

INDOLENT NON-HODGKIN LYMPHOMA (NHL)
and
CHRONIC LYMPHOCYTTIC LEUKEMIA (CLL)

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Facts and Figures

NHL

- 6th most common type of cancer in the US¹
- Most common blood cancer
- 65,980 new cases expected in the US in 2009²
- 85% are B-cell disorders³
- Follicular lymphoma = 2nd most common type, ~25% of all diagnoses⁴

CLL

- Most common adult leukemia in the US¹
- 15,000 new cases expected in the US in 2009²
- 100% are B-cell disorders³

¹ <http://www.cancer.gov/cancertopics/commoncancers#1>

² American Cancer Society. *Cancer Facts & Figures 2009*.

³ ACS. Detailed Guide (revised January 21, 2000): Non-Hodgkin's Lymphoma.

⁴ Blood 89: 3909, 1997

Causes

NHL

Possible cause(s):

- chemical exposures (pesticides, fertilizers or solvents)
- individuals with compromised immune systems
- heredity
- infections
- most patients have no clear risk factors
- IN MOST CASES, THE EXACT CAUSE IS UNKNOWN

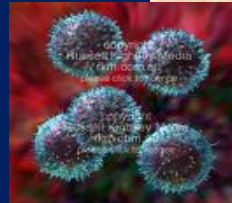
CLL

Possible cause(s):

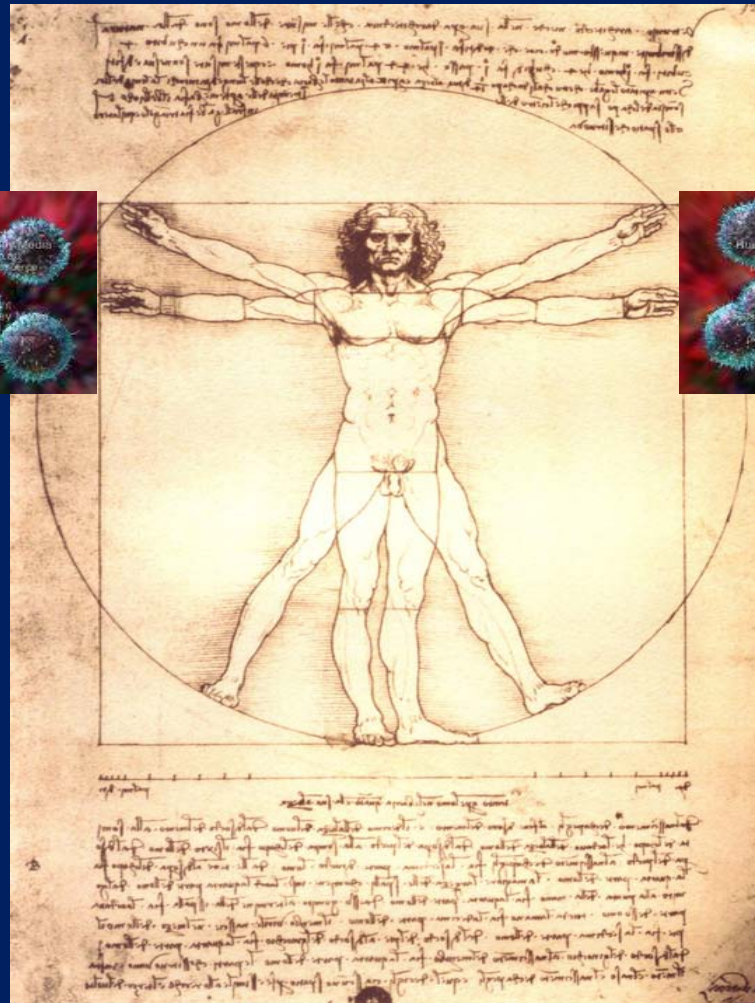
- UNKNOWN

The Immune System

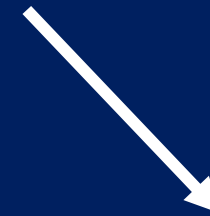
T- CELLS



Cellular immunity:
helper + cytotoxic T-cells

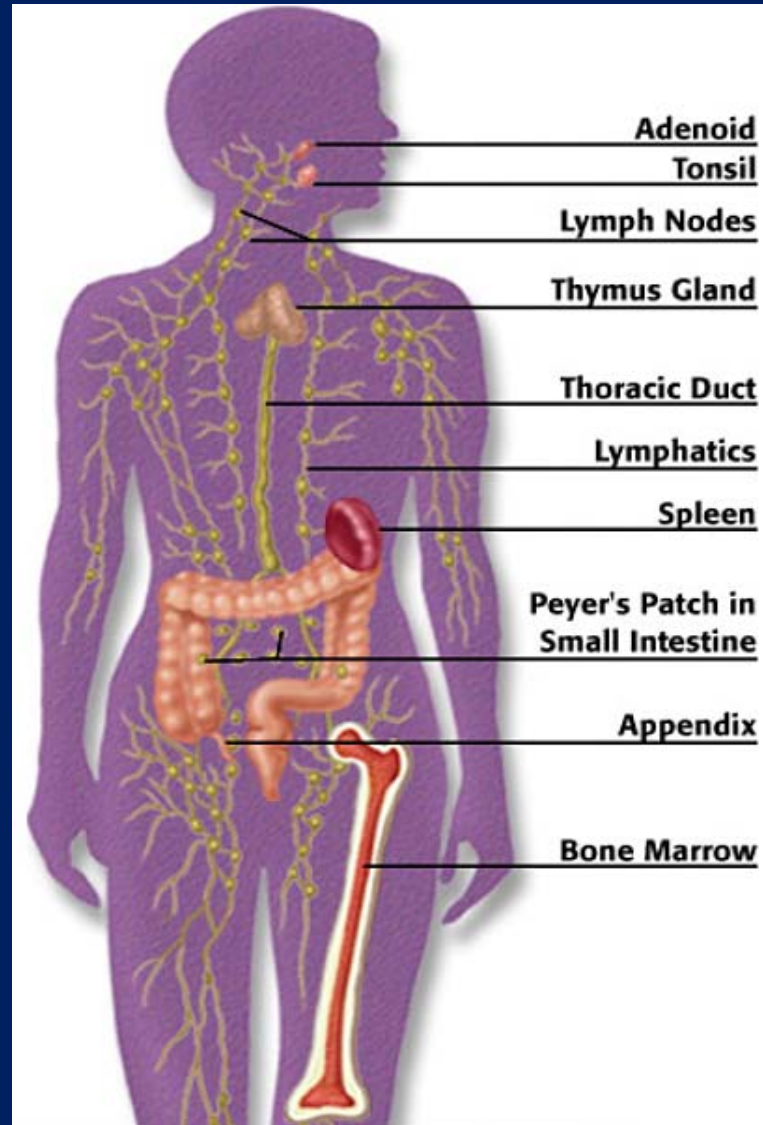


B- CELLS

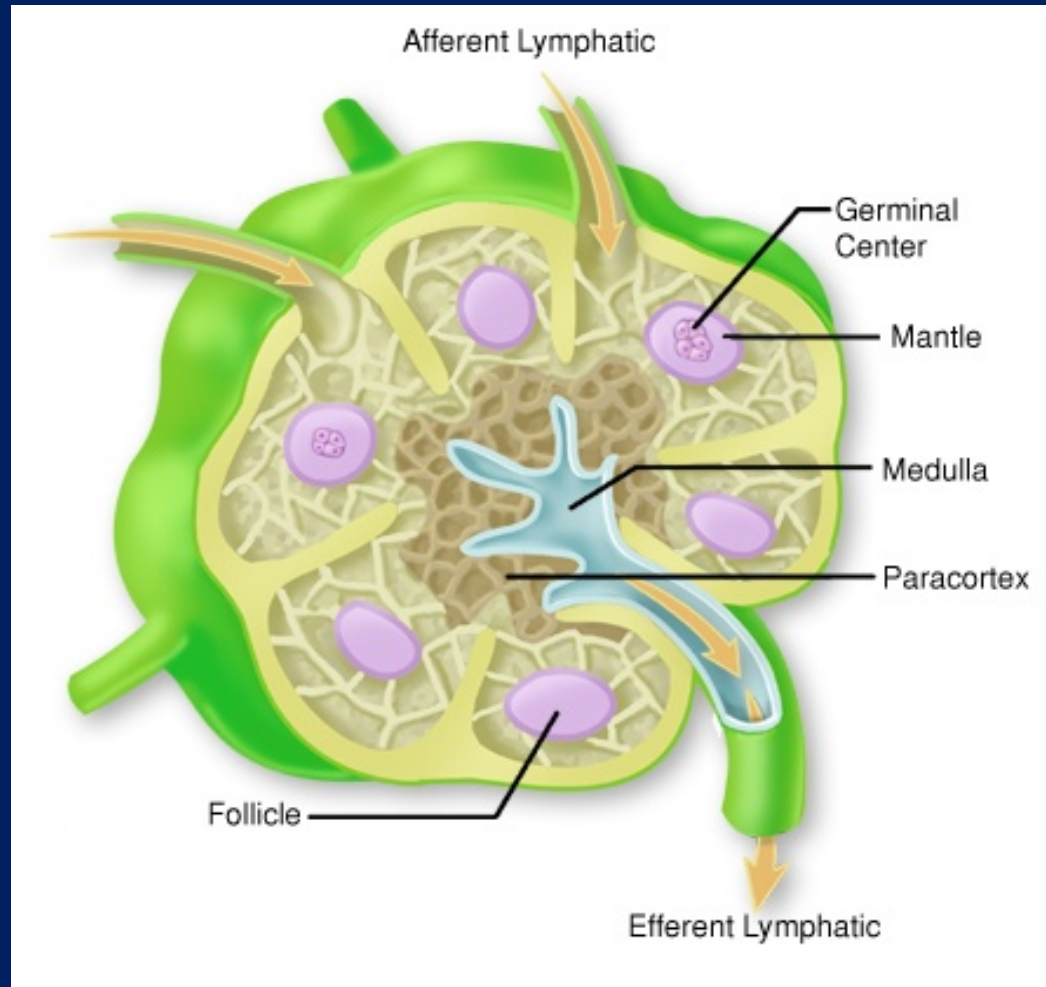


Humoral immunity:
antibodies

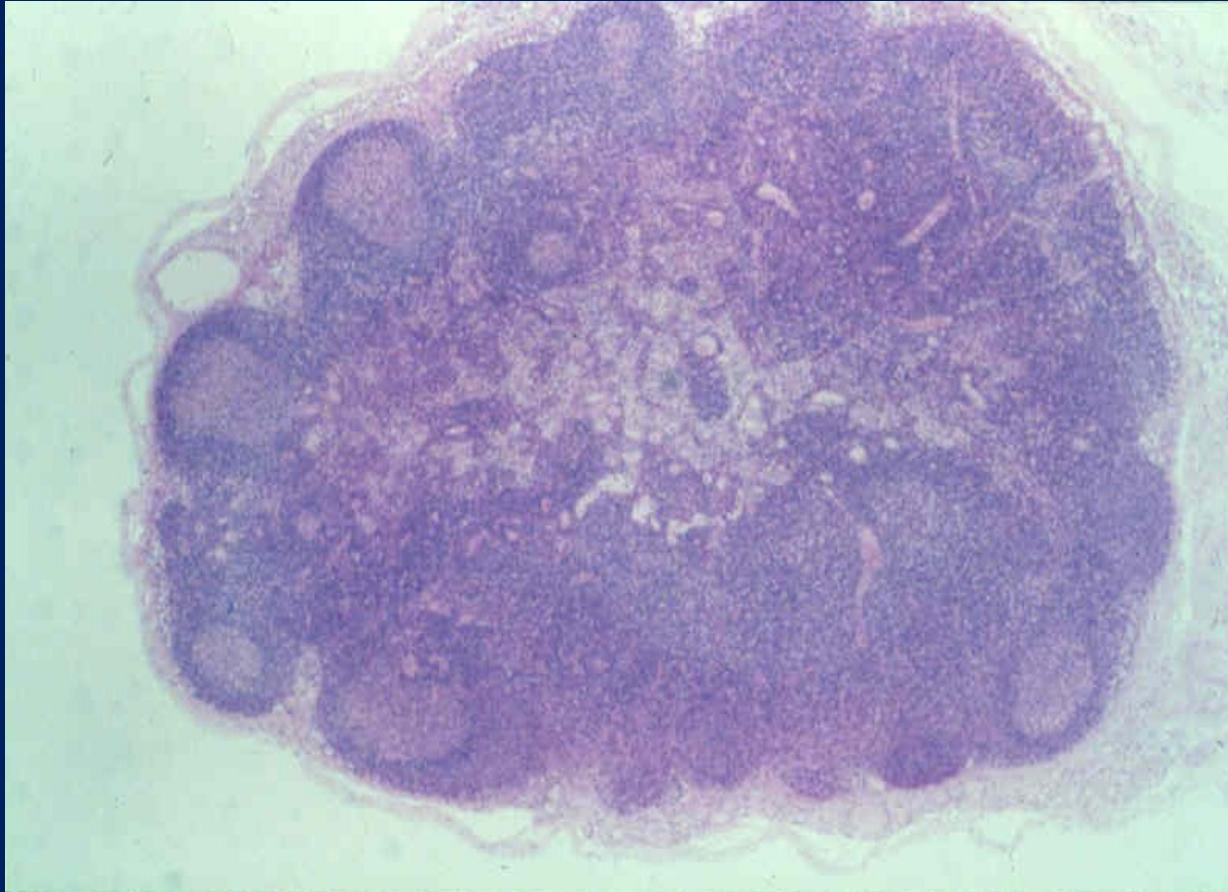
Lymphatic System



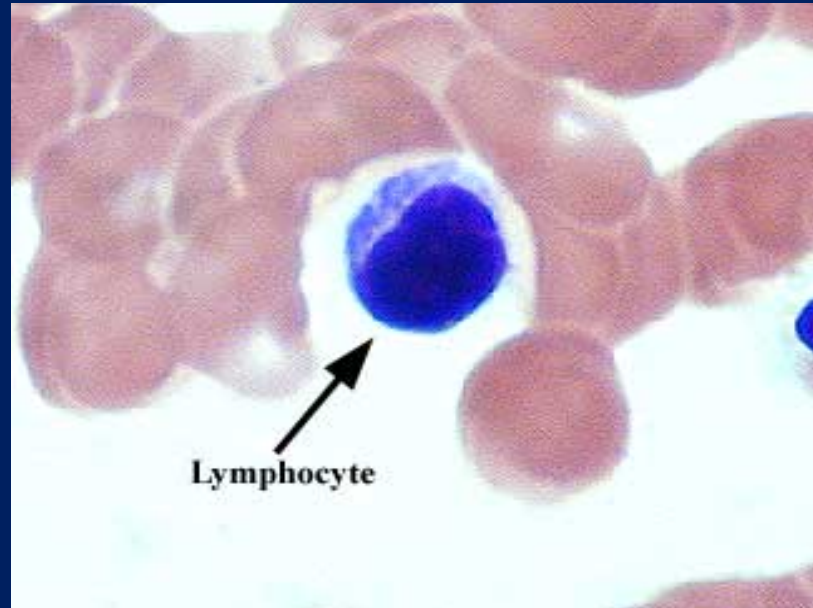
Lymph Node Anatomy



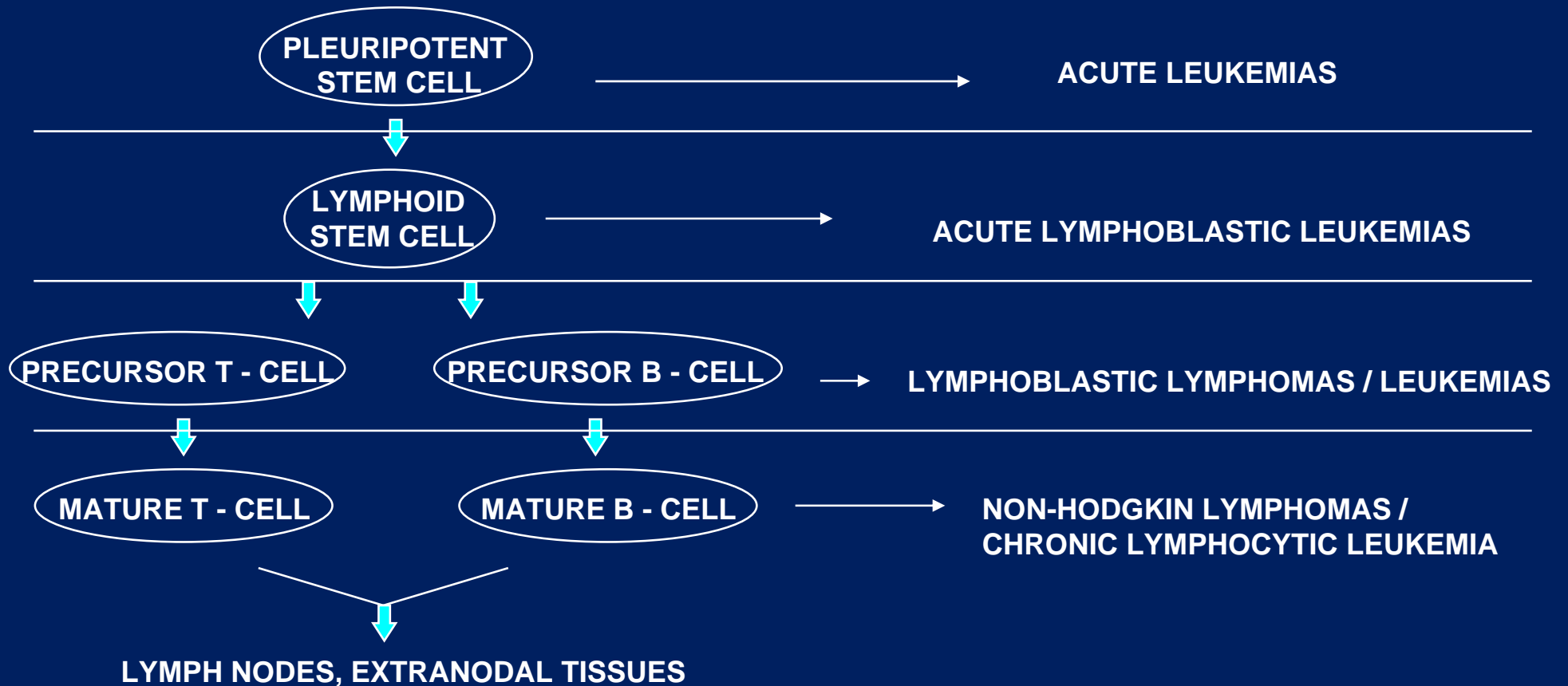
Lymph Node: Microscopic View



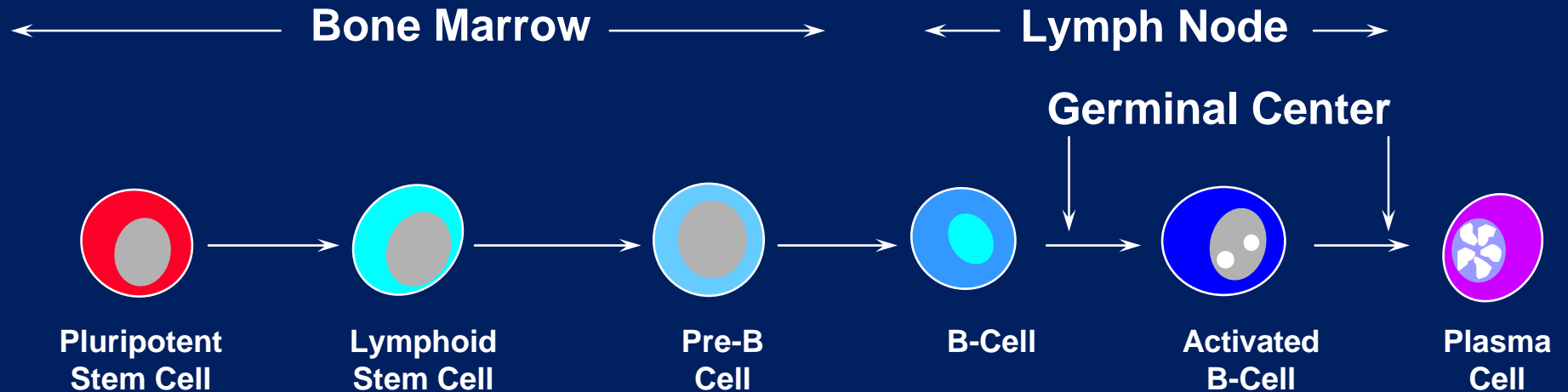
Lymphocyte: Microscopic View



CELLULAR ORIGINS OF LYMPHOMAS / LEUKEMIAS



Normal B-Cell Life Cycle and Related Lymphoid Malignancy



Antigen Expression:

CD20
CD22

CD20
CD22
CD80

Precursor B-Cell
Acute Leukemias

NHL
CLL

Myeloma

NON-HODGKIN LYMPHOMAS: WHO CLASSIFICATION

MATURE (PERIPHERAL) B-CELL NEOPLASMS

- **B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA / SMALL LYMPHOCYTIC LYMPHOMA**
- B-CELL PROLYMPHOCYTIC LEUKEMIA
- **LYMPHOPLASMACYTIC LYMPHOMA (WALDENSTROM'S)**
- **SPLENIC MARGINAL ZONE B-CELL LYMPHOMA (+/- VILLOUS LYMPHOCYTES)**
- HAIRY CELL LEUKEMIA
- PLASMA CELL MYELOMA / PLASMACYTOMA
- **EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMA OF MALT TYPE**
- **NODAL MARGINAL ZONE B-CELL LYMPHOMA**
- **FOLLICULAR LYMPHOMA (GRADES I, II, III)**
- MANTLE CELL LYMPHOMA
- DIFFUSE LARGE B-CELL LYMPHOMA
MEDIASTINAL LARGE B-CELL LYMPHOMA
PRIMARY EFFUSION LYMPHOMA
- BURKITT'S LYMPHOMA / BURKITT CELL LEUKEMIA

MATURE (PERIPHERAL) T-CELL NEOPLASMS

- T-CELL PROLYMPHOCYTIC LEUKEMIA
- T-CELL GRANULAR LYMPHOCYTIC LEUKEMIA
- AGGRESSIVE NK-CELL LEUKEMIA
- ADULT T-CELL LYMPHOMA / LEUKEMIA (HTLV I +)
- EXTRANODAL NK/T-CELL LYMPHOMA NASAL TYPE
- ENTEROPATHY-TYPE T-CELL LYMPHOMA
- HEPATOSPLENIC GAMMA-DELTA T-CELL LYMPHOMA
- SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA
- MYCOSIS FUNGOIDES / SEZARY SYNDROME
- ANAPLASTIC LARGE-CELL LYMPHOMA, T/NULL CELL, PRIMARY CUTANEOUS TYPE
- PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE CHARACTERIZED
- ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA
- ANAPLASTIC LARGE-CELL LYMPHOMA, T/NULL CELL, PRIMARY SYSTEMIC TYPE

Non-Hodgkin Lymphomas: Clinical Groups

- “INDOLENT” - SURVIVAL MEASURED IN YEARS
- “AGGRESSIVE” - SURVIVAL MEASURED IN MONTHS
- “HIGHLY AGGRESSIVE” - SURVIVAL MEASURED IN WEEKS

“INDOLENT” LYMPHOMAS: WHO CLASSIFICATION

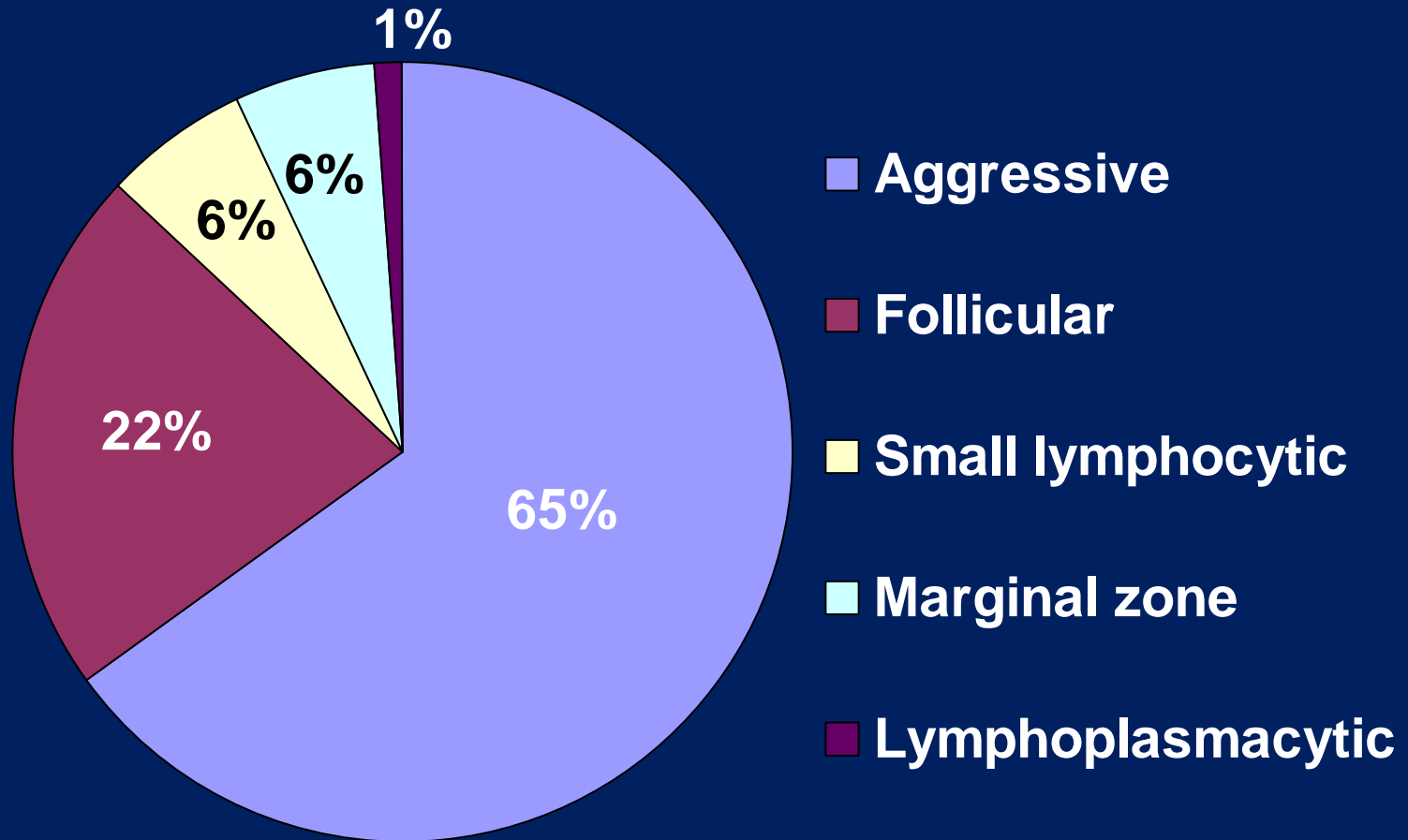
MATURE (PERIPHERAL) B-CELL NEOPLASMS

- B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA / SMALL LYMPHOCYTIC LYMPHOMA
- LYMPHOPLASMACYTIC LYMPHOMA
- SPLENIC MARGINAL ZONE B-CELL LYMPHOMA (+/- VILLOUS LYMPHOCYTES)
- HAIRY CELL LEUKEMIA
- EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMA OF MALT TYPE
- NODAL MARGINAL ZONE B-CELL LYMPHOMA (+/- MONOCYTOID B-CELLS)
- FOLLICULAR LYMPHOMA (GRADES I AND II)

MATURE (PERIPHERAL) T-CELL NEOPLASMS

- T-CELL GRANULAR LYMPHOCYTIC LEUKEMIA
- MYCOSIS FUNGOIDES / SEZARY SYNDROME
- ANAPLASTIC LARGE-CELL LYMPHOMA, T/NULL CELL, PRIMARY CUTANEOUS TYPE

Relative Frequency of Types of Lymphomas



Characteristics of “Indolent” Lymphomas

- GENERALLY MALIGNANCIES OF SMALL, MATURE LYMPHOCYTES
- MOST COMMONLY B-CELL TUMORS
- HIGH PROPORTION OF NON-DIVIDING CELLS WITH LOW PROLIFERATION RATE
- LYMPHOID DISEASES WITH HETEROGENEOUS HISTOLOGIES
- FREQUENT INVOLVEMENT OF BLOOD AND BONE MARROW
- LONG MEDIAN SURVIVAL
- INITIAL SENSITIVITY TO CHEMOTHERAPY AND RADIOTHERAPY
- ADVANCED STAGE AT DIAGNOSIS

Diagnosis of non-Hodgkin Lymphomas

LYMPH NODE OR TISSUE BIOPSY FOR EVALUATION OF:

- HISTOLOGY (CELL TYPE, TISSUE ARCHITECTURE, PATTERN OF LYMPHOID INFILTRATION)
- PHENOTYPING OF TUMOR CELLS
- GENOTYPING OF TUMOR CELLS

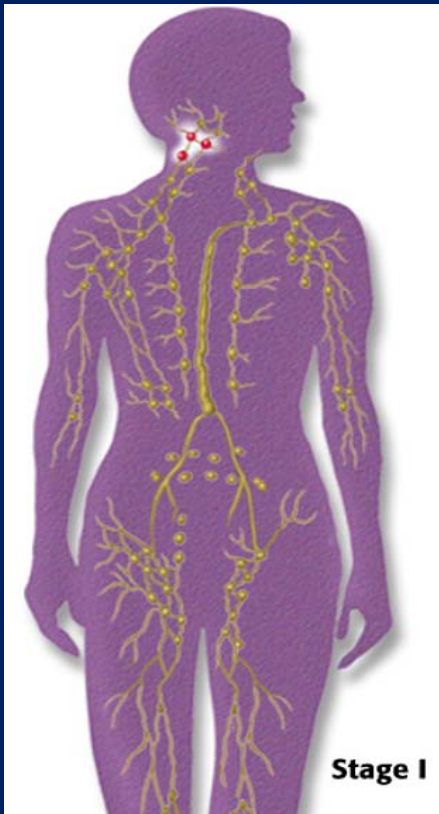
Staging of Lymphomas

- PHYSICAL EXAM WITH ATTENTION TO LN AREAS, LIVER, SPLEEN
- BLOOD COUNT WITH EVALUATION OF BLOOD SMEAR
- SERUM CHEMISTRIES
- CHEST X-RAY
- CT SCANS OF NECK, CHEST, ABDOMEN AND PELVIS
- ADDITIONAL RADIOLOGIC STUDIES AS INDICATED (*e.g.*, PET SCAN)
- BONE MARROW BIOPSIES
- DETERMINATION OF ANN ARBOR STAGE

Staging of Lymphomas

Stage I

single lymph node region / organ



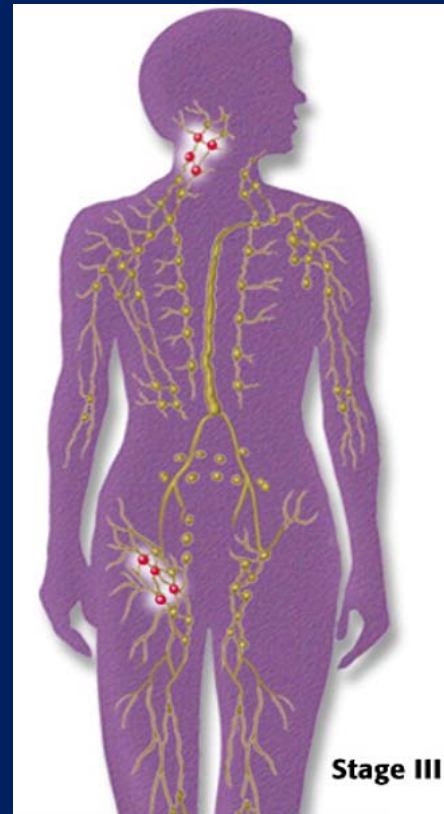
Stage II

2 adjacent lymph node regions



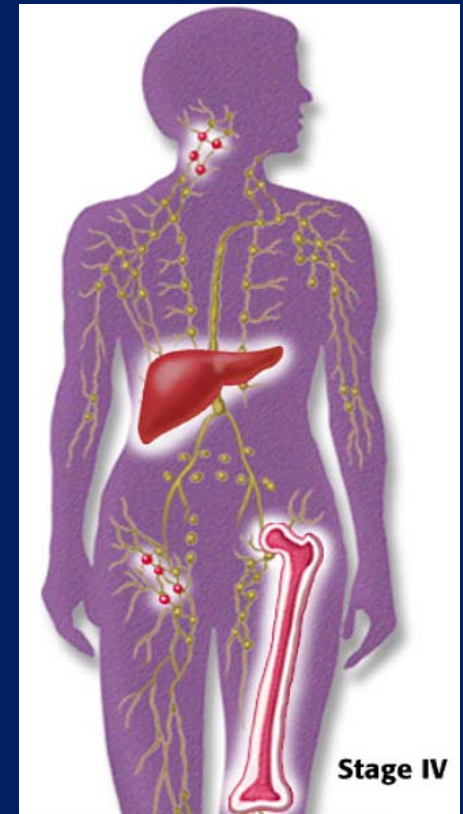
Stage III

≥ 2 lymph node regions in different parts of the body



Stage IV

widespread disease + / - lymph node involvement



Prognosis of non-Hodgkin Lymphomas

- INDOLENT LYMPHOMAS
 - advanced stage considered incurable, but long survival.
- AGGRESSIVE LYMPHOMAS
 - frequently curable.
- HIGHLY AGGRESSIVE LYMPHOMAS
 - frequently curable.

Follicular Lymphoma

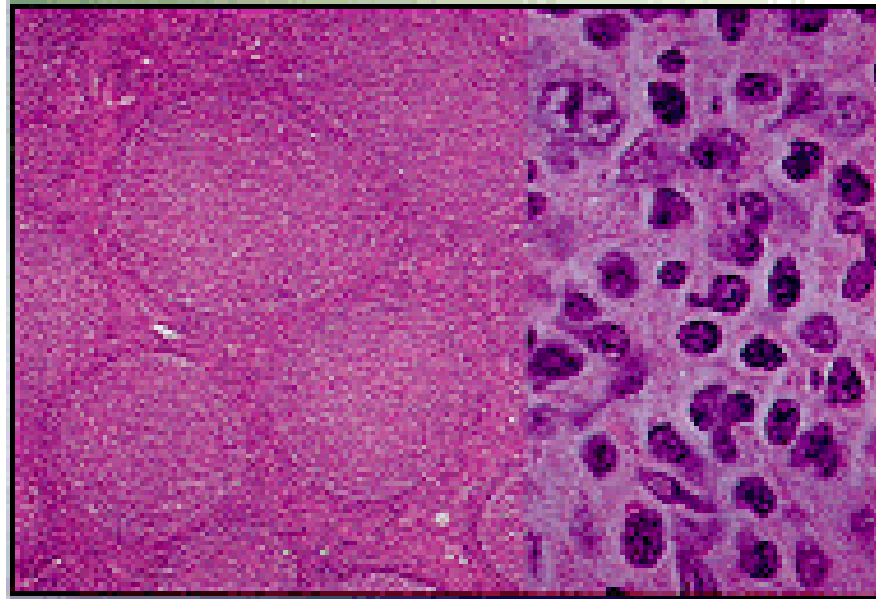
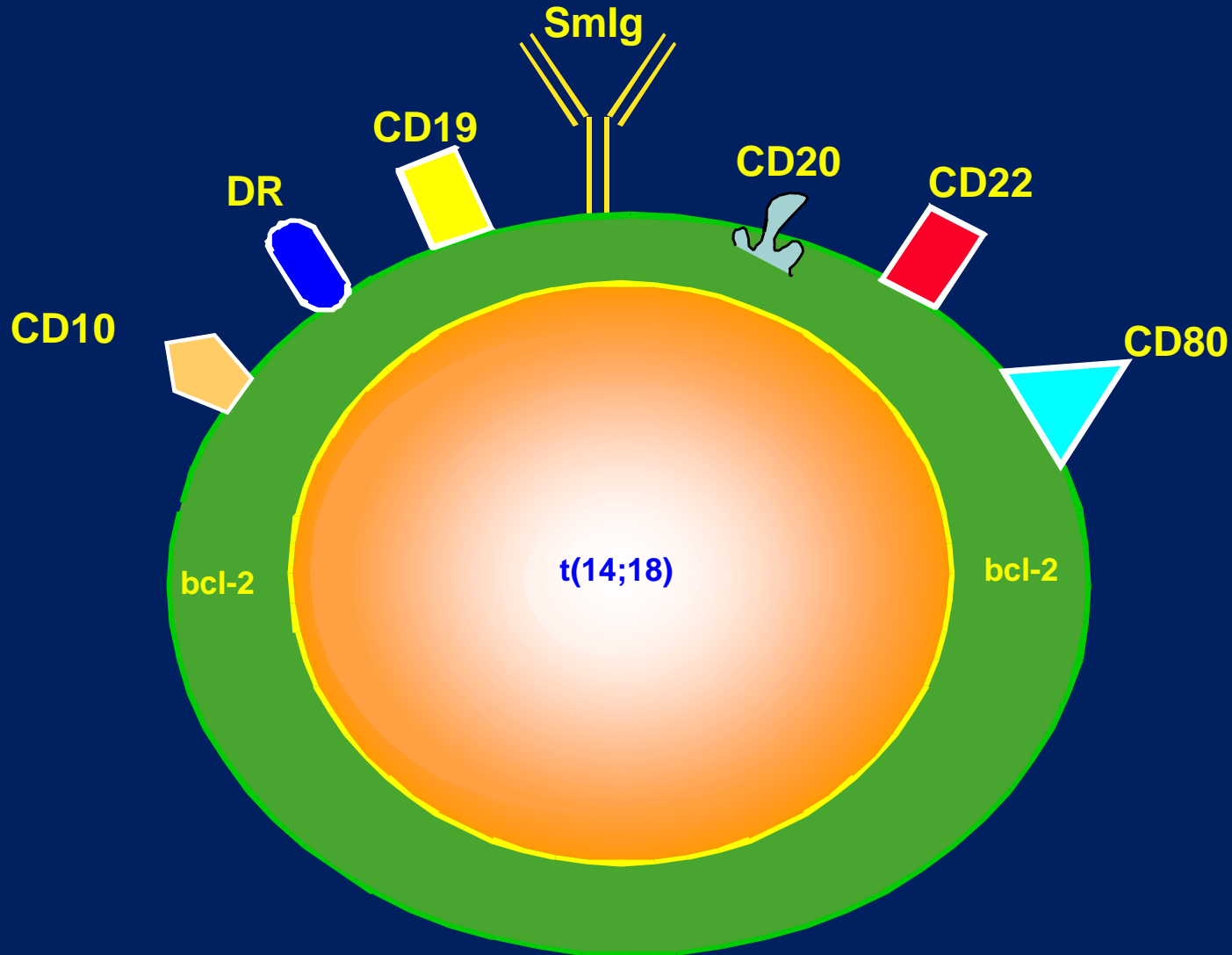


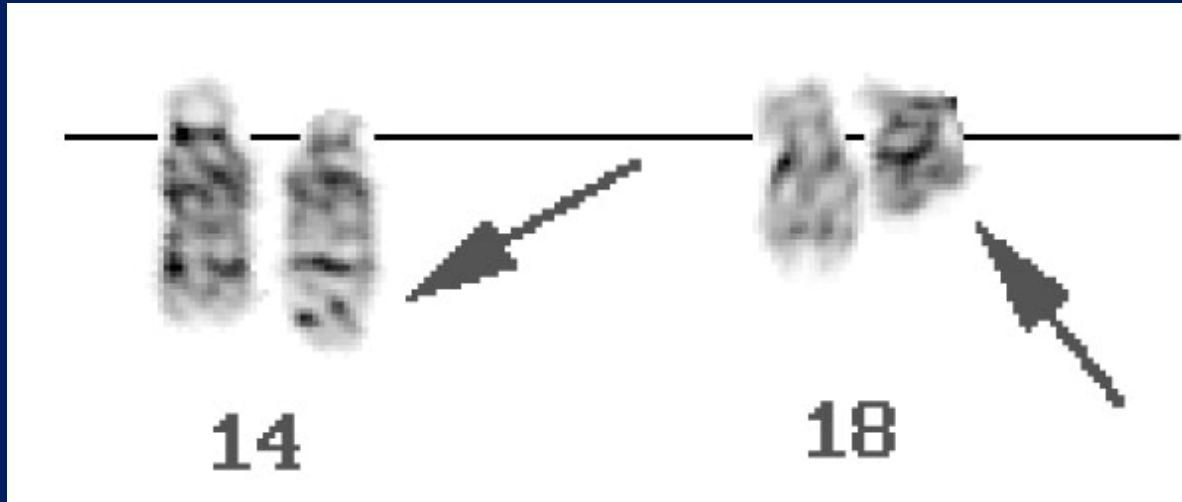
Fig 6. — Follicular lymphoma. Normal architecture is replaced by numerous, fairly uniform, and closely apposed follicles. The follicles show mainly small cleaved cells and a single, large noncleaved cell (hematoxylin-eosin 40x, x 400).

Follicular Lymphoma Cell



Follicular Lymphoma

t(14;18)



Follicular Lymphoma

HISTOLOGY: SMALL CLEAVED AND LARGER NONCLEAVED LYMPHOCYTES ARRANGED IN NODULAR AGGREGATES; THE NUMBER OF LARGE CELLS PRESENT DETERMINES THE TUMOR GRADE (I, II or III).

IMMUNOPHENOTYPE: CD5-, CD10+, CD19/20+, CD23-, SIg+.

CYTOGENETICS: t(14;18).

EPIDEMIOLOGY: 22% OF NHL; MEDIAN AGE 55.

CLINICAL: ADVANCED STAGE AT DX (80%); PROGRESSION MORE RAPID IN MIXED AND LARGE CELL TYPES; TRANSFORMATION TO AGGRESSIVE LYMPHOMA IN 25% PATIENTS.

MEDIAN SURVIVAL: 7, 5, AND 3 YEARS FOR GRADES I, II AND III RESPECTIVELY.

TREATMENT: NO SURVIVAL ADVANTAGE TO EARLY Rx FOR ADVANCED GRADE I (OR II) DISEASE. STANDARD FIRST THERAPIES FOR ADVANCED GRADE I (OR II) DISEASE INCLUDE RITUXAN, CVP + RITUXAN, R-CHOP, OR CHLORAMBUCIL; FOR GRADE III FOLLICULAR NHL (AND FREQUENTLY GRADE II) R-CHOP IS A STANDARD FIRST THERAPY.

Lymphoplasmacytic lymphoma (Waldenstrom's)

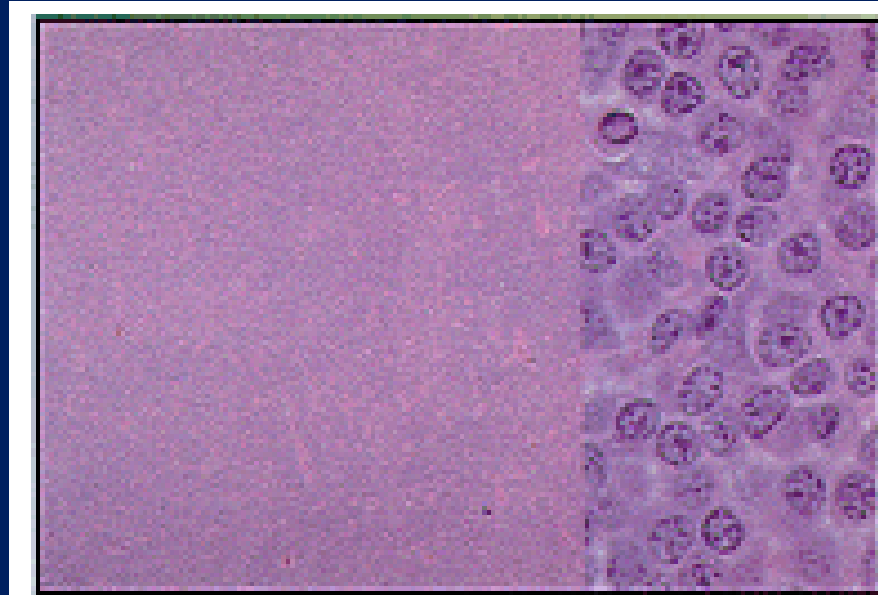


Fig 2. — SLL/PL. Lymph node architecture is effaced by diffuse proliferation of plasmacytoid lymphocytes with moderately abundant cytoplasm. High-power magnification shows uniform plasmacytoid cells and a single Dutcher body (hematoxylin-eosin 40x, x 400).

Lymphoplasmacytic lymphoma (Waldenstrom's)

HISTOLOGY: SMALL BENIGN-APPEARING LYMPHOCYTES WITH PLASMACYTIC DIFFERENTIATION.

IMMUNOPHENOTYPE: CD5+ or -, CD10-, CD19/20+, CD23-, SIg+, CIg+.

CYTOGENETICS: t(9;14)(p13;q32).

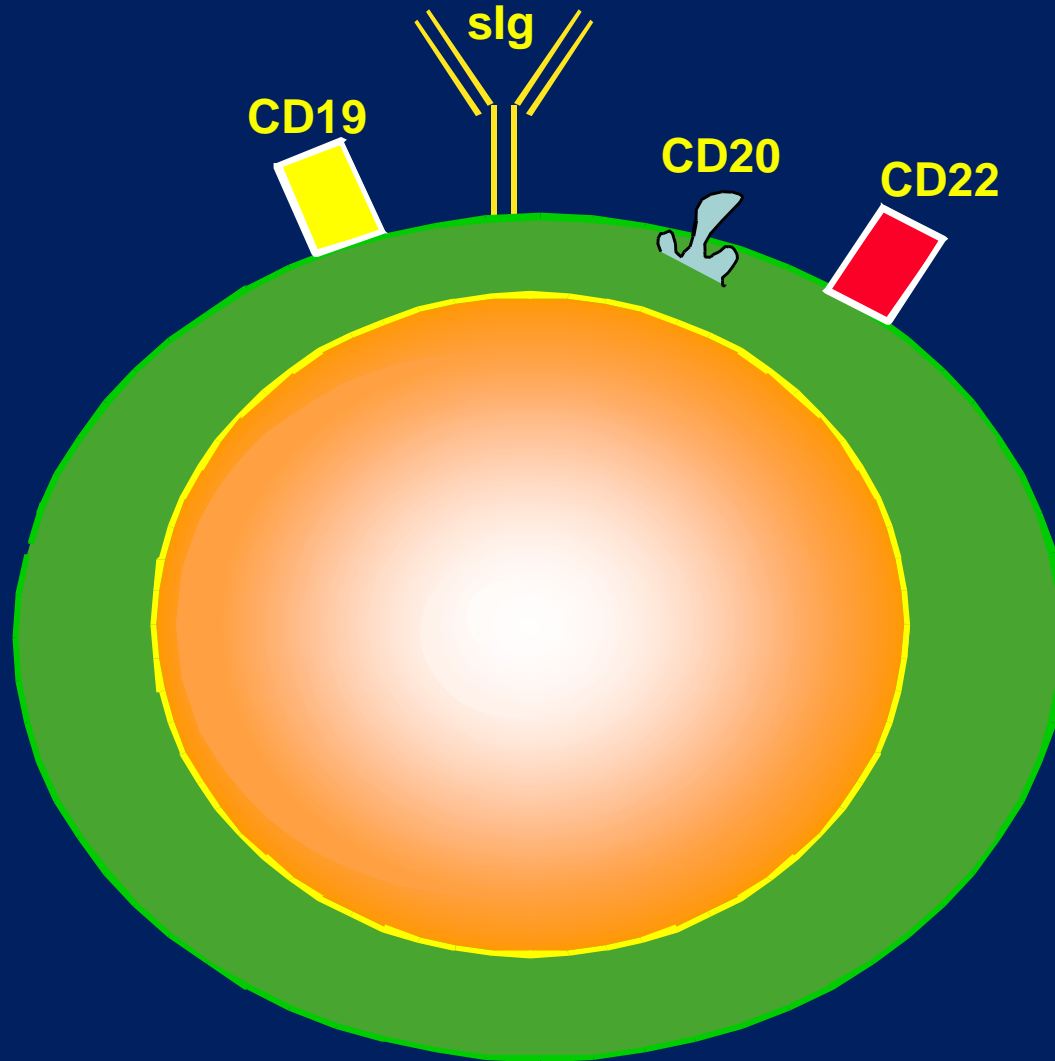
EPIDEMIOLOGY: <5% OF NHL; MEDIAN AGE 55 - 65; POSSIBLE ROLE OF Hep C.

CLINICAL: USUALLY ADVANCED STAGE AT DX; PARAPROTEINEMIA (WALDENSTROM'S).

MEDIAN SURVIVAL: >6 - 7 YEARS.

TREATMENT: NO ADVANTAGE TO EARLY Rx. TREAT FOR SYMPTOMS OR REAL/IMPENDING ORGAN DYSFUNCTION. STANDARD FIRST THERAPIES INCLUDE RITUXAN, FLUDARABINE (ALONE OR IN COMBINATION) OR CHLORAMBUCIL.

Lymphoplasmacytic lymphoma (Waldenstrom's)



Extranodal Marginal Zone Lymphoma (MALT)

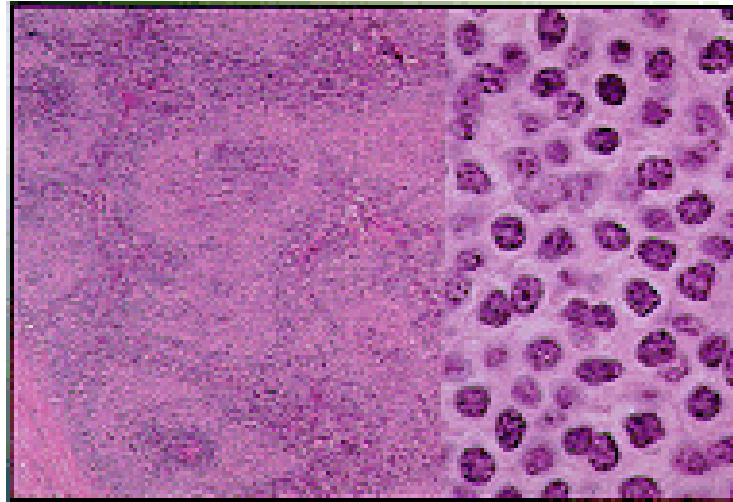


Fig 3. — Marginal-zone lymphoma. Lymph node is infiltrated by monocytonoid B cells surrounding germinal centers. This appearance also is referred to as the "inverted follicular" pattern. The monocytonoid B cells have abundant, lightly staining cytoplasm and irregular nuclei (hematoxylin-eosin 40x, x 400).

Extranodal Marginal Zone Lymphoma (MALT)

HISTOLOGY: ASSO. WITH EPITHELIAL TISSUE (MALT-LYMPHOMA) OR OTHER EXTRANODAL SITES. CELLULAR HETEROGENEITY INC. SMALL LYMPHOCYTES, PLASMA CELLS, MONOCYTOID B-CELLS. LYMPHOEPITHELIAL LESIONS SEEN IN MALT-LYMPHOMAS.

IMMUNOPHENOTYPE: CD5-, CD10-, CD19/20+, CD23+/-, SIg+, CIg+/-.

CYTOGENETICS: TRISOMY 3 IN 60% OF CASES.

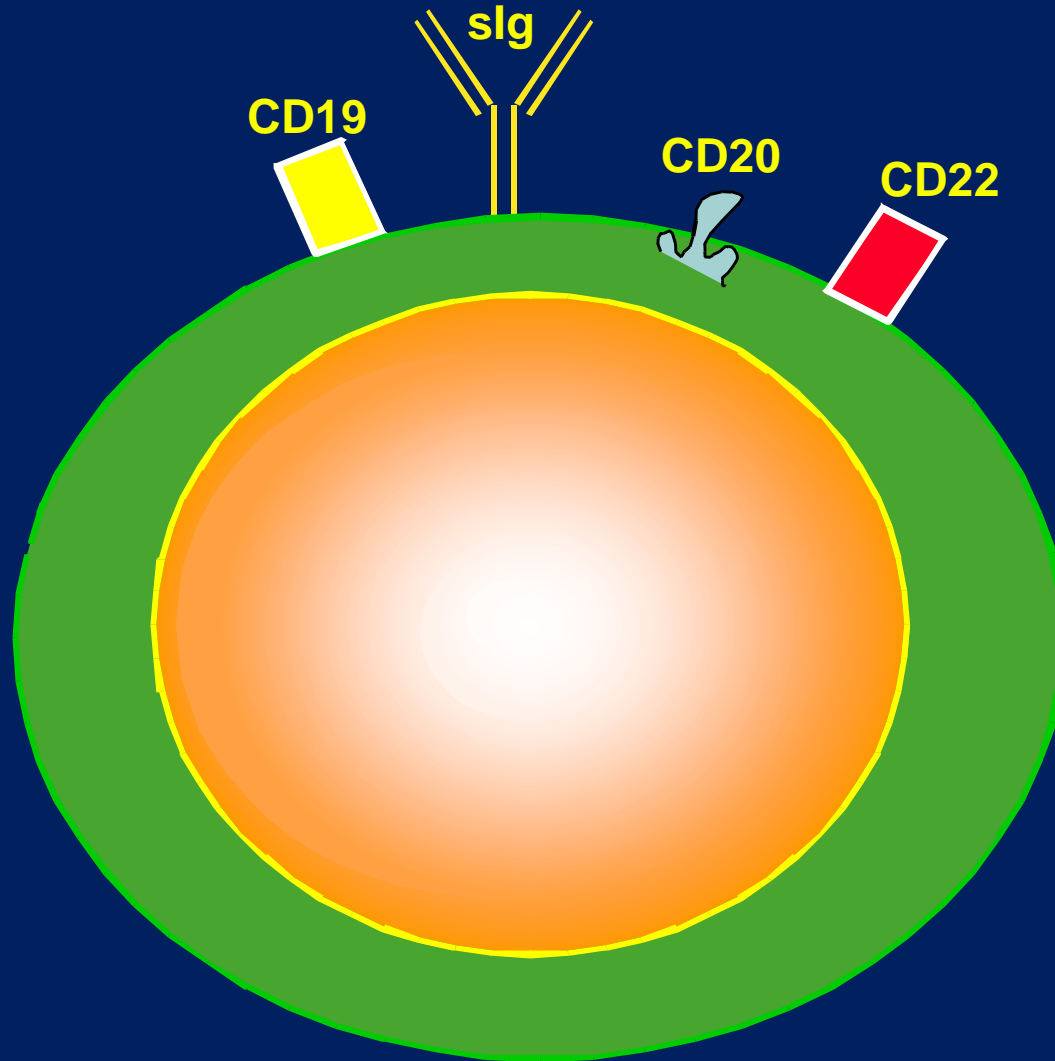
EPIDEMIOLOGY: GASTRIC MALT LYMPHOMA IS ASSO. WITH H. PYLORI INFECTION. NONGASTRIC MALT LYMPHOMA IS ASSO. WITH AUTOIMMUNE DISEASE.

CLINICAL: GASTRIC MALT LYMPHOMA FREQUENTLY LOCALIZED AT DIAGNOSIS. NONGASTRIC MALT LYMPHOMA IS LESS COMMONLY EARLY STAGE AT DIAGNOSIS. MEDIAN AGE AT DIAGNOSIS IS 50 – 60s.

MEDIAN SURVIVAL: 5-YEAR SURVIVAL 80 - 100% FOR EARLY STAGE MALT LYMPHOMA. SURVIVAL IN ADVANCED DISEASE IS SIMILAR TO OTHER INDOLENT NHLs.

TREATMENT: ANTIBIOTICS FOR EARLY STAGE H. PYLORI ASSO. GASTRIC MALT LYMPHOMA. IN SOME CASES, SURGERY, RADIATION THERAPY AND /OR CHEMOTHERAPY ARE ALSO APPROPRIATE THERAPIES .

Marginal Zone Lymphoma (MALT)



Chronic lymphocytic leukemia / Small lymphocytic lymphoma

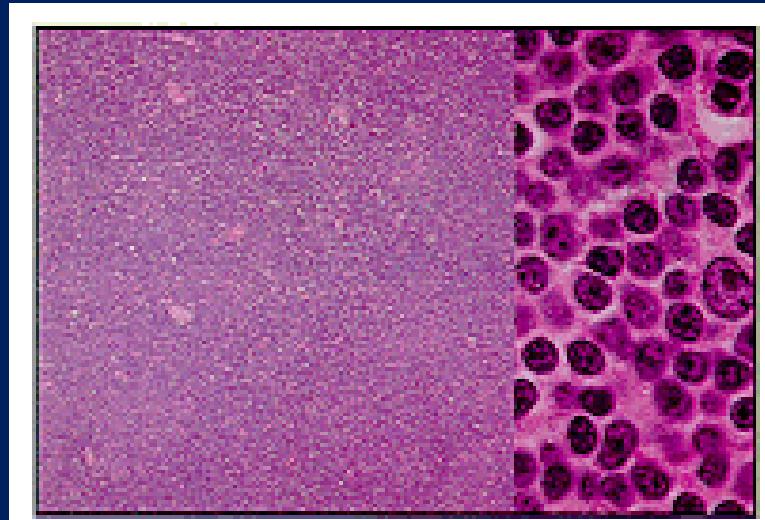


Fig 1. — SLL/CLL. There is diffuse effacement of lymph node architecture, with scattered, pale, staining growth centers, a characteristic pattern of SLL/CLL. No residual germinal centers are present. At higher magnification, uniform infiltration by small, round lymphocytes with scant cytoplasm admixed with larger cells with prominent nucleoli (paraimmunoblasts) is demonstrated (hematoxylin-eosin 40x, x 400).

Chronic lymphocytic leukemia / Small lymphocytic lymphoma

HISTOLOGY: SMALL ROUND BENIGN-APPEARING LYMPHOCYTE.

IMMUNOPHENOTYPE: CD5+, CD10-, CD19/20+, CD23+, SIg+/-.

CYTOGENETICS: OCC. TRISOMY 12; del13q; del11q; del17p.

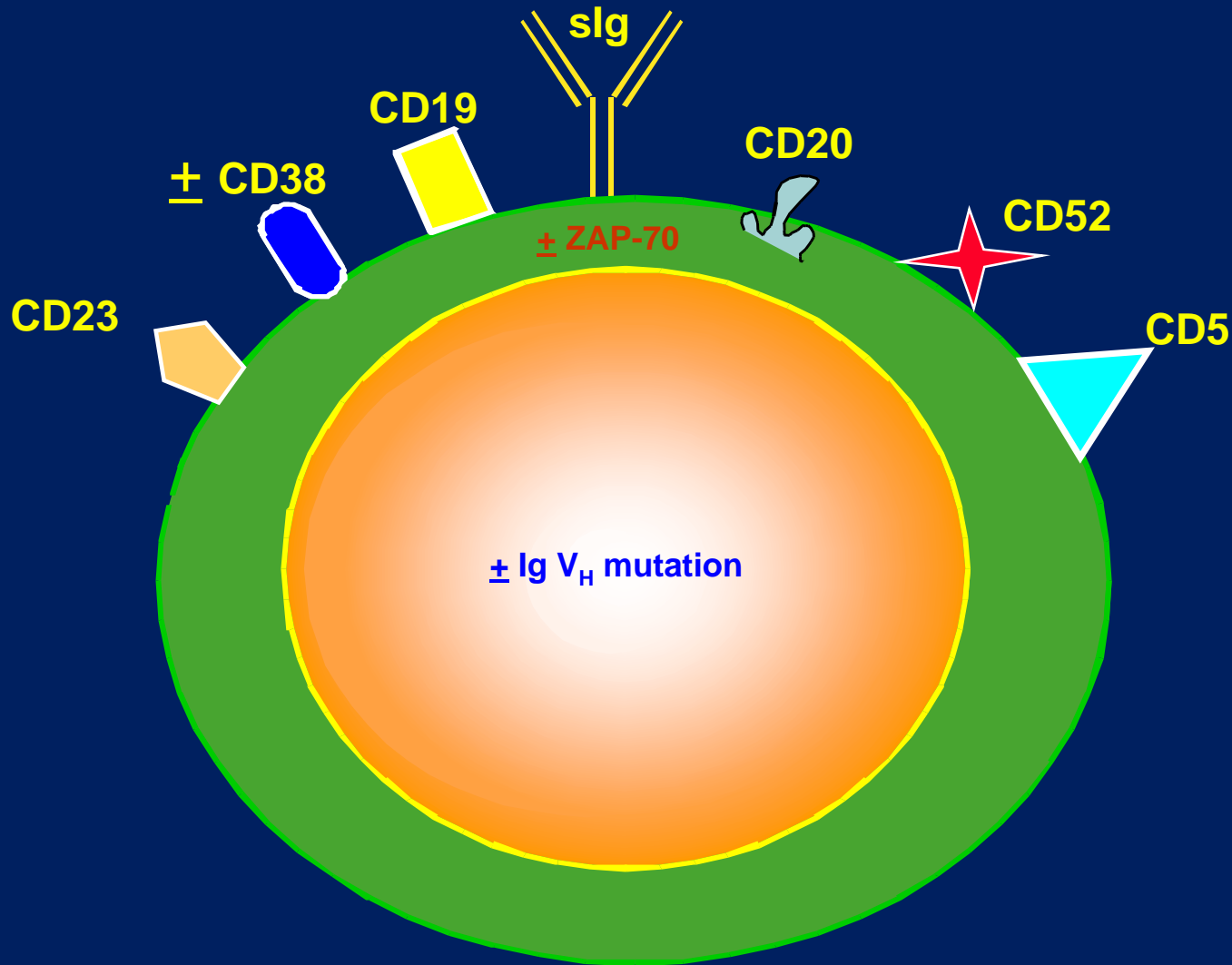
EPIDEMIOLOGY: 5% OF NHL; MEDIAN AGE 60.

CLINICAL: ADVANCED STAGE AT DX (>60 - 80%); FREQ. BLOOD INVL. (CLL).

MEDIAN SURVIVAL: >5 - 8 YEARS.

TREATMENT: NO ADVANTAGE TO EARLY Rx. TREAT FOR SYMPTOMS OR REAL/IMPENDING ORGAN DYSFUNCTION. STANDARD FIRST THERAPIES INCLUDE FLUDARABINE COMBINATIONS USUALLY WITH RITUXAN AND/OR CYTOXAN, CHLORAMBUCIL, CVP.

Chronic lymphocytic leukemia / Small lymphocytic lymphoma



Non-Hodgkin Lymphomas: Treatment Overview

- Watch and wait (for indolent lymphomas)
- Chemotherapy
- Radiation therapy
- Monoclonal antibody therapy
- Combination therapies
- Radioimmunotherapy (RIT)
- Bone marrow and stem cell transplants
- Investigational therapies

Standard Therapeutic Approaches to non-Hodgkin Lymphomas

INDOLENT LYMPHOMAS: *palliative approach in general*

advanced stage: watch & wait or palliative therapies (applicable to CLL)

early stage: regional radiation

AGGRESSIVE LYMPHOMAS: *curative therapy*

advanced stage: combination chemotherapy (e.g., CHOP or R-CHOP)

early stage: combined modality therapy (radiation + R-CHOP)

HIGHLY AGGRESSIVE LYMPHOMAS: *curative therapy*

Older “Standard” Approaches to Treatment of Indolent Lymphomas

LIMITED STAGE DISEASE

- INVOLVED FIELD OR REGIONAL IRRADIATION

ADVANCED-STAGE DISEASE

- DEFERRED THERAPY (WATCH AND WAIT)
- SINGLE ALKYLATING AGENT
- TOTAL BODY OR TOTAL NODAL IRRADIATION
- COMBINATION CHEMOTHERAPY (CVP, CHOP, C-MOPP)

Newer and Investigational Approaches for Indolent NHL and CLL

- NEWER CHEMOTHERAPEUTIC AGENTS AND COMBINATIONS

- NUCLEOSIDE ANALOG COMBINATIONS
- BENDAMUSTINE (TREANDA)
- BORTEZOMIB (VELCADE)

- MONOCLONAL ANTIBODY THERAPY

- MONOCLONAL ANTIBODY MONOTHERAPY: anti-CD20
- MONOCLONAL ANTIBODY: RITUXAN + CHEMOTHERAPY
- RADIOLABELLED MONOCLONAL ANTIBODIES: ZEVALIN; BEXXAR
- COUNTLESS NEW MONOCLONAL ANTIBODIES: anti-CD22, -CD74, -CD80, etc.

- ADOPTIVE IMMUNOTHERAPY USING AUTOLOGOUS T-CELLS

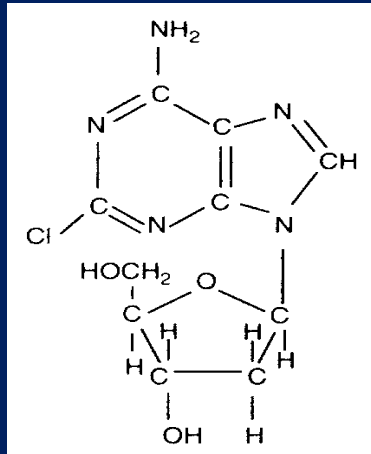
- IMMUNOMODULATORY AGENTS

- LENALIDOMIDE (REVLIMID)

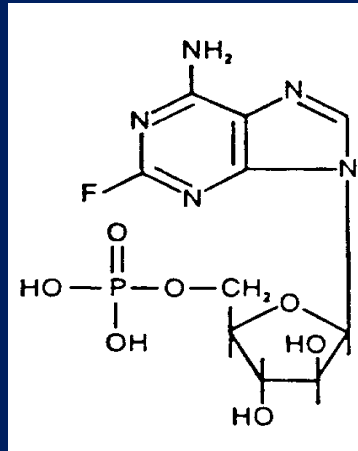
- VACCINES

- TRANSPLANTATION – will not discuss

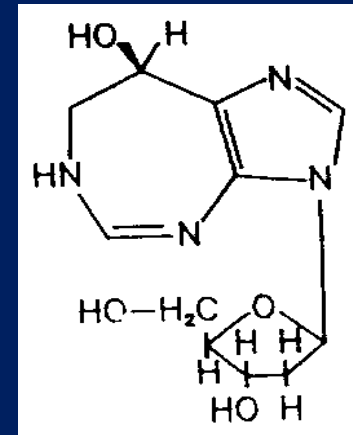
Purine Nucleoside Analogs



CLADRIBINE



FLUDARABINE



PENTOSTATIN

Purine Analog Therapy for Indolent non-Hodgkin Lymphomas

AGENT	# PTS	PRIOR THERAPY	CR%	PR%
Fludarabine	326	yes	12	45
		no	39	69
Cytosin-Fludarabine	27	no	89	100

From: CHESON, B. D. ASH EDUCATION PROGRAM BOOK, 1999.

Initial Therapy for Chronic Lymphocytic Leukemia

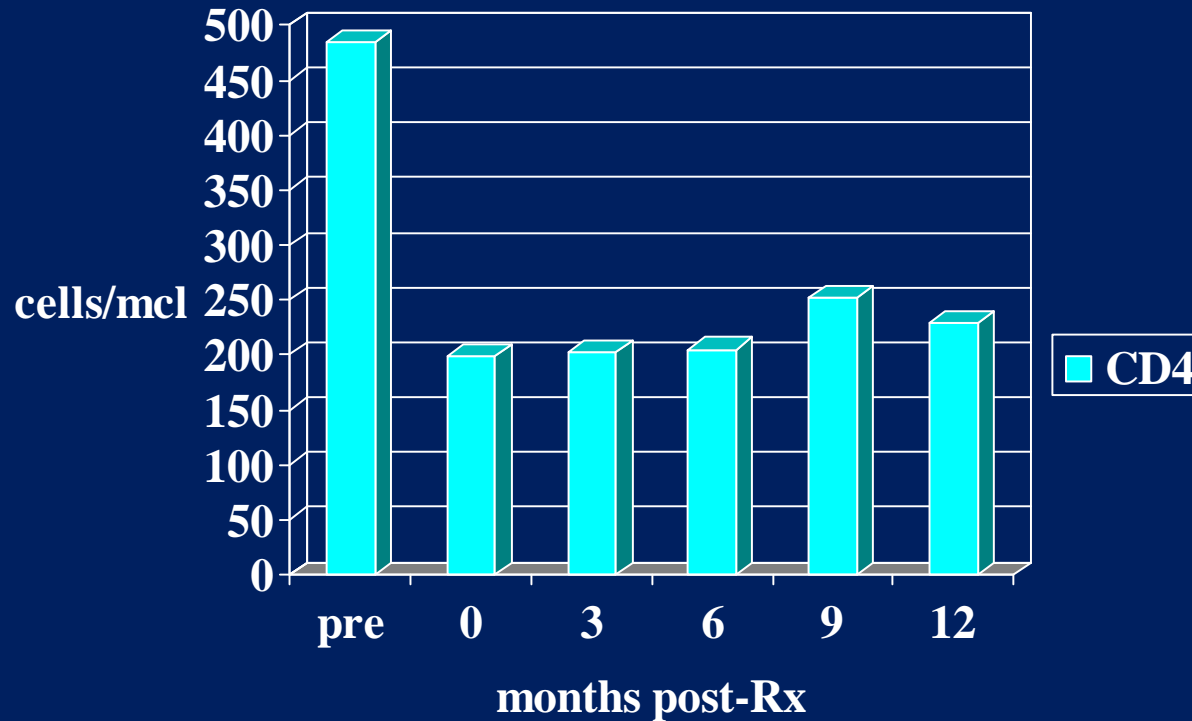
	Chlorambucil ¹	Fludarabine ¹	Fludarabine + Cytosan ²	Fludarabine + Cytosan + Rituxan ³
ORR (%)	37	63	94	95
CR (%)	4	20	24	70
PFS	median @ 14 mo	median @ 20 mo	median @ 48 mo	69% @ 48 mo

1. Rai et al. *N Engl J Med.* 2000; 343: 1750.

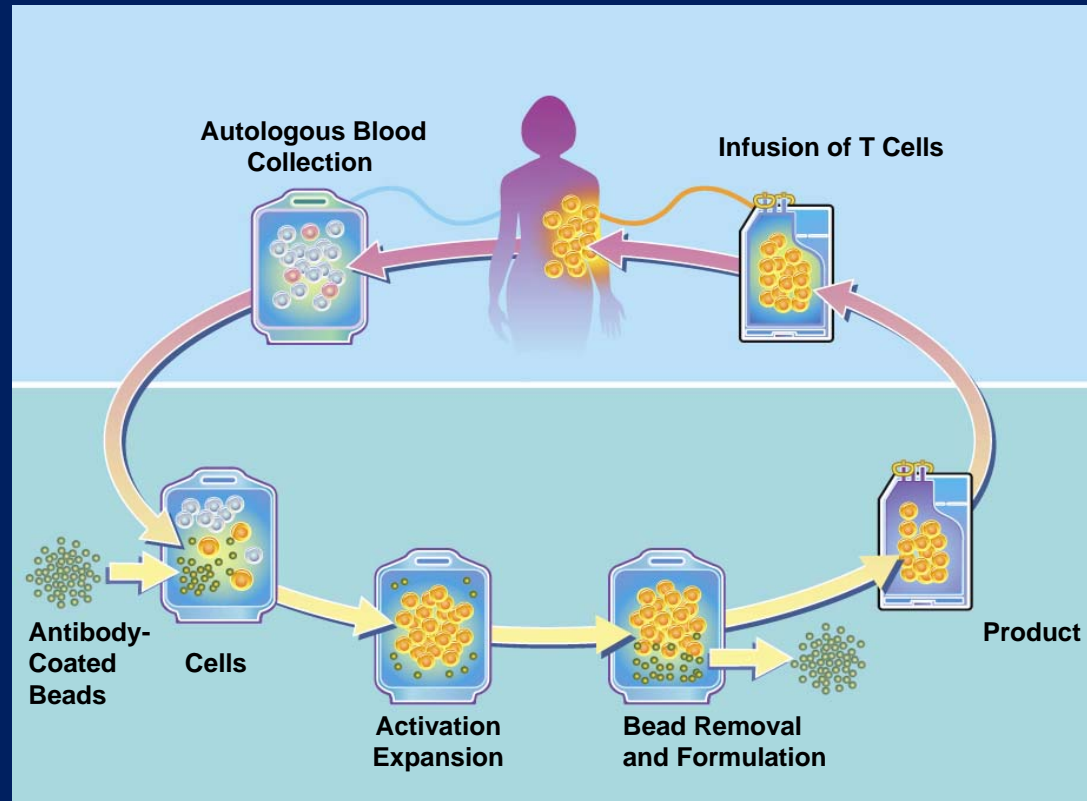
2. Eichorst et al. *Blood.* 2006; 107:885.

3. Keating et al. *J Clin Onc.* 2005; 18:4079.

Immunosuppression After Cytoxan - Fludarabine

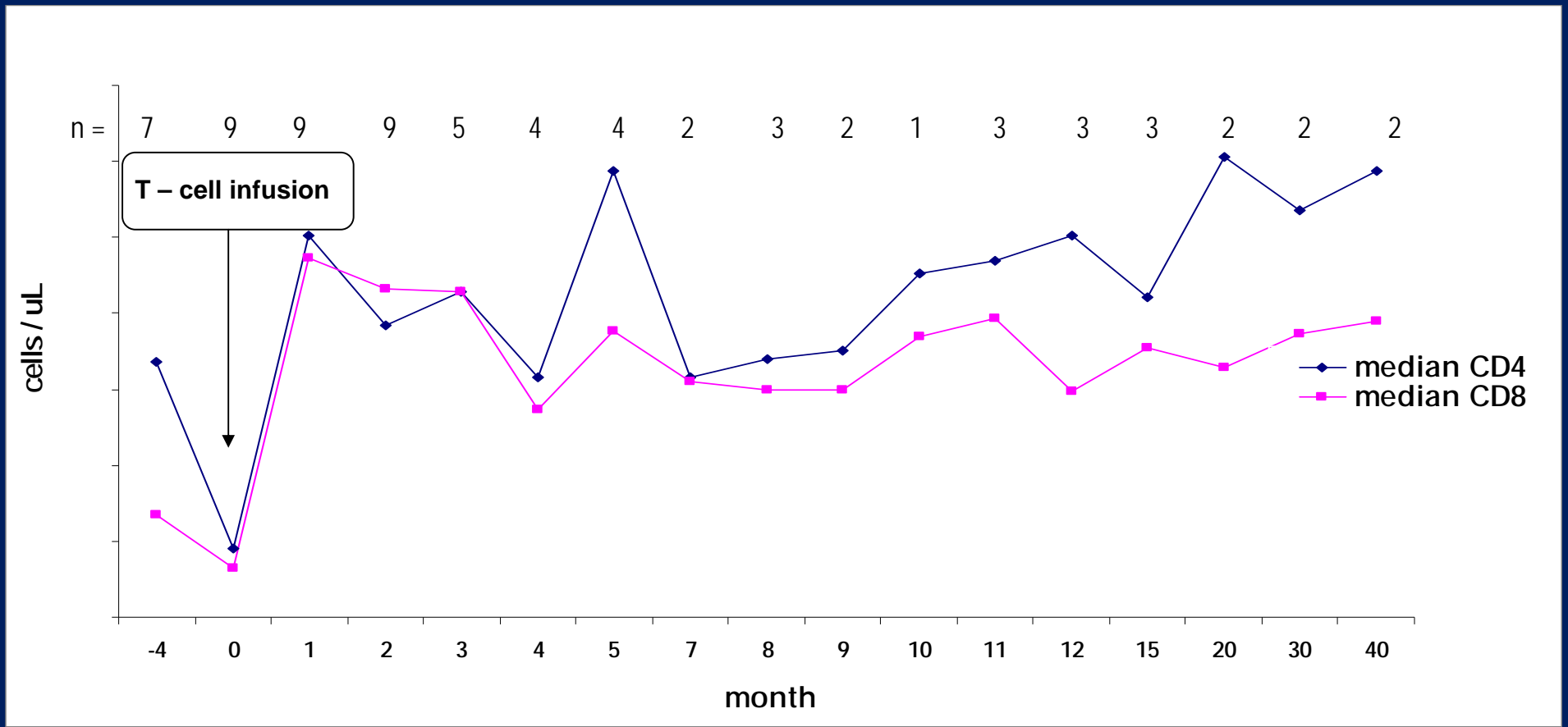


Ex Vivo T-Cell Expansion



Technology developed by Dr. Carl June

CD4 and CD8 Counts Over Time



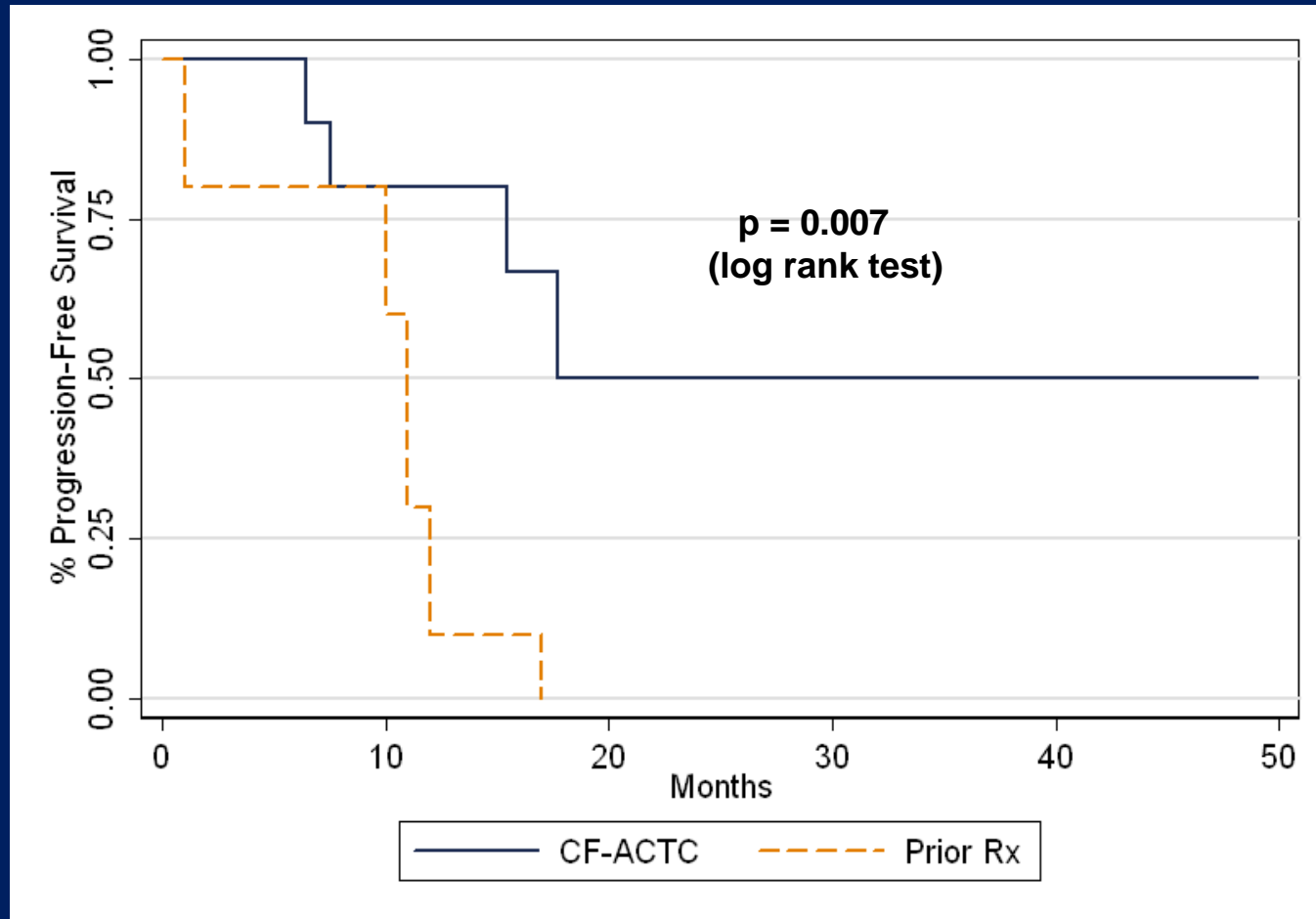
DTH Candida Skin Test Results

n = 10



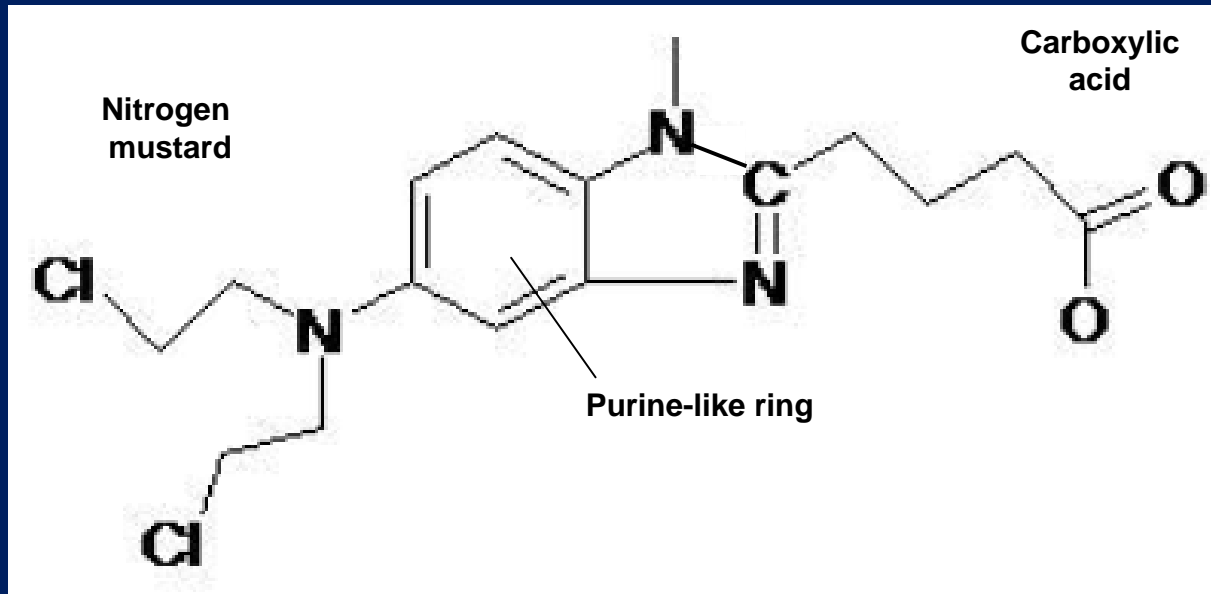
	POSITIVE	NEGATIVE
PRE-CHEMO Rx	0	10
POST-CF-ACTC	5	5

Progression-Free Survival



Bendamustine

- Purine-like nucleus with a bifunctional alkylating nitrogen mustard group
 - induces DNA damage resulting in apoptosis and mitotic catastrophe
- Lacks cross resistance with other agents (including alkylators)



Phase II Trial: Bendamustine Monotherapy in Relapsed Indolent NHL

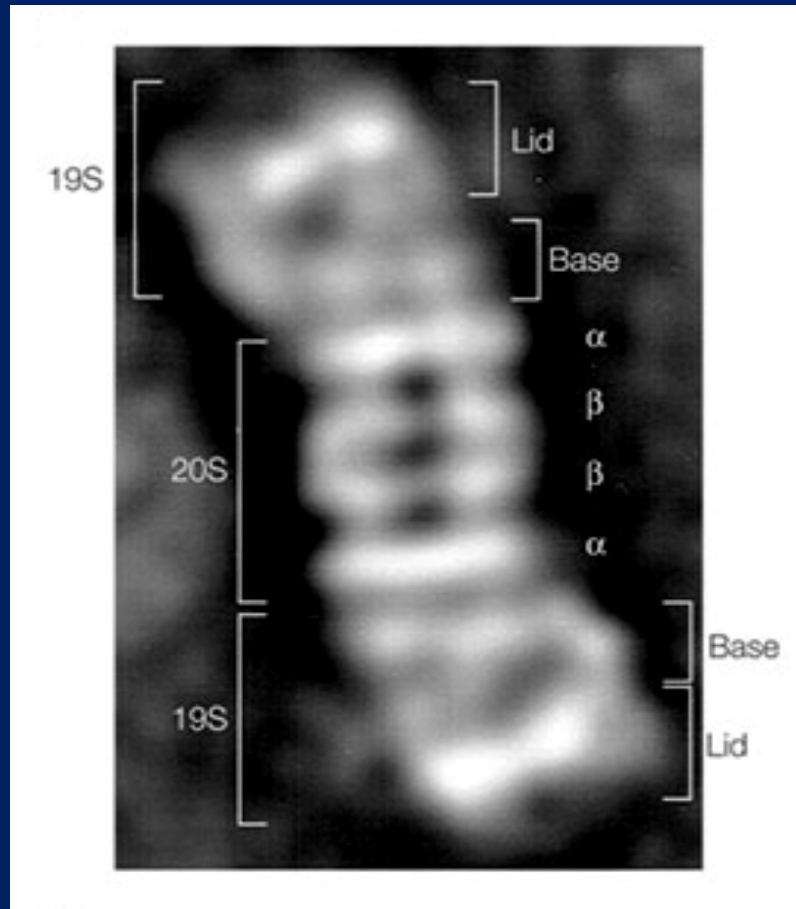
Trial	N	CR	PR	Relapse-Free Survival
Heider, 2001	58	11%	62%	16 months
Cohen, 2005	60	23%	55%	Not reported
Friedberg, 2005	75	25%	49%	9.3 months*
	10/15 (67%) refractory patients had an overall response (OR)			

*DOR

CR = complete response; PR = partial response

Heider. *Anticancer Drugs*. 2001;12:725; Cohen. ASCO 2005 (abstr 6564); Friedberg. ASH 2005 (abstr 229).

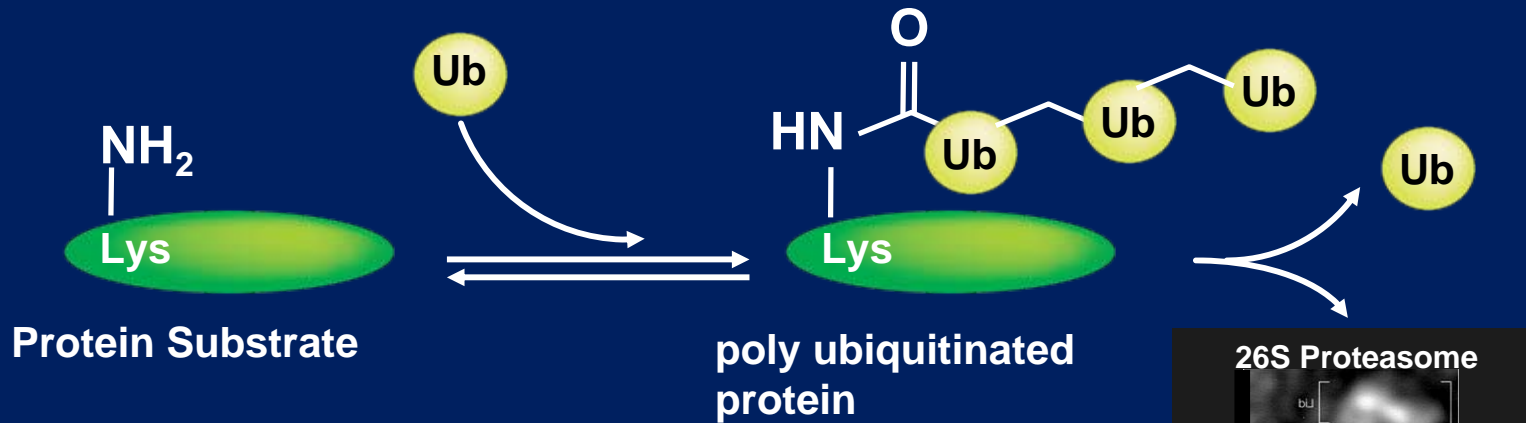
Proteasome



26S Proteasome

- 26S proteasome is abundant in all cells.
- uses the ubiquitin - proteasome pathway to regulate the intracellular concentrations of specific proteins

Ubiquitin - Proteasome Pathway



Ub = ubiquitin

Lys = lysine

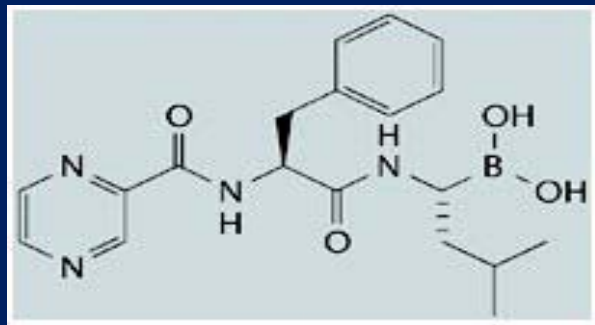


degraded proteins

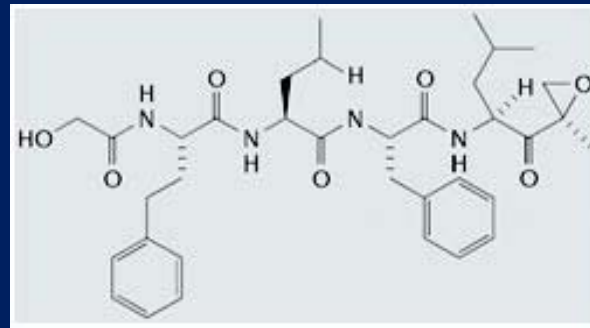
Proteasome Inhibitors in Indolent Lymphoma

Rationale

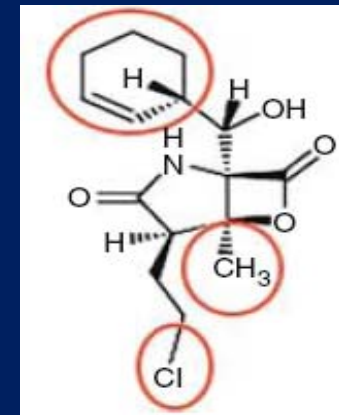
- Disrupts pathways involved in pathogenesis of lymphoma
- Preclinical models show sensitivity of lymphoma cell lines to proteasome inhibitors



Bortezomib
Reversible Inhibitor
Approved for MCL



Carfilzomib (PR-171)
Irreversible Inhibitor
Phase I testing



NPI-0052
Irreversible Inhibitor
Early phase I testing

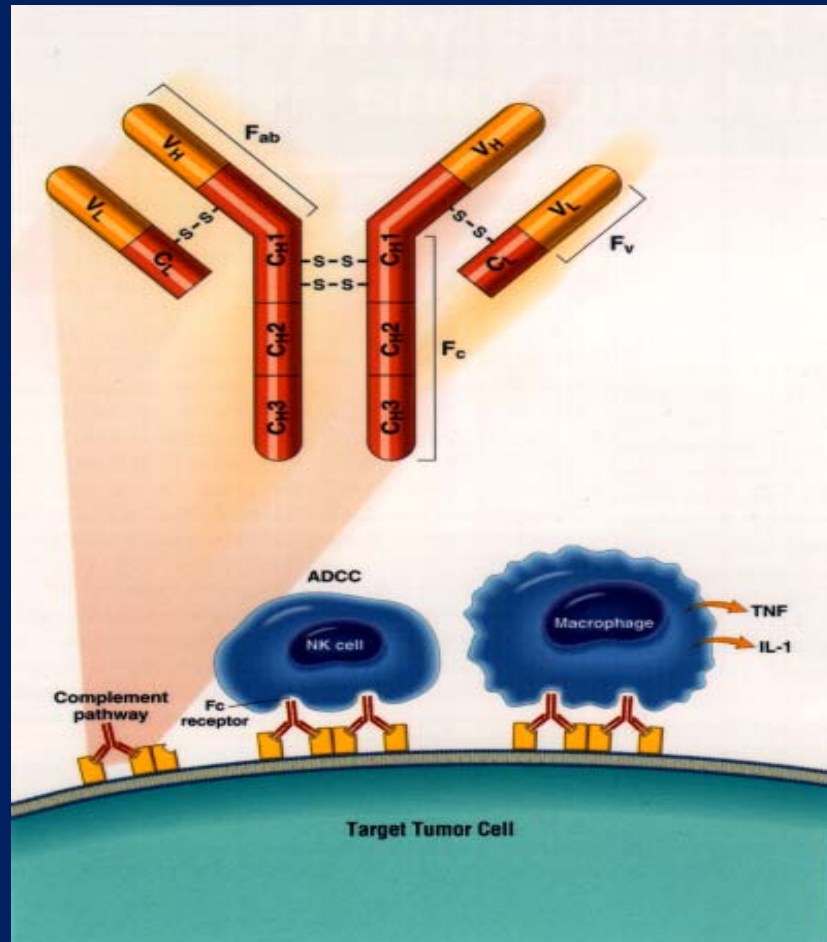
O'Connor. *Clin Lymphoma Myeloma*. 2005;6:191; Leonard. *Int J Cancer*. 2006;119:971; Velcade [package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; Demo. *Cancer Res*. 2007;67:6383; Ahn. *Blood*. 2007 [Epub ahead of print]; Stewart. ASCO 2007 (abstr 8003); Chauhan. *Br J Cancer*. 2006;95:961.

Single-Agent Bortezomib in Relapsed Lymphomas

Study	Subtype	Evaluable Patients (N)	CR/CRu	PR	OR
O'Connor, 2005	FL	9	1/1	5	7 (77%)
	MZL	2	0	2	2 (100%)
	SLL	3	0	0	0
	MCL	10	0/1	4	5 (50%)
Goy, 2005	FL	5	0/1	0	1 (20%)
	SLL	4	1/0	0	1 (25%)
	WM	2	0	1	1 (50%)
	MCL	29	6	6	12 (41%)
Strauss, 2006	FL	11	0	2	2 (18%)
	WM	5	0	2	2 (40%)
	MCL	24	1	6	7 (29%)

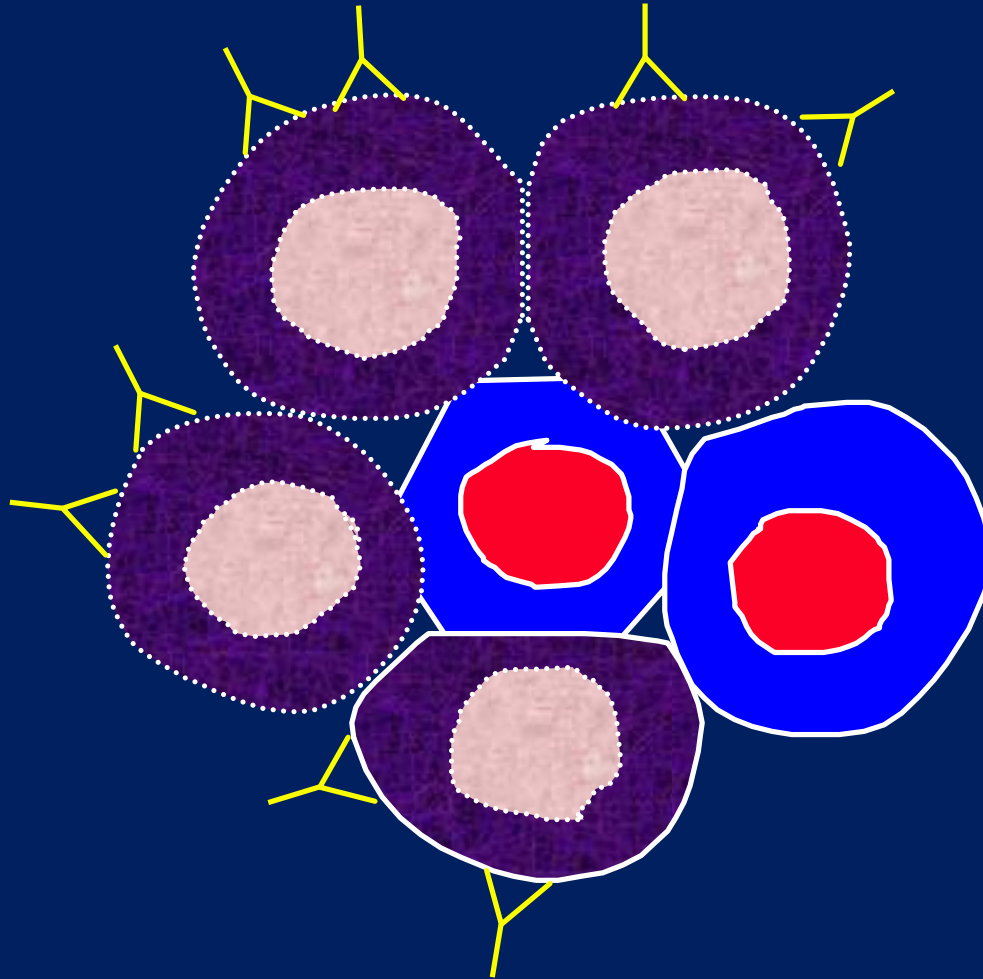
O'Connor. *J Clin Oncol.* 2005;23:676; Goy. *J Clin Oncol.* 2005;23:667; Strauss. *J Clin Oncol.* 2006;24:2105.

Antibody Structure and Function

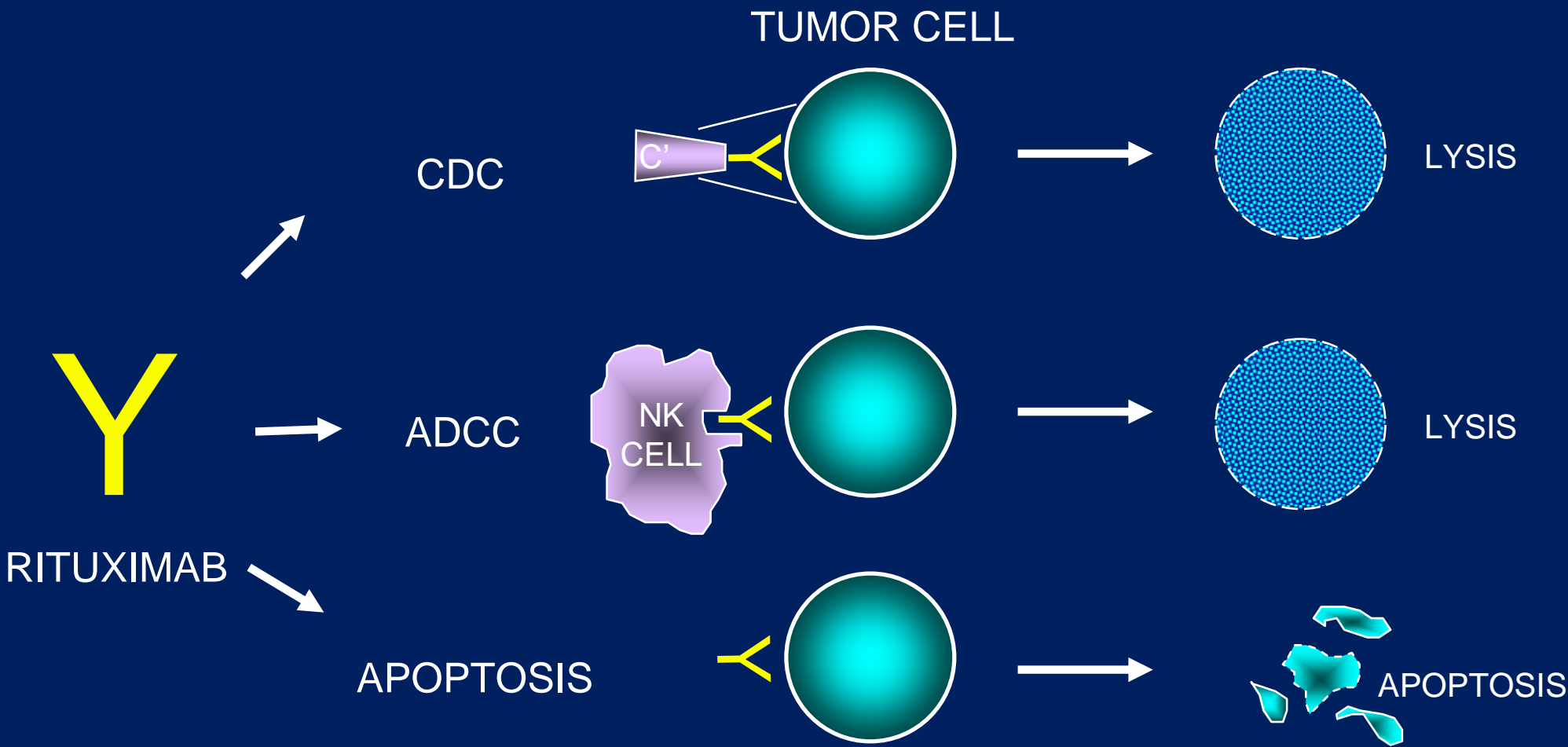


From *Biological Therapy of Lymphoma* 3(4): 2000
Baylor-Charles A. Sammons Cancer Center

Rituxan (Rituximab) an antibody for CD20



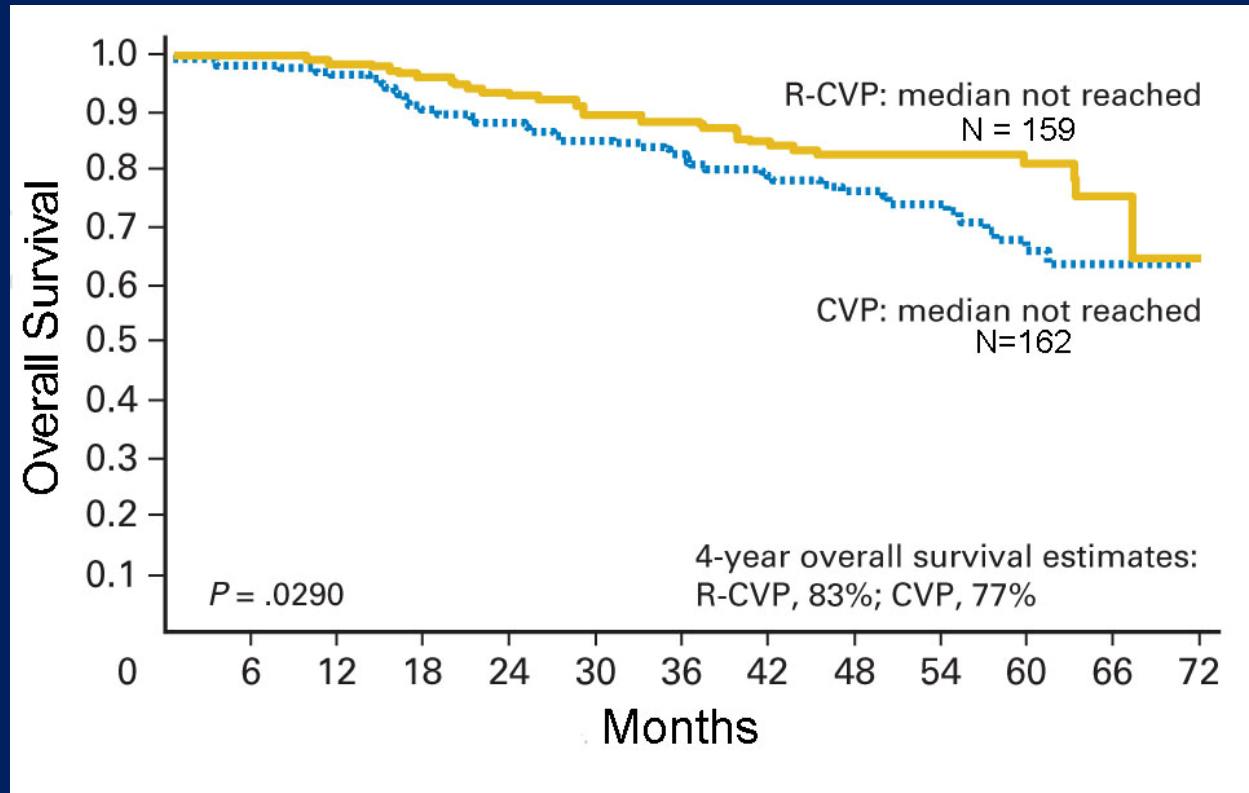
Rituximab Mechanisms



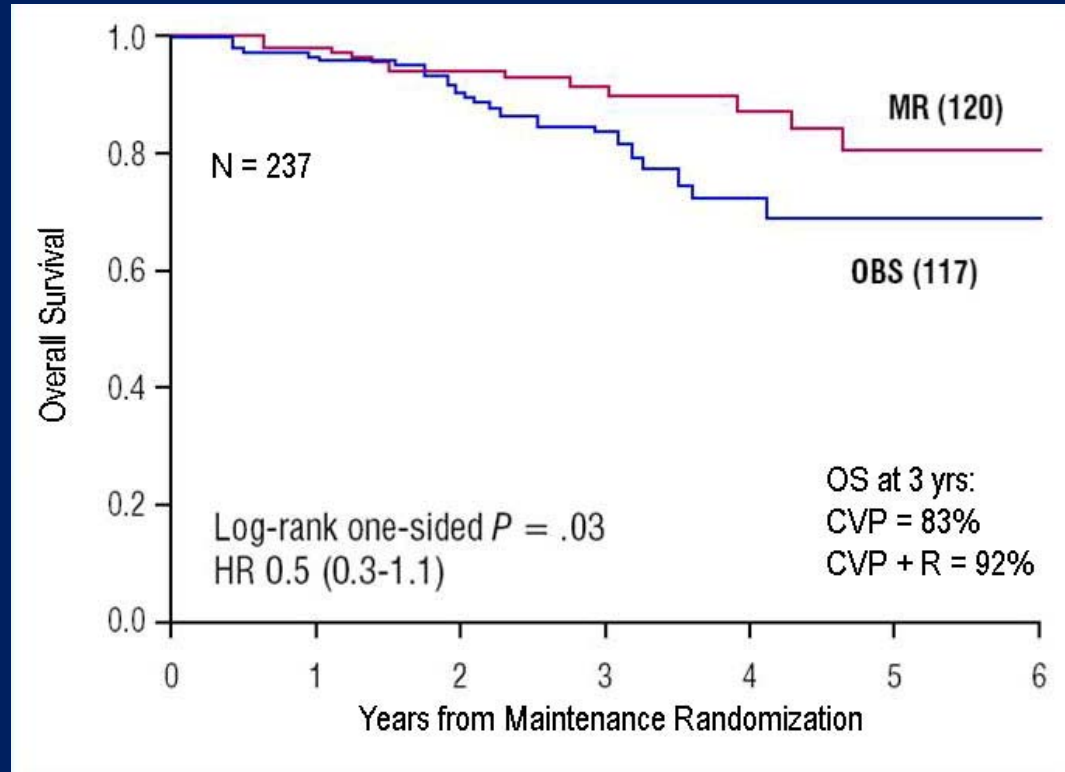
Rituximab Monotherapy for Indolent non-Hodgkin Lymphomas

<u>AUTHOR</u>	<u># PTs</u>	<u>CR</u>	<u>PR</u>
MALONEY	34	3 (4%)	14 (41%)
MCLAUGHLIN	151	9 (6%)	67 (44%)
COLOMBAT	50	10 (20%)	23 (47%)
HAINSWORTH	62 (1 ST Rx)	4 (7%)	24 (40%)
	60 (Rx x4)	22 (37%)	22 (37%)

R-CVP v. CVP as first therapy for follicular lymphoma



CVP-R v. CVP as first therapy for follicular lymphoma



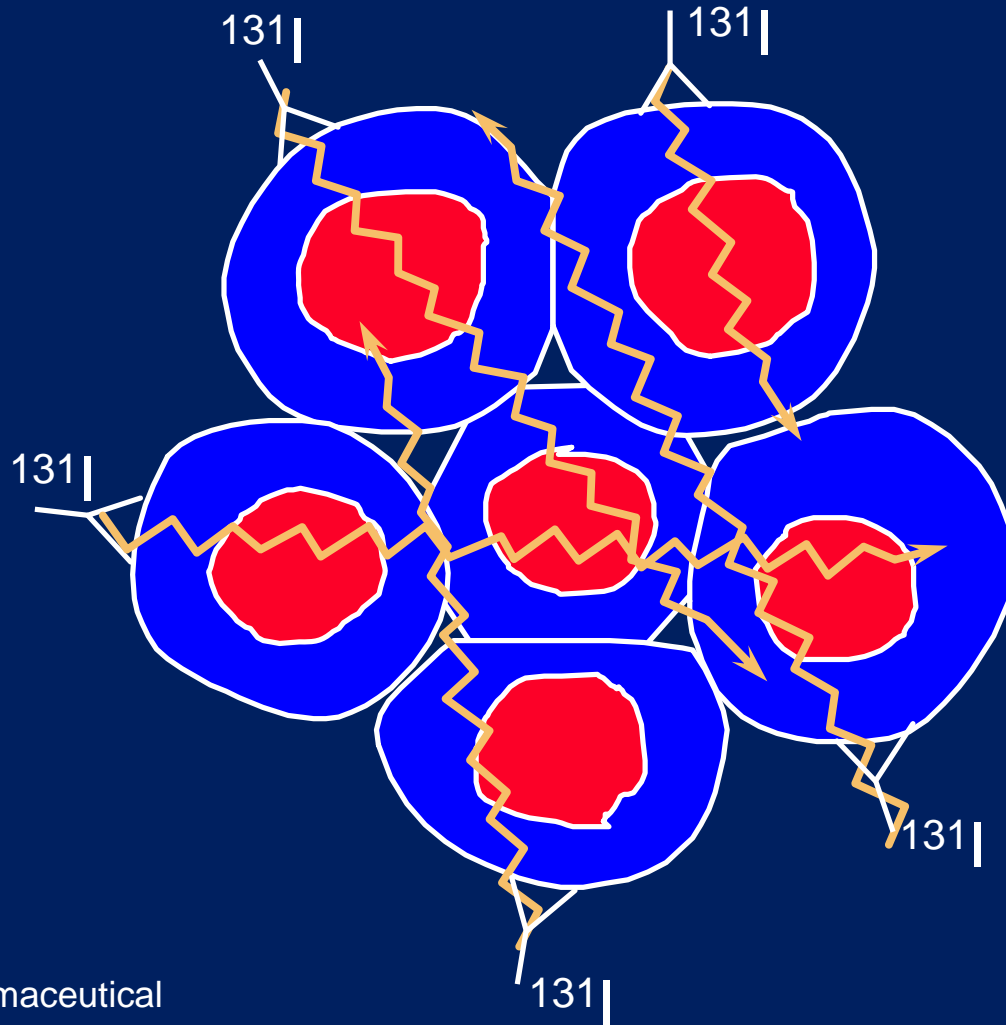
Radioimmunotherapy

- Monoclonal antibodies with radioactive elements (isotopes) attached
- Delivers radiation therapy targeted to tumor cells
 - Bexxar[®] - tositumomab and iodine ¹³¹I tositumomab
 - Zevalin[®] - Rituxan[®] and ⁹⁰Y ibritumomab tiuxetan

Radioimmunotherapy of B-cell non-Hodgkin Lymphomas: Scientific Rationale

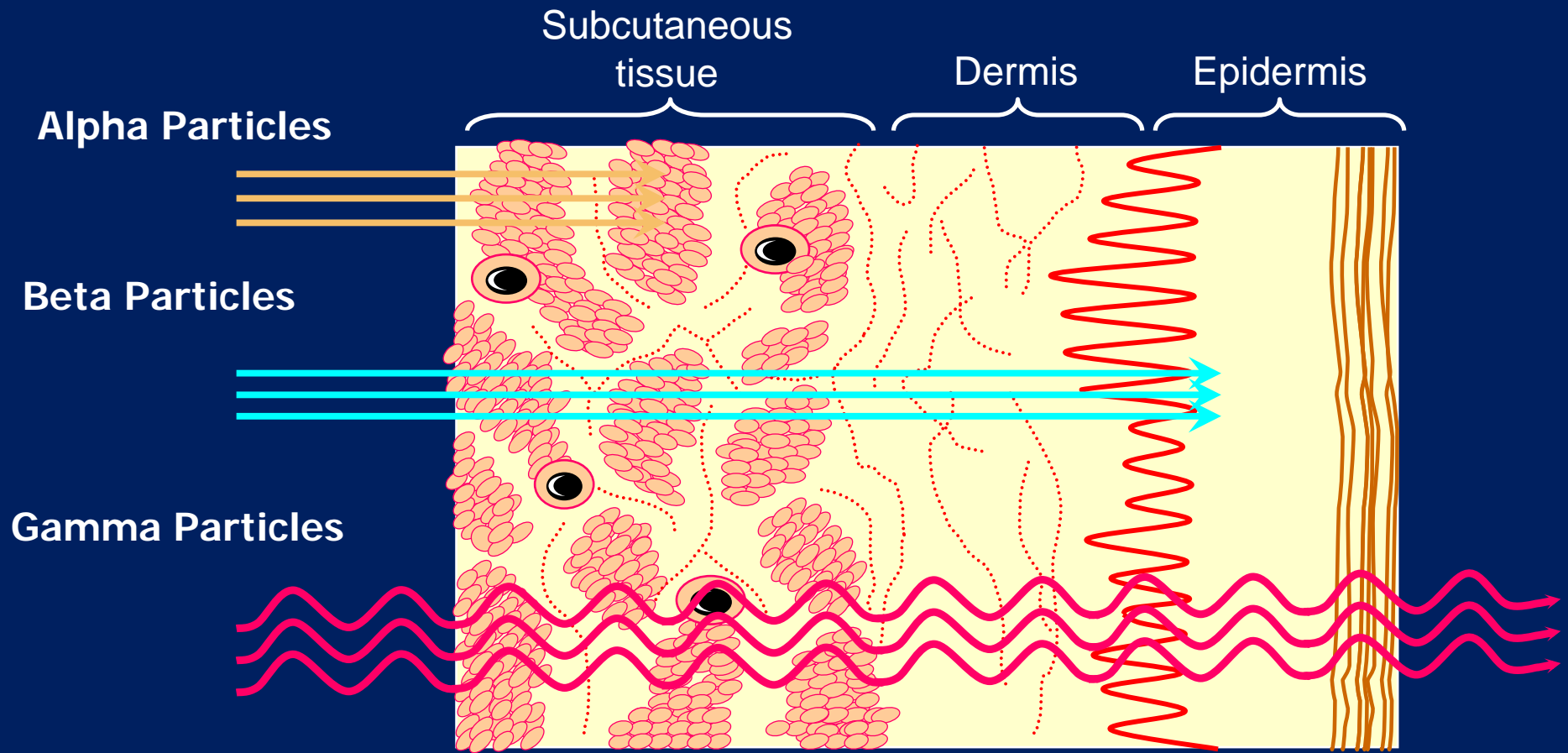
1. LYMPHOMA CELLS ARE HIGHLY SENSITIVE TO RADIATION.
2. MONOCLONAL ANTIBODIES ARE AVAILABLE THAT BIND SPECIFICALLY TO ANTIGENS PRESENT EXCLUSIVELY ON LYMPHOMA CELLS (AND NORMAL LYMPHOCYTES).
3. RADIONUCLIDE-LABELED MONOCLONAL ANTIBODIES CAN TARGET RADIATION TO LYMPHOMA CELLS, LIMITING RADIATION TO OTHER CELLS.

Radioimmunotherapy



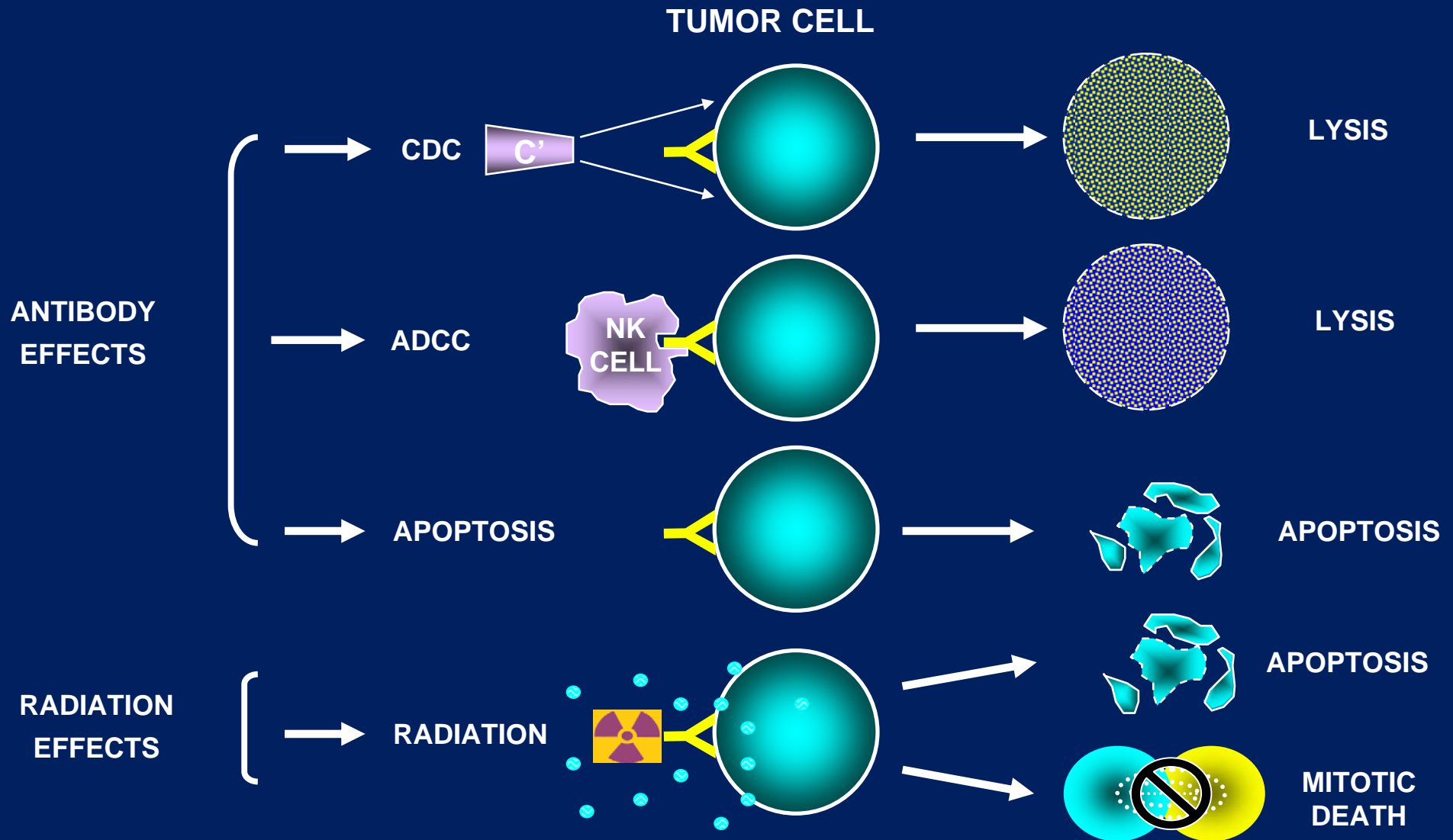
Courtesy of Coulter Pharmaceutical

Penetration of Particulate and Electromagnetic Radiation

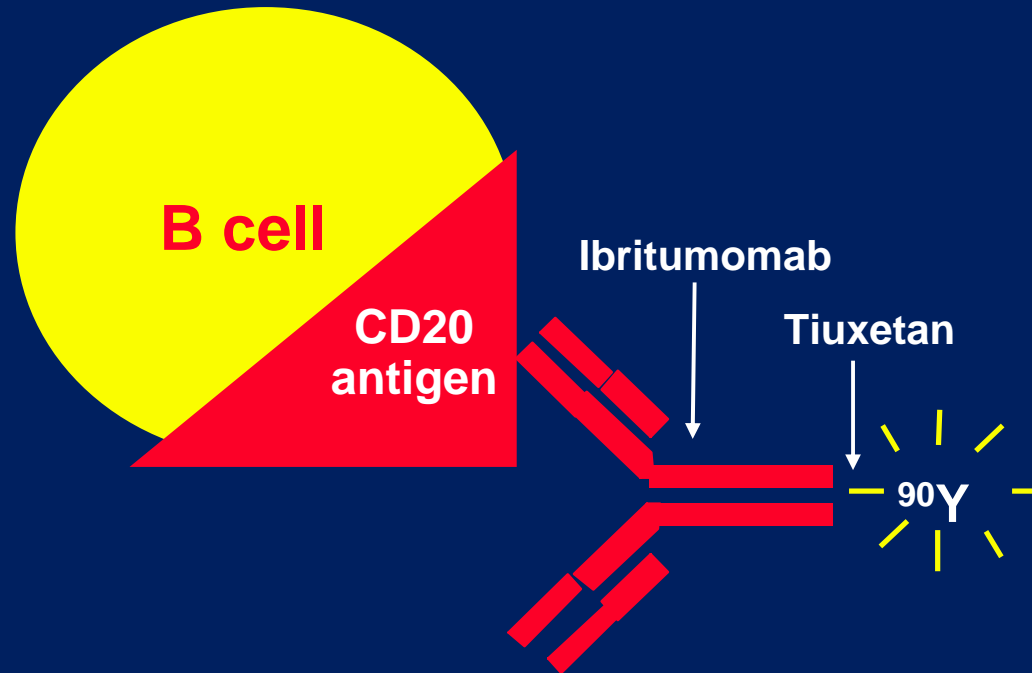


Adapted from Wootton. *Radiation Protection of Patients*. 1993.

Radioimmunotherapy: Mechanisms of Action



^{90}Y Ibritumomab: Zevalin[®]



Approved in the US, February 2002

ZEVALIN®: RESPONSE RATES, DURABLE REMISSIONS

Study (n)	Overall responses		CR, CRu		Ongoing CR, CRu
	%	Median DR (mo)	%	Median DR (mo)	Range of ongoing response (mo)
Phase 1-2 (51)	73	11.7	29*	23*	60+ to 74+
Phase 2 (30)	83	11.5	47	23	41+ to 55+
Phase 3 (73)	80	13.9	34	23	43+ to 60+

*Patients with CR only.

^{131}I Tositumomab: Bexxar[®]

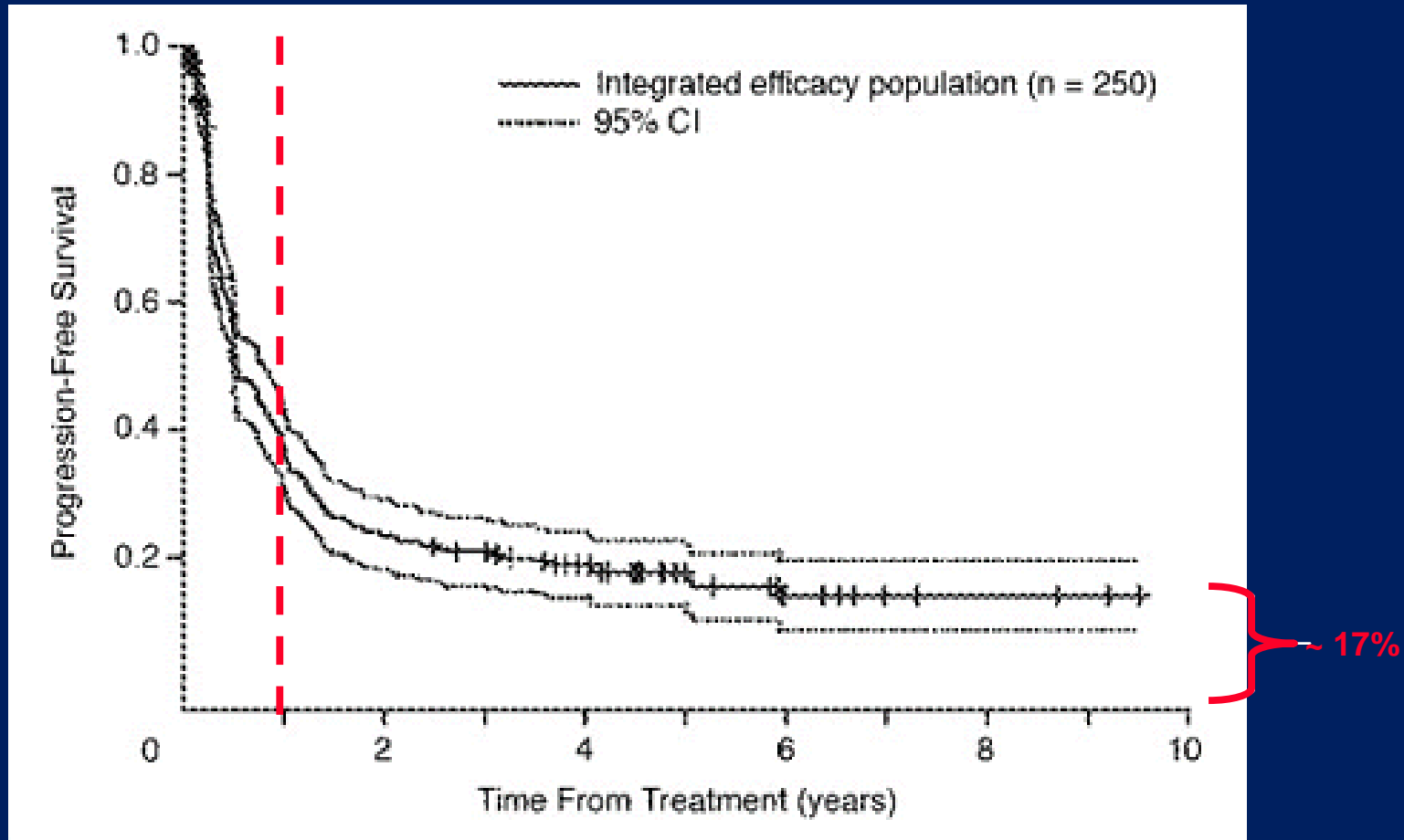


Bexxar[®]: Integrated Efficacy Data (n = 250)

Efficacy Data: Integrated Efficacy Population (N = 250)		
	No.	%
Response	141	56
Duration of response, months		
Median*	12.9	
Range	10.6-17.3	
Complete response	75	30
Duration of complete response, months		
Median*	58.4	
Range	28.3-NR	

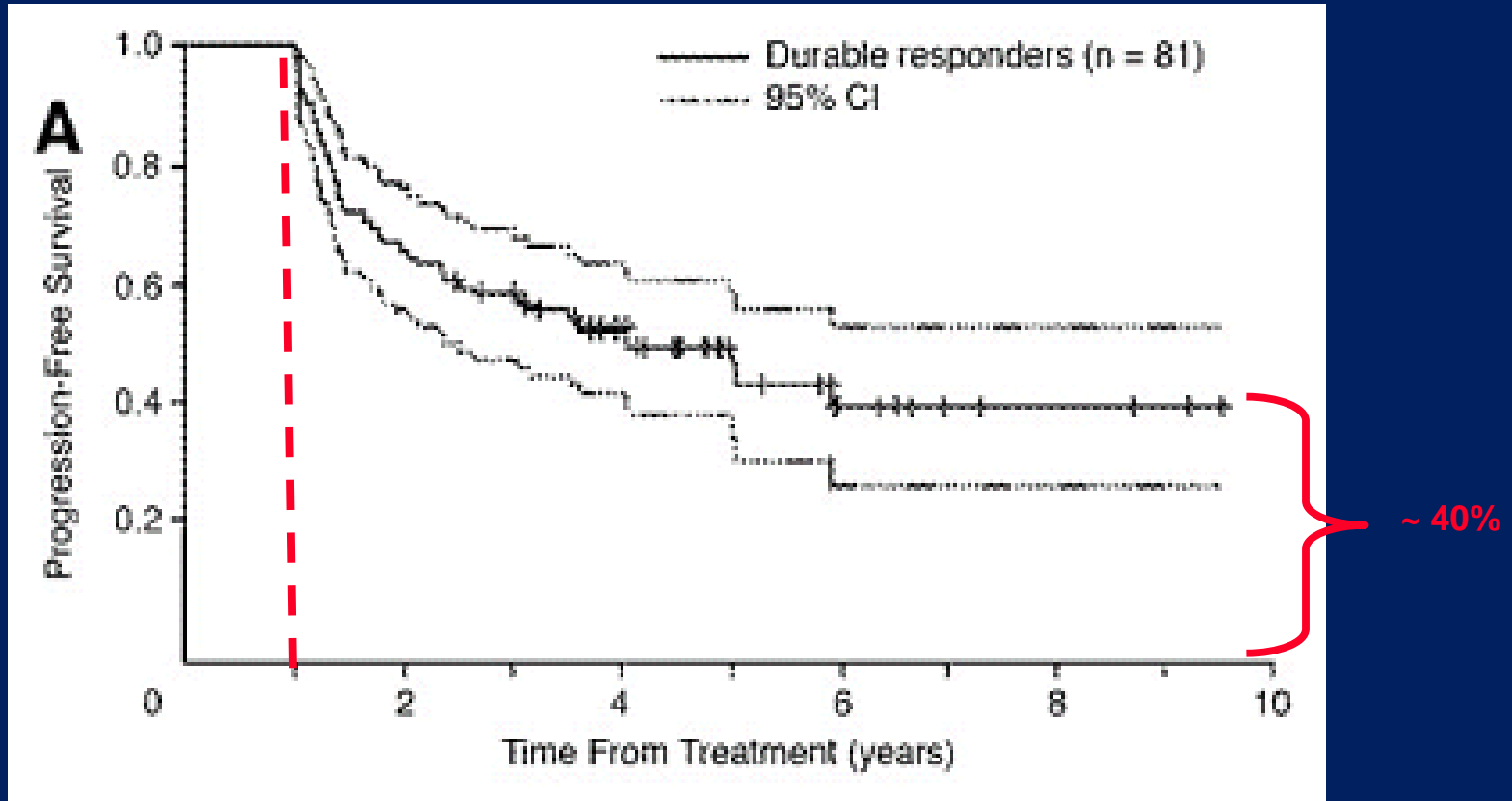
Abbreviation: NR, not reached.
*95% CI.

Bexxar[®]: Integrated Progression-Free Survival



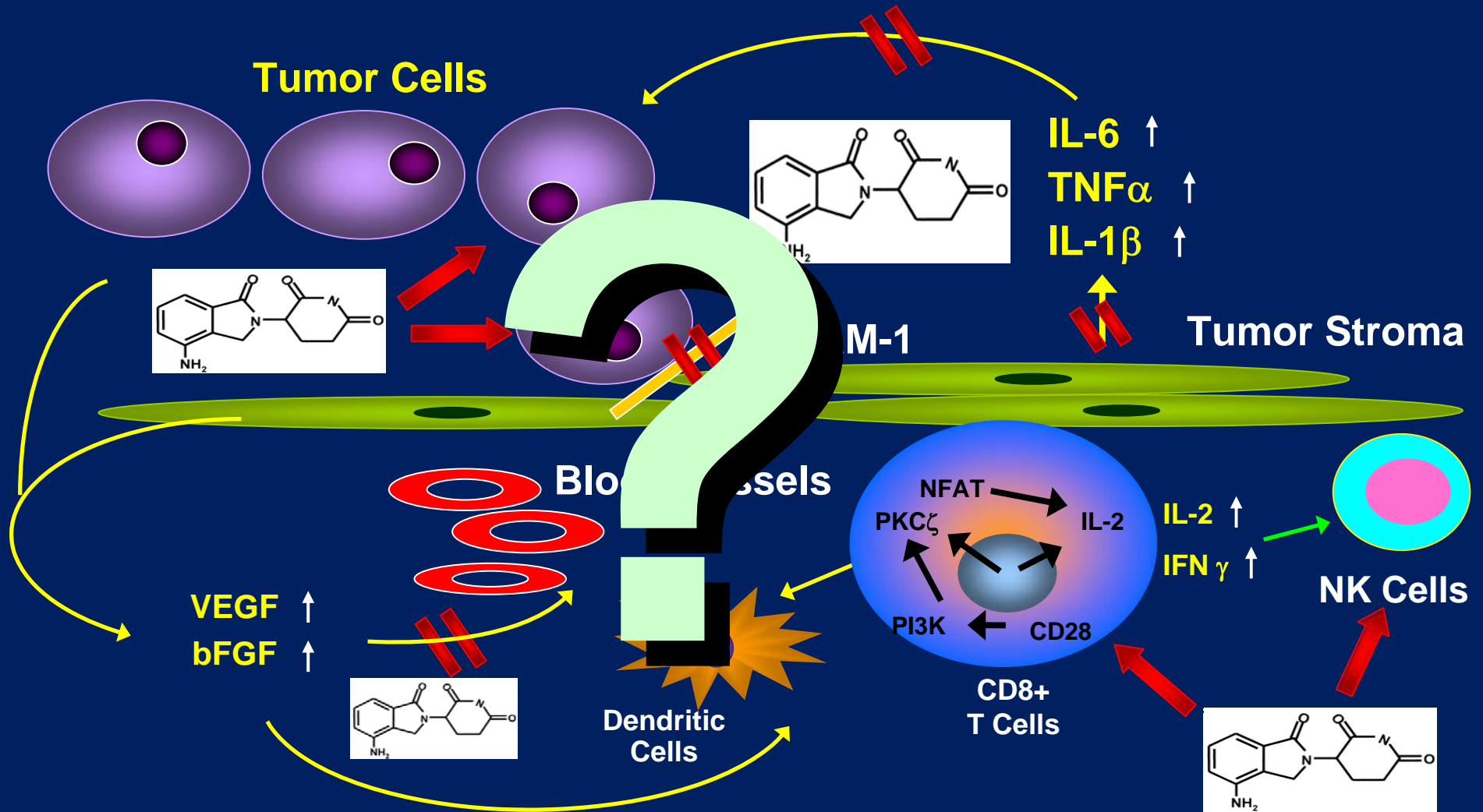
PFS at 5 years = 17%

Bexxar[®]: PFS for Durable Responders



44% remain in PFS from ≥ 2.7 to ≥ 10.2 years

Lenalidomide: It Works, but HOW??



Phase II Trial: Lenalidomide in Recurrent Follicular Lymphoma

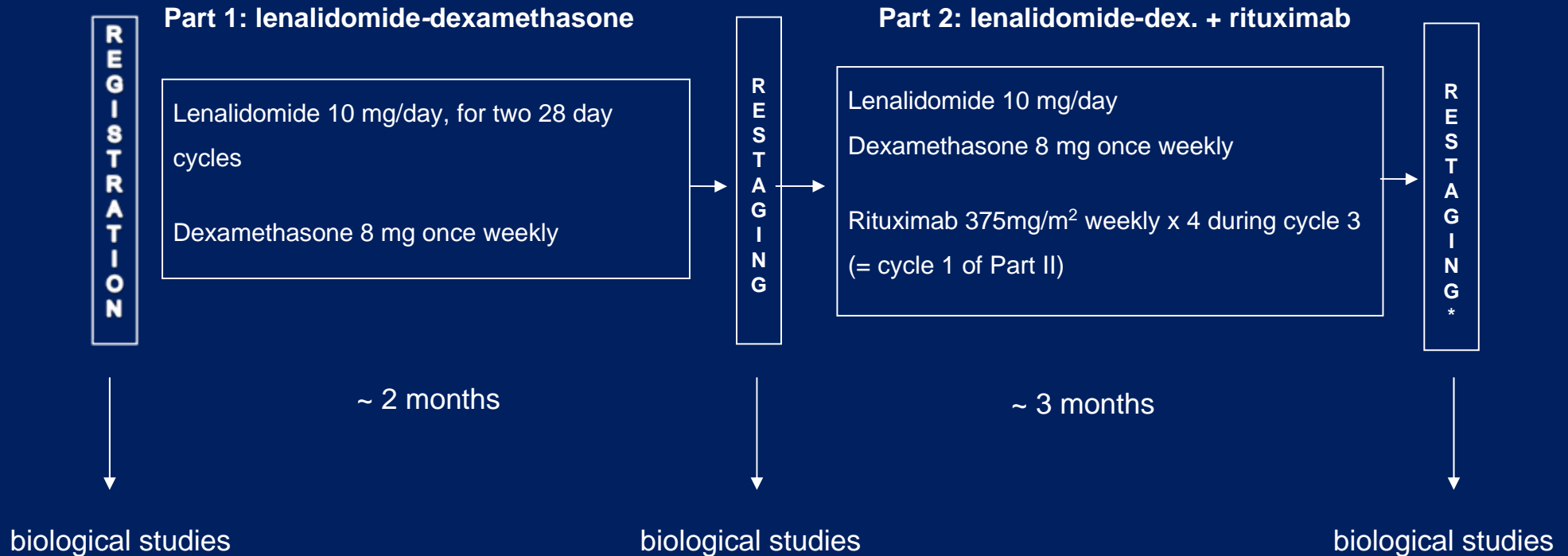
- 27 evaluable patients, 12 with follicular lymphoma
- Lenalidomide 25 mg/d, days 1-21 of 28-day cycle up to 1 year or progressive disease

	n	ORR, %	CR, n	PR, n
Follicular Lymphoma	12	25%	2	1

Phase II Trial of Lenalidomide - Dexamethasone +
Rituximab in Recurrent Small B-Cell Lymphomas
Resistant to Rituximab (UPCC 02408)

Lymphoma Program
Abramson Cancer Center
University of Pennsylvania

Protocol design (UPCC 02408)



* Three months after first dose of rituximab

Response Assessment (UPCC 02408): Follicular Subset (Part 1: n=10; Part 2: n=9)

After Part 1, 10 patients evaluable:

- Overall response to lenalidomide-dexamethasone:
2/10 (20%; both CR)

After Part 2, 9 patients evaluable:

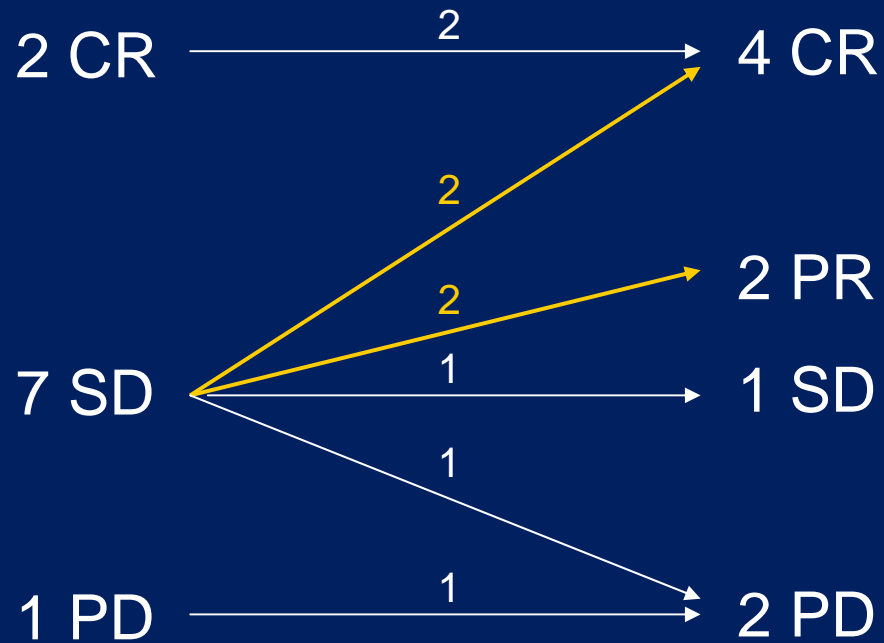
- Overall response to lenalidomide-dexamethasone + rituximab:
6/9 (66%; 4 CR; 2 PR)

*Follow-up: 5 – 14 months (CR/PR/SD)

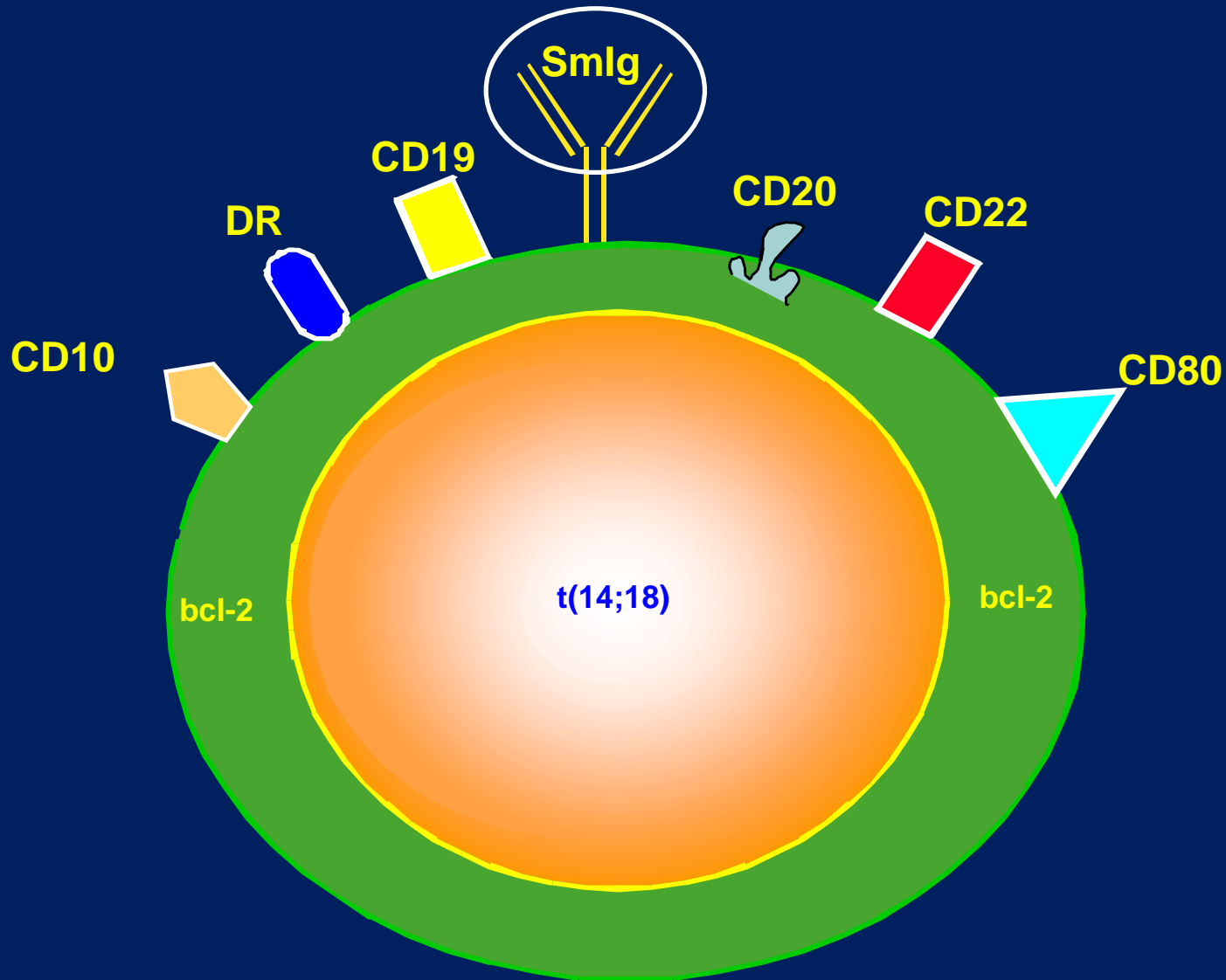
Response Assessment (UPCC 02408)

PART 1 response
n=10

PART 2 response
n=9

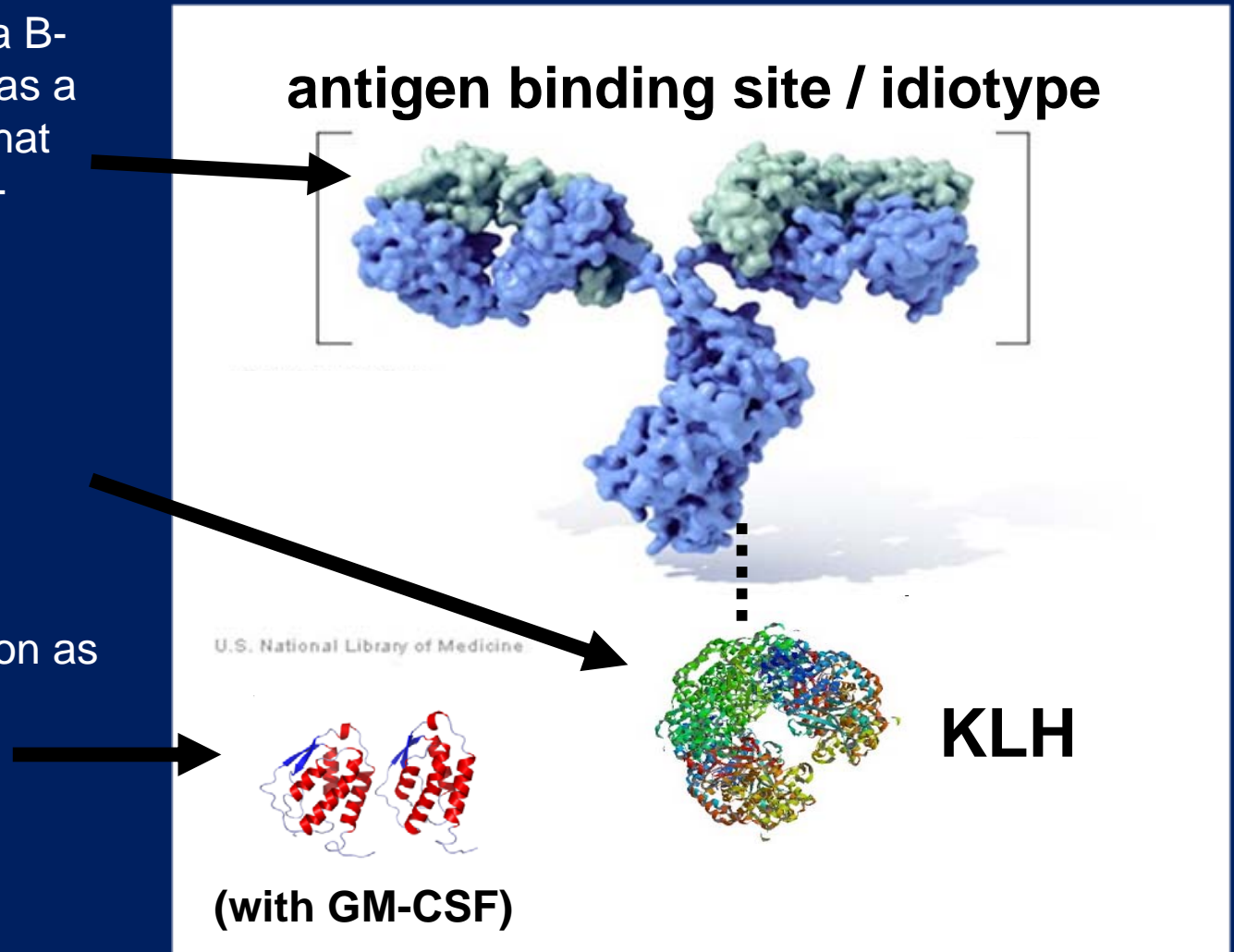


Follicular Lymphoma Cell

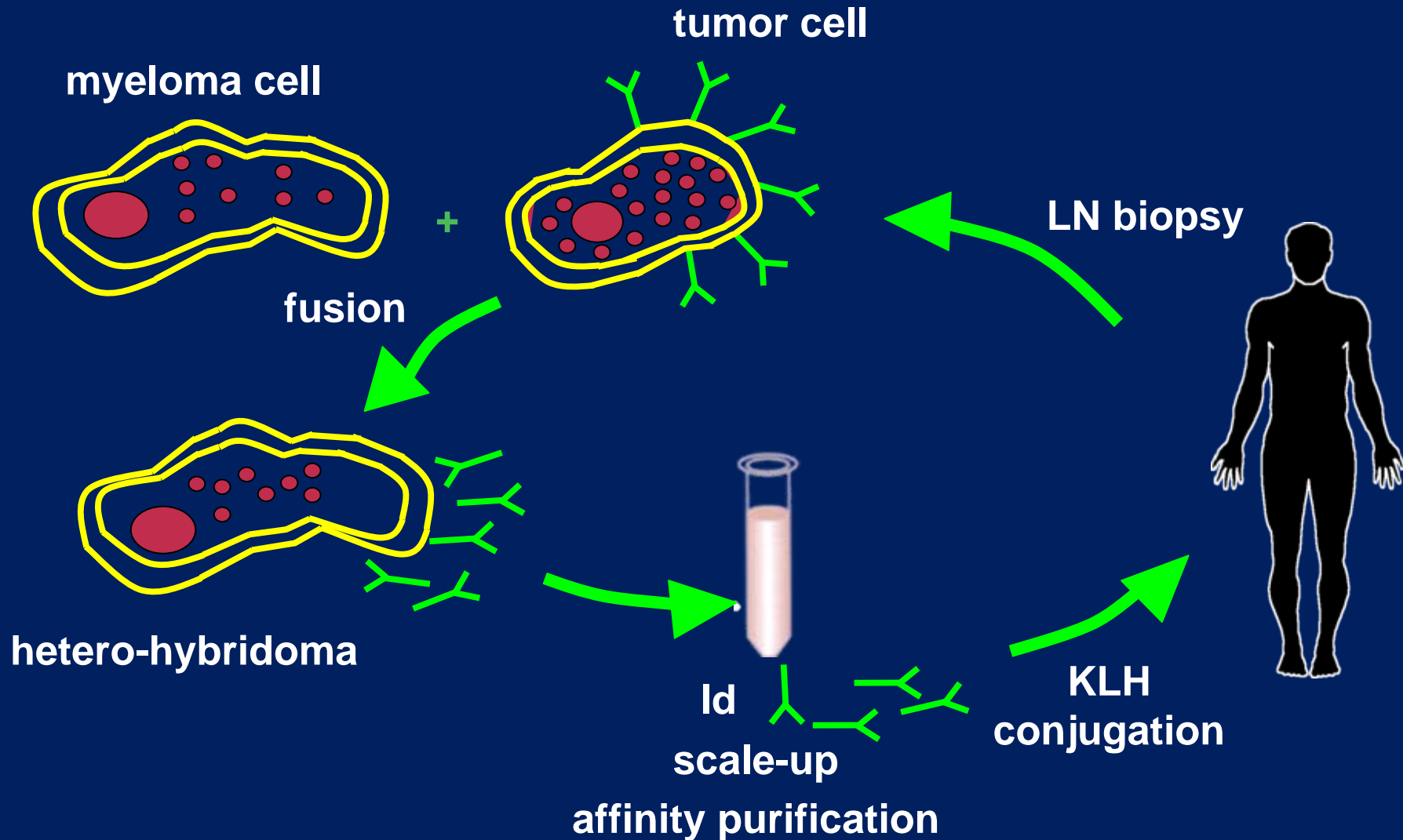


Id+KLH Protein Vaccines

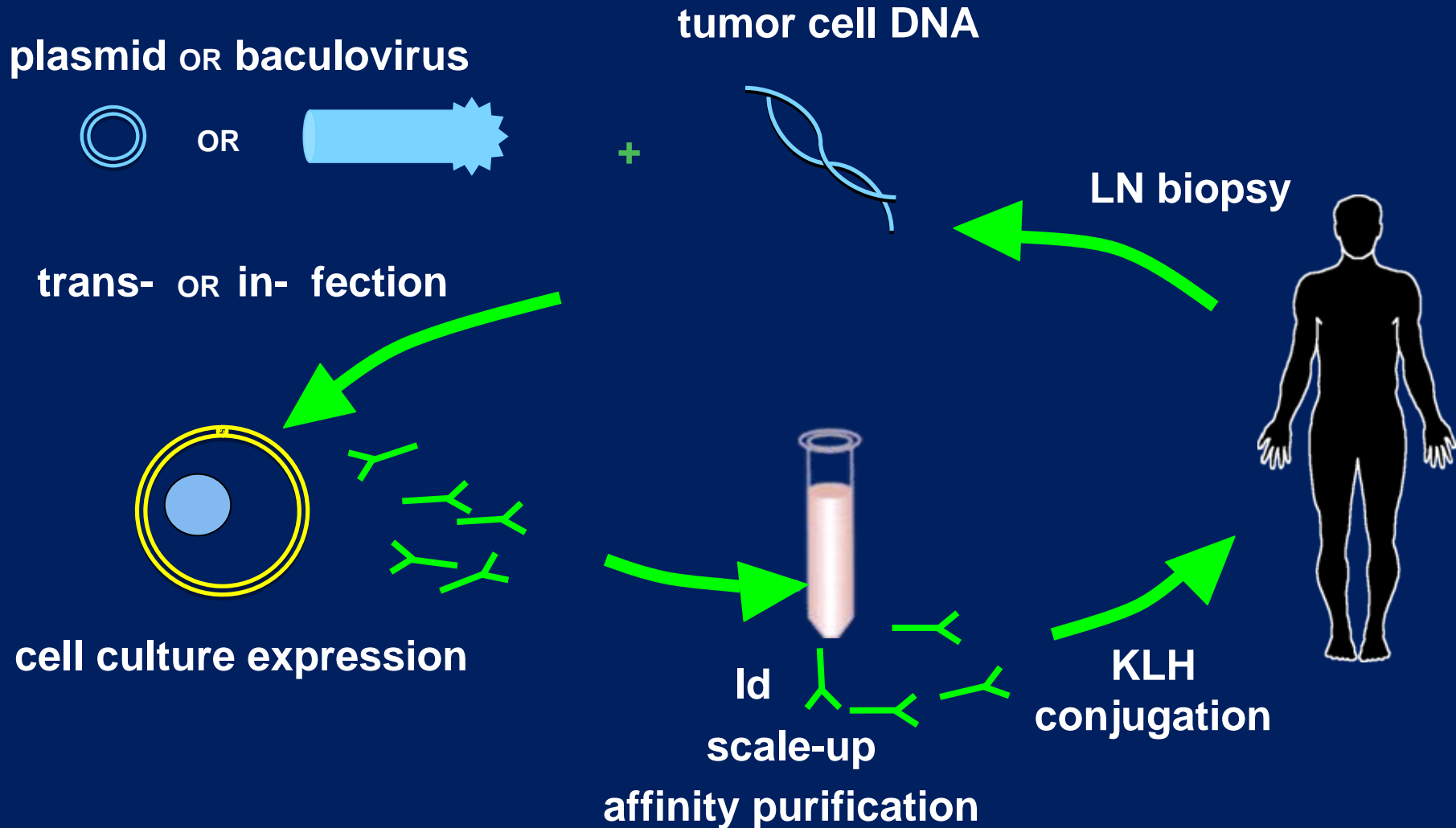
- The idiotype of the Smlg of a B-cell lymphoma can be used as a tumor-specific immunogen that induces immunity against Id-bearing tumor cells
- Keyhole limpet hemocyanin (KLH) carrier serves as an immune stimulant
- GM-CSF administered concurrently at site of injection as an adjuvant



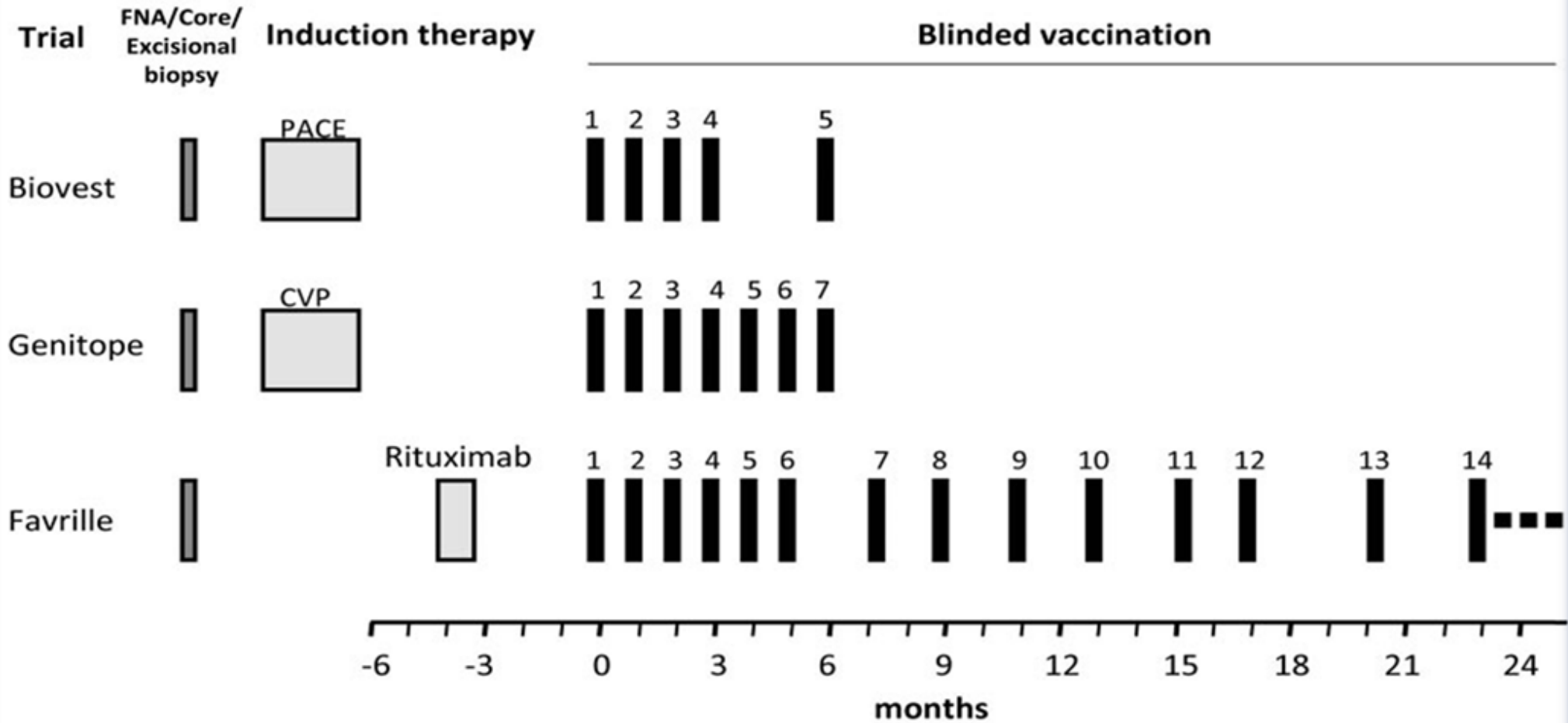
Id Vaccine Production by Hybridoma



Id Vaccine Production by Recombinant DNA



Phase III Randomized Trials of Id Vaccination in Follicular Lymphoma



Phase III Randomized Trials of Id Vaccination in Follicular Lymphoma

Study	Id protein production	N	Eligible	Induction Rx	Pts. randomized	Endpoint	Results
Biovest ¹	hetero-hybridoma	117	untreated	PACE	CR, CRu	DFS	44.2 vs. 30.6 mo. (p = 0.045)
Genitope ²	baculovirus, insect cell	278	untreated	CVP	CR, CRu, PR	PFS	NS
Favrille ³	plasmid, mammalian cell	315	untreated relapsed refractory	rituximab	CR, CRu, PR, SD	TTP	NS

¹ Schuster SJ, Neelapu SS, Gause BL, *et al.* J Clin Oncol. 2009; 27:18s (abstract 2).

² Levy R, Robertson M, Leonard J, *et al.* Ann Oncol. 2008;19:Suppl.4:iv101-102.

³ Freedman AS, Neelapu S, Nichols CR, *et al.* Blood. 2008;112:94 (abstract 236).



Patient Education and Support Services

- The Leukemia & Lymphoma Society
 - www.LLS.org
 - Information Resource Center: 1-800-955-4572
- Lymphoma Research Foundation
 - www.lymphoma.org
 - helpline@lymphoma.org
 - 1-800-500-9976
- National Cancer Institute
 - www.cancer.gov
 - Cancer Information Service: 1-800-422-6237

Questions