapping study of the MHC region in NHL.
- Aim to work on genetic risk factors for T and NK/T cell lymphoma

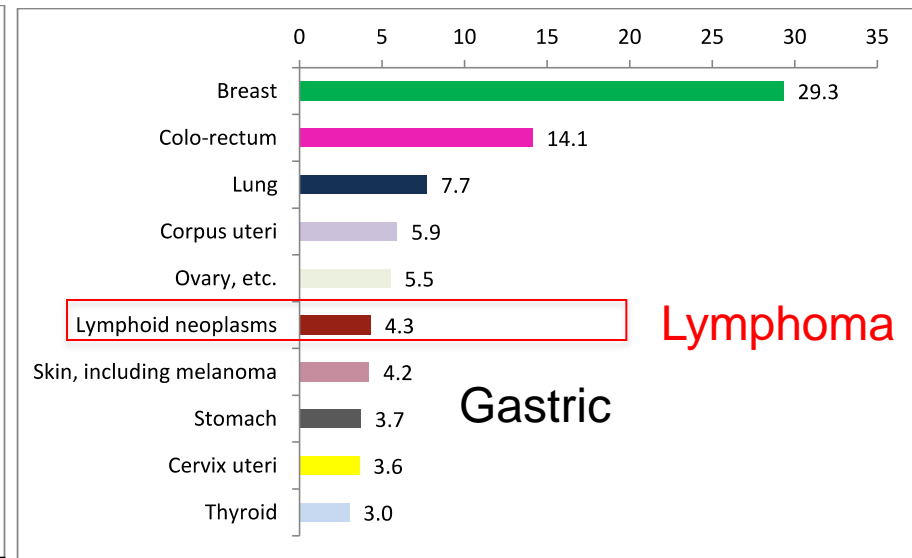


A National Concerted Effort Needed: Rising Incidence of NHL

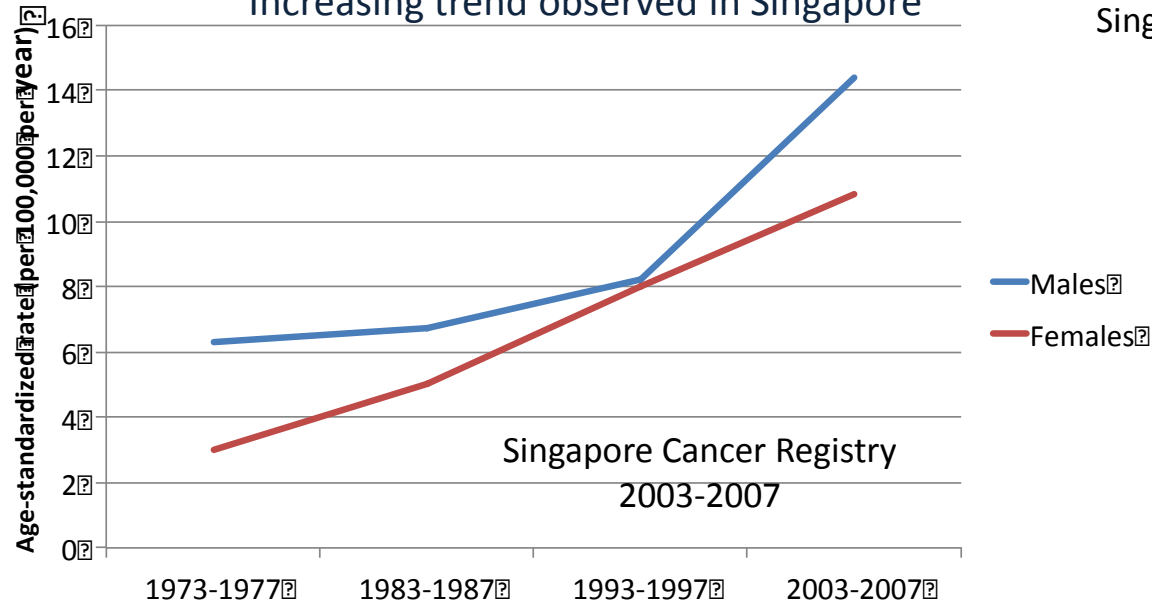
5th most common in Singaporean Males



6th most common in Singaporean Females



Increasing trend observed in Singapore



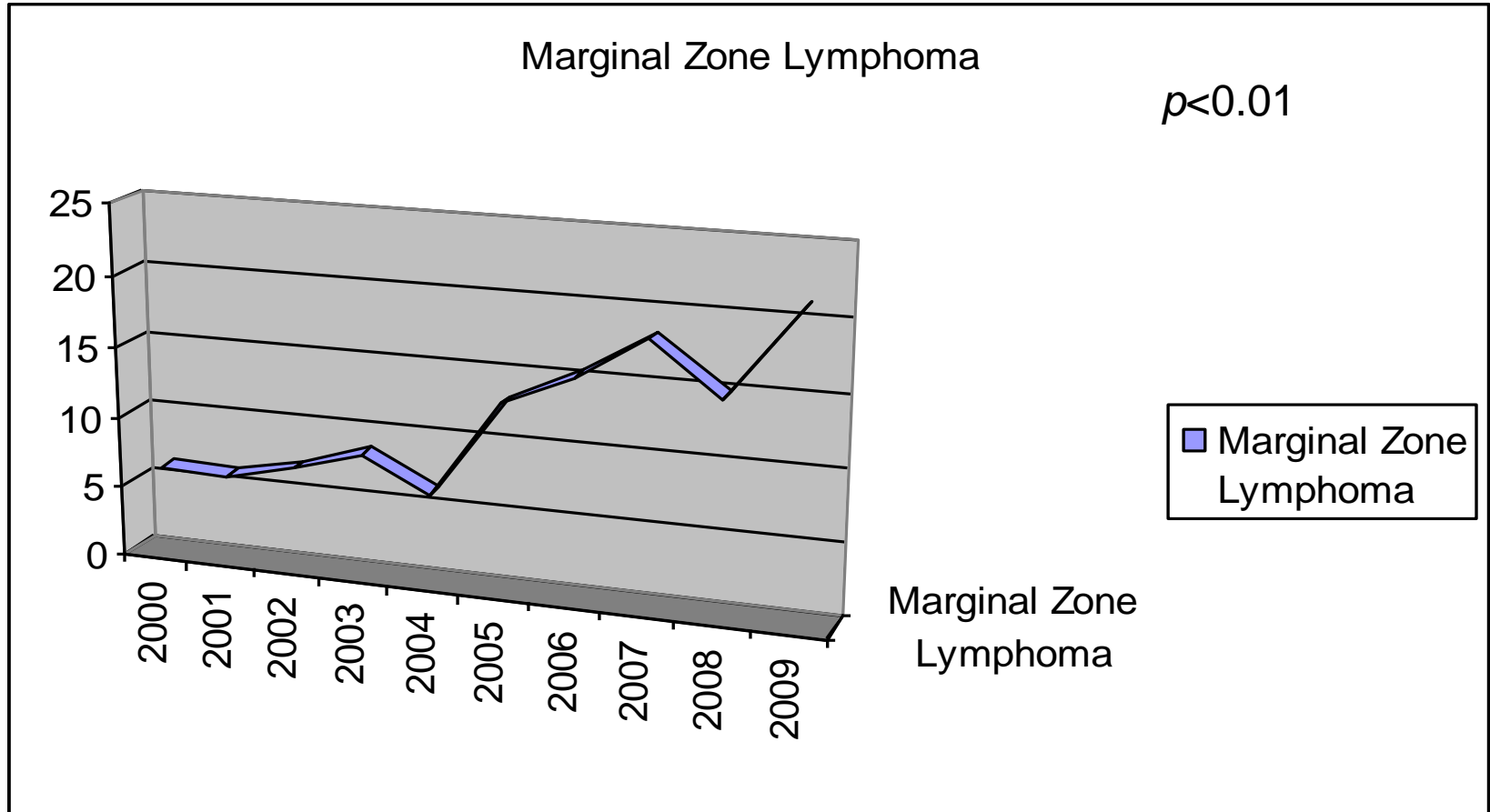
Singapore Cancer Registry
2008-2012

Singapore Cancer Registry
2003-2007

Reasons for the Increase in Incidence of NHL?

- The increasing incidence of NHL is poorly understood.
- Improved diagnostic techniques?
- Effects of the human immunodeficiency virus epidemic?
- Increase in immunosuppressive therapies?
- Environment: pesticides and solvents?
- Research to define reasons for this increase is extensive, but has not yet resolved them.

Marginal zone lymphoma: Increasing Trend?



Pathogenesis of Extranodal Marginal Zone (MALT) Lymphomas

Often arise in sites devoid of native lymphoid tissue



Lymphoid tissue acquired

- Hashimoto's thyroiditis
- H. pylori induced gastritis



Chronic Lymphoid Hyperplasia

Genetic "events":
chromosomal
errors



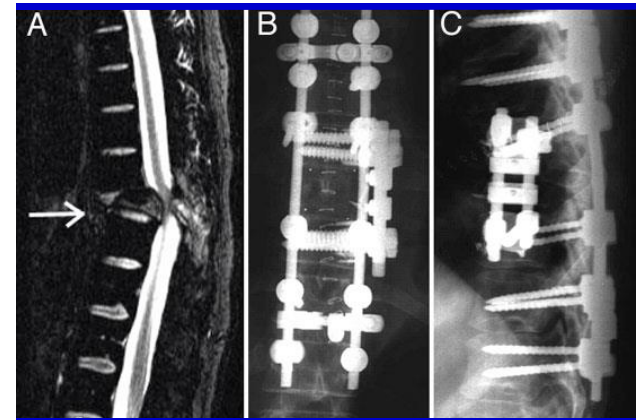
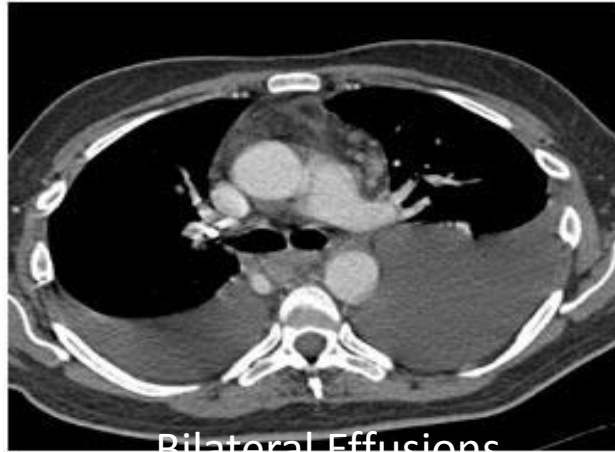
MALIGNANT LYMPHOMA

Exposure to
environmental
mutagens (?)

Clinical Features

- Variable
 - severity: asymptomatic to extremely ill
 - time course: evolution over weeks, months, or years
- Generalized Symptoms
 - fever, night sweats, weight loss, anorexia, pruritis
 - B symptoms
- Local symptoms
 - Due to enlarged lymph node causing pain or obstruction

Other Complications of Lymphoma



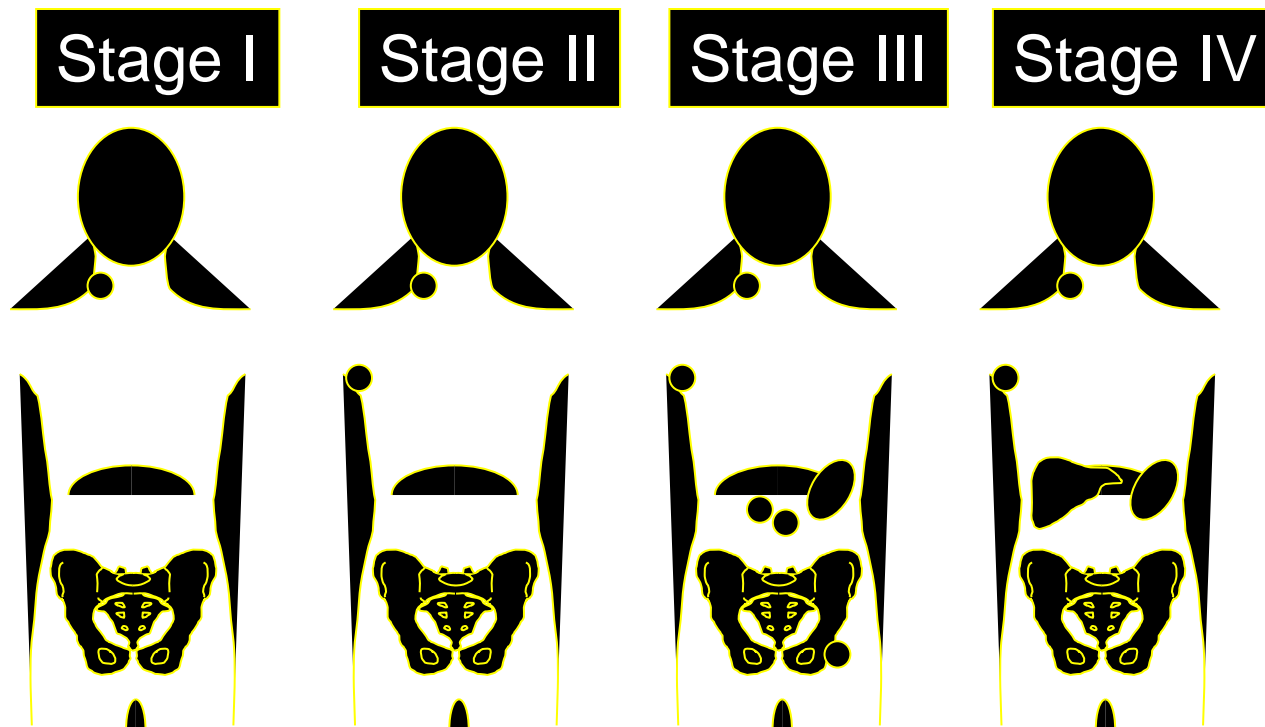
CHOICE OF BIOSPY

- Fine needle aspiration biopsy
- Trucut Biopsy
- Excision Biopsy
- Incisional Biopsy

Excisional biopsy

- Most ideal in patients with accessible peripheral lymph nodes
- provides more tissue for evaluation
- permits the hematopathologist to evaluate the architecture of the lymph node.
- Note that it is wise to ask the surgeon to send the excised node to the lab in transport media (not fixative), as this will allow you to obtain a full range of diagnostic studies.

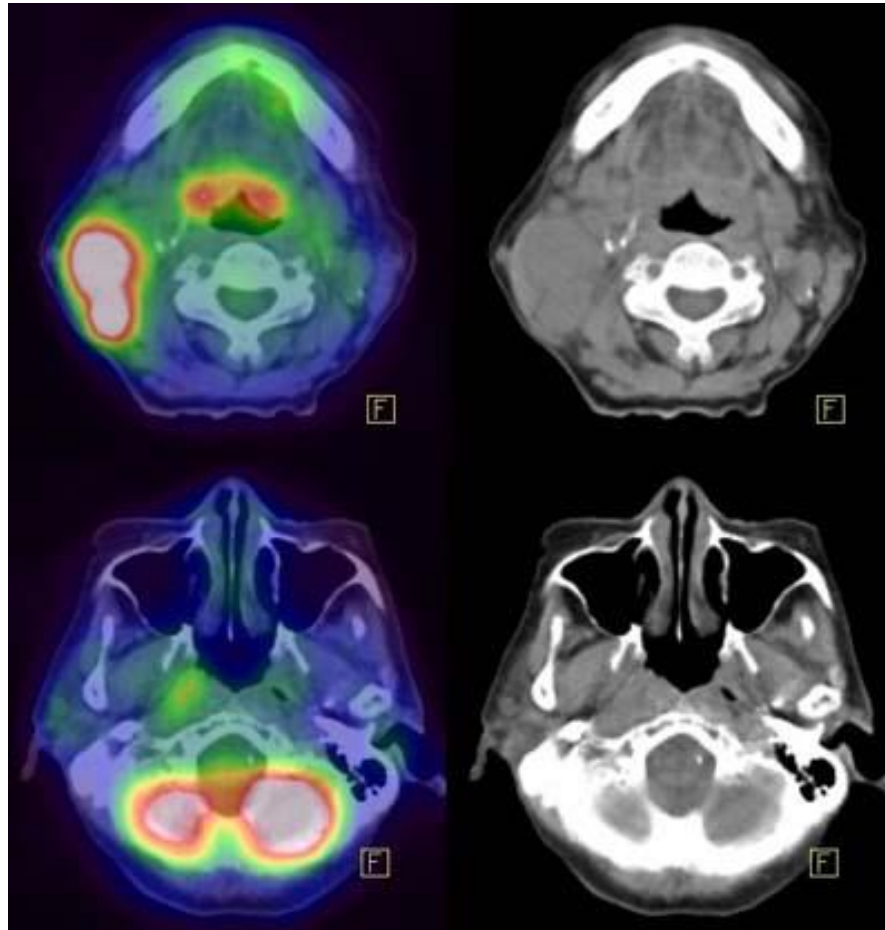
Staging of Lymphoma



A: absence of B symptoms

B: fever, night sweats, weight loss

PET Scan in Staging Lymphoma

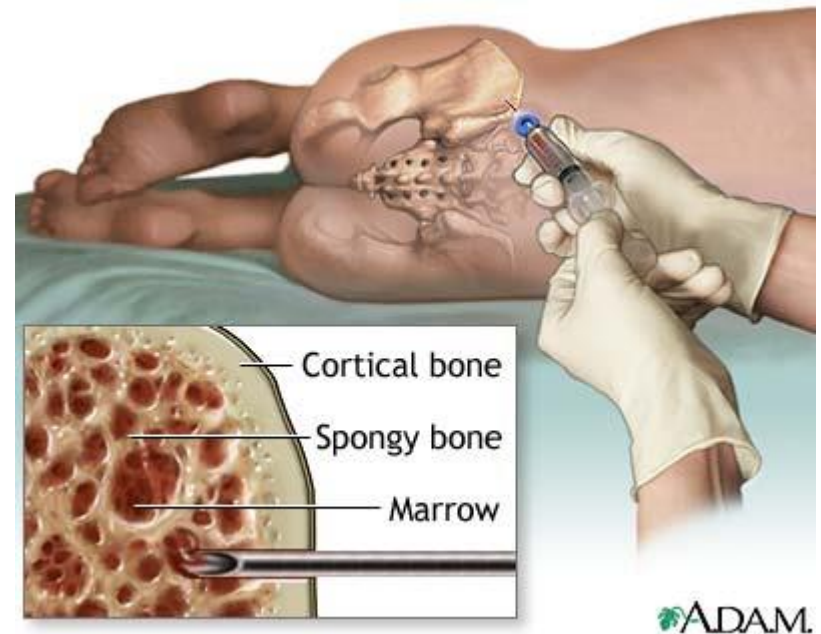


PET Scan for Lymphoma Staging

Histology		No of patients (%)	Median Age (yrs) (range)	No. of patients upstaged by PET/CT (%)
Aggressive B-NHL (n=63)	DLBCL	55 (45%)	57 (21-80)	10 (18)
	Mantle cell	3 (3)	59 (57-69)	0
	Burkitt's Lymphoma	5 (4)	52 (51-67)	2 (40)
Indolent B-NHL (n= 21)	CLL	2 (2)	51 (38-64)	0
	Follicular lymphoma	11 (9)	59 (22-76)	0
	Marginal Zone/MALT	8 (7)	58 (25-75)	0
T-NHL		17 (14)	52 (24-79)	3 (43)
Hodgkin Lymphoma		21 (17)	28 (17-71)	6 (29)

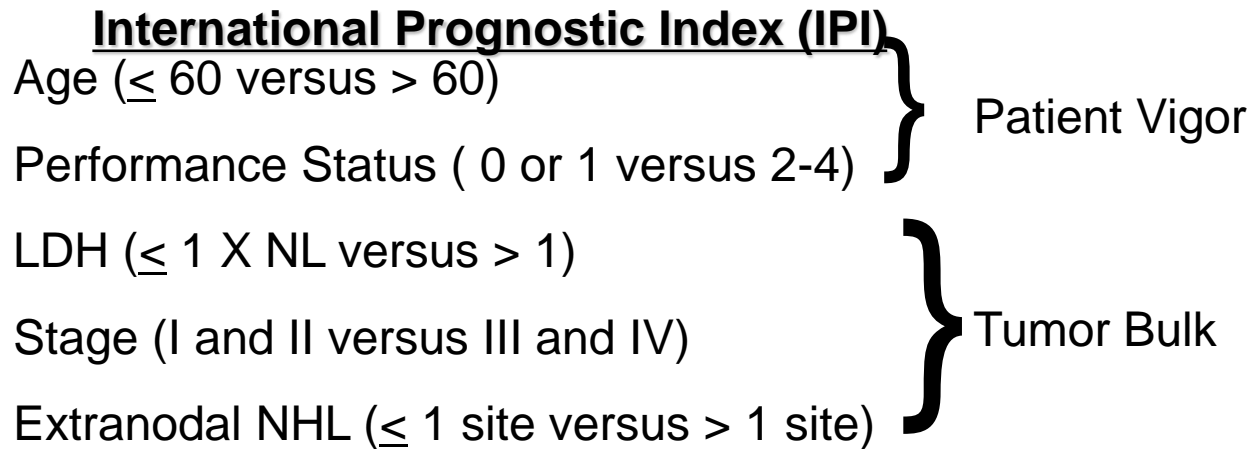
Bone Marrow Examination

- Bone Marrow aspirate
- Bone Marrow Trephine Biospy
- Bone Marrow Flow Cytometry
- Bone Marrow Cytogenetics



What are my chances?

Prognostic Model: Aggressive Lymphoma



Age Adjusted International Index (pts ≤ 60 years)

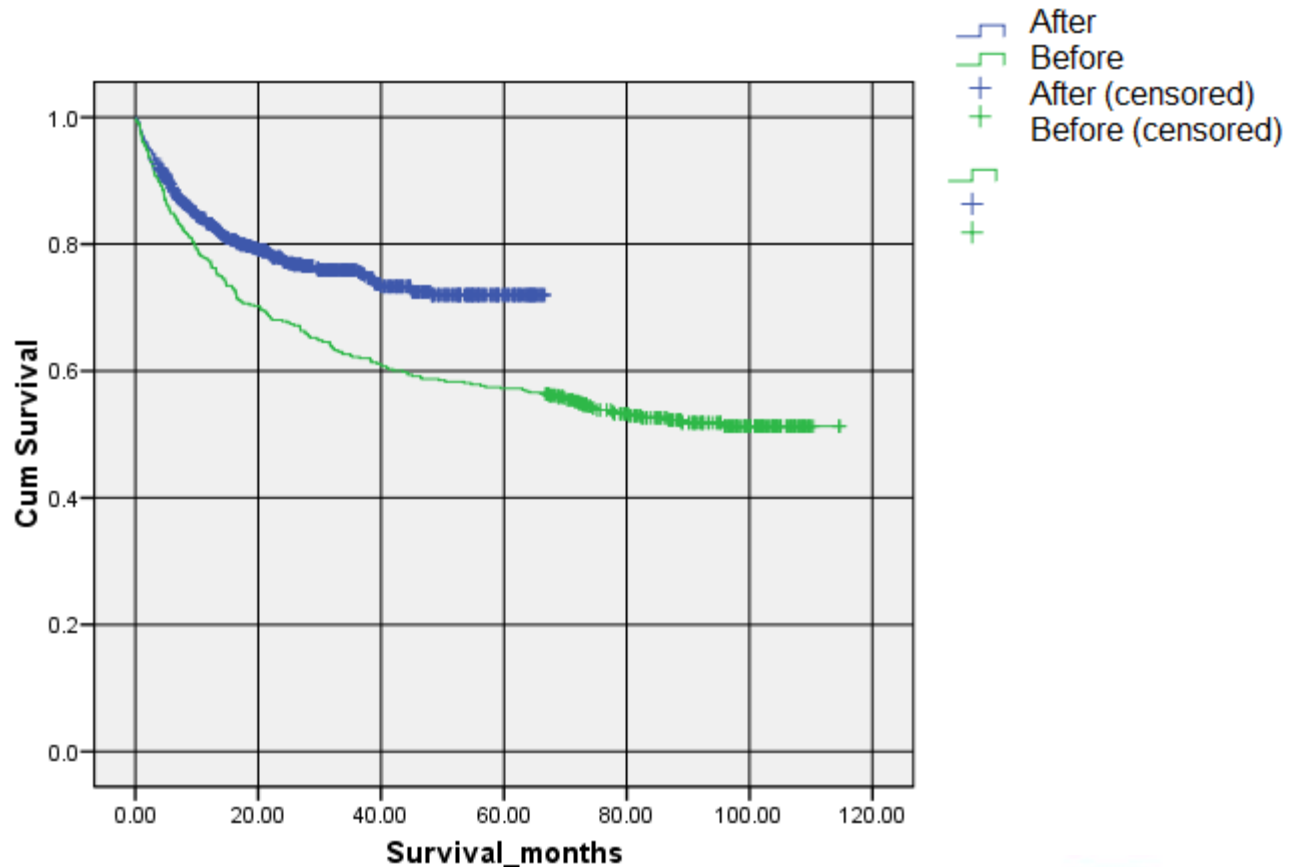
Stage

LDH

Performance Status

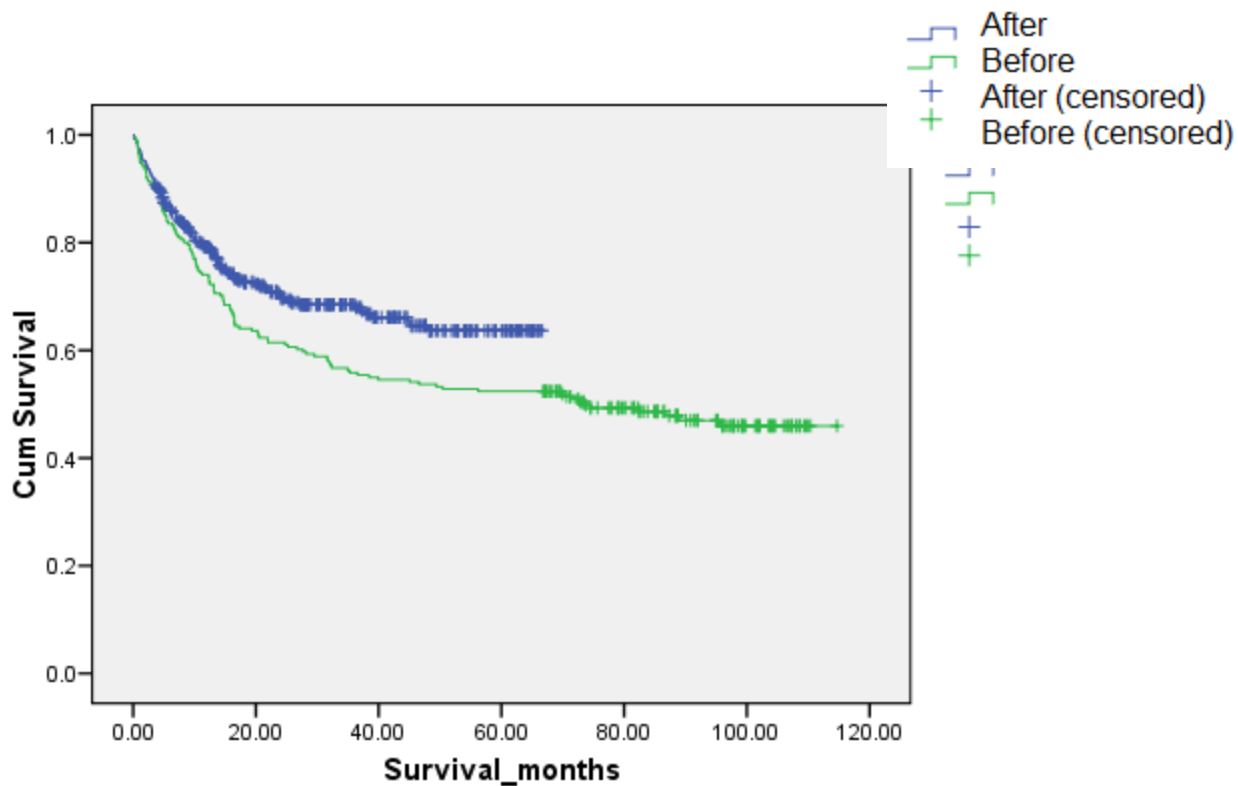
Significant Improvement in Survival over Time: Overall

- 5-yr OS: 72% vs 56% ($p < 0.001$)



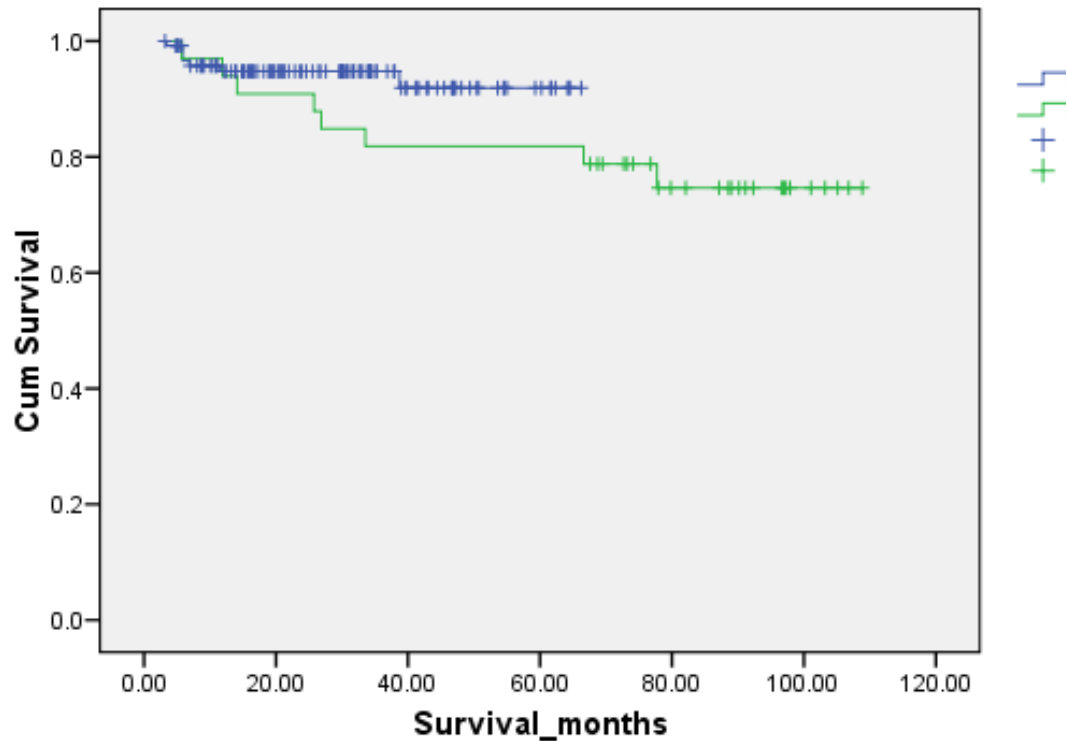
Improvement in Survival: DLBCL

5-yr OS: 64% vs 52% ($p=0.01$)



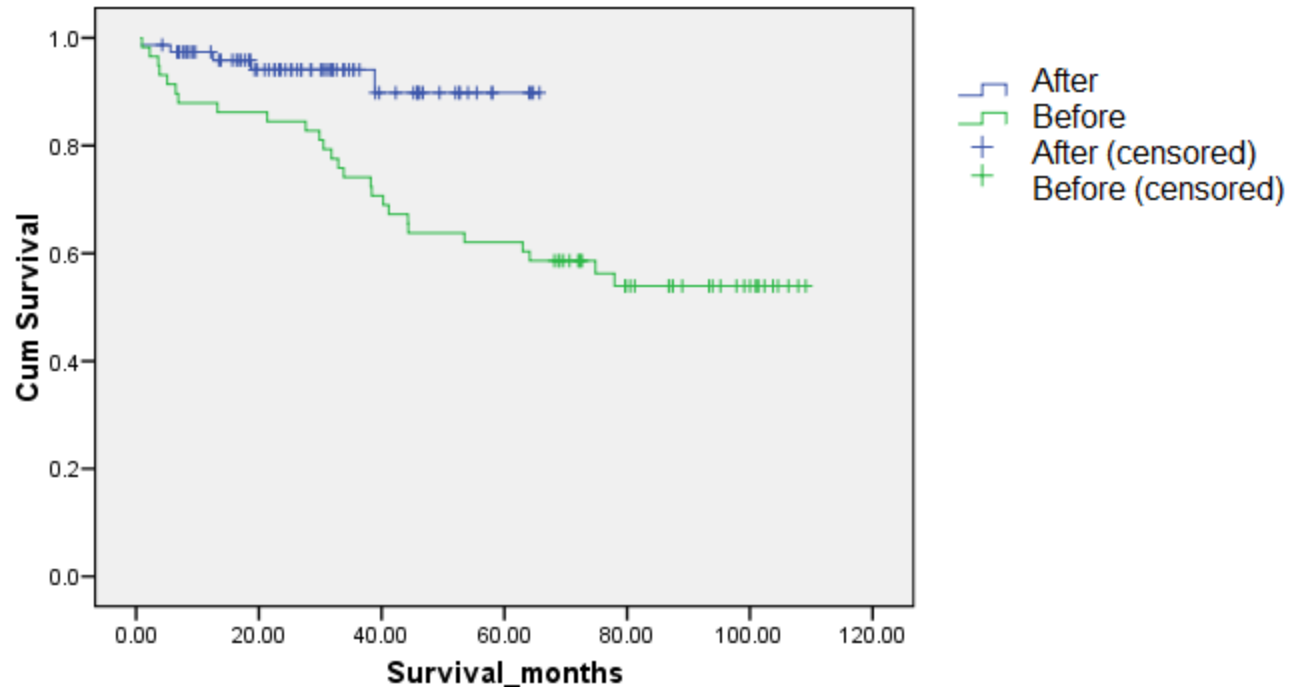
Improvement in Survival: Marginal zone lymphoma

5-yr OS: 92% vs 79 %



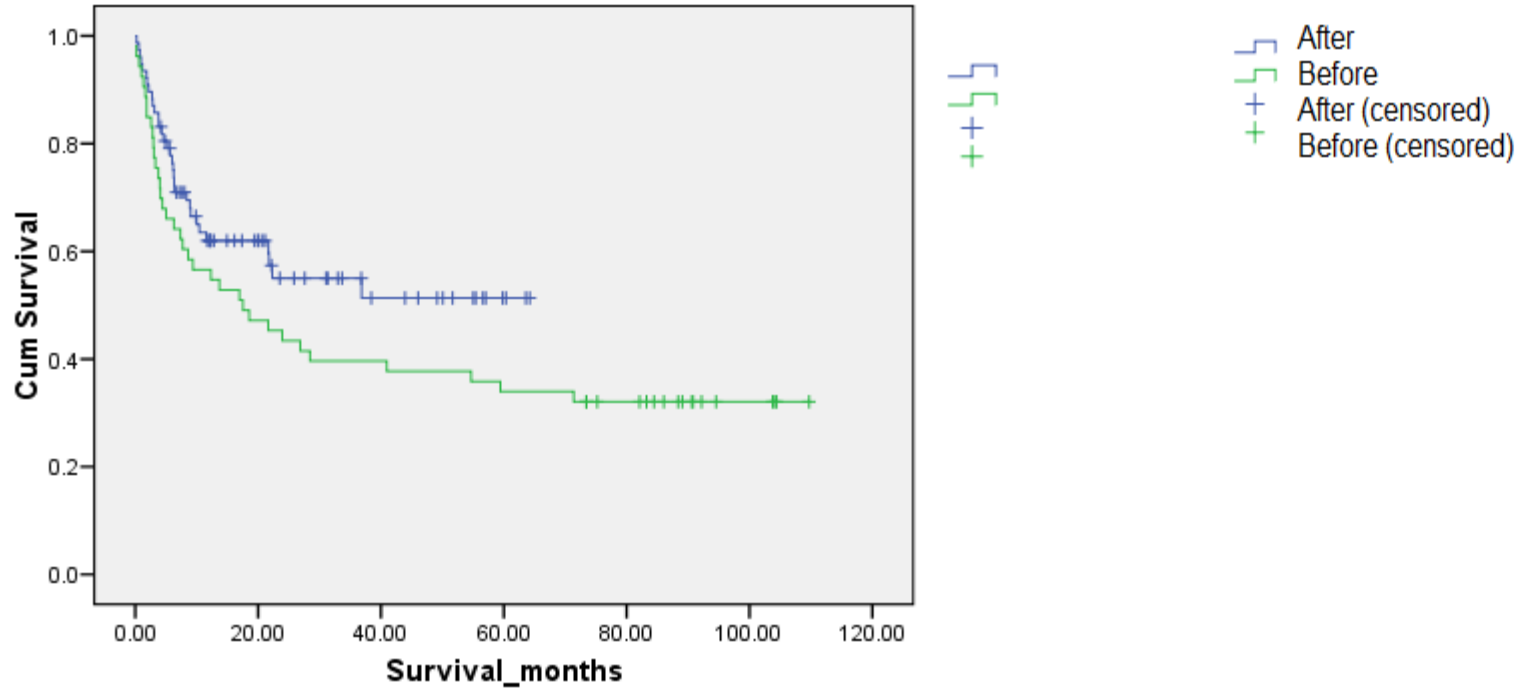
Improvement in Survival: Follicular Lymphoma

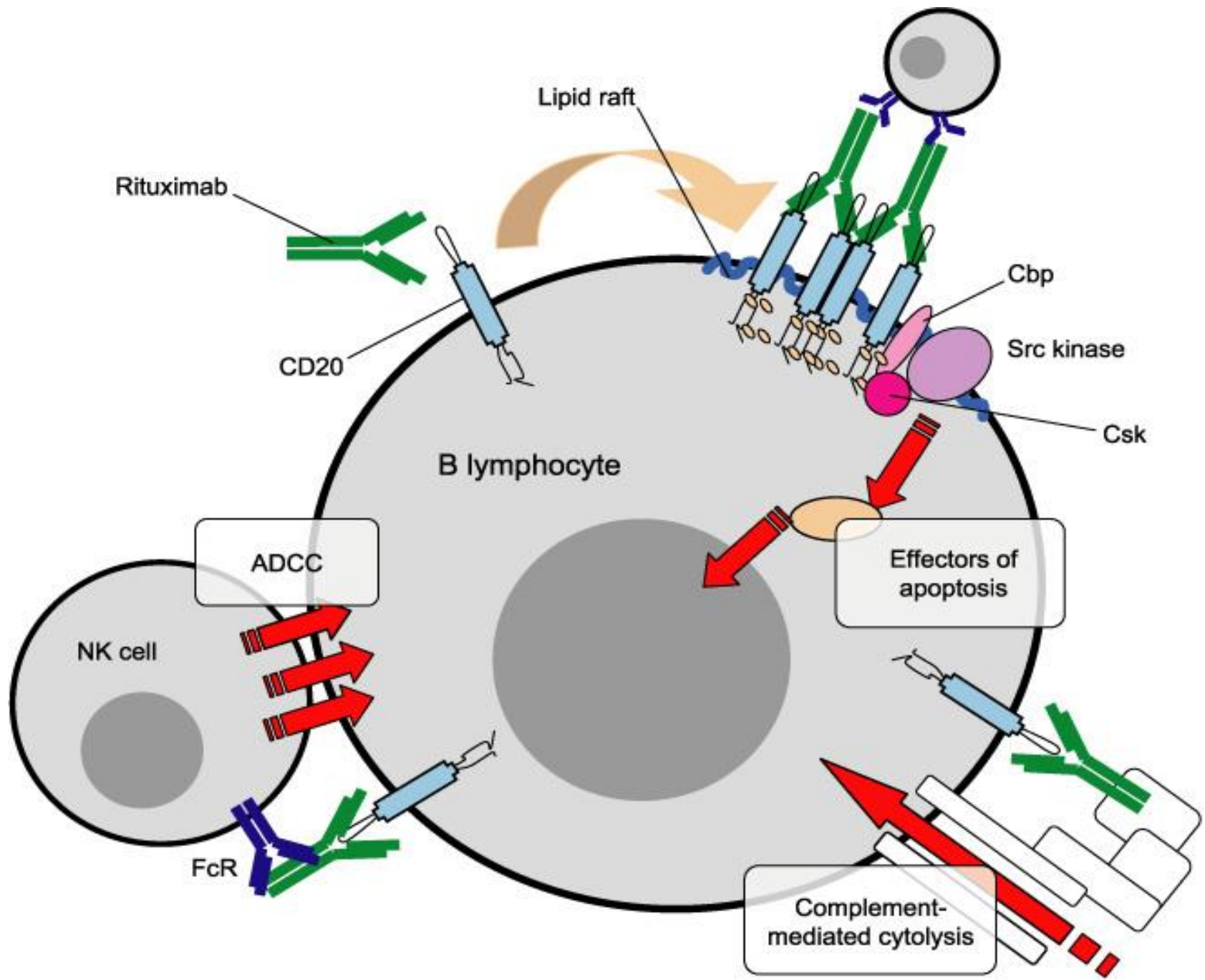
5-yr OS: 90% vs 59% ($p < 0.01$)



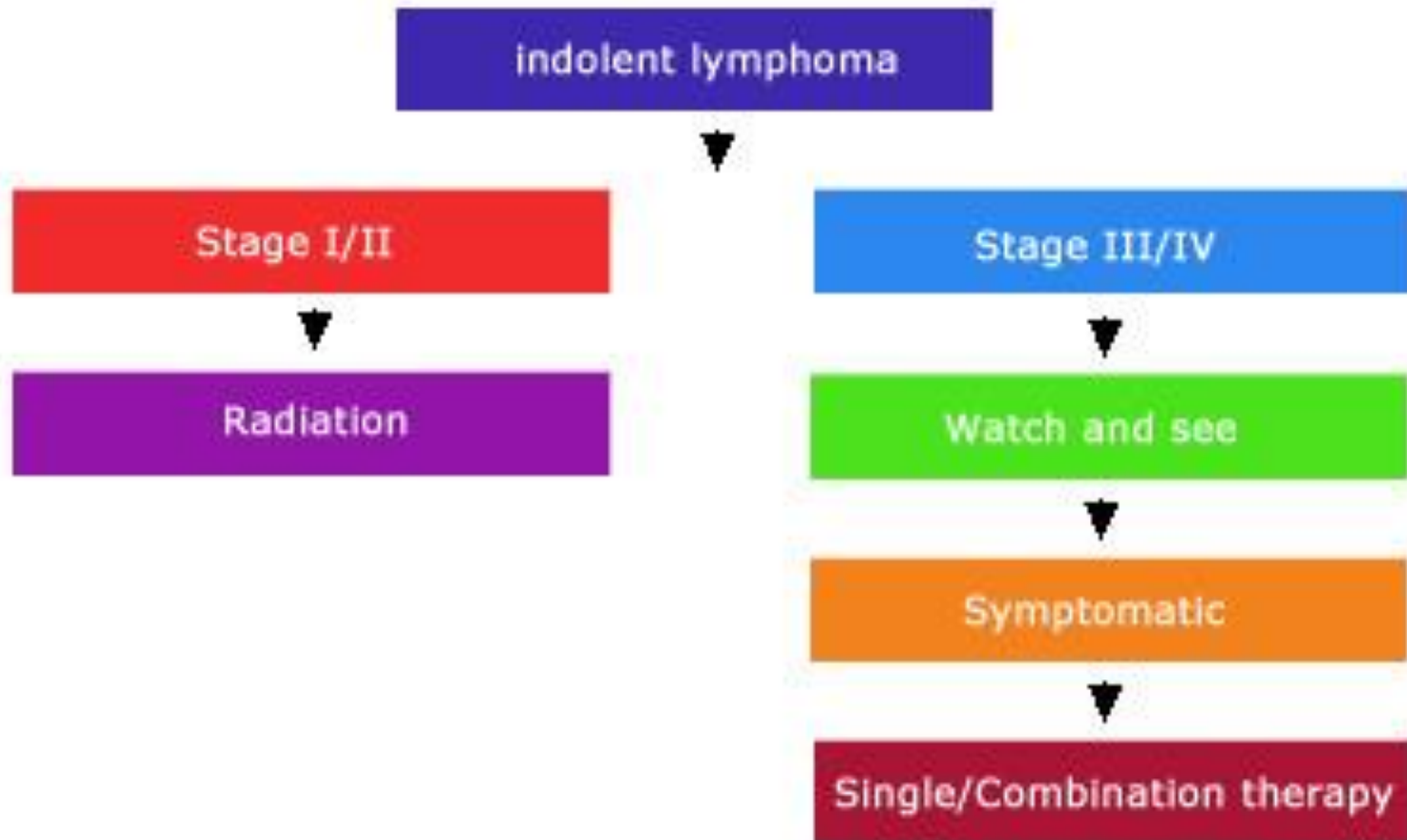
No improvement in survival of T-cell Lymphoma

5-yr OS: 32% vs 51% ($p=0.103$)





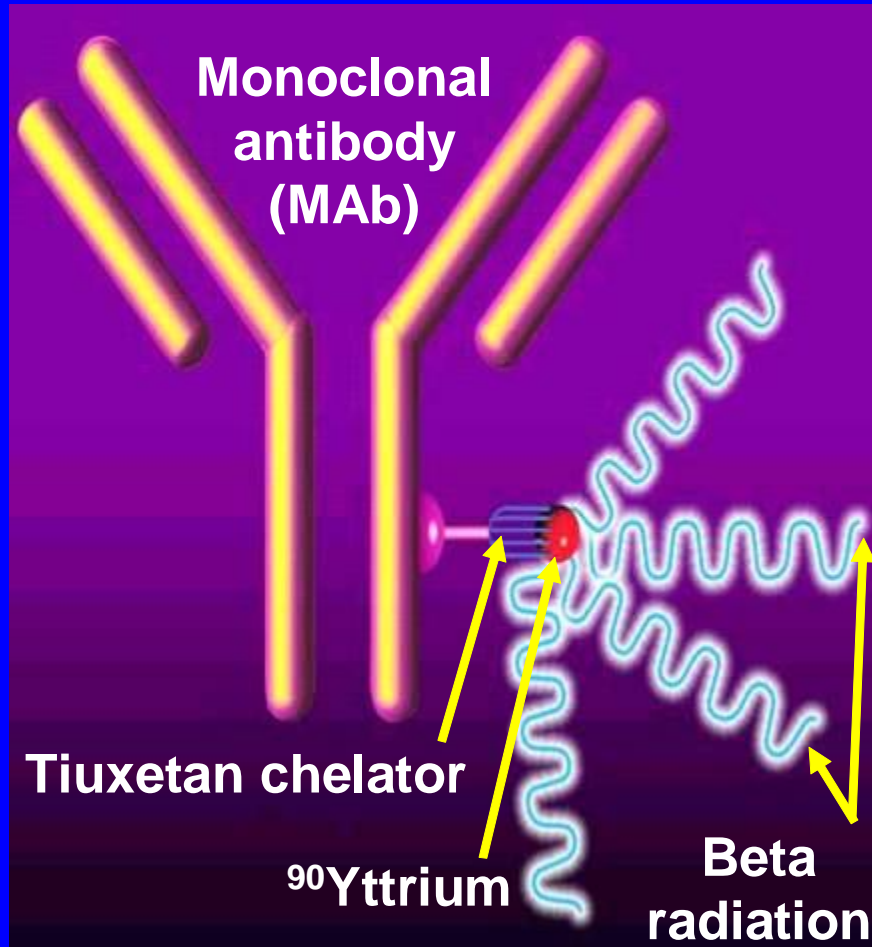
Treatment of Low Grade Lymphoma



Rituximab + Chemotherapy in First-Line Therapy of Advanced Stage FL Improves Clinical Outcomes

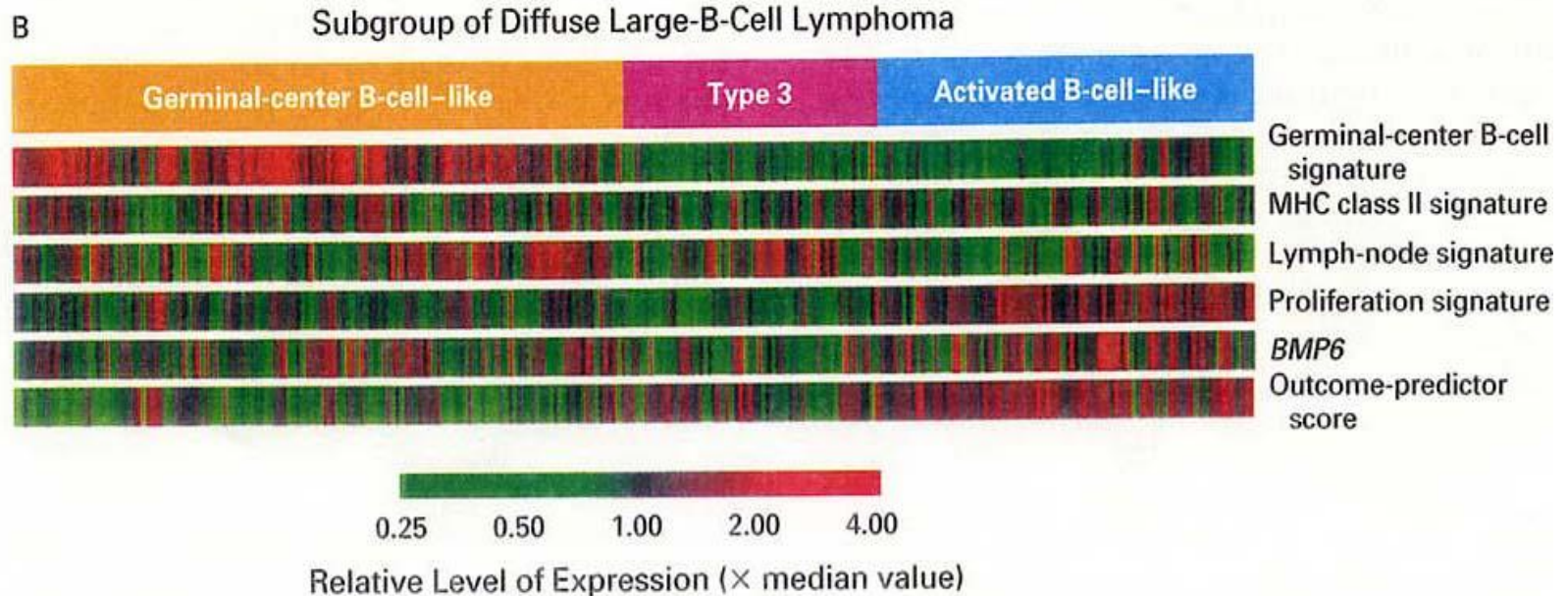
Author	Regimen		P
Hiddemann et al	CHOP (n = 205)	R-CHOP (n = 223)	
Response rate	90%	96%	0.011
Median TTF	31 months	Not reached	< .0001
Marcus et al	CVP (n = 159)	R-CVP (n = 162)	
Response rate	57%	81%	< .0001
Median TTF	7 months	27 months	< .0001
Herold et al	MCP (n = 96)	R-MCP (n = 105)	
Response rate	75%	92%	< .001
Median EFS	19 months	Not reached	< .0001
Salles et al	CHVP/IFN- (n = 175)	R-CHVP/IFN- (n = 184)	
Response rate	85%	94%	< .0001

Zevalin[®] – ⁹⁰Yttrium-Labelled Ibritumomab Tiuxetan



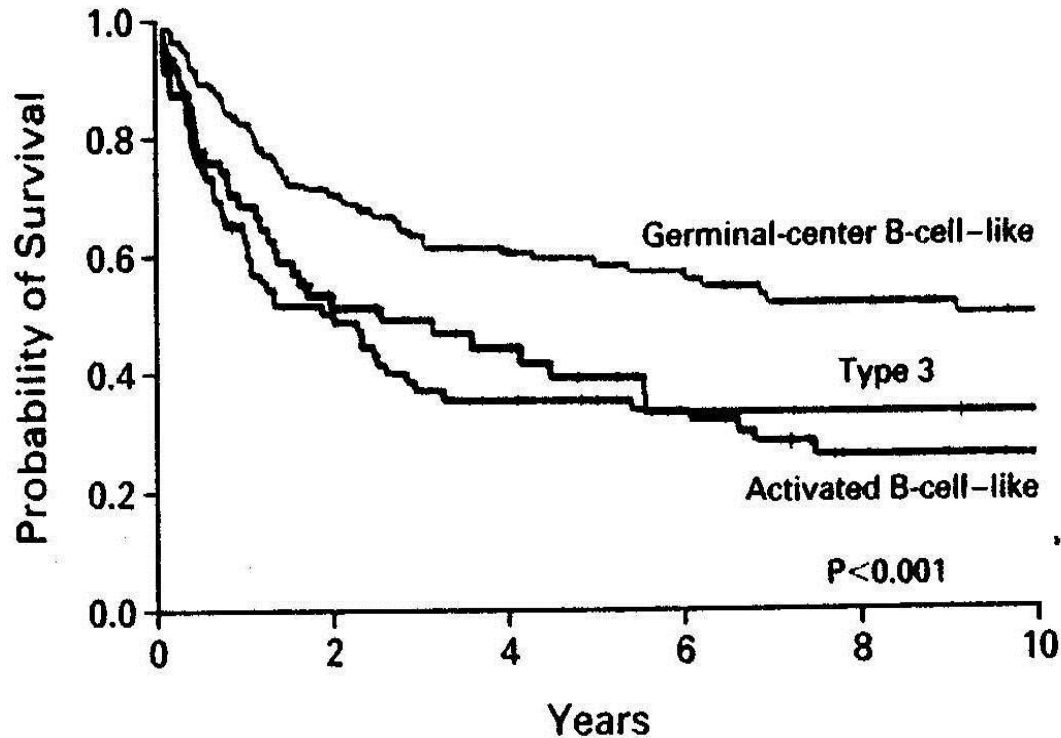
- **Ibritumomab:**
 - Anti-CD20 murine MAb that targets malignant B-cells
- **Tiuxetan:**
 - A high-affinity chelator that ensures a stable bond between MAb and ⁹⁰Yttrium
- **⁹⁰Yttrium (⁹⁰Y):**
 - Emits beta radiation that reaches malignant B-cells, 90% deposited within 5 mm (11 mm maximum path length)

Gene Expression Patterns: Molecular Subgroups of DLBCL

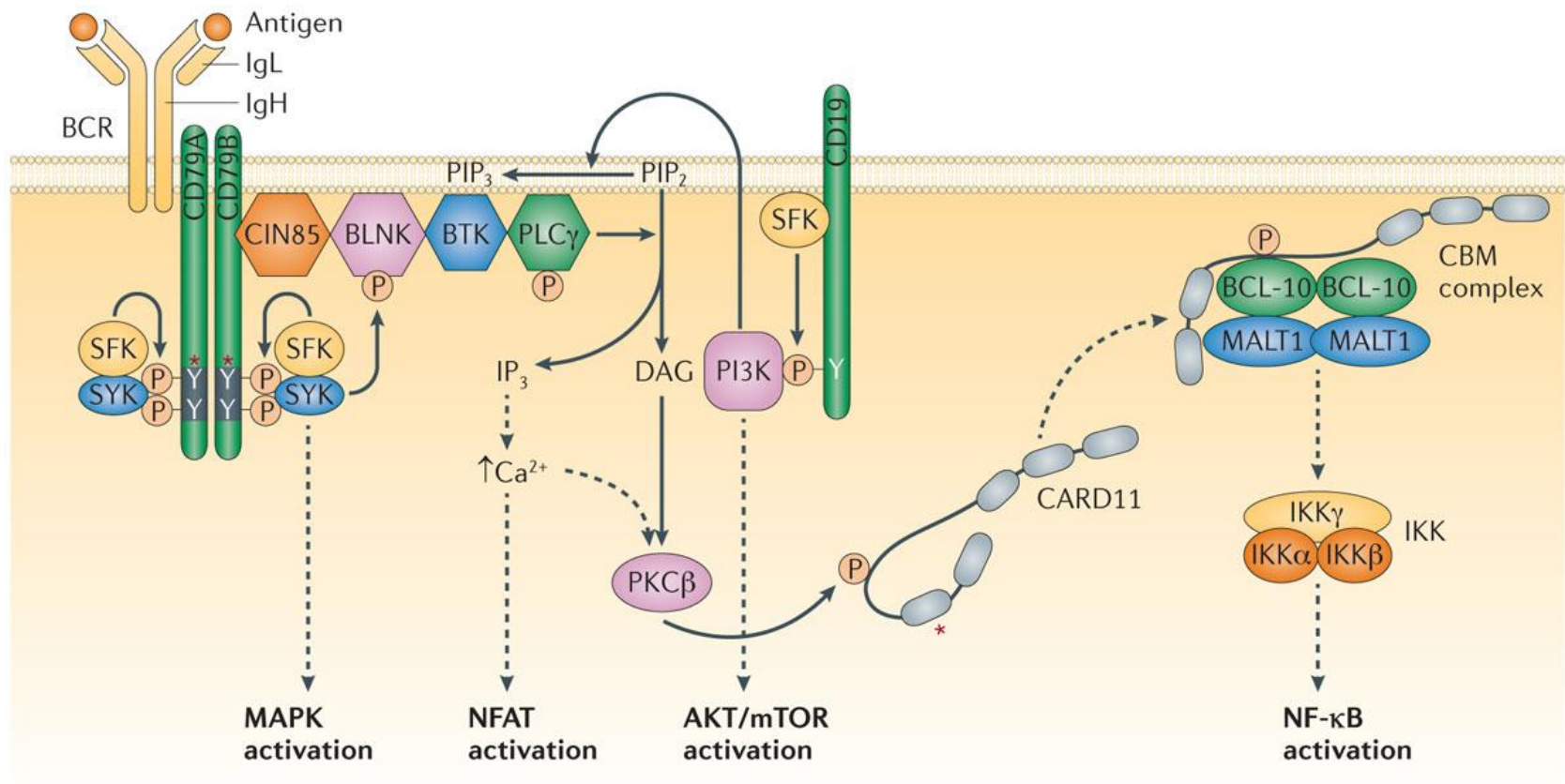


Ref: Rosenwald A, et al: NEJM 2002; 346:1937-47

Survival Based Upon Molecular Sub-Type of DLBCL



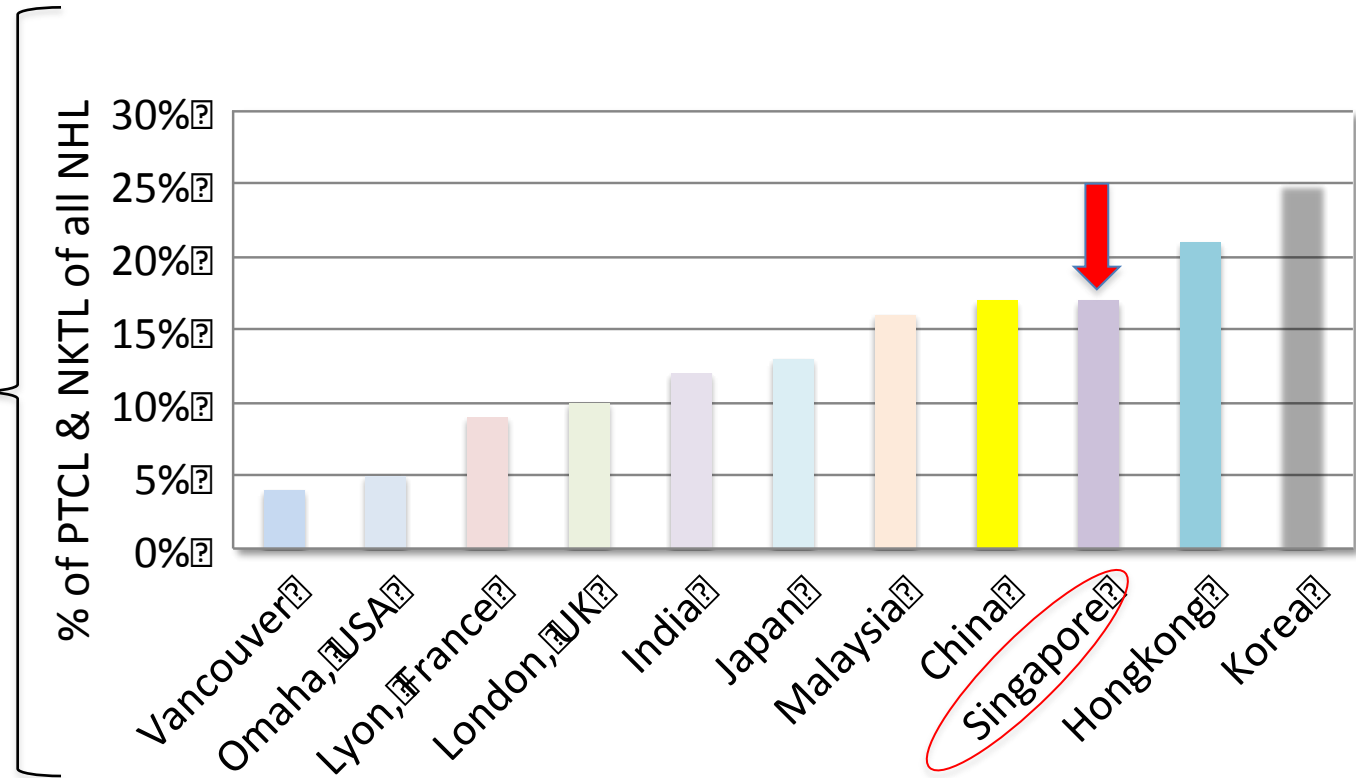
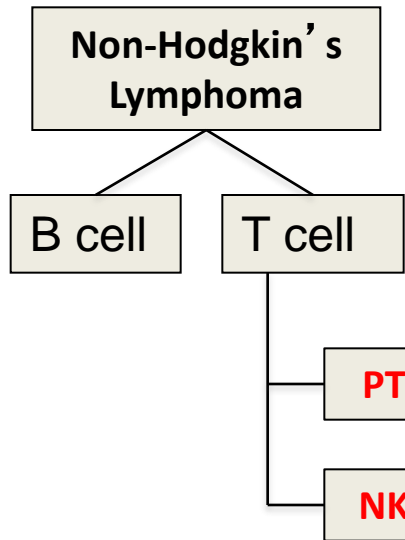
Ref: Rosenwald A, et al: *NEJM* 2002; 346:1937-47



Target	Inhibitor	Manufacturers	Clinical trials
<i>Chronic active BCR signalling</i>			
BTK	Ibrutinib (PCI-32765)	Pharmacyclics/Janssen Research & Development	Phase III
	Dasatinib	Bristol-Myers Squibb	Approved
	AVL-292	Celgene	Phase I
PKC β	Sotrastaurin (AEB071)	Novartis	Phase I
PI3K δ	GS-1101 (CAL-101)	Calistoga Pharmaceuticals/Gilead Sciences	Phase II
<i>Chronic active and tonic BCR signalling</i>			
SYK	Fostamatinib (R788)	Rigel Pharmaceuticals/AstraZeneca	Phase II
	PRT062607	Portola Pharmaceuticals/Biogen Idec	Phase I
Pan-PI3K	BKM120	Novartis	Phase I*
	GDC-0941	Genentech	Phase Ib*
	XL147	Exelixis	Phase I*
	ZSTK474	Zenyaku Kogyo Co.	Phase I*
SRC family	Saracatinib	AstraZeneca	Phase II
	KX01	Kinex Pharmaceuticals	Phase II
	Dasatinib	Bristol-Myers Squibb	Approved
TORC1	Rapamycin (sirolimus)	Wyeth/Pfizer	Approved
	Everolimus	Novartis	Phase III
	Temsirolimus	Wyeth/Pfizer	Approved

BCR, B cell receptor; BTK, Bruton tyrosine kinase; PI3K, phosphoinositide 3-kinase; PKC β , protein kinase C β ; TORC1, target of rapamycin complex 1. *Clinical trials in solid tumours only.

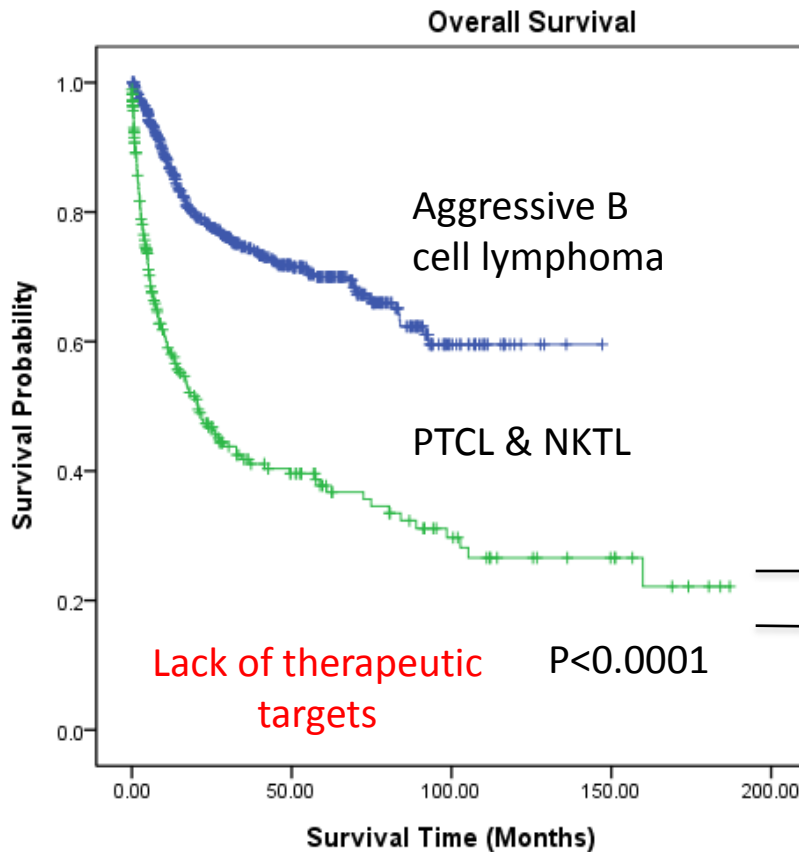
Peripheral T Cell and NK/T cell Lymphoma (PTCL & NKTL): Geographical Distribution



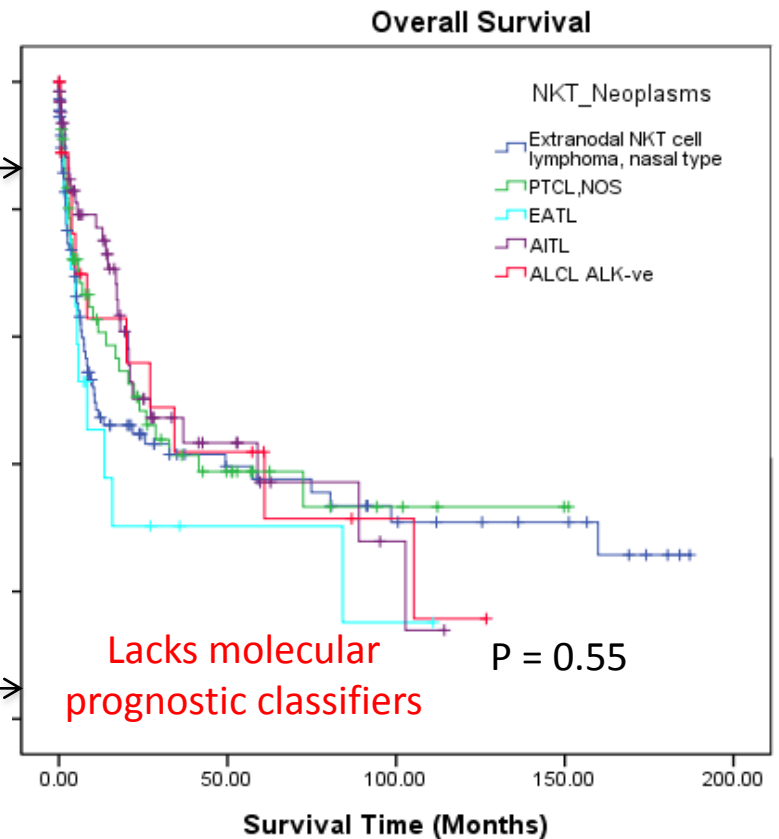
Frequencies of PTCL and NKTL in Asia and the Far West

PTCL and NKTL: An Unmet Need Globally and Asia in particular

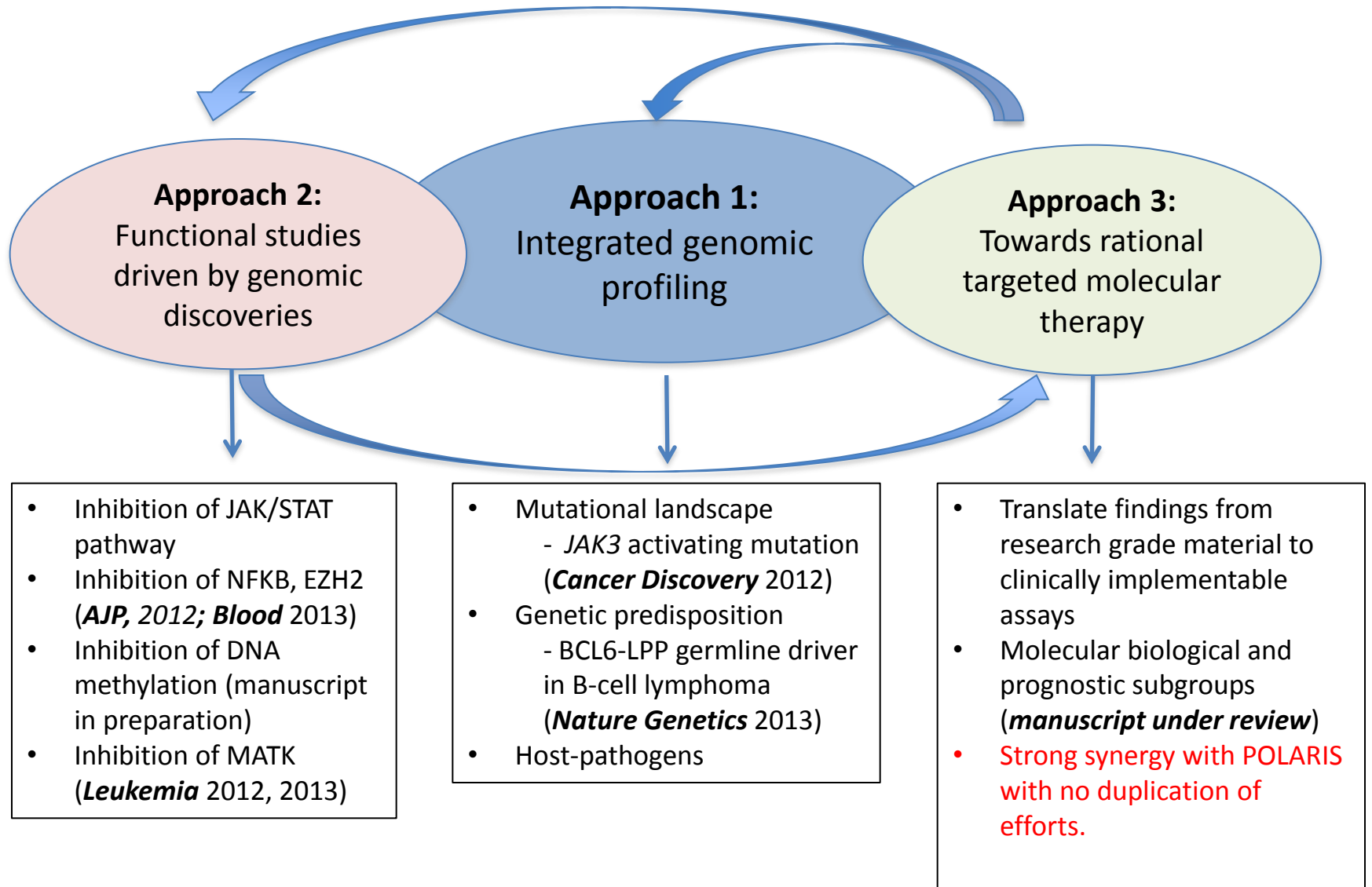
Inferior survival of PTCL & NKTL compared to aggressive B cell NHL



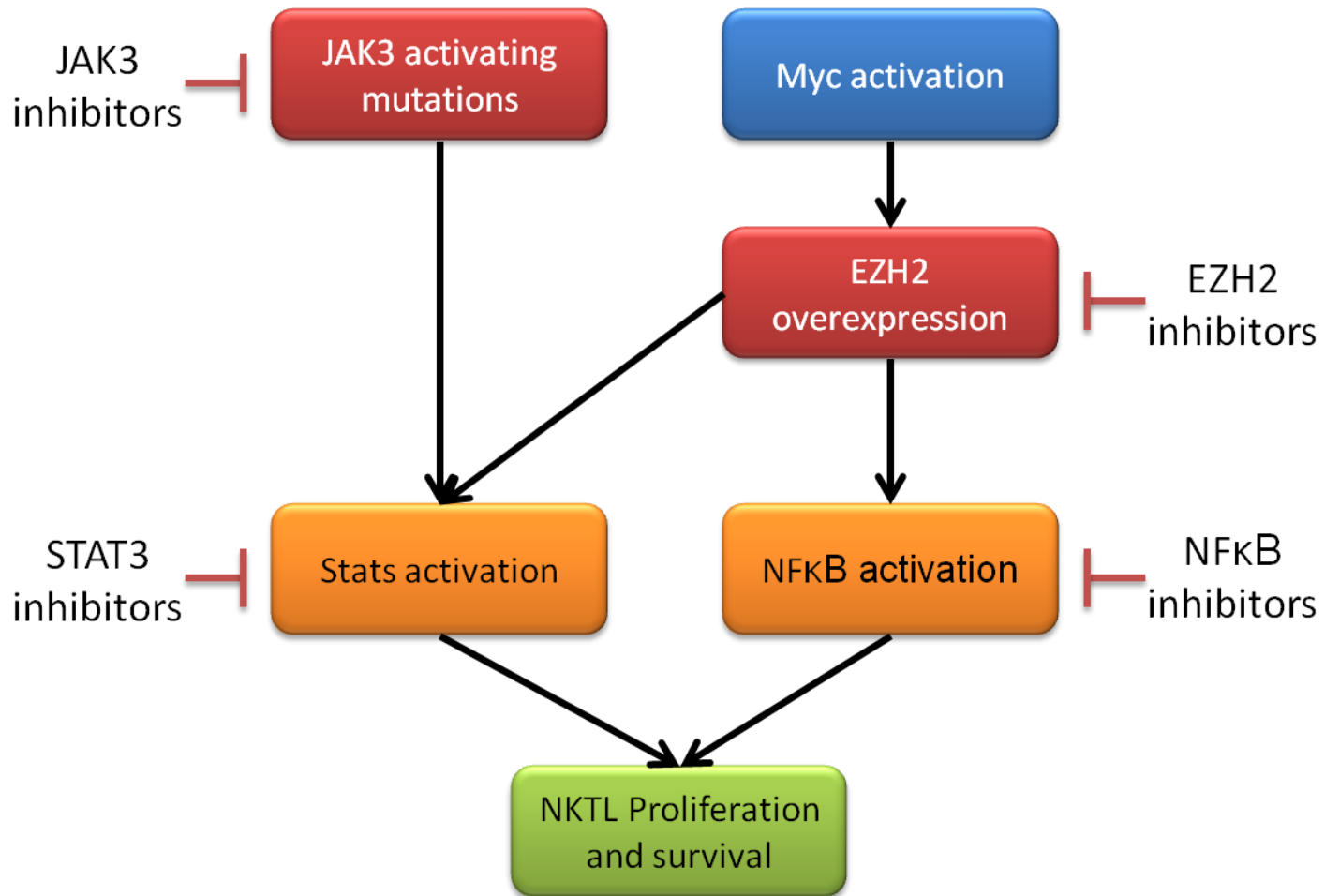
Poor survival across major subtypes of PTCL and NKTL



Unraveling Mature T Cell Lymphoma: Three-prong approach



Proposed Model of NKTL Pathogenesis and Strategies of Targeted Therapy



The Singapore Lymphoma Study Group

National Lymphoma Translational Research Program: From Genomics to Therapeutics

