



Memorial Sloan Kettering  
Cancer Center

# Lymphoma biology and therapy

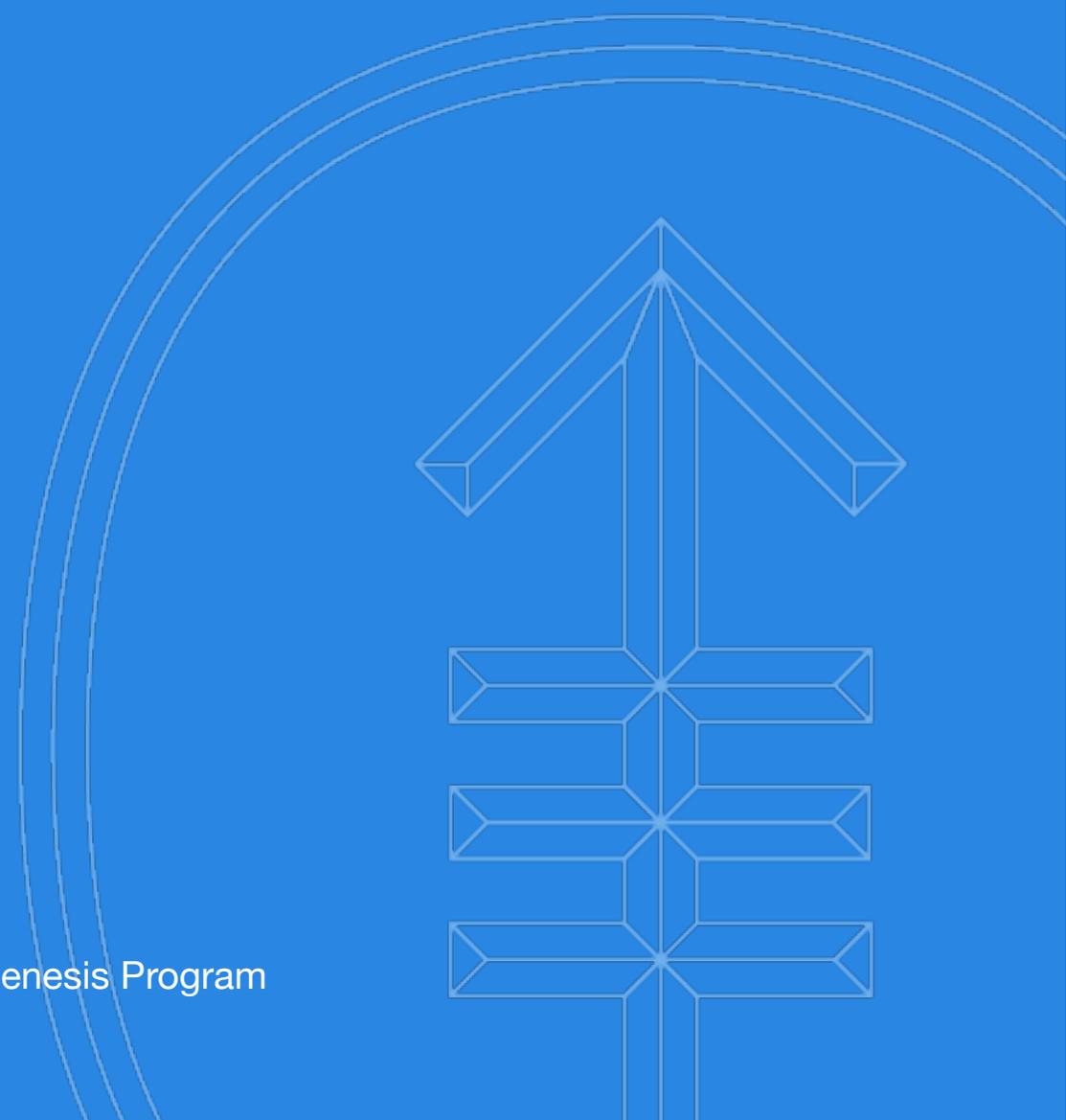
GSK Lecture

March 30, 2026

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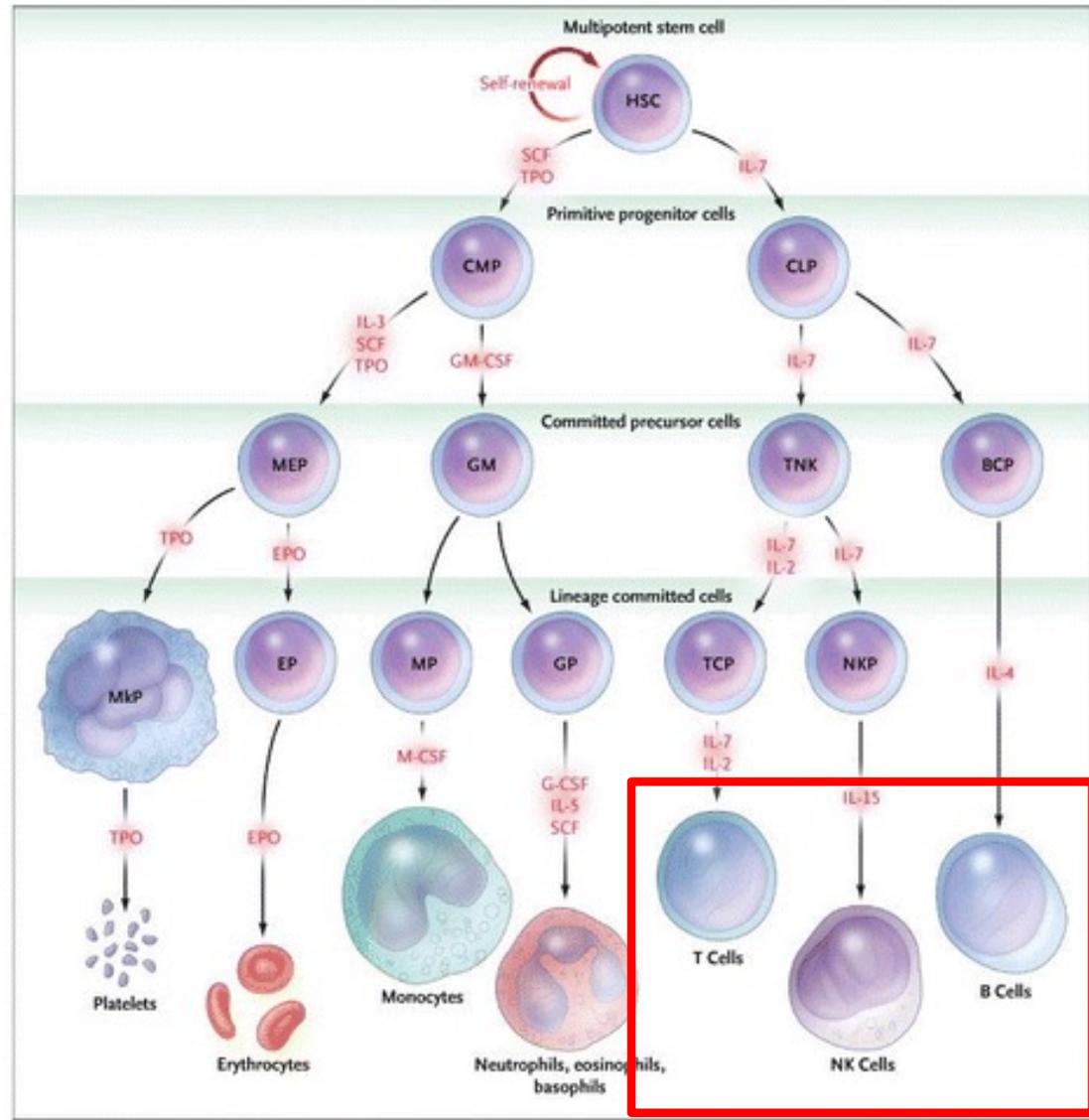


# Overview

- Normal B cell biology and lymphoma pathogenesis
- Clinical features and standard therapies
  - Hodgkin lymphoma (existing therapies are highly effective but too toxic)
  - Diffuse large B cell lymphoma (existing therapies are not effective enough for many patients)
- Progress toward precision medicine for lymphoma

# Definition

Lymphomas are cancers arising from mature lymphocytes (B, T, or NK cells)



# There are >70 different types of lymphoma (and the # keeps increasing)

## Classification

**Table 1**

### **WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2008)**

#### Mature B-Cell Neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- *Splenic lymphoma/leukemia, unclassifiable\**
  - ▶ *Splenic diffuse red pulp small B-cell lymphoma\**
  - ▶ *Hairy cell leukemia-variant\**
- Lymphoplasmacytic lymphoma
  - ▶ Waldenström's macroglobulinemia
- Heavy chain diseases
  - ▶ Alpha heavy chain disease
  - ▶ Gamma heavy chain disease
  - ▶ Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extracranial plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT type)
- Nodal marginal zone lymphoma
  - ▶ *Pediatric nodal marginal zone lymphoma\**
- Follicular lymphoma
  - ▶ *Pediatric follicular lymphoma\**
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - ▶ T-cell/histiocyte-rich large B-cell lymphoma
  - ▶ Primary DLBCL of the CNS
  - ▶ Primary cutaneous DLBCL, leg type
  - ▶ *EBV positive DLBCL of the elderly\**
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

This list of 38 is just B cell non-Hodgkin...

[Continued on next page](#)

# There are >70 different types of lymphoma (and the # keeps increasing)

## Classification

### *Table 1 continued*

#### Mature T-Cell and NK-Cell Neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
  - ▶ *Chronic lymphoproliferative disorder of NK-cells\**
- Aggressive NK cell leukemia
- Systemic EBV-positive T-cell lymphoproliferative disorder of childhood
- Hydroa vacciniforme-like lymphoma
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
  - ▶ Lymphomatoid papulosis
  - ▶ Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma\**
- *Primary cutaneous CD4-positive small/medium T-cell lymphoma\**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large-cell lymphoma, ALK positive
- *Anaplastic large-cell lymphoma, ALK negative\**

#### Hodgkin Lymphoma

- Nodular lymphocyte-predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - ▶ Nodular sclerosis classical Hodgkin lymphoma
  - ▶ Lymphocyte-rich classical Hodgkin lymphoma
  - ▶ Mixed cellularity classical Hodgkin lymphoma
  - ▶ Lymphocyte-depleted classical Hodgkin lymphoma

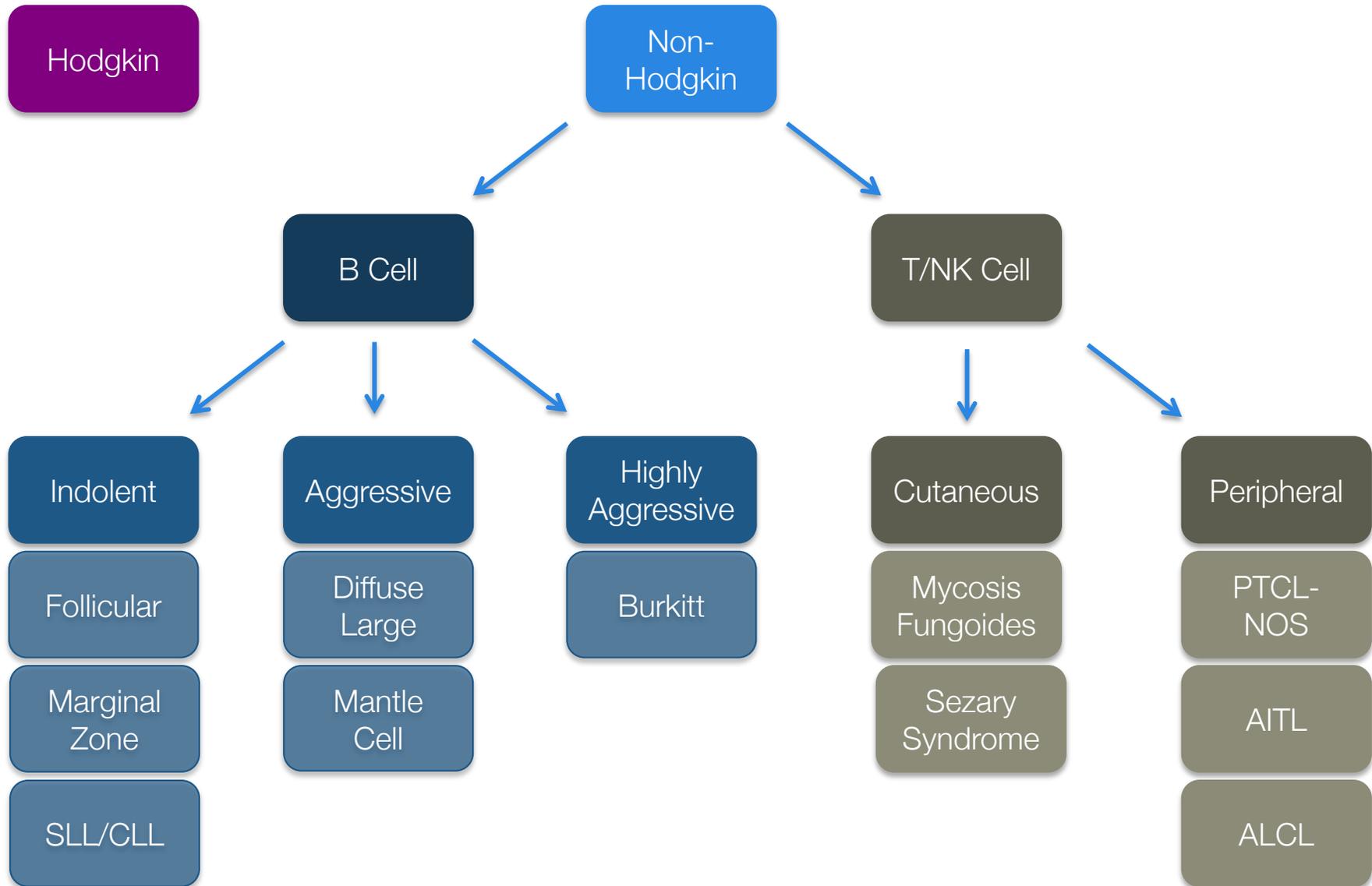
#### Post-Transplant Lymphoproliferative Disorders (PTLD)

- Early lesions
  - ▶ Plasmacytic hyperplasia
  - ▶ Infectious mononucleosis-like PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)#
- Classical Hodgkin lymphoma type PTLD#

From Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds): World Health Organization Classification of Tumours of the Haematopoietic and Lymphoid Tissues. IARC Press: Lyon 2008.

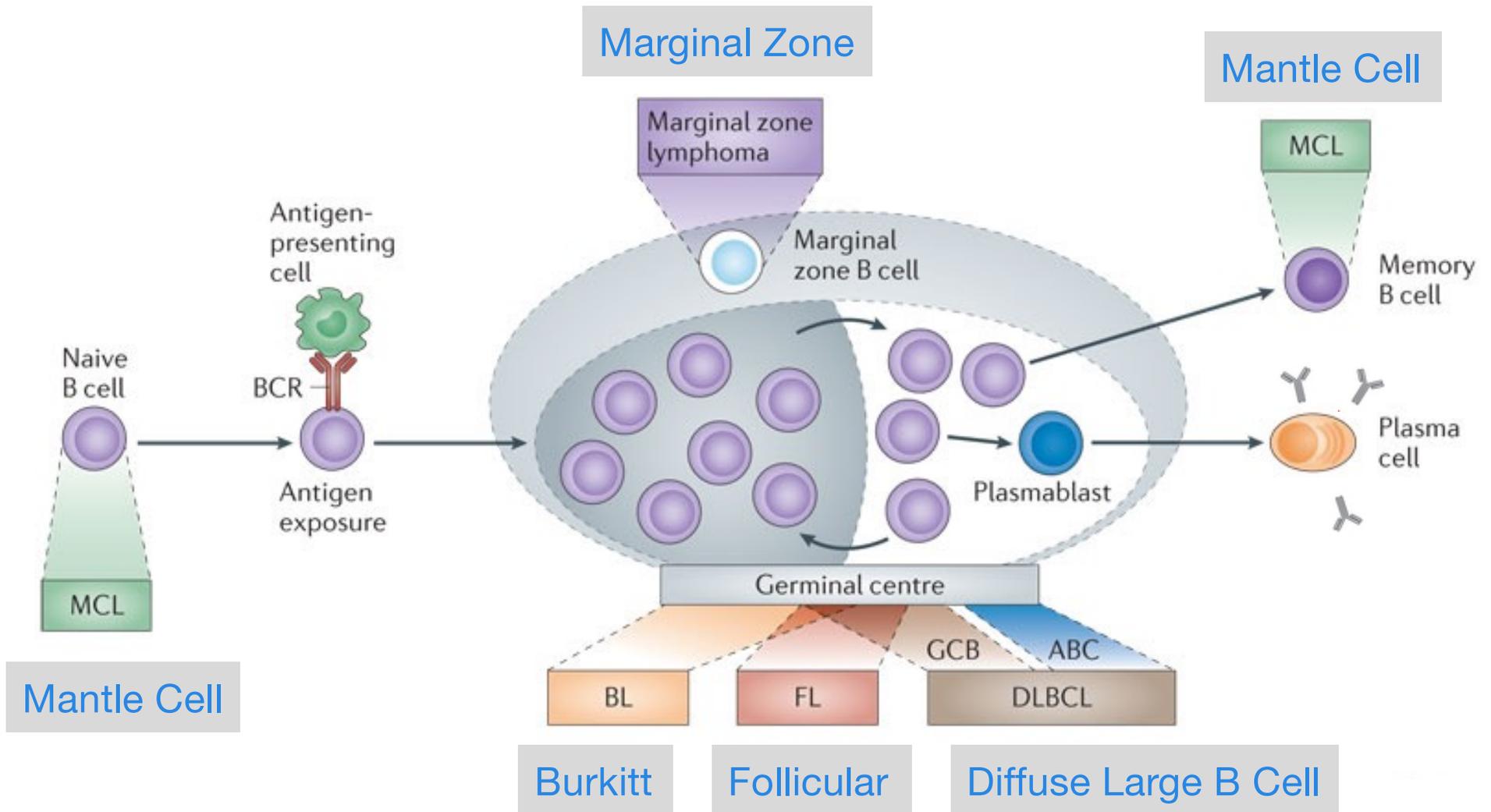
5 types of Hodgkin lymphoma,  
22 types of T/NK cell lymphoma,  
5 types of post-transplant lymphoma

# Simplified lymphoma classification

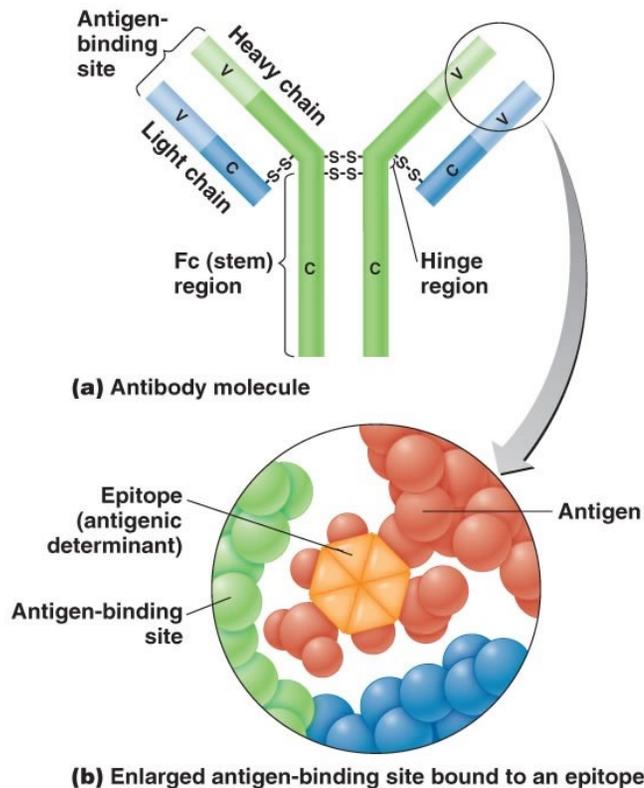


# Why are there so many types of lymphoma?

Each arises from a distinct stage of lymphocyte development/differentiation



# Pathogenesis: B cells live dangerously



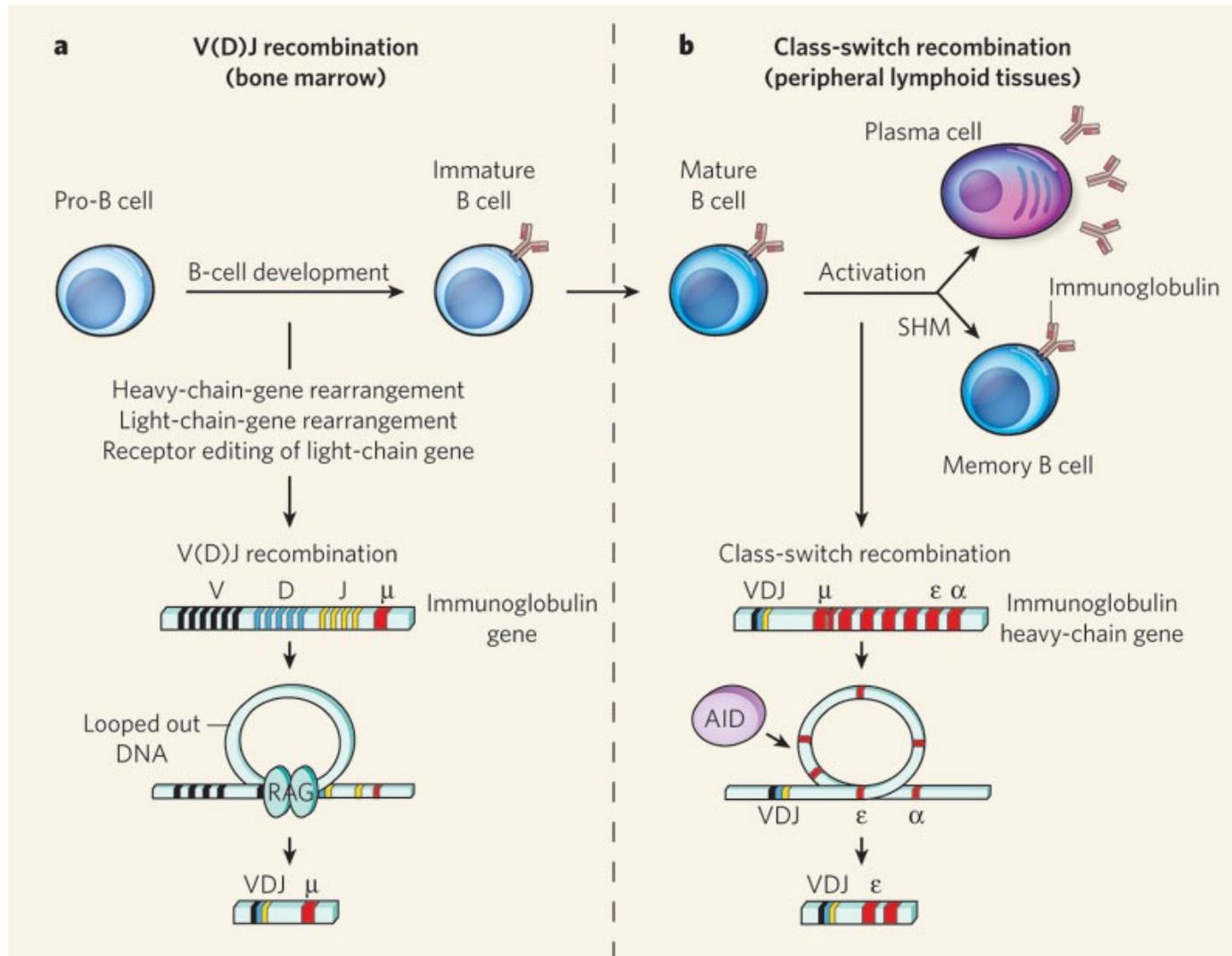
Copyright © 2010 Pearson Education, Inc.

B cells intentionally break/repair and mutate their DNA

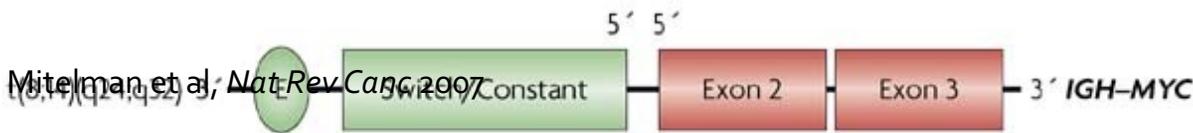
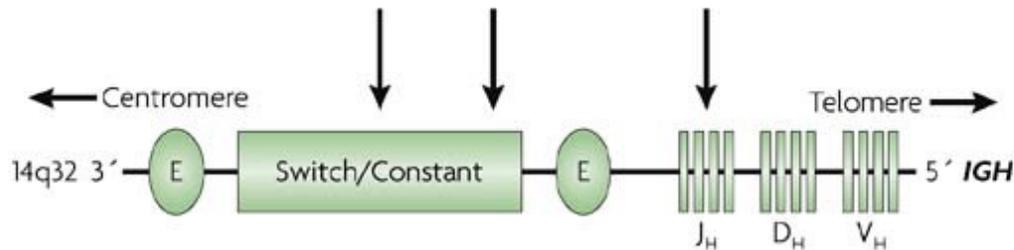
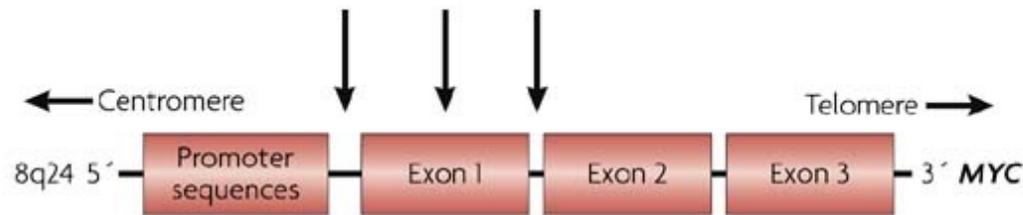
- **VDJ recombination** -> generates a functional B cell receptor which becomes an antibody when secreted
- **Isotype class switching** -> IgM antibodies change to IgG, IgA, or IgE isotypes with specialized effector functions
- **Somatic hypermutation** -> random point mutations in DNA encoding the antigen recognition motif of the BCR/antibody; function to increase antibody affinity

These processes are critical for generating an antibody repertoire that effectively defends against the diverse universe of pathogens

# Pathogenesis: B cells live dangerously



# Pathogenesis: Mistakes in DNA repair lead to oncogenic translocations



Chromosomal karyotype



**8 t(8;14) 14**

Promoters/enhancers that normally drive high-level antibody expression are accidentally juxtaposed upstream of oncogenes like c-Myc

# Pathogenesis: Characteristic translocations in B cell lymphomas

	Translocation	Gene	Oncogenic Effect
Burkitt	t(8;14)	c-Myc	Anabolic metabolism
Mantle	t(11;14)	Cyclin D1	Cell cycle progression
Follicular	t(14;18)	Bcl2	Blocks apoptosis

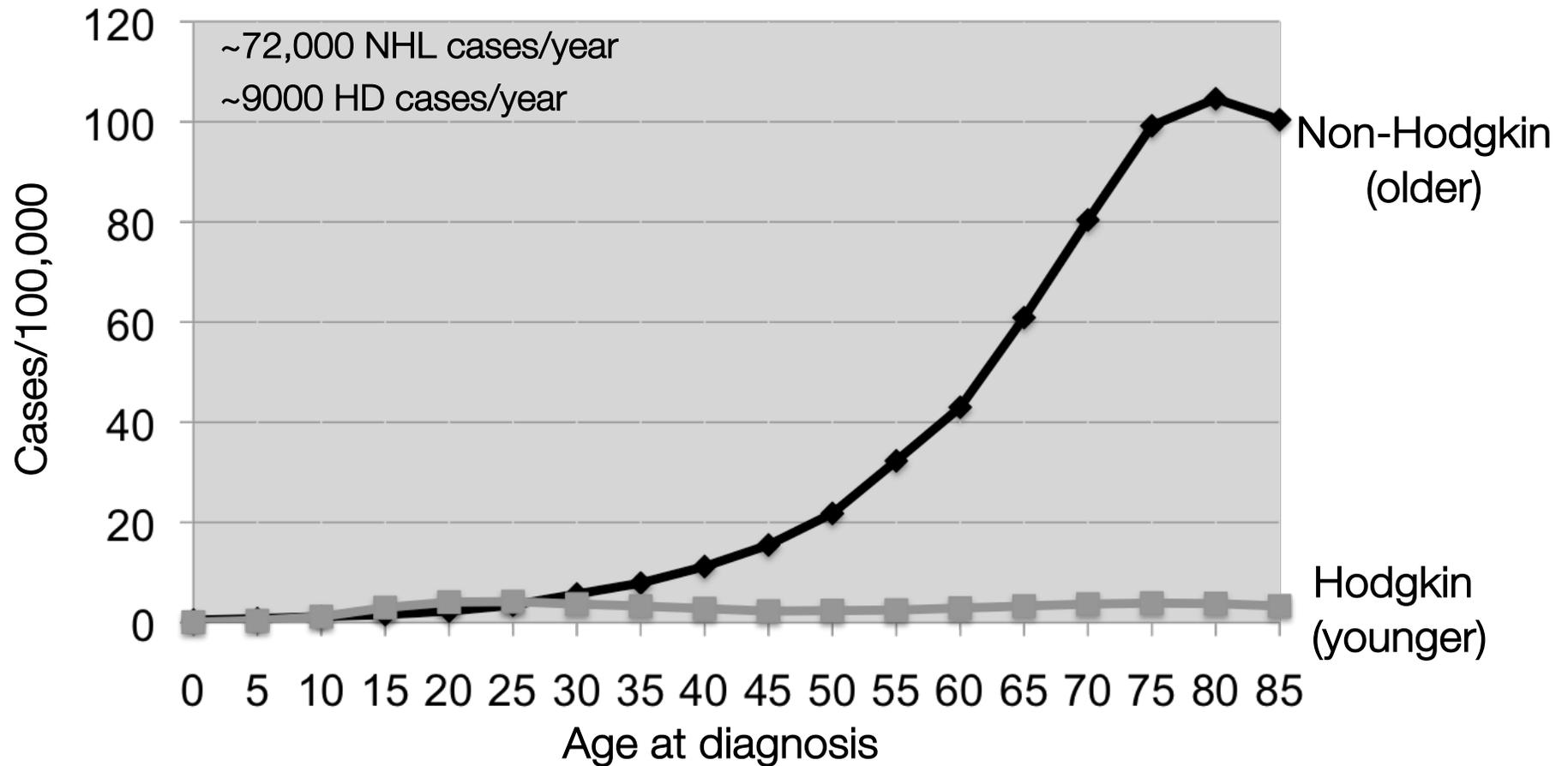
Chromosome 14 = immunoglobulin heavy chain

Additional oncogenic gene mutations accumulate, more on that later...

# Epidemiology: Incidence and mortality

Type of cancer	Cases in 2015	Deaths in 2015
Breast	232,000	40,000
Prostate	221,000	28,000
Lung	221,000	158,000
Colorectal	133,000	50,000
Lymphoma	81,000	21,000
• Hodgkin	• 9,000	• 1,000
• Non-Hodgkin	• 72,000	• 20,000
Melanoma	74,000	10,000
Bladder	74,000	16,000
Thyroid	62,000	2,000
Kidney	62,000	14,000
Uterus	55,000	10,000
Leukemia	54,000	24,000
Pancreas	49,000	41,000

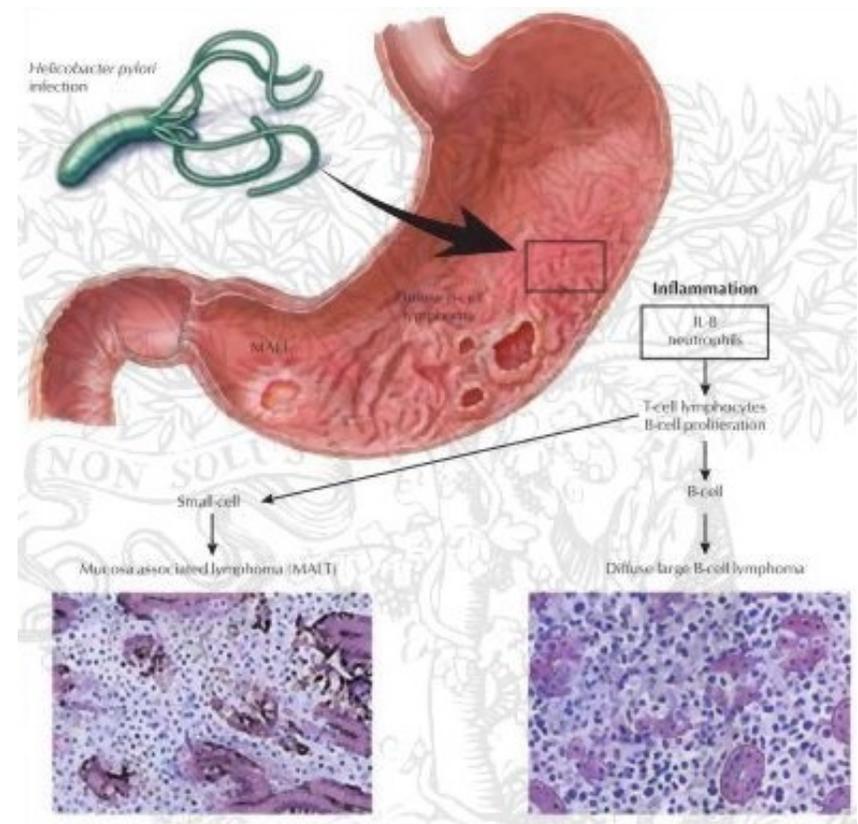
# Epidemiology: Relation to age



# Epidemiology: Potential risk factors

- Occupational/Environmental
  - Pesticides/herbicides
  - Hair dyes (pre-1980)
- Immunosuppression
  - HIV/AIDS
  - Transplant-related
  - Prior chemotherapy/radiotherapy
- Viral/Bacterial
  - EBV, HTLV-1, HHV8, Hepatitis C
  - Helicobacter pylori
- Autoimmune disease
- Familial

## H. Pylori infection of stomach



Gastric mucosal-associated lymphoid tissue (MALT) lymphoma (type of marginal zone)

Diffuse large B cell lymphoma (DLBCL)

# Clinical presentation

Most common presenting symptoms

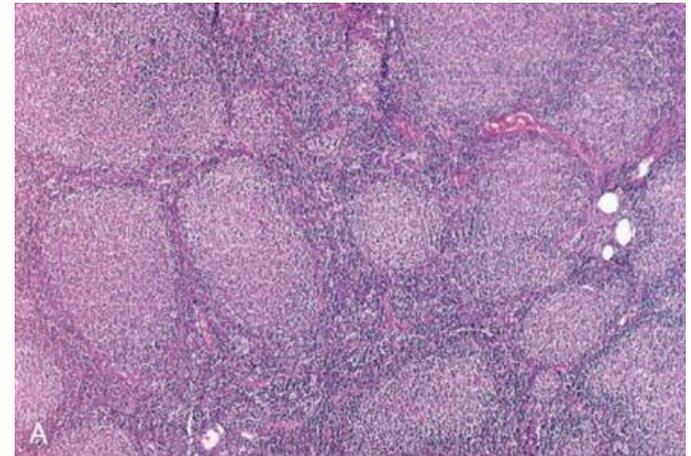
- Painless lymphadenopathy
- Presence of B symptoms
  - Fevers
  - Night sweats
  - Weight loss
- Splenomegaly (enlarged spleen)
- Hepatomegaly (enlarged liver)
- Compressive symptoms
  - Unexplained pain
  - Cough
  - Lower extremity swelling



# Diagnosis: Adequate biopsy is key

- Biopsy
  - Adequate tissue imperative
  - Excisional biopsy (optimal)
  - Multiple core biopsy may be acceptable
  - Fine needle aspiration is unacceptable

Example: Follicular lymphoma; lymph node architecture must be intact to make diagnosis

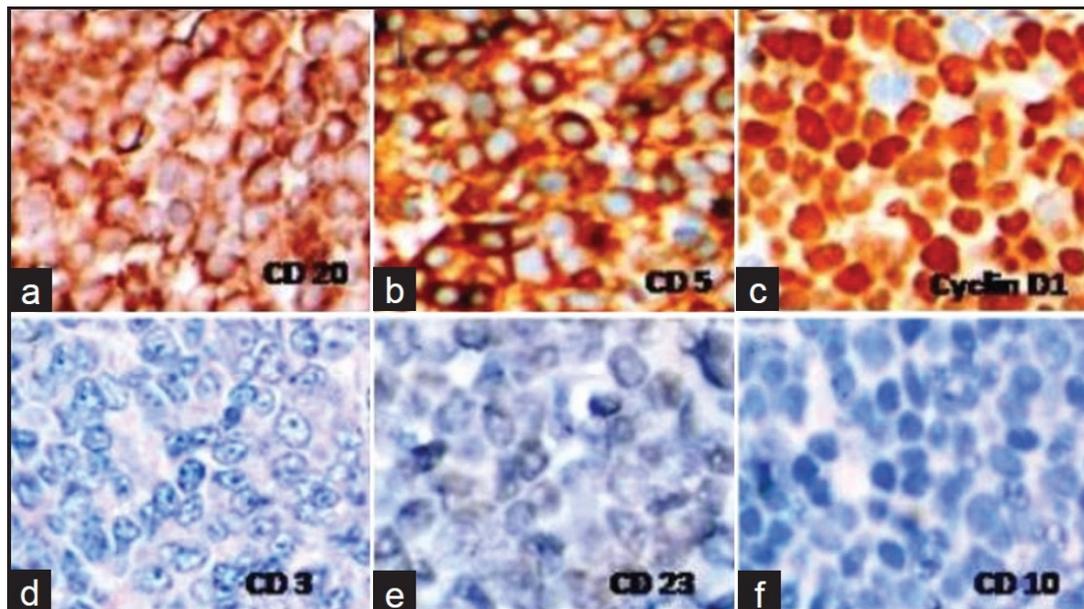
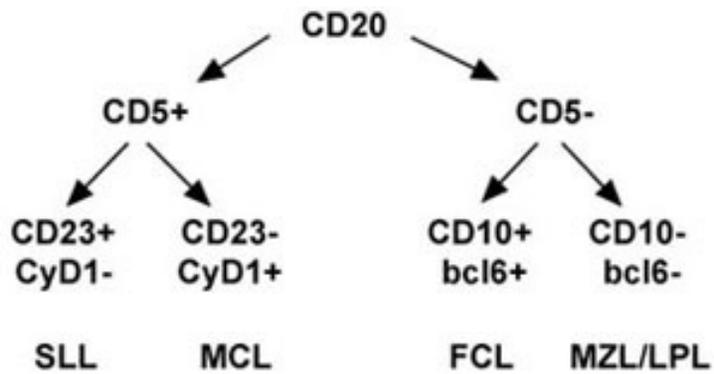


## Diagnosis: Assays performed on biopsy specimen(s)

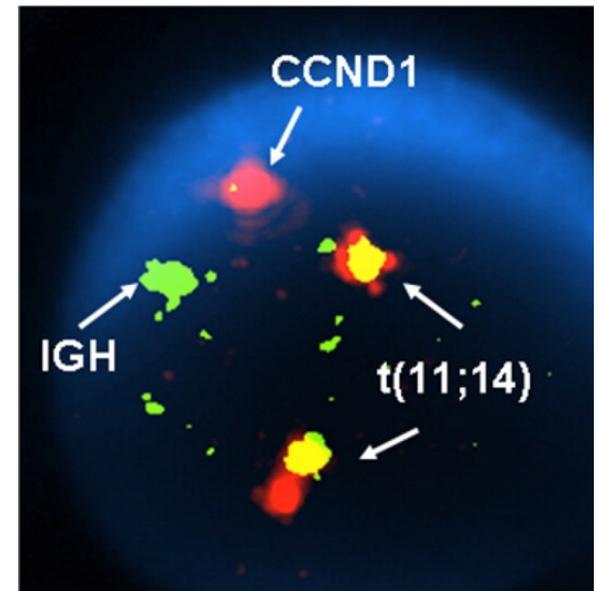
Method	Findings
Routine histologic study	Morphologic classification
Immunoperoxidase staining	Lineage, subtyping by protein expression (CD markers, e.g. CD10, CD30)
Flow cytometry	Lineage, evaluation principally of cell surface protein (CD markers)
Molecular biologic methods (PCR)	Clonality by immune receptor gene and chromosomal rearrangements
Cytogenetics/FISH	Chromosomal abnormalities including translocations

# Diagnosis: Example of assays at work

## Distinguishing mantle cell lymphoma from small lymphocytic lymphoma



Immunohistochemistry



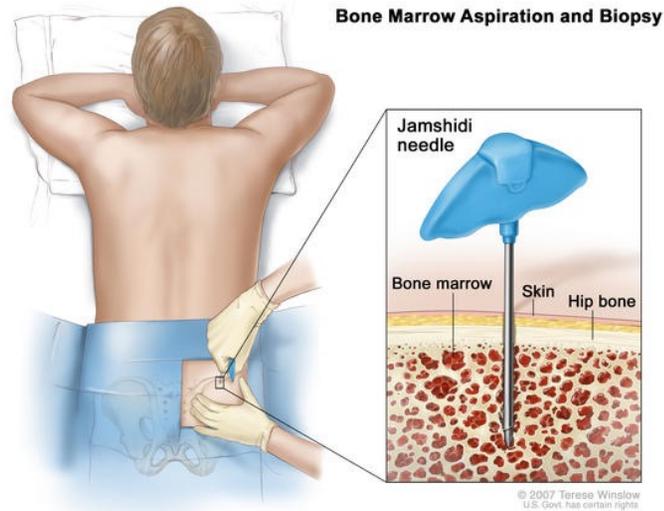
FISH (fluorescence in-situ hybridization)

## Staging: Comprehensive evaluation of the patient

- History and complete physical examination
- Laboratory evaluation: Standard blood studies
  - Complete blood count, differential blood count, blood smear examination
  - LDH and  $\beta$ 2-microglobulin levels
  - Liver function tests
  - Renal function tests
  - Serum electrolyte, calcium, and uric acid levels
- Bone marrow
  - Bilateral bone marrow biopsies or unilateral (at least 2-cm specimen)  $\pm$  flow cytometry
- Radiologic studies
  - CT scans (abdomen, pelvis, and thorax)/PET in selected histologies

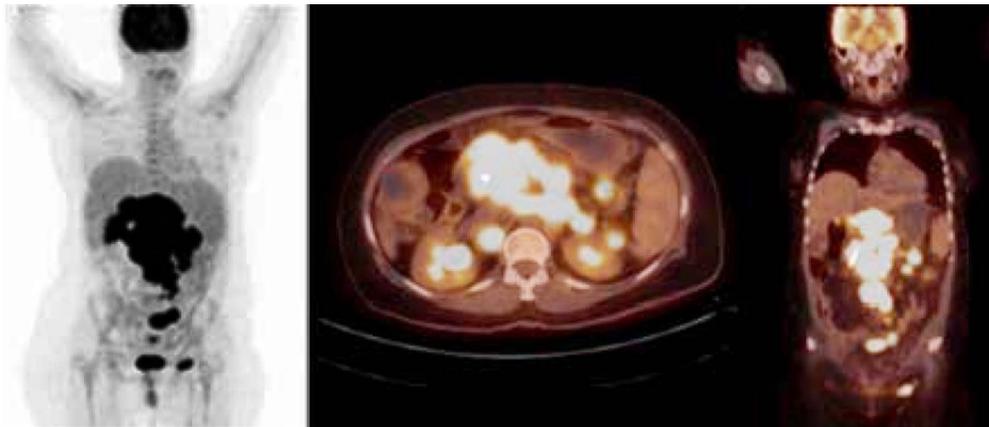
# Staging: Bone marrow biopsy and FDG PET scan

Bone marrow biopsy



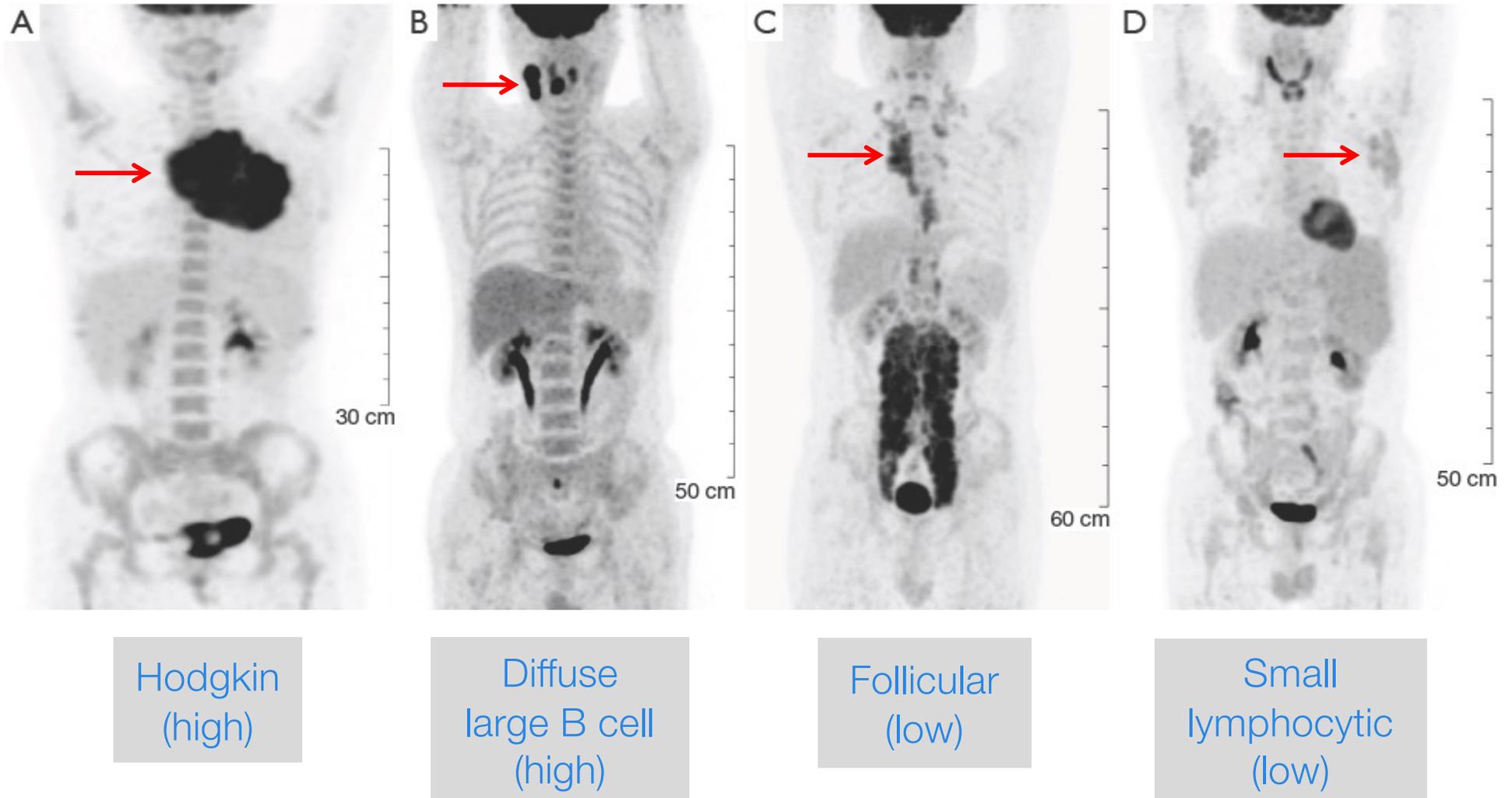
- Aspirate liquid marrow for microscopic examination of smear, flow cytometry, and molecular studies
- Harvest ~2cm portion of intact bone for microscopic examination

FDG PET scan



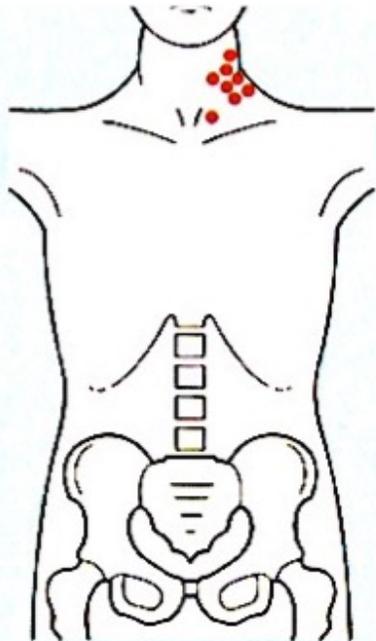
- Fluorodeoxyglucose (FDG) administered IV to patient
- Metabolically active cancer cells uptake FDG which is visualized by positron emission tomography
- Computed tomography (CT) scan provides anatomic detail

# Staging: FDG PET uptake varies according to grade of lymphoma

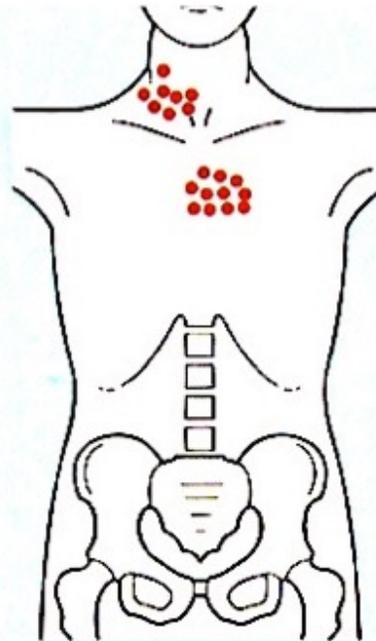


PET is also an important way to monitor response to therapy

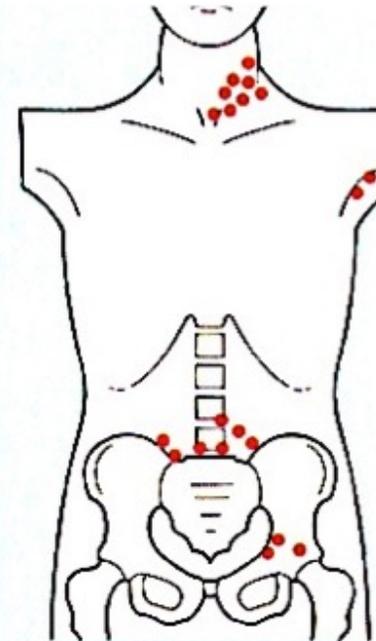
# Staging: Ann Arbor staging for lymphomas



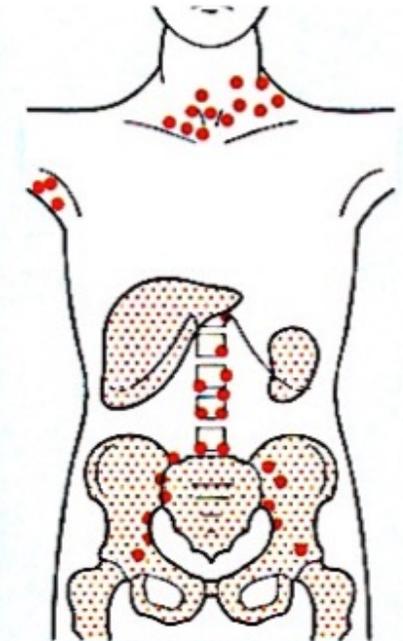
**Stage I:**  
involvement of single lymph node region or single extralymphatic site (I<sub>E</sub>)



**Stage II:**  
involvement of two or more lymph node regions on same side of diaphragm; may include localized extralymphatic



**Stage III:**  
involvement of lymph node regions on both sides of the diaphragm; may include spleen (III<sub>S</sub>) or localized



**Stage IV:**  
diffuse extralymphatic disease (e.g. in liver, bone marrow, lung, skin)

From [www.studyblue.com](http://www.studyblue.com)

A = absence of B symptoms

B = presence of B symptom(s) (fevers, sweats, or weight loss)

# Prognosis: Clinical factors that predict outcome

## International Prognostic Score (IPS) for advanced-stage (III/IV) Hodgkin

Patients with advanced disease are risk stratified using the IPS, which includes the following risk factors (for each factor present, the patient receives 1 point):

- Albumin <4 g/dL
- Hemoglobin <10.5 g/dL
- Male
- Age  $\geq$ 45 y
- Stage IV disease
- Leukocytosis: WBC count  $>15,000/\text{mm}^3$
- Lymphopenia: lymphocyte count  $<8\%$  of WBC count and/or absolute lymphocyte count  $<600 \text{ cells}/\text{mm}^3$

HL, Hodgkin lymphoma; IPS, International Prognostic Score; WBC, white blood cell  
Adapted from *N Engl J Med*. 1998;339(21):1506-1514.

## International Prognostic Index (IPI) for non-Hodgkin

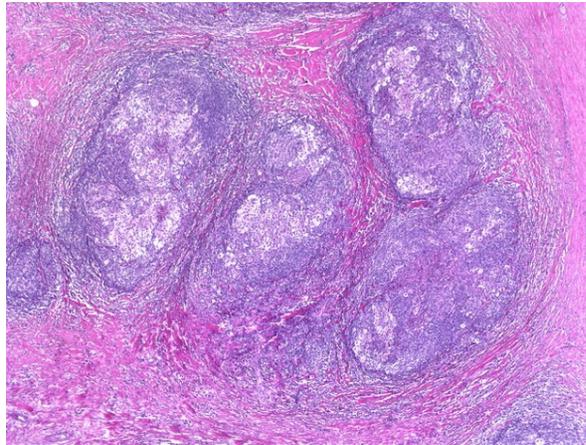
### IPI (Large Cell Lymphoma)

Age  $>60$  yr  
Stage III or IV  
Performance status  $>1$   
Extranodal involvement  $>1$  site  
Serum LDH level  $>1x$  normal

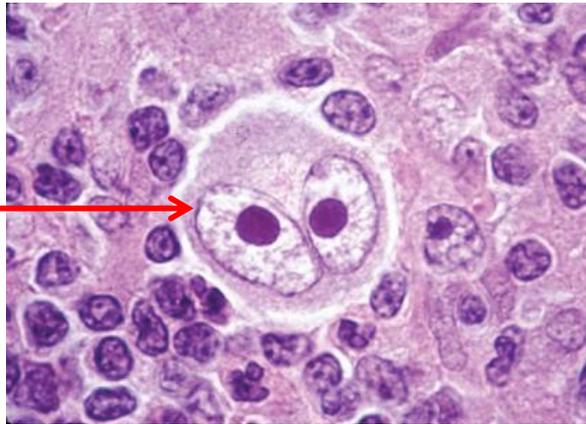
Risk Categories (Factors)	5-yr Overall Survival
Low (0-1)	73
Low Intermediate (2)	51
High Intermediate (3)	43
High (4-5)	26

# Hodgkin lymphoma: Disease features

Low magnification showing  
“nodular sclerosis”



High magnification showing  
Reed-Sternberg cell  
with “owl eyes”



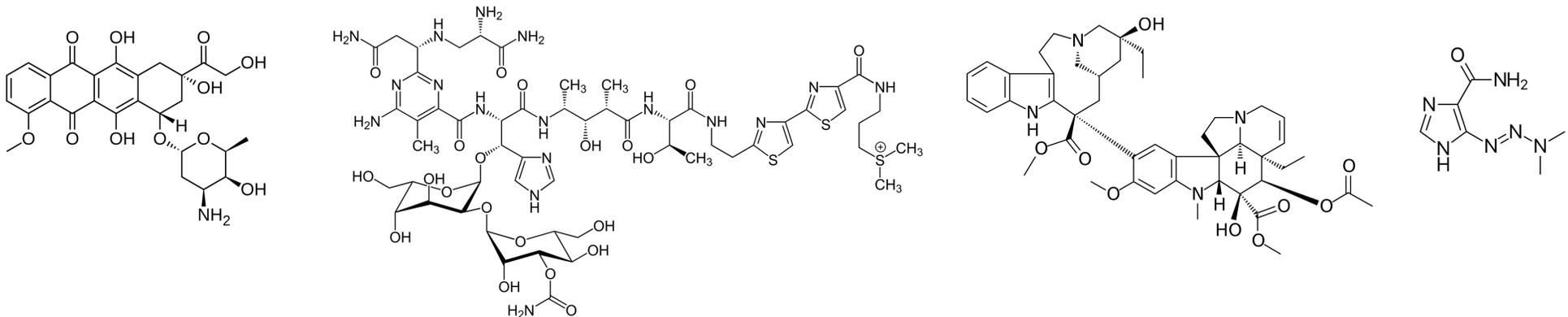
- ~10-12% of lymphomas
- ~9000 cases per year in US
- Typically occurs in young adults
  - 20-30 years old
  - outcomes are excellent
- Older adults have poor outcome
- Reed-Sternberg is malignant cell
  - small fraction of tumor
  - CD15+ CD30+
  - CD20–
- Believed to arise from thymic B cell

# Hodgkin lymphoma: Standard-of-care ABVD chemotherapy

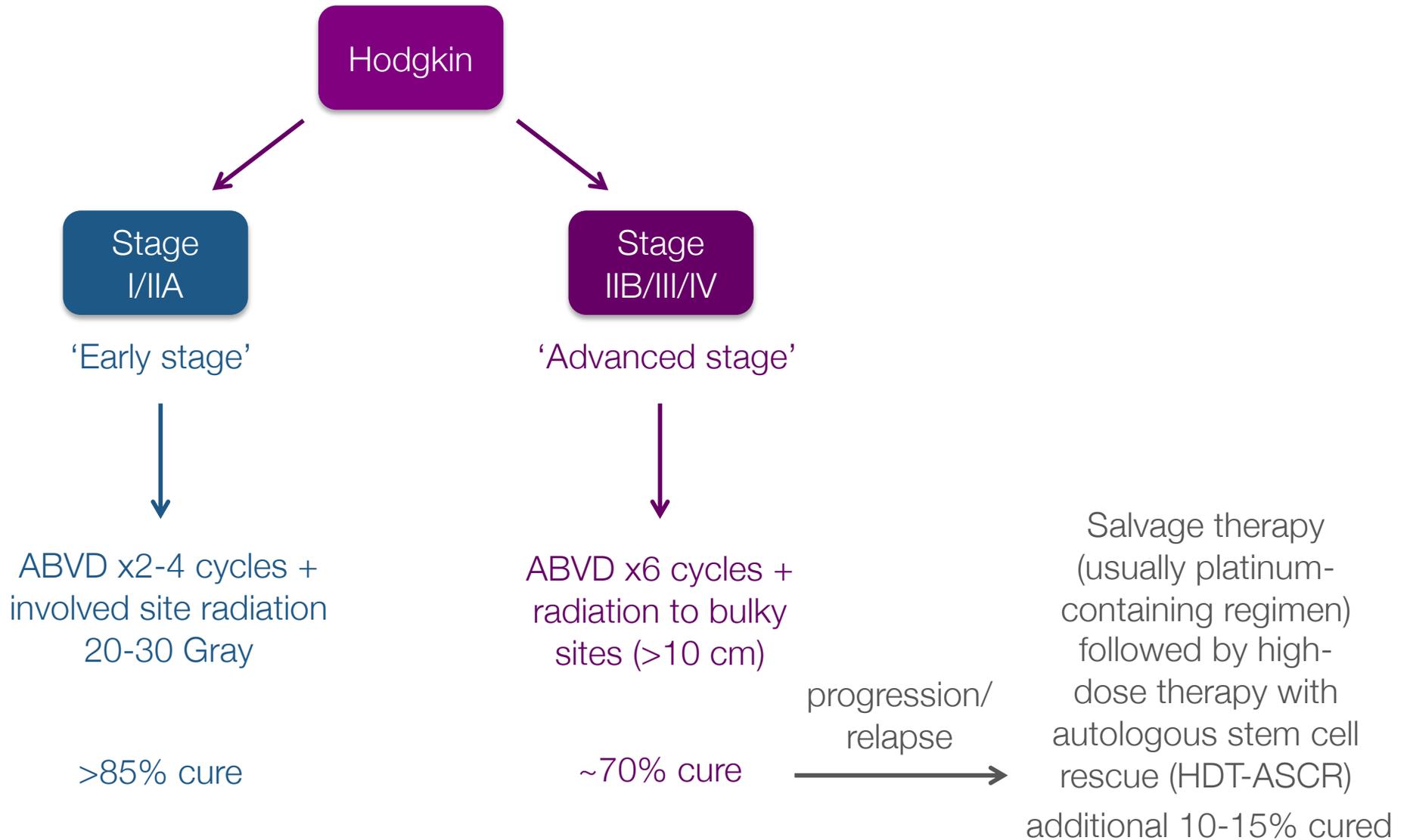
Chemotherapeutic agent	Class	Mechanism	Toxicities
<b>A</b> driamycin (doxorubicin)	anthracycline	DNA intercalator	heart failure; secondary leukemia
<b>B</b> leomycin	peptide	DNA damage via free radicals	pulmonary fibrosis
<b>V</b> inblastine	vinca alkaloid	microtubule disruption	neuropathy; constipation (severe)
<b>D</b> acarbazine	alkylator	methylates DNA	nausea

All have side effects of bone marrow suppression and infertility

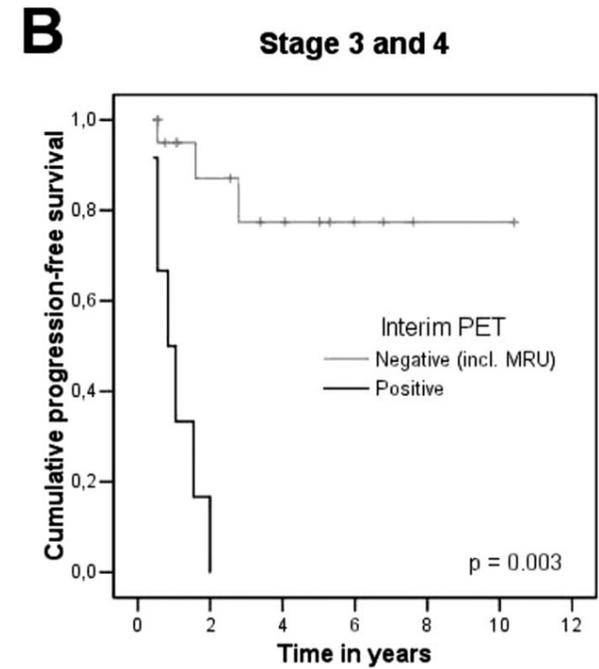
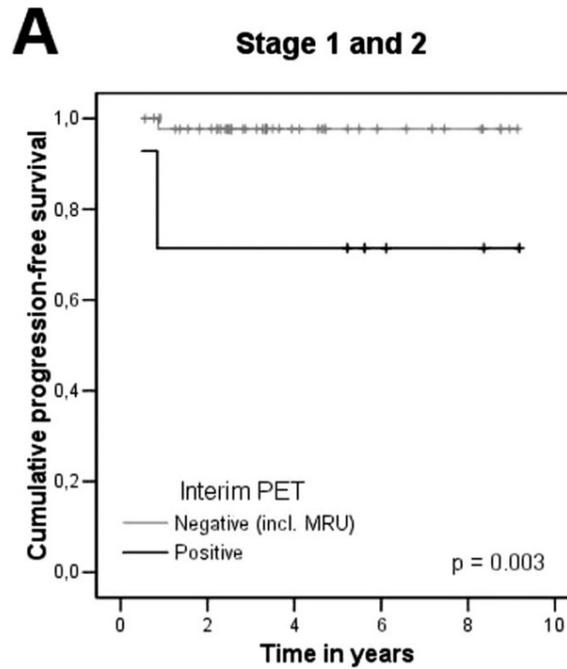
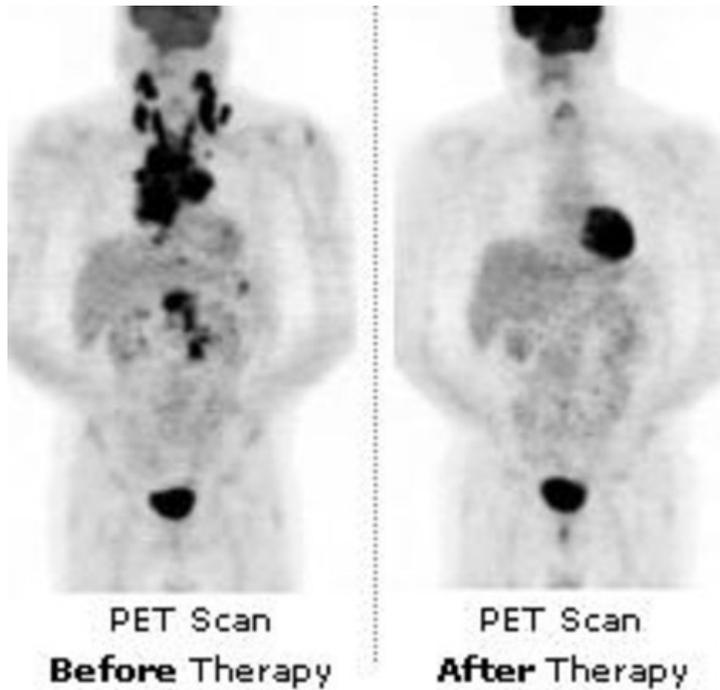
- Fertility preservation prior to treatment is key in young patients



# Hodgkin lymphoma: Treatment algorithm

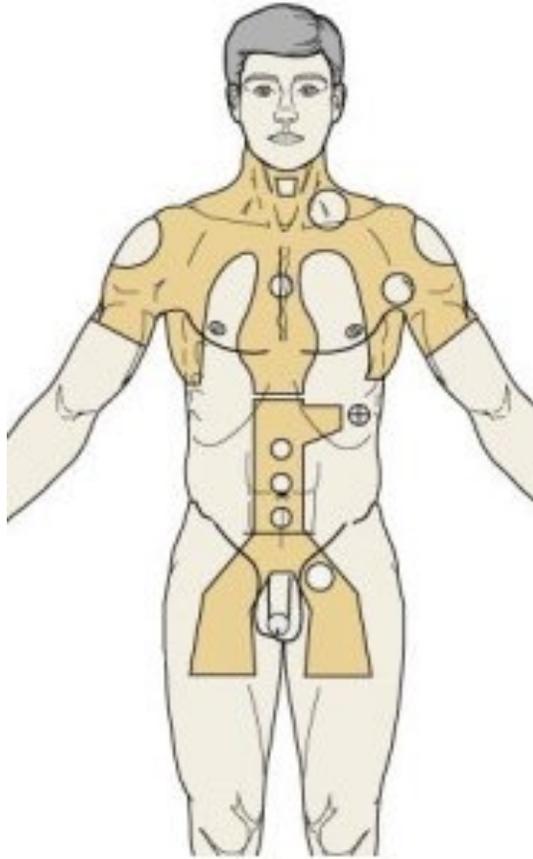


# Hodgkin lymphoma: FDG PET response to treatment predicts outcome



Hutchings et al, *Blood* 2006

# Hodgkin lymphoma: Long-term complications after treatment (historical)



'Mantle' radiation

## Second malignancies

- Thyroid
- Breast
- Lung
- Sarcoma of muscle or bone

## Cardiac atherosclerosis

Restrictive heart failure (epicardial fibrosis)

Lung fibrosis

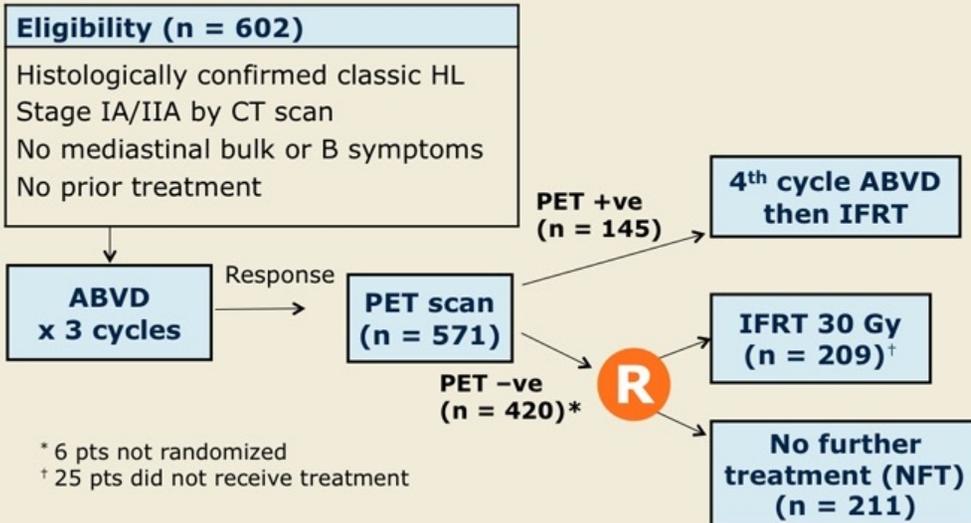
Infertility

Hypothyroidism

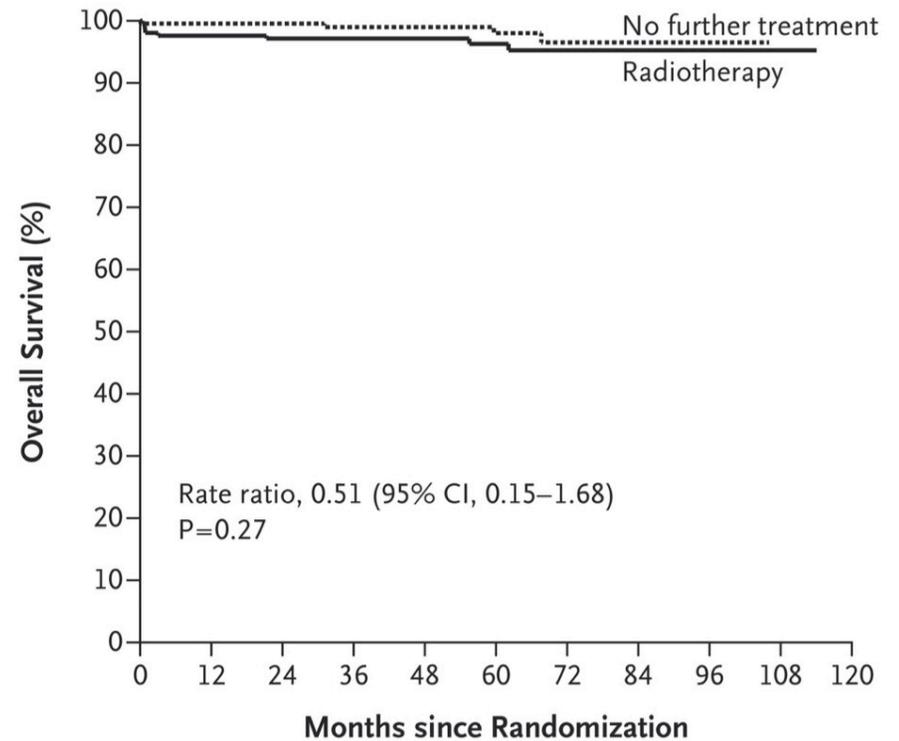
# Hodgkin lymphoma: Current strategies to reduce treatment toxicities

## Eliminating radiation from early stage (I/IIA) HL

### Phase III RAPID Study Design



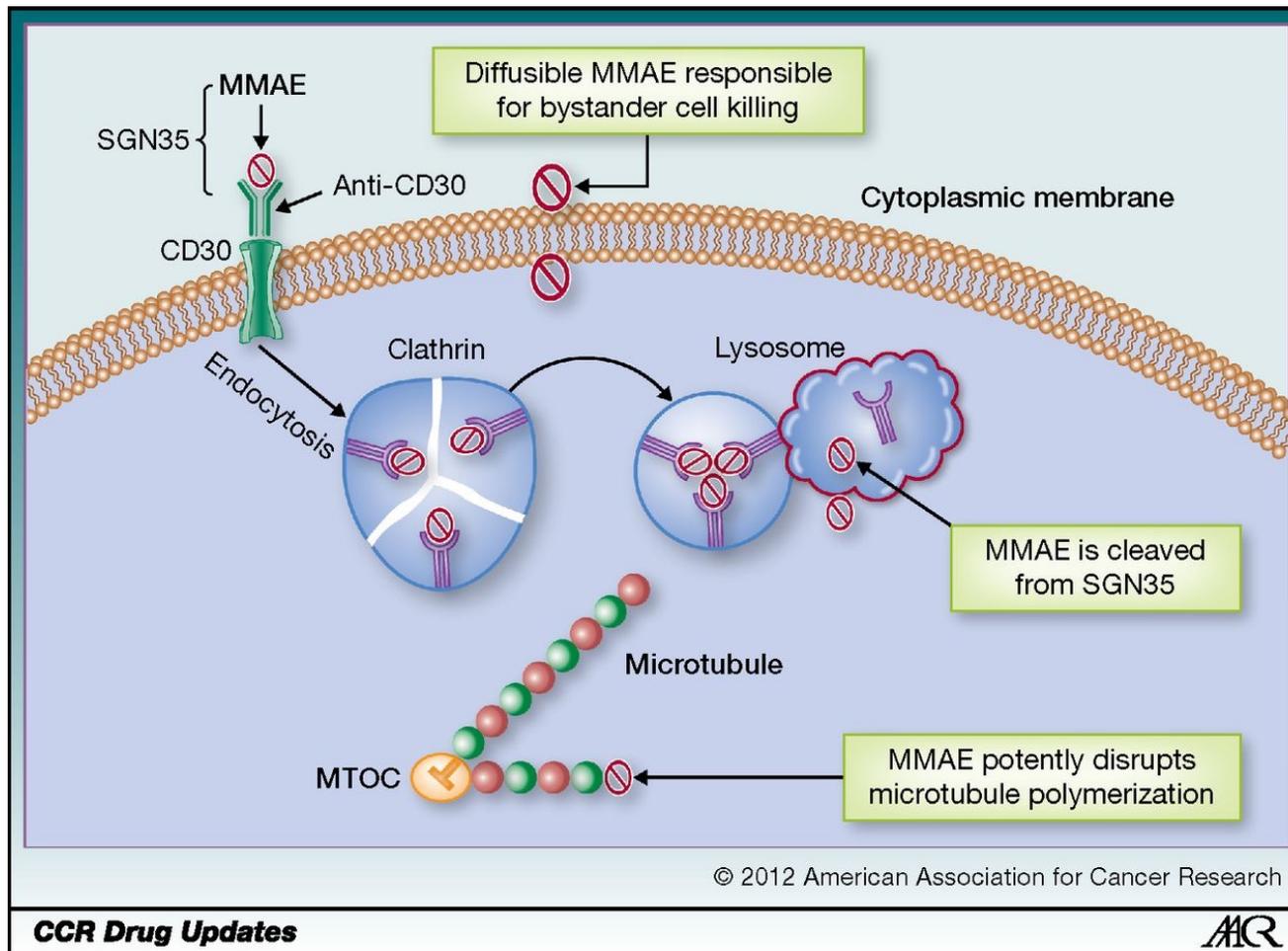
Radford J et al. *Proc ASH* 2012;Abstract 547.



Radford et al, *NEJM* 2015

# Hodgkin lymphoma: Novel treatment strategies

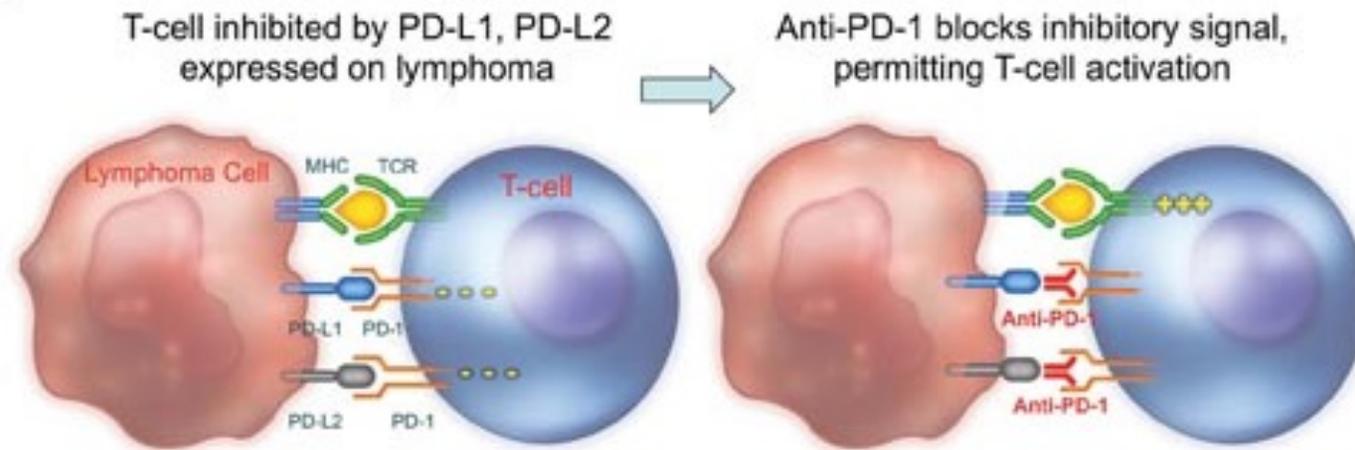
## Brentuximab vedotin (anti-CD30 antibody-drug conjugate)



‘Smart’ targeting of chemotherapy maximizes efficacy and limits toxicity

# Hodgkin lymphoma: Novel treatment strategies

## Immune checkpoint blockade with anti-PD-1/PD-L1

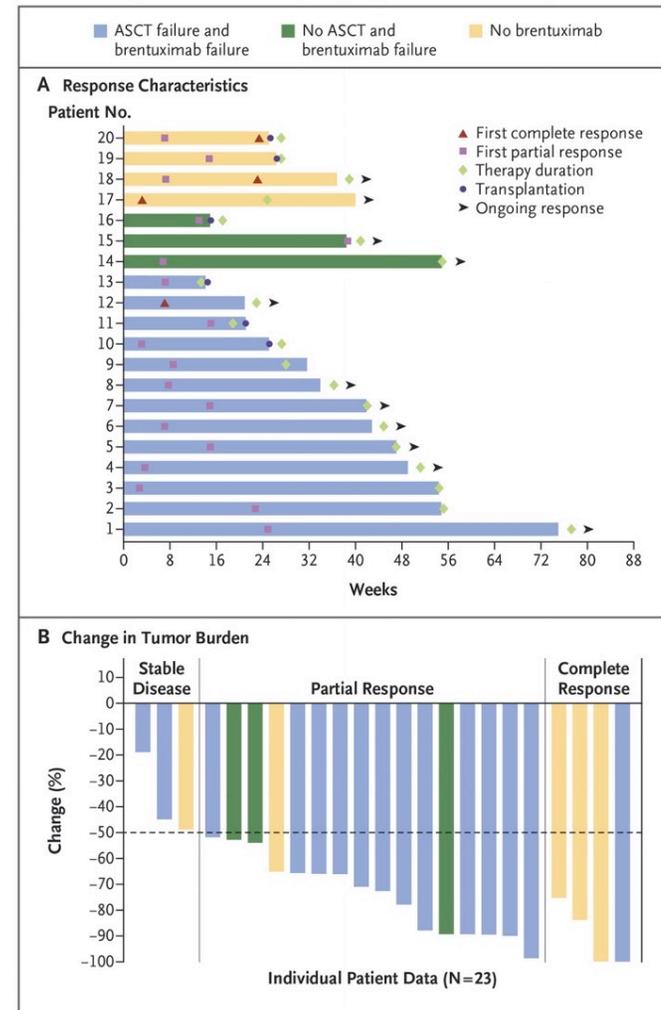
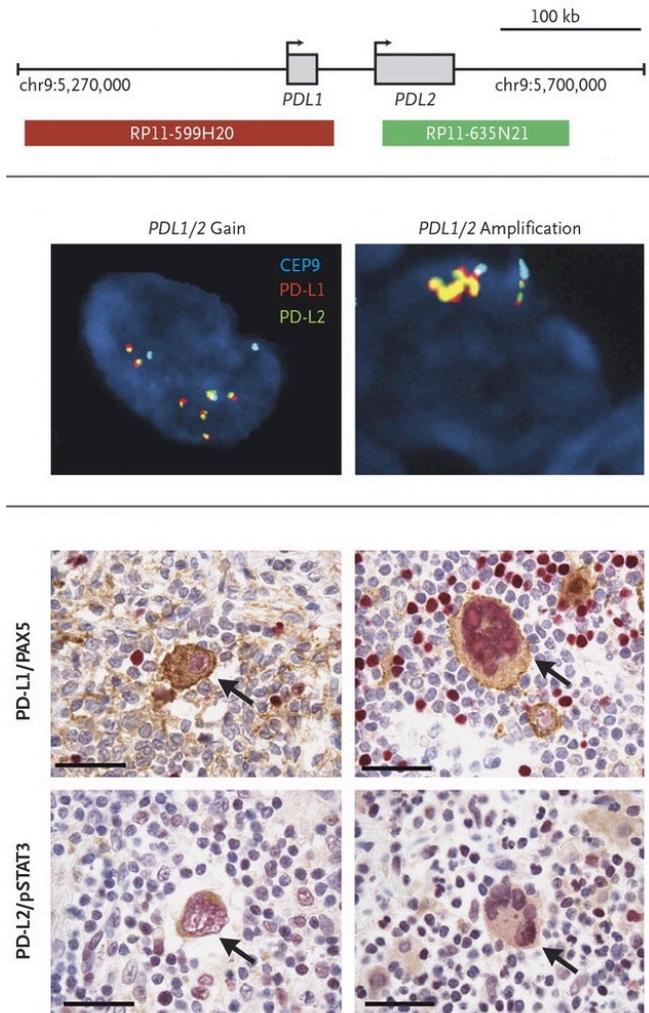


Johnson et al, *Hematologist* 2014

PD1/PDL1 blockade unleashes the immune system to attack cancer cells

# Hodgkin lymphoma: Novel treatment strategies

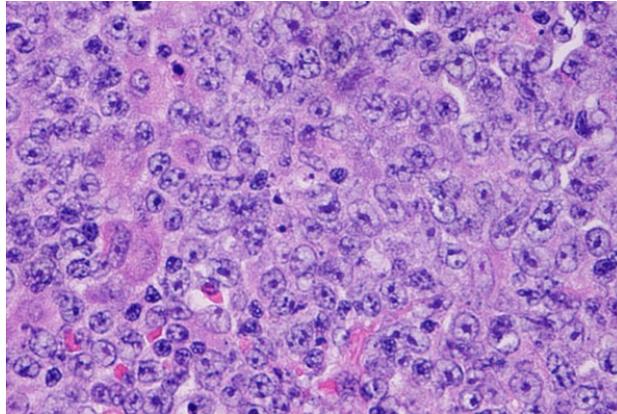
## Immune checkpoint blockade with anti-PD-1/PD-L1



Ansell et al, *NEJM* 2015

# Diffuse large B cell lymphoma (DLBCL): Disease features

Biopsy: Monotonous population of large, atypical lymphocytes

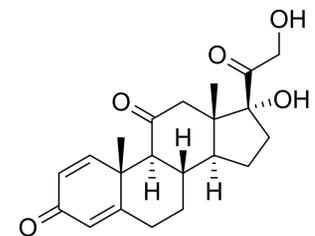
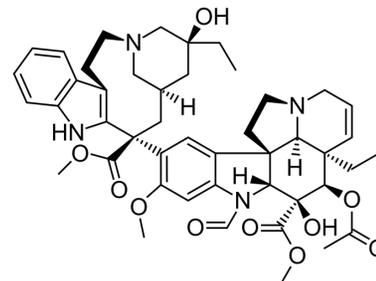
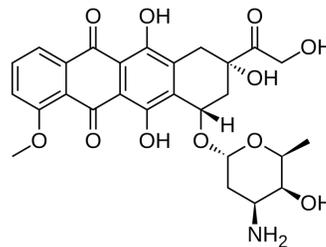
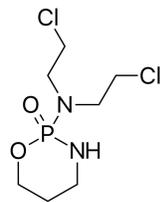
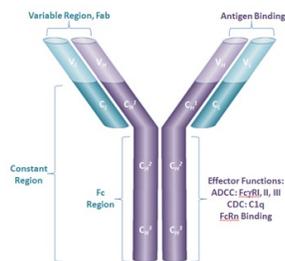


FDG PET: high-level uptake of tracer indicates metabolically active, rapidly dividing cells

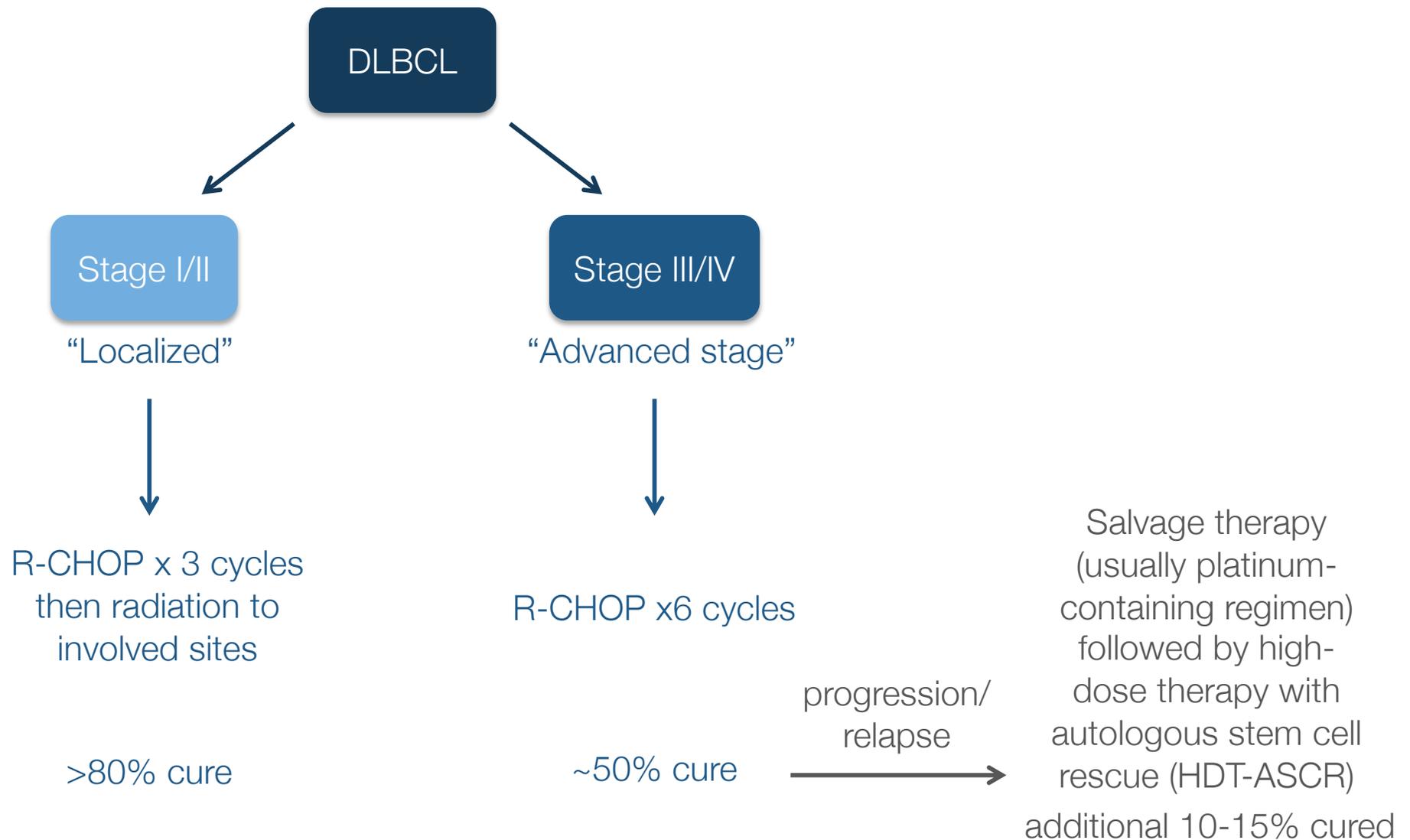
- Most common type of lymphoma (~30%)
- Average age at diagnosis 64
- Typical scenario: progressively enlarging lymph nodes and B symptoms for several weeks
- Aggressive disease but potentially curable
  - Patients will die in a matter of months if untreated
- 30% patients stage I-II
- 70% stage III-IV
- Malignant cells are CD20+

# DLBCL: Standard-of-care R-CHOP chemotherapy

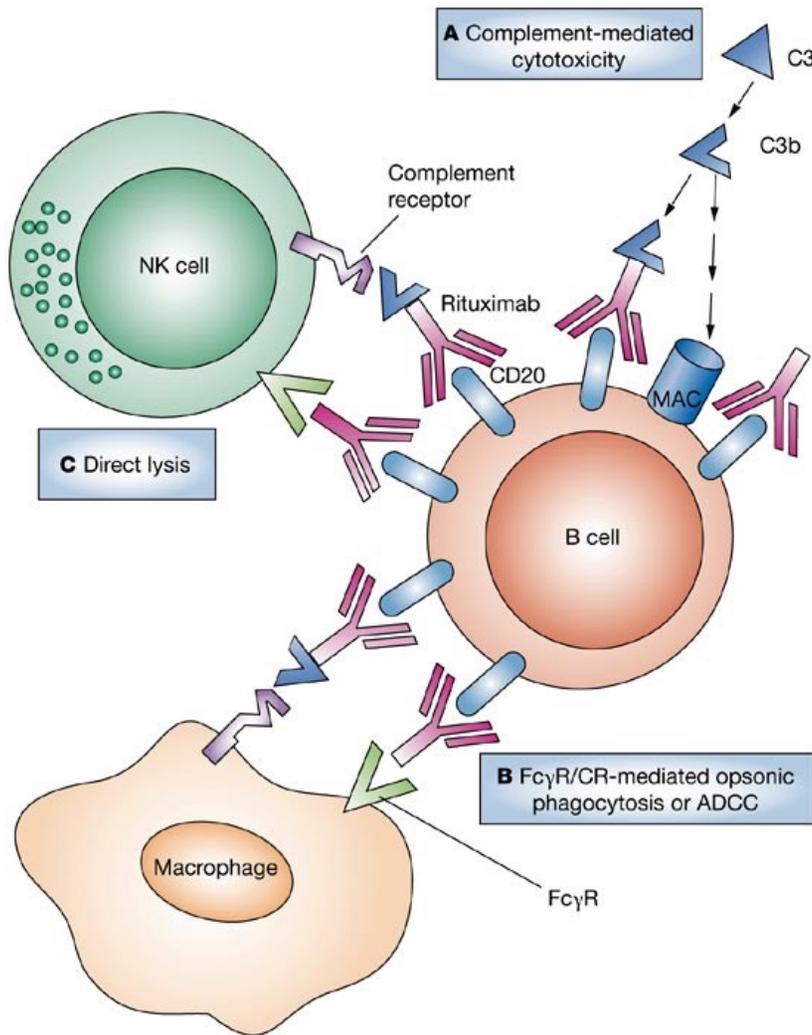
Chemotherapeutic agent	Class	Mechanism	Toxicities
<b>R</b> ituximab	anti-CD20 monoclonal antibody	kills CD20+ cells by multiple mechanisms	immune suppression; infusion reactions
<b>C</b> yclophosphamide	alkylator	DNA crosslinker	bladder hemorrhage; hair loss; infertility; nausea/vomiting
<b>H</b> ydroxydaunorubicin (doxorubicin)	anthracycline	DNA intercalator	heart failure; secondary leukemia
<b>O</b> ncovin (vincristine)	vinca alkaloid	microtubule disruption	neuropathy; constipation
<b>P</b> rednisone	steroid	lymphotoxic by multiple mechanisms	diabetes; osteoporosis; insomnia; stomach ulcers; cataracts



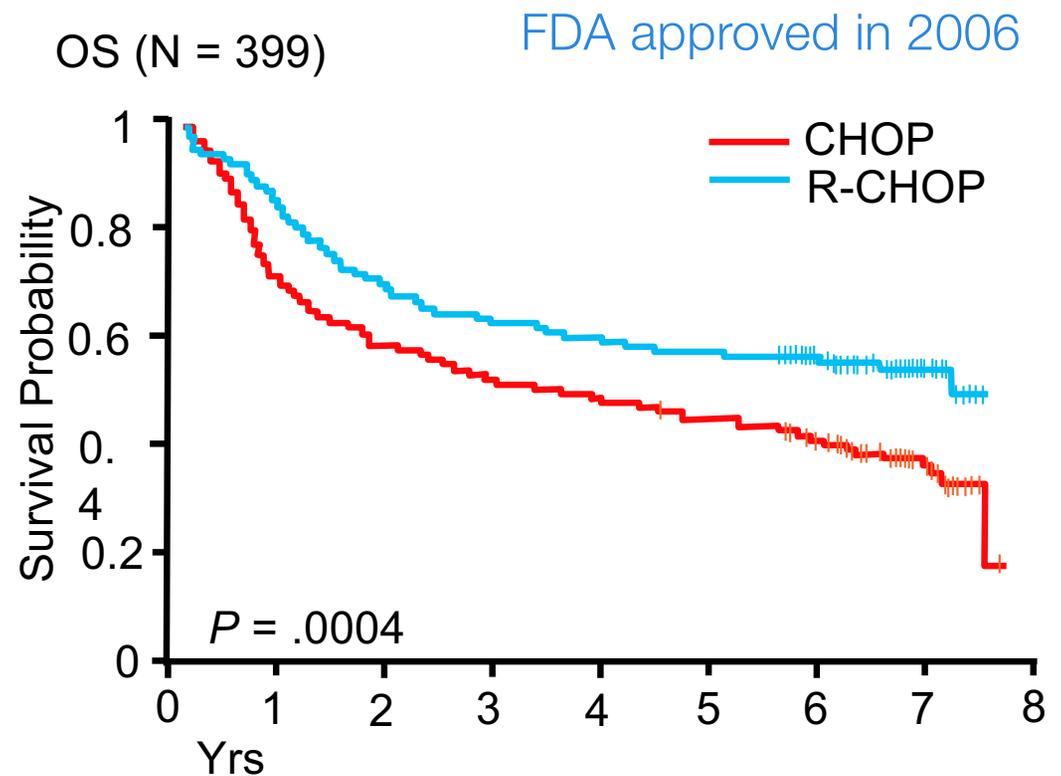
# Diffuse large B cell lymphoma (DLBCL): Treatment algorithm



# DLBCL: Rituximab was only therapeutic advance for a long time

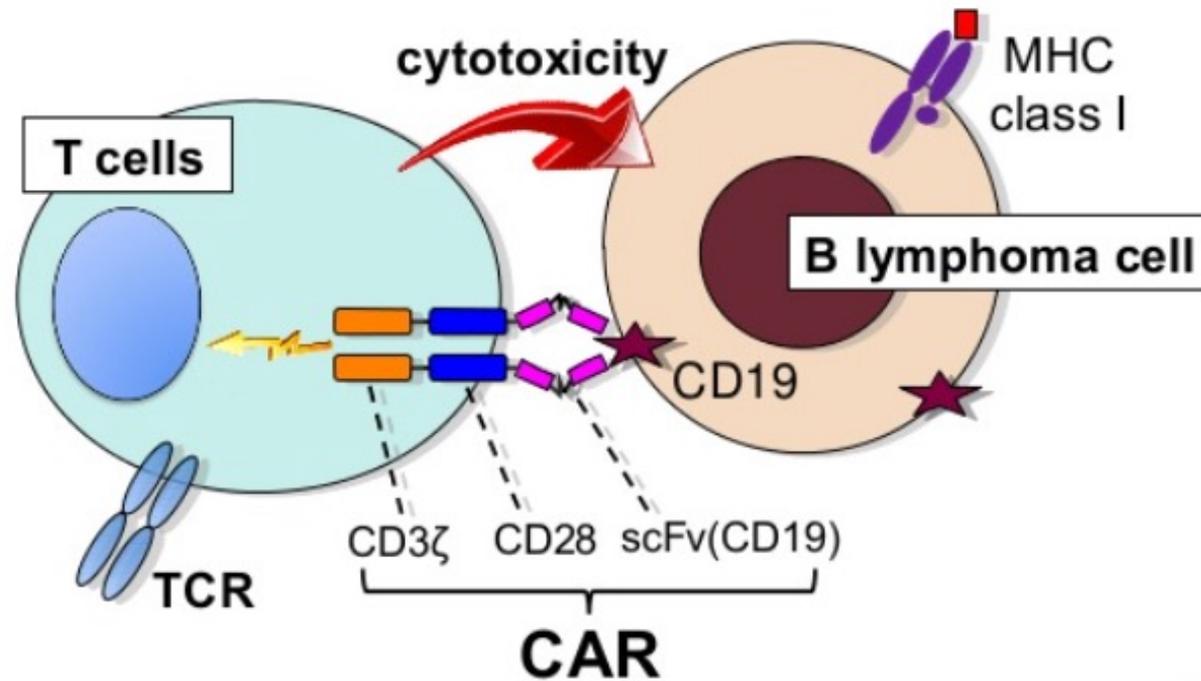


Taylor and Lindorfer, *NCPR* 2007



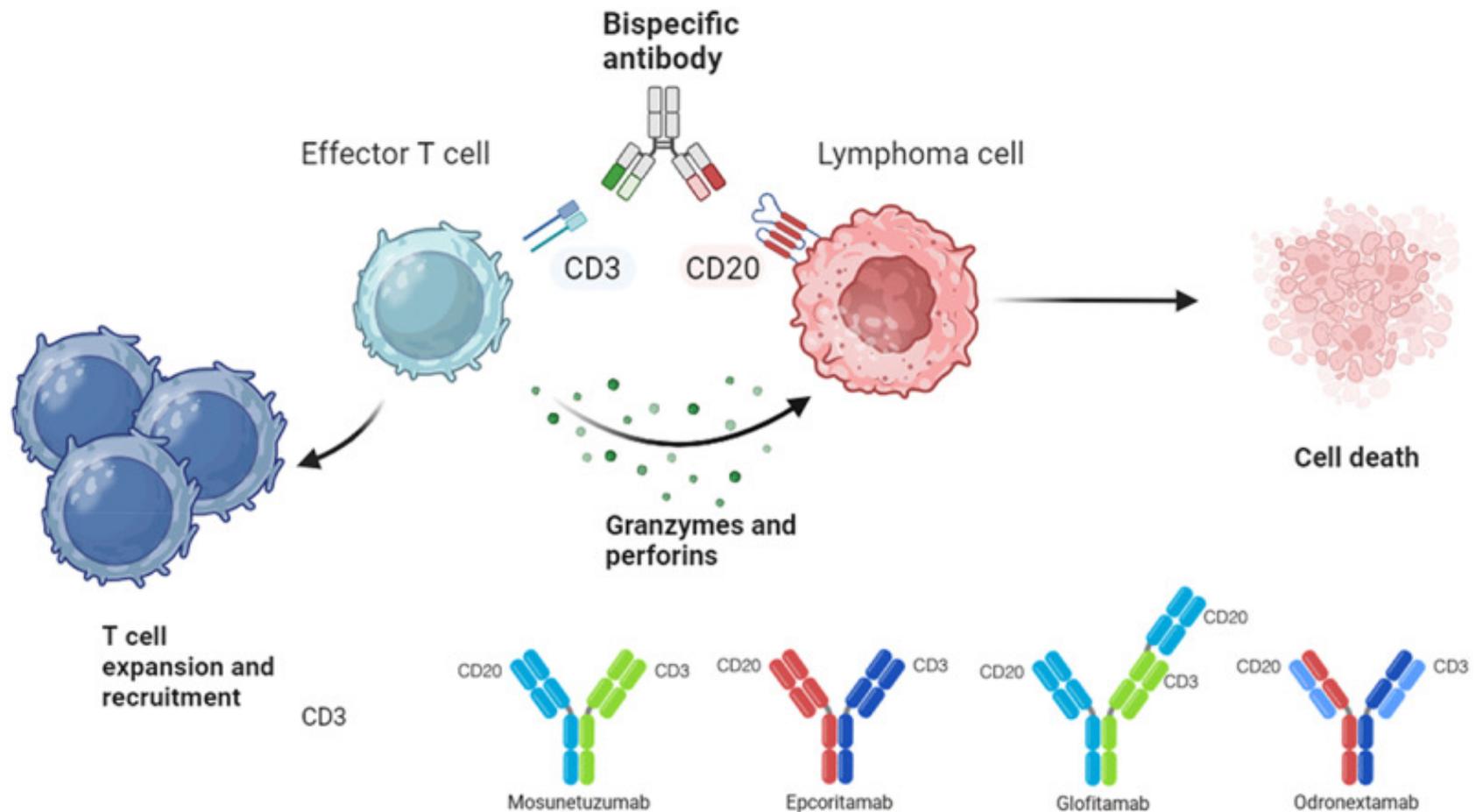
Coiffier B et al, *NEJM* 2002; *Blood* 2010

# DLBCL: CAR T cells recently approved (2017/2018)

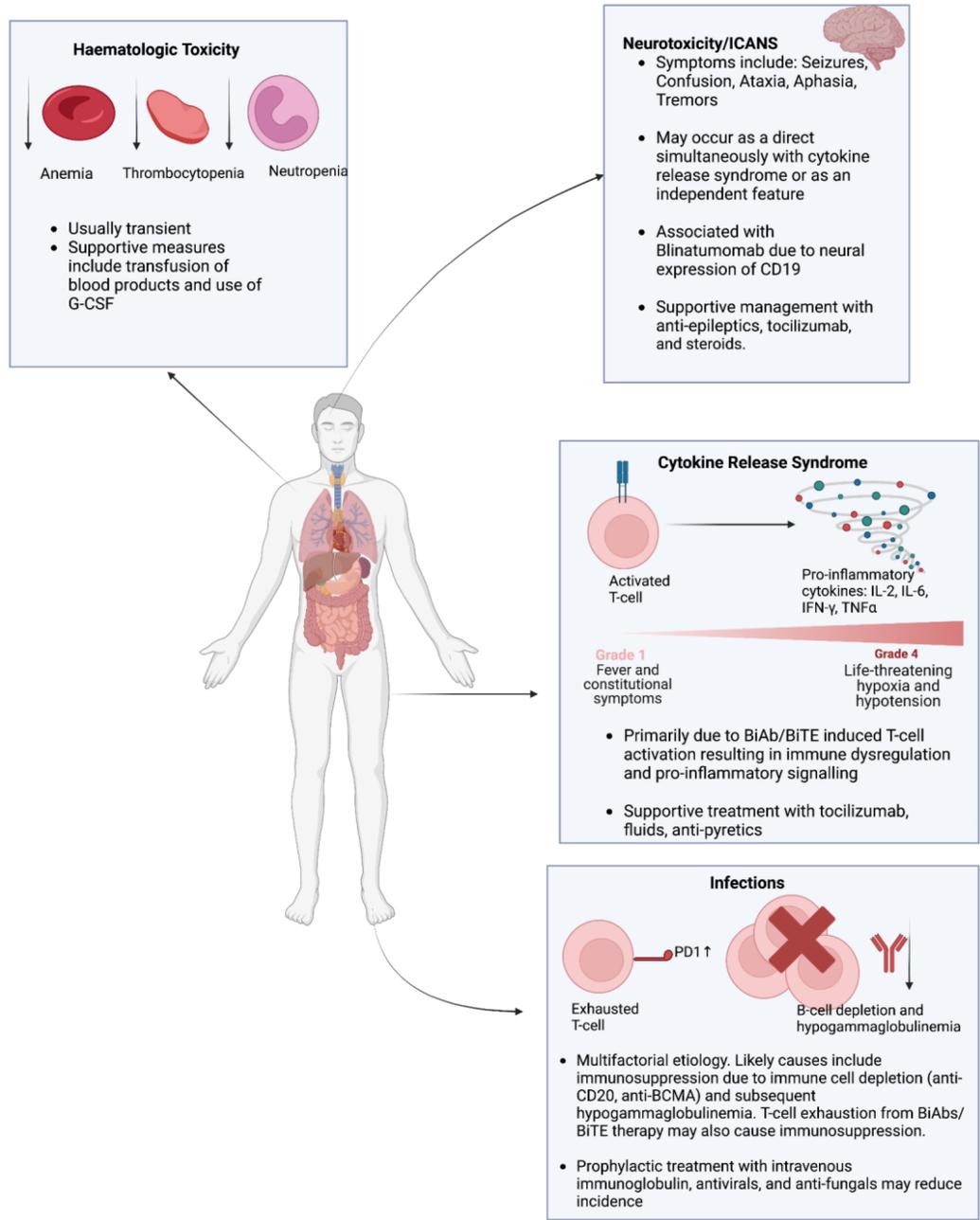


CD19-CAR T cells, which are engineered to express extracellular single-chain immunoglobulin variable fragments to CD19, linked to cytoplasmic T cell activation domains including CD3- $\zeta$ , showed remarkable therapeutic benefits toward CD19<sup>+</sup> B cell malignancies.

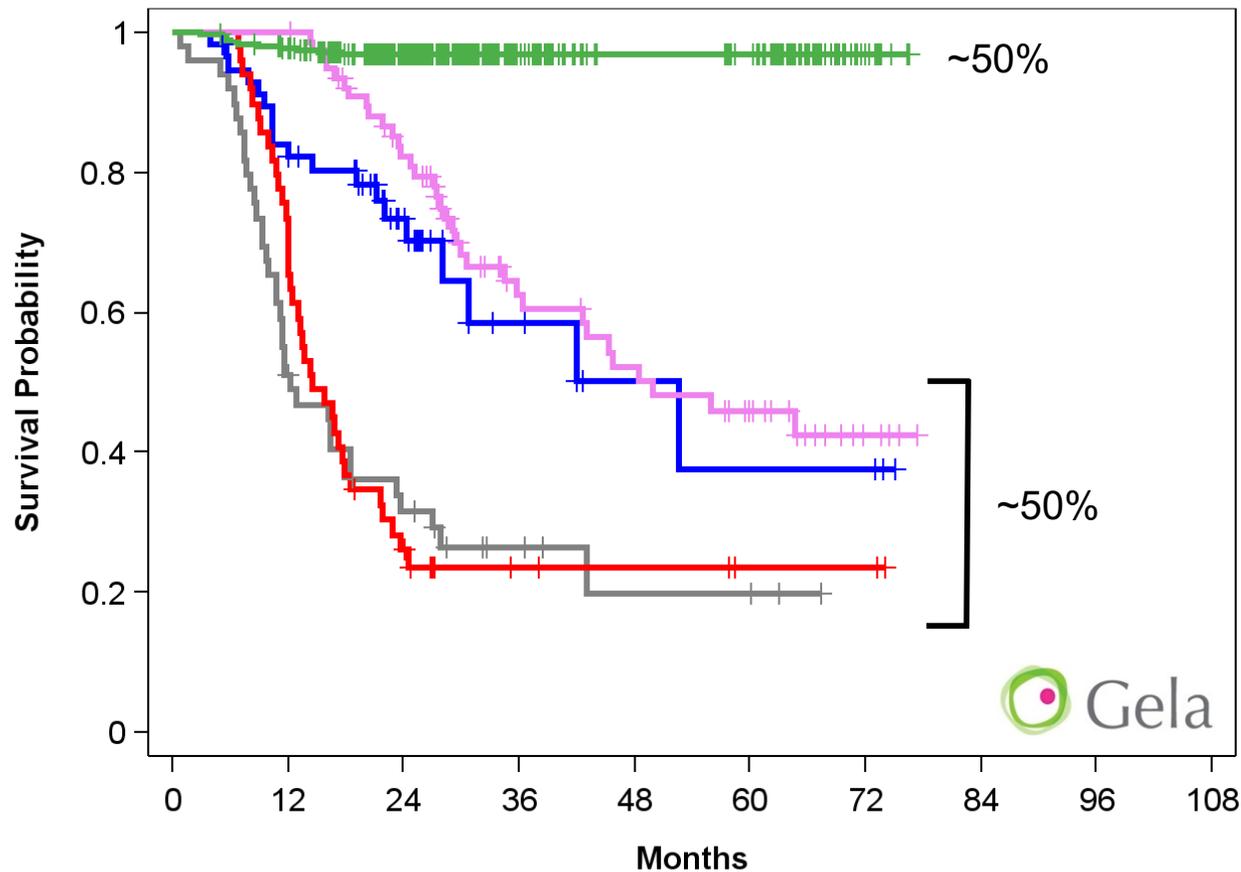
# B cell lymphomas: Bispecific T cell engagers (BiTEs)



# Toxicities of CART and BiTEs



# DLBCL: What explains the heterogeneous outcomes?



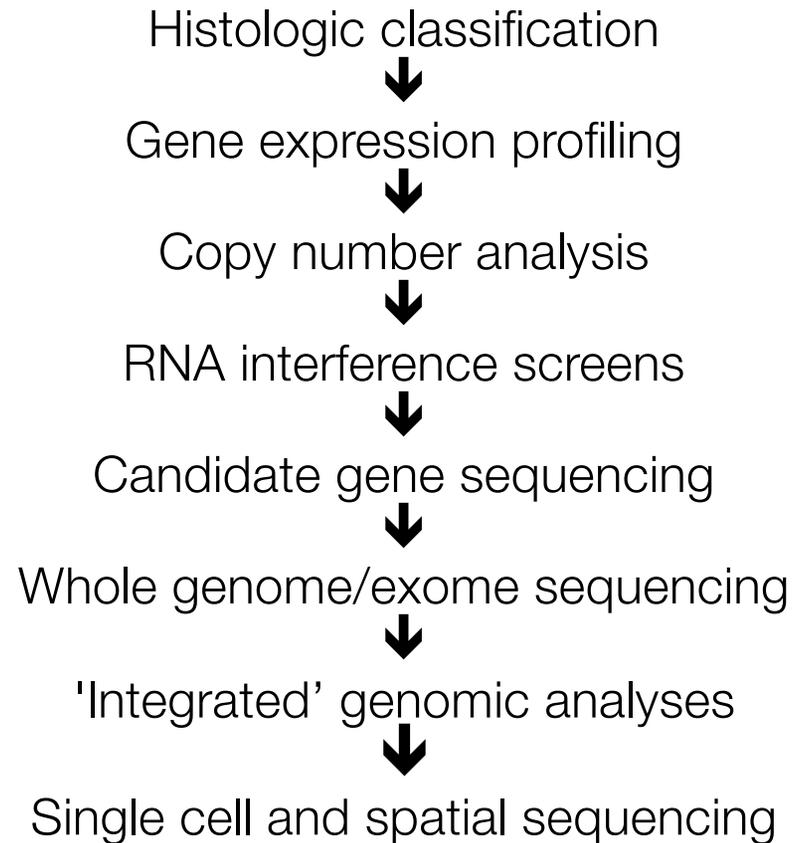
Advanced stage DLBCL outcomes with R-CHOP

- No relapse
- Late relapse
- Partial response
- Early relapse
- Refractory

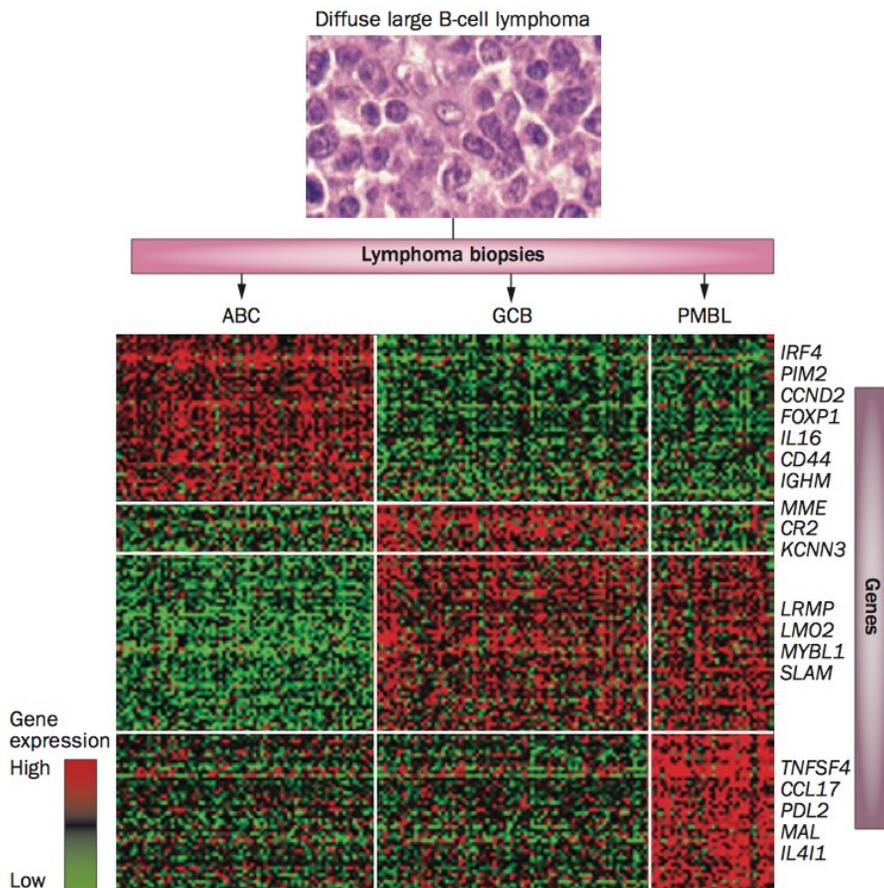
What molecular features distinguish these patients?

# DLBCL: What explains the heterogeneous outcomes?

Answer: The disease is molecularly heterogeneous  
How did we figure that out?

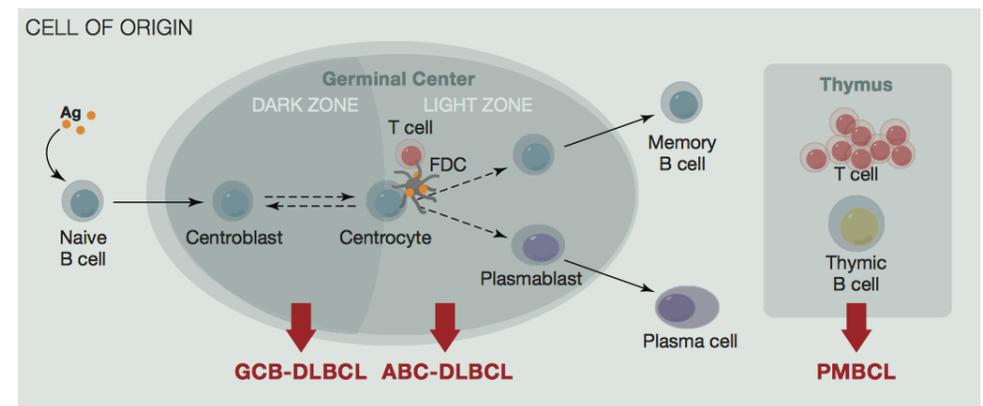


# DLBCL: Gene-expression profiling identifies distinct molecular subtypes



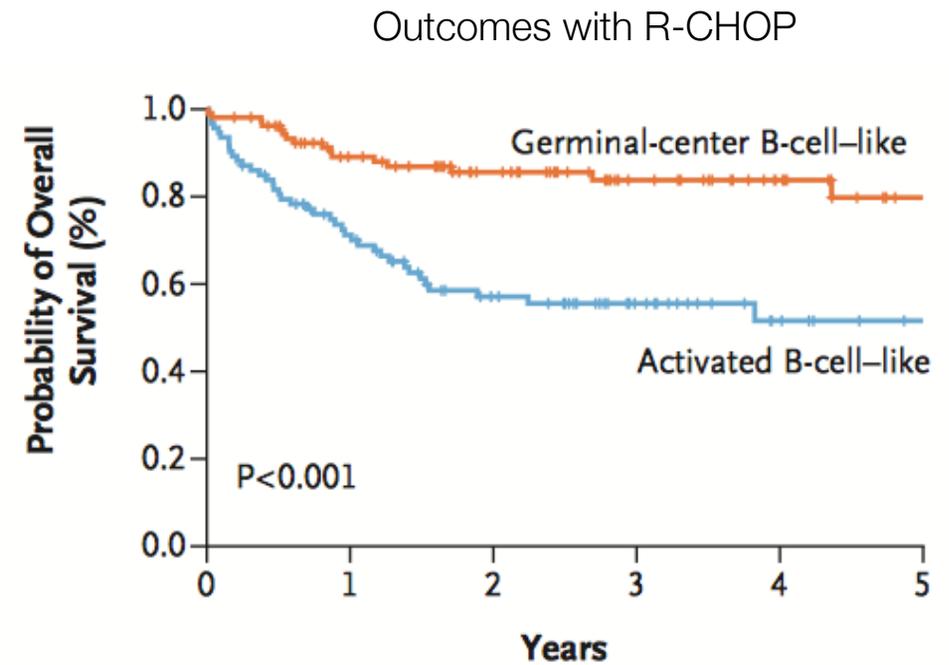
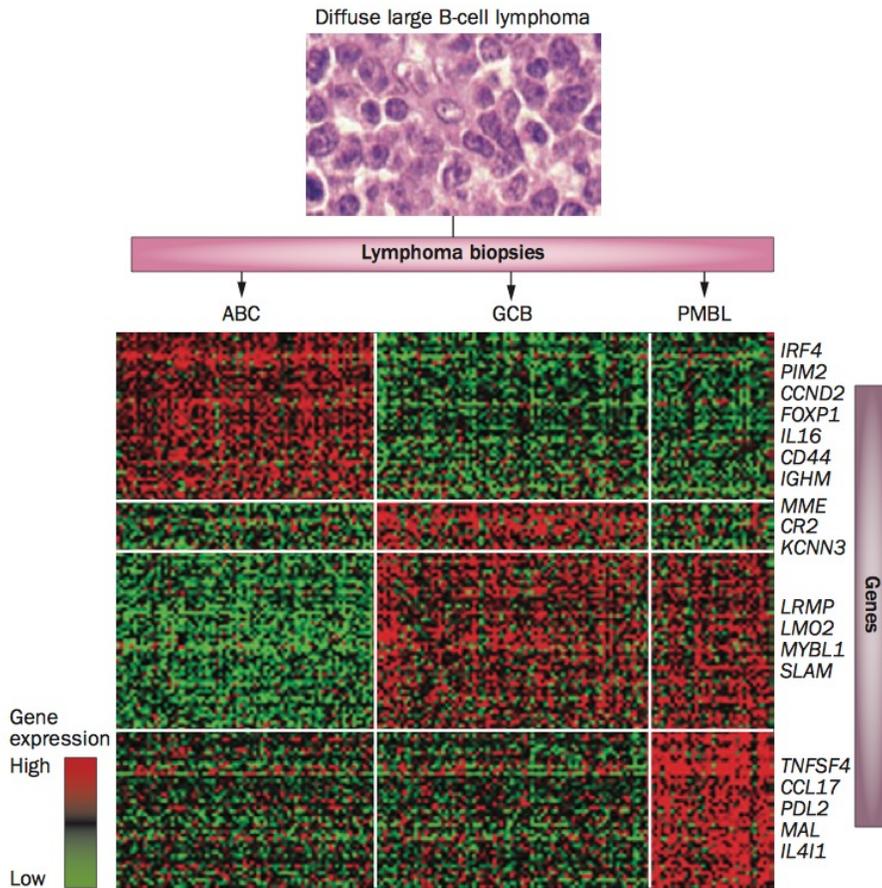
Alizadeh et al, *Nature* 2000  
 Roschewski et al, *NRCO* 2014

GCB = Germinal center B cell-like  
 ABC = Activated B cell-like



Pasqualucci et al, *Cancer Cell* 2014

# DLBCL: Gene-expression profiling identifies distinct molecular subtypes

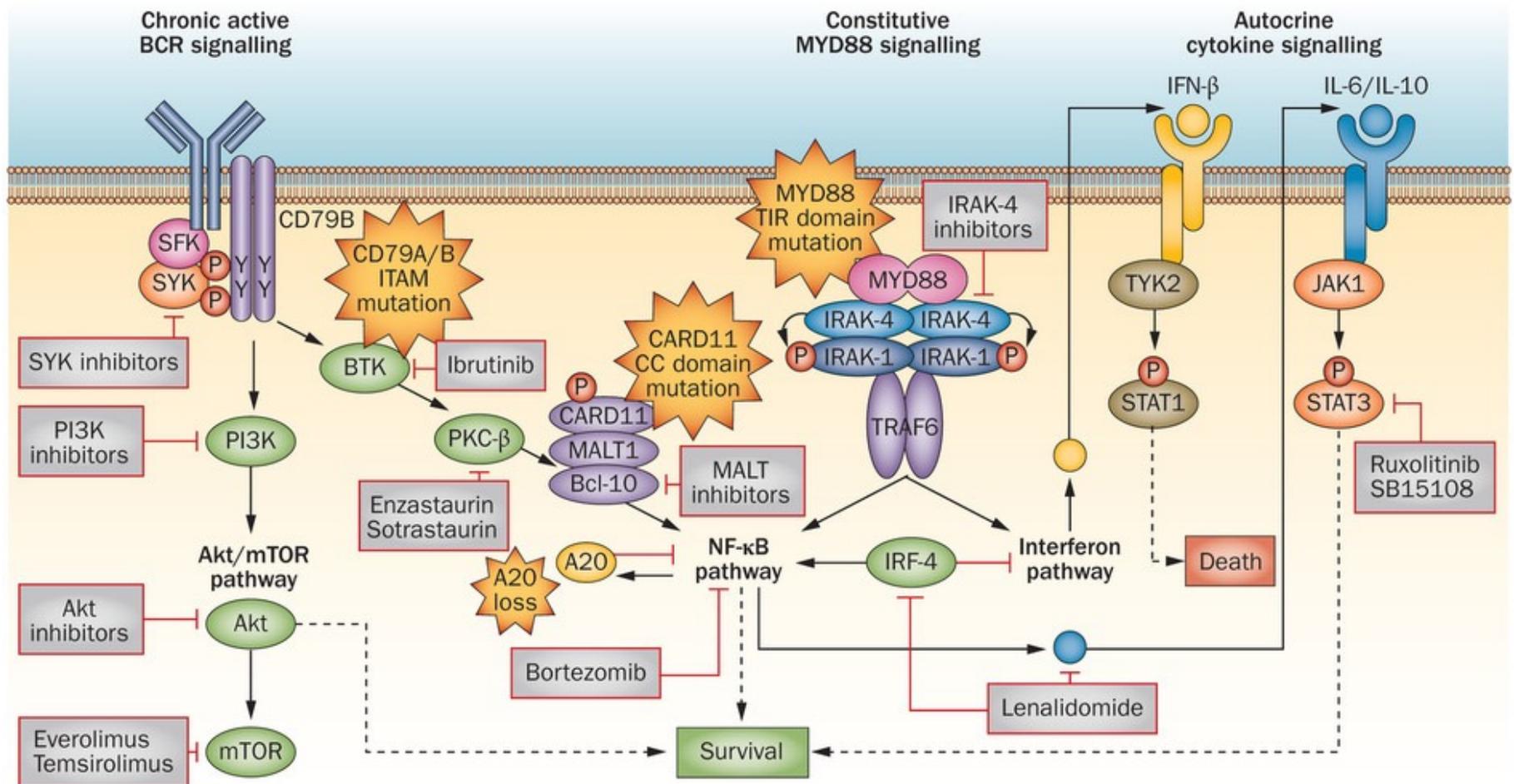


Lenz et al, *NEJM* 2008

Alizadeh et al, *Nature* 2000

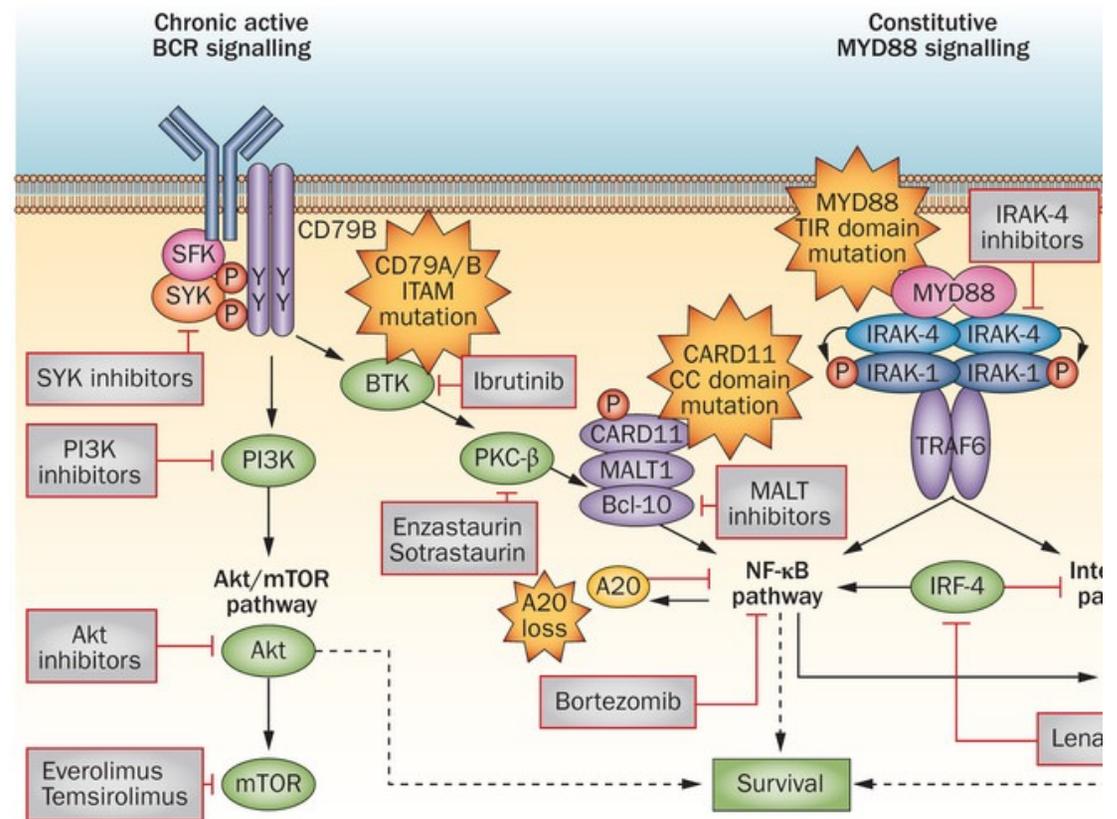
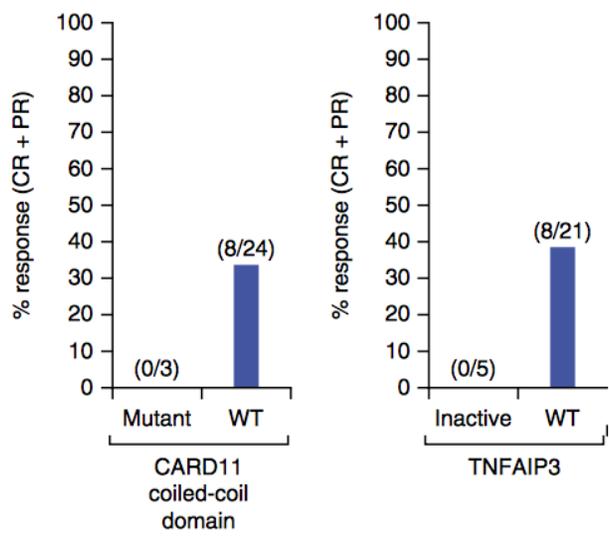
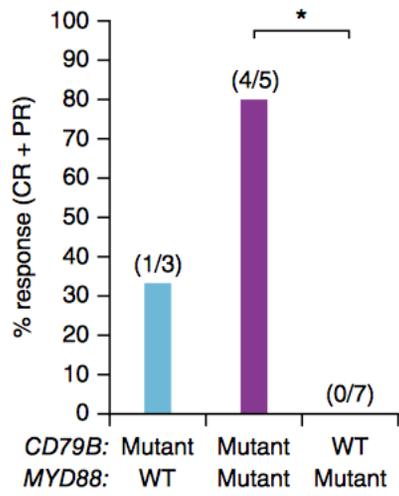
Roschewski et al, *NRCO* 2014

# DLBCL: Precision targeting of oncogenic “driver” mutations





# Negative selection of patients likely to be resistant: Learning from clinical trials



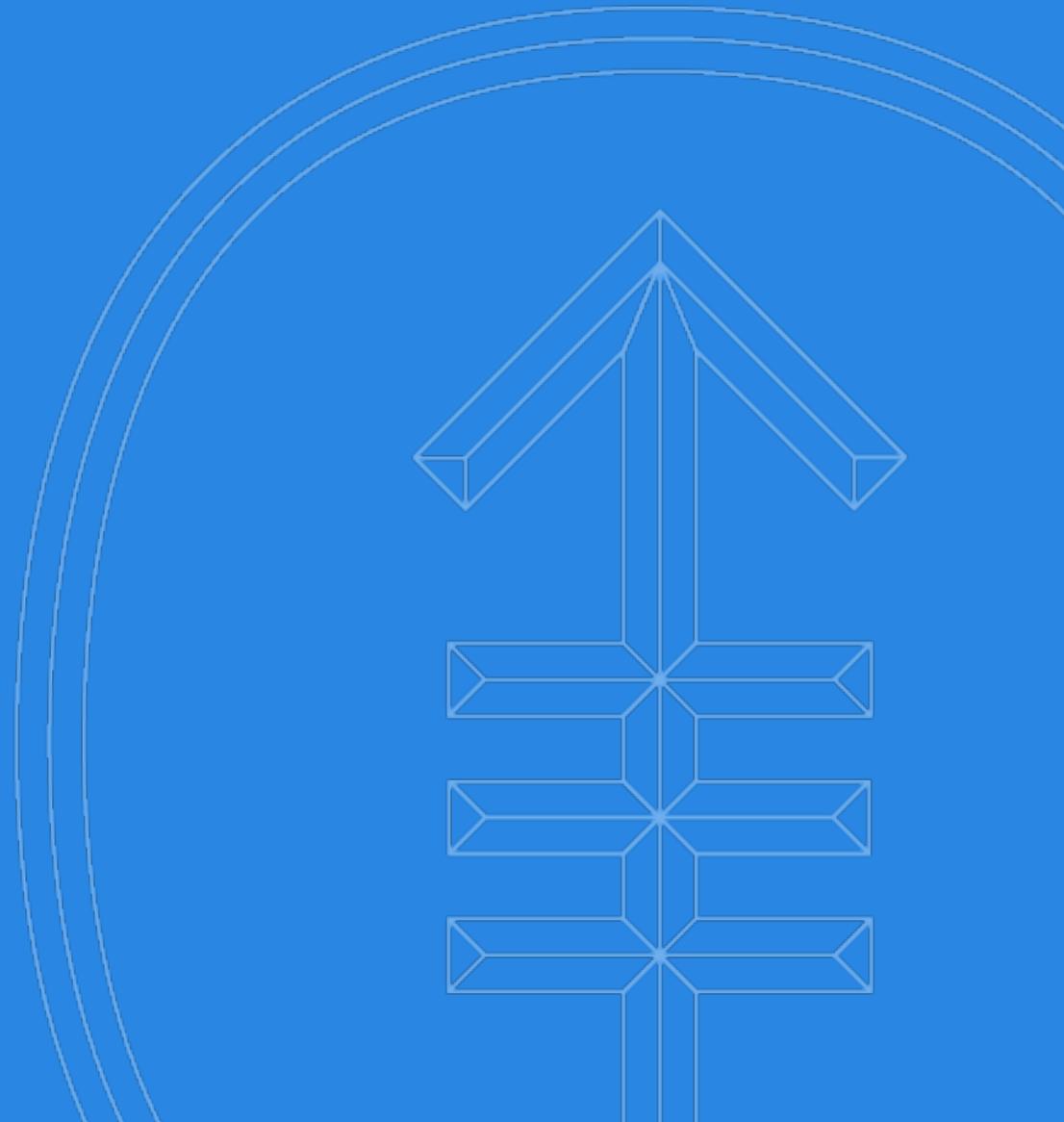
Roschewski et al, *NRCO* 2014

# Conclusions

- Lymphomas are a diverse and challenging group of diseases where advances in science and medicine are rapidly changing treatment paradigms and improving the lives of patients
- Progress toward precision medicine for lymphoma
  - **Hodgkin lymphoma** -> reducing toxicities with novel treatment approaches for a highly curable disease
  - **Diffuse large B cell lymphoma** -> dissecting molecular mechanisms and individualizing therapy to improve outcomes for a genetically heterogeneous disease

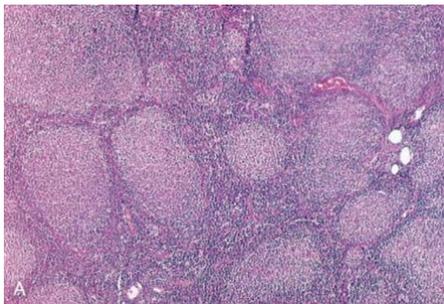


Memorial Sloan Kettering  
Cancer Center

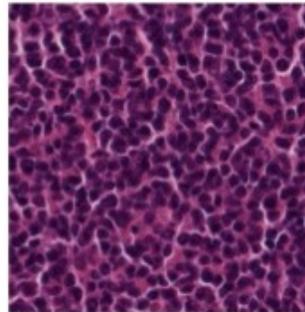


# Follicular lymphoma: The prototypical indolent lymphoma

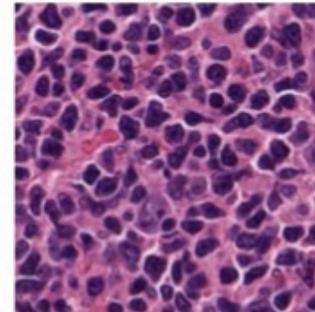
Morphology	<ul style="list-style-type: none"><li>• Grades 1 (small-cleaved cell), 2 (mixed small and large cell), and 3 (large cell)</li></ul>
Immunophenotyping	<ul style="list-style-type: none"><li>• CD20+, CD10+, CD5-, CD3-</li></ul>
Genetic features	<ul style="list-style-type: none"><li>• t(14;18) bcl2 oncogene (in 70%-95%)</li><li>• Aberrant Bcl2 expression blocks apoptosis, causing gradual accumulation of malignant cells that cannot die</li></ul>
Clinical features	<ul style="list-style-type: none"><li>• 2<sup>nd</sup> most common lymphoma (~25% of NHL)</li><li>• Equal number of men and women</li><li>• Presents with disseminated lymphadenopathy</li><li>• Stochastic transformation to DLBCL, actuarial risk up to 65% at 10 years</li><li>• Spontaneous regression in up to 30%</li><li>• Incurable -&gt; goal of treatment is long-term remission</li></ul>



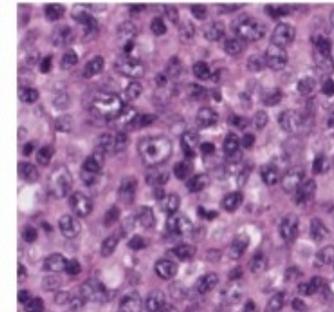
low magnification



Grade 1

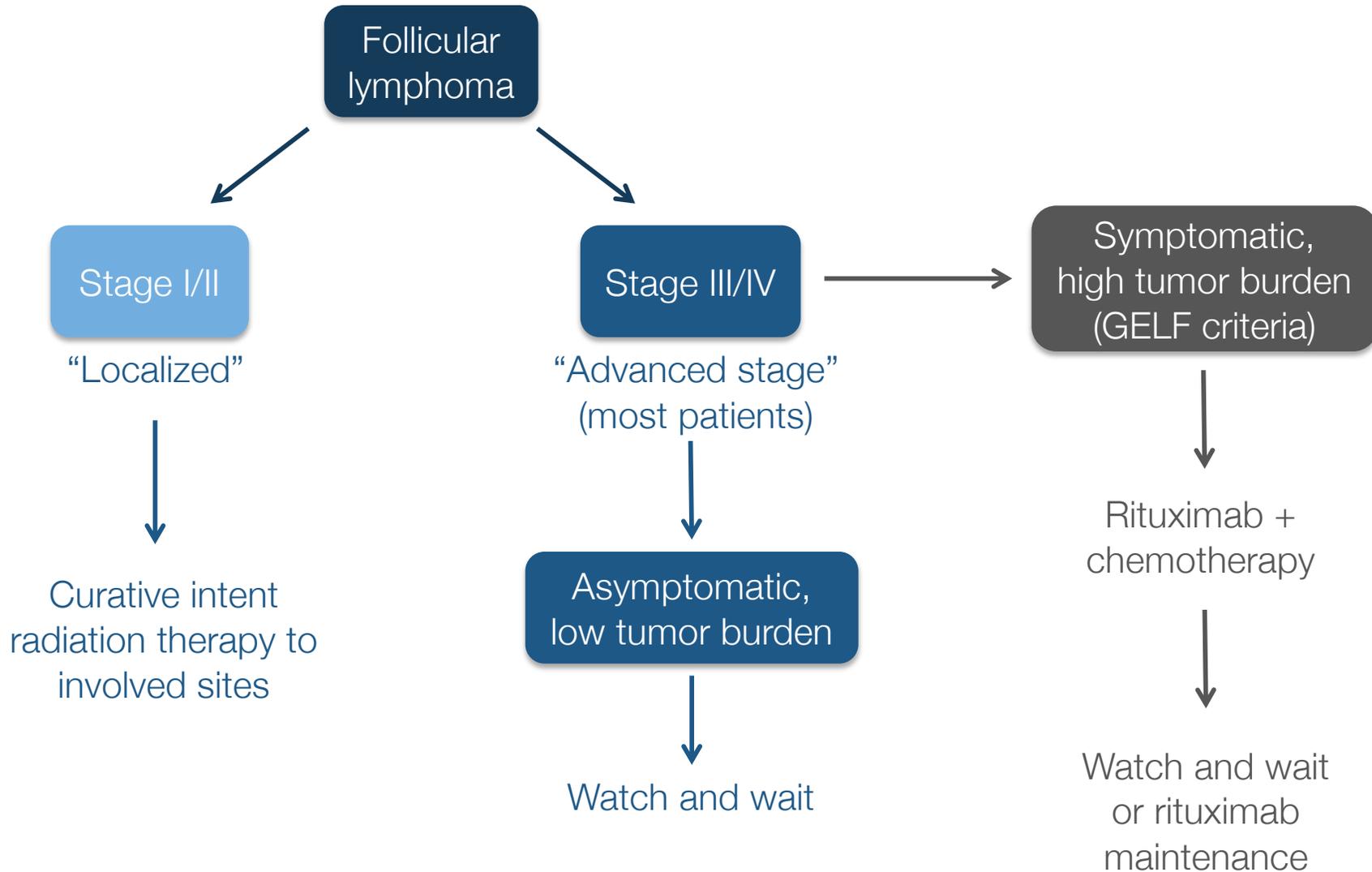


Grade 2



Grade 3

# Follicular lymphoma: Treatment algorithm



# Follicular lymphoma: Individualized treatment planning

- Follicular lymphoma is a disease of paradoxes
  - Incurable but a long natural history
  - Highly responsive to therapy but relapse inevitable
  - Current potentially curative therapy (alloSCT) associated with a high risk of treatment related mortality

## • Patient Characteristics

- Age
- Symptoms
- Short & long term goals
- Co-morbidity
- Preserve future options
- Reimbursement

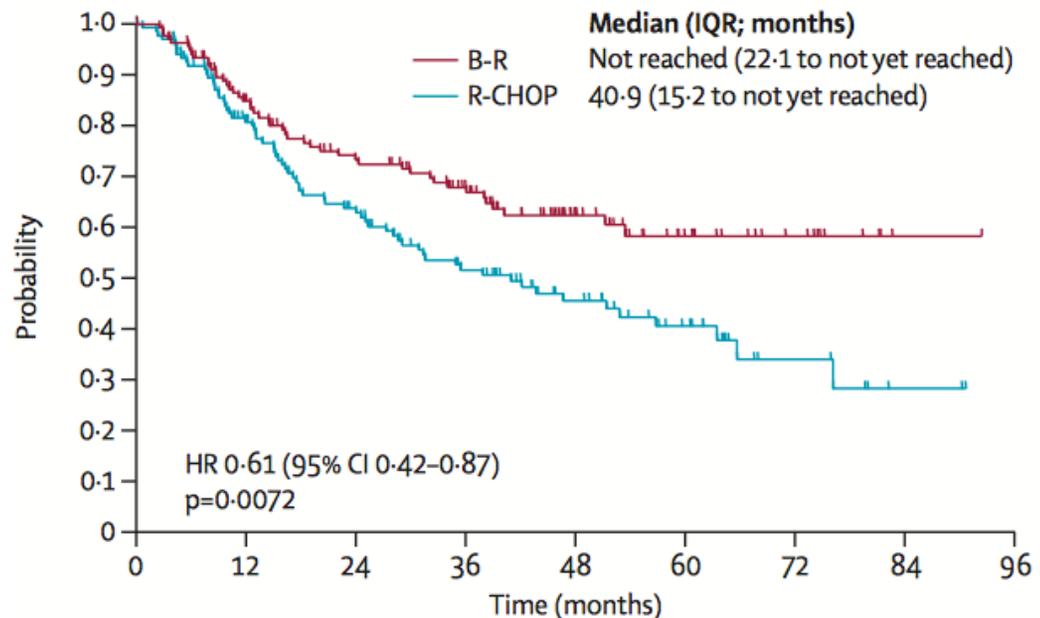
## • Disease Characteristics

- Stage
- FL IPI
- Transformation
- Sites of involvement
- Prior therapy
- Time from prior therapy

# Follicular lymphoma: Standard-of-care BR (or R-CHOP)

Chemotherapeutic agent	Class	Mechanism	Toxicities
<b>Rituximab</b>	anti-CD20 monoclonal antibody	kills CD20+ cells by multiple mechanisms	immune suppression; infusion reactions
<b>Bendamustine</b>	alkylator	DNA crosslinker	Skin rash; diarrhea; immune suppression

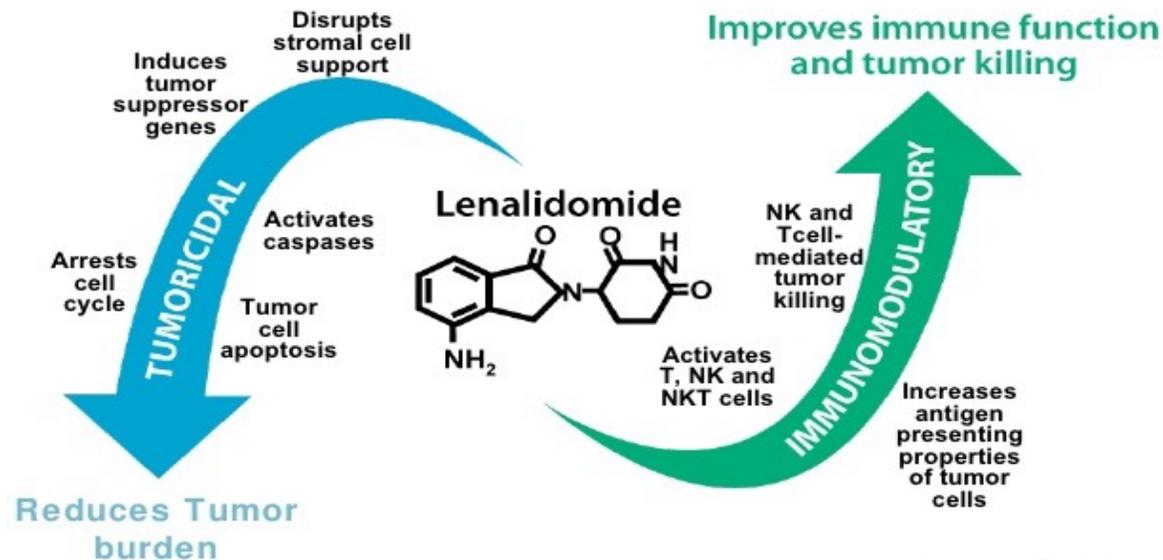
R-CHOP was previous standard of care but recent studies show that BR is at least as good and maybe better (controversial) in terms of efficacy and better tolerated than R-CHOP



# Follicular lymphoma: Moving to a 'chemotherapy-free' treatment approach



## Lenalidomide mechanism of action

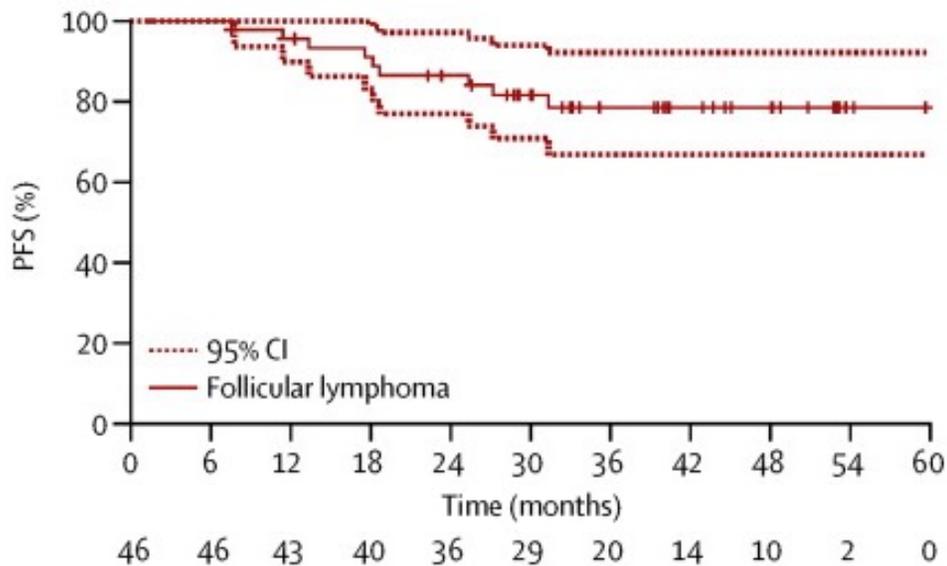


Stathis, *EASO* 2011

Notable side effects: teratogenic (birth defects) -> same class of drug as thalidomide

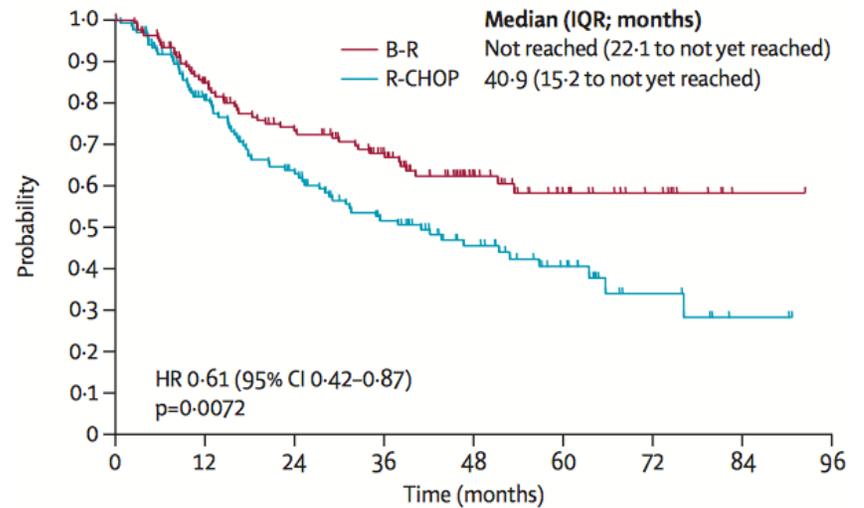
# Follicular lymphoma: Moving to a 'chemotherapy-free' treatment approach

Lenalidomide + rituximab (R<sup>2</sup>)



Fowler et al, *Lancet Onc* 2014

Benadmustine + rituximab (BR)



Rummel et al, *Lancet* 2013

R<sup>2</sup> vs BR now being tested in head-to-head randomized trial