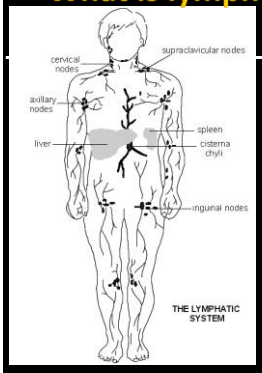
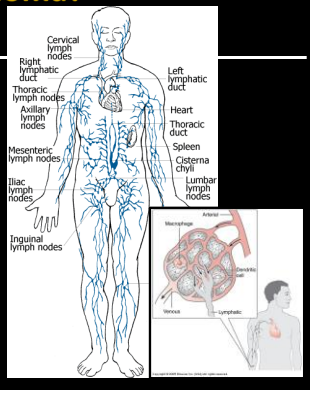
Introduction to the Biology and Management of Lymphoproliferative Disorders

Pallawi Torka, MD
Assistant Professor of Oncology
Lymphoma/Myeloma Division, Department of Medicine
Roswell Park Cancer Institute

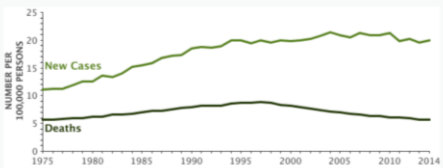
What is lymphoma?





Trends over time.....we are making a difference!

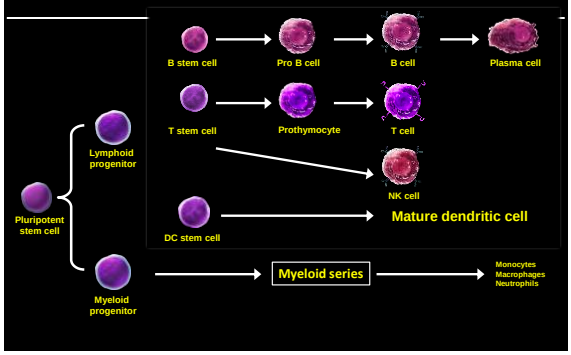
New Cases, Deaths and 5-Year Relative Survival — NHL — View Data Table

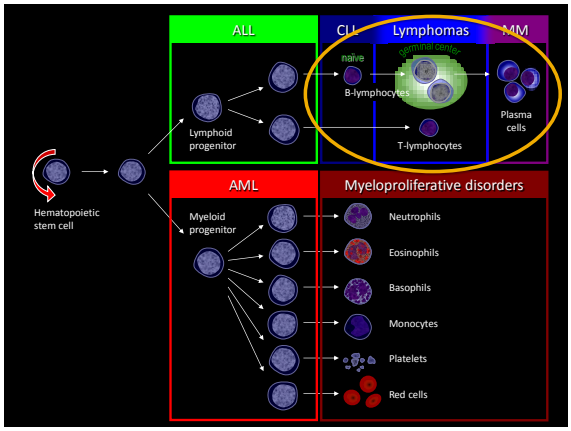


Year	1975	1980	1985	1990	1995	2000	2005	2009
5-Year Relative Survival	45.7%	49.1%	52.4%	49.7%	51.9%	63.8%	71.6%	74.0%

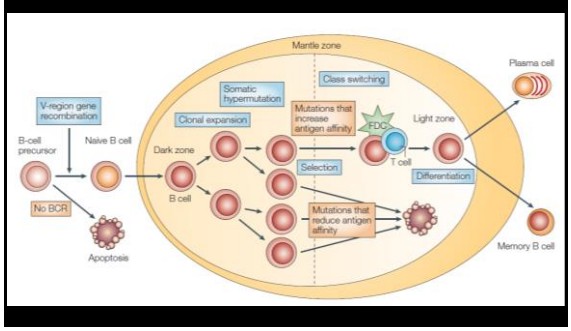
SEER 9 Incidence & U.S. Mortality 1975-2014, All Races, Both Sexes. Rates are Age-Adjusted.

Lymphocyte development is a complex process that occurs in discrete steps[1-3]

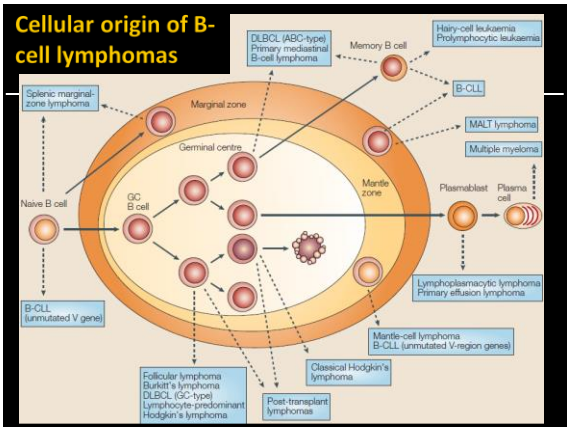




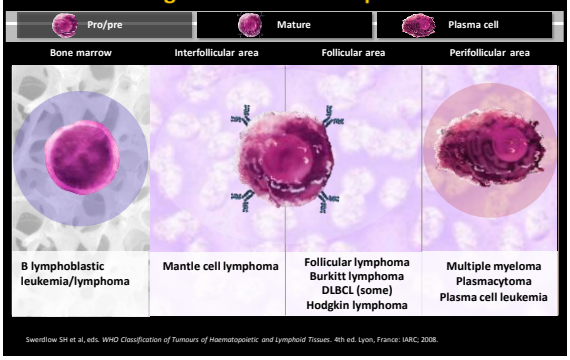
Stages of B-cell development



Cellular origin of B-cell lymphomas

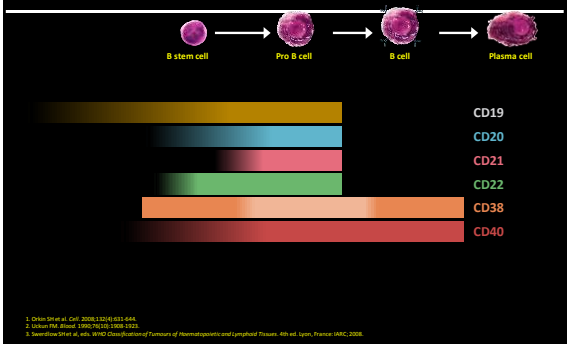


Lymphoma subtypes arise from different stages of B-cell development



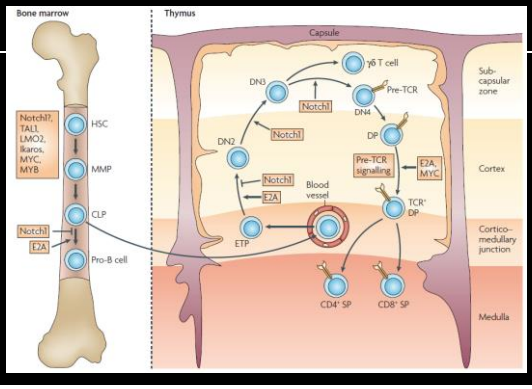
Swerdlow SH et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC; 2008.

Stages of B-cell development are defined by surface antigen expression[1-3]

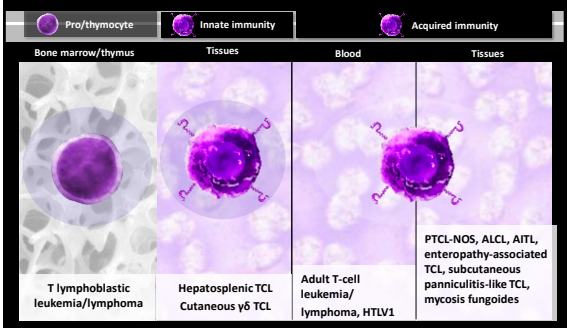


1. Orkin SH et al. *Cell*. 2008;132(4):631-644.
2. Uckun FM. *Blood*. 1990;76(10):1908-1923.
3. Swerdlow SH et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC; 2008.

T cell development



Lymphoma subtypes arise from different stages of T-cell development[1,2]



1. Swerdlow SH et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC; 2008.
2. de Leval L et al. *Histopathology*. 2011;58(1):49-68.

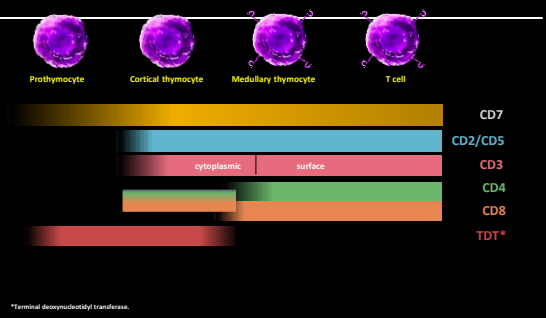
Table 2 NK and T-cell subsets and the classification of peripheral T-cell and NK-cell neoplasms

Innate immune system	*Adaptive immune system*
Does not require antigen sensitization	Characterized by specificity and memory
NK cells, NK/T cells, γδ T cells	Effector and memory T cells
Cell-mediated cytotoxicity	Act principally through cytokines and chemokines
Mainly cutaneous and other extranodal sites	Mainly nodal lymphomas
Children and adults	More often in adults

- Aggressive NK cell leukemia
- Systemic EBV positive T-cell lymphoproliferative disease
- Hepatosplenic γδ TCL

Most other T cell lymphomas

Stages of T-cell development are defined by surface antigen expression



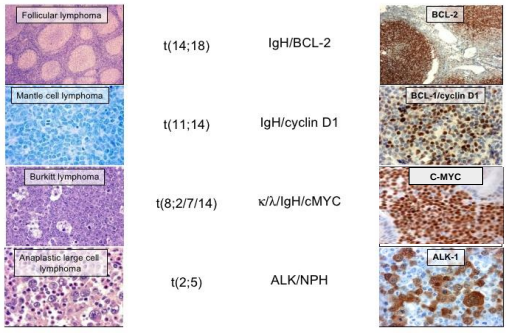
*Terminal deoxynucleotidyl transferase.

Swerdlow SH et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC; 2008.

Transforming events

- Reciprocal chromosomal translocations
  - Oncogene comes under control of active Ig Locus, causing a deregulated, constitutive expression of oncogene
- Mutations in tumor suppressor genes
- Genomic amplifications (such as REL)
- Translocations not involving Ig loci
- Viruses

Genetic alterations determine lymphoma entities



Classification

- Historically- a mess
  - 1940s Gail and Mallory
  - 1950s Rappaport
  - 1970s Lukes-Collins
  - 1970s Kiel
  - 1982 Working
  - 1994 REAL
  - WHO- currently used

WHO classification for lymphomas

- Universal, consensual
- Collaborative work between clinicians & pathologists from different countries
- Accurate criteria, updated
- All haematopoietic neoplasms (NHL, Hodgkin, myeloid & histiocytic neoplasms)

- **About ~60 entities of lymphomas**

Lymphoma classification (WHO)

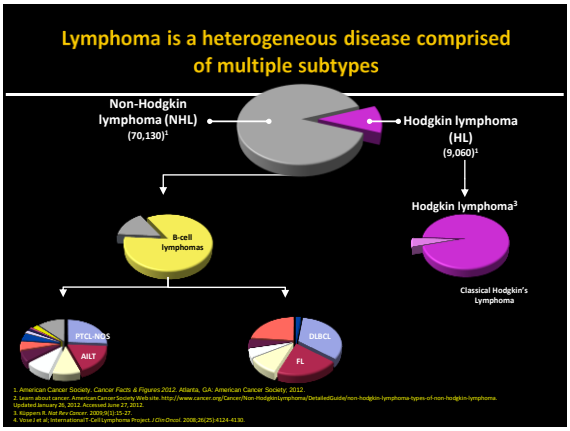
- B-cell neoplasms
  - precursor
  - mature
- T-cell & NK-cell neoplasms
  - precursor
  - mature

Non-Hodgkin Lymphomas

- **Hodgkin lymphoma**

WHO 2016 Classification

Lymphoma is a heterogeneous disease comprised of multiple subtypes



1. American Cancer Society. *Cancer Facts & Figures 2012*. Atlanta, GA: American Cancer Society; 2012.
2. Learn about cancer. American Cancer Society Web site. http://www.cancer.org/Cancer/Non-HodgkinLymphoma/DetailedGuide/non-hodgkin-lymphoma-types-of-non-hodgkin-lymphoma. Updated January 26, 2012. Accessed June 27, 2012.
3. Küppers R. *Nat Rev Cancer*. 2009;9(1):15-27.
4. Vose J et al; International T-Cell Lymphoma Project. *J Clin Oncol*. 2008;26(25):4124-4130.

Risk factors for NHL

- immunosuppression or immunodeficiency
- connective tissue disease
- infectious agents
- ionizing radiation

Clinical manifestations

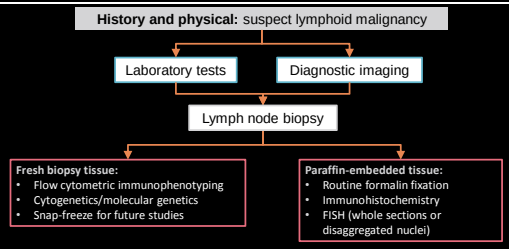
- Variable
  - severity: asymptomatic to extremely ill
  - time course: evolution over weeks, months, or years
- Systemic manifestations
  - fever, night sweats, weight loss, anorexia, pruritis
- Local manifestations
  - lymphadenopathy, splenomegaly most common
  - any tissue potentially can be infiltrated

Other complications of lymphoma

- bone marrow failure (infiltration)
- CNS infiltration
- immune hemolysis or thrombocytopenia
- compression of structures (eg spinal cord, ureters)
- pleural/pericardial effusions, ascites

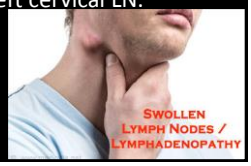
How to make the diagnosis?

A systematic approach to diagnosing suspected lymphoid cancers is recommended[1,2]

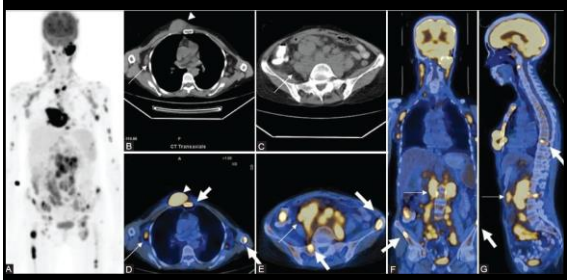


Case study 1

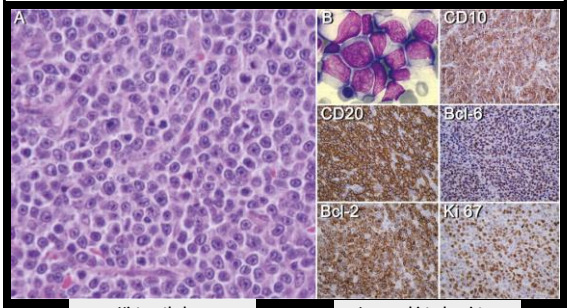
- A 50 year old previously healthy man presents with rapidly enlarging right sided neck lymph node for the past 1 month. He has lost 10 lb despite a good appetite and reports drenching night sweats.
- On exam, he has a 5 cm left cervical LN.
- No LAP elsewhere.
- No hepatosplenomegaly



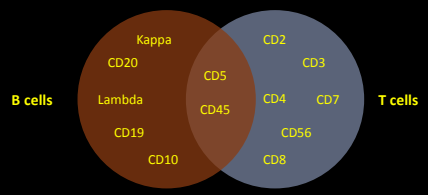
- Labs show a LDH of 1600, rest wnl.
- PET-CT



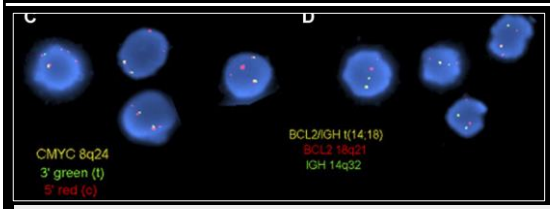
Lymph node biopsy



Immunophenotyping lymphomas involves multiple cell surface antigens[1,2]



Molecular diagnostics- MYC and BCL2 rearrangements



Final diagnosis

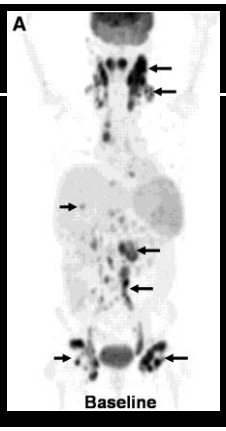
Till 2015: Double hit DLBCL
2016 onwards: High grade B- cell lymphoma with myc and BCL-2 rearrangements

Treatment: high dose chemotherapy +/- autologous stem cell transplant

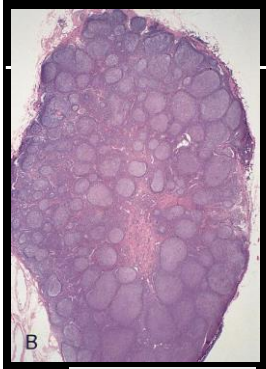
Case study 2

- A 75 year old man presents with a cervical LN which has been growing gradually for past 2 years. Over the past year, he has also noticed swellings in his groin on both sides.
- On exam he has non-tender cervical and inguinal lymphadenopathy.
- Labs (including LDH) are normal

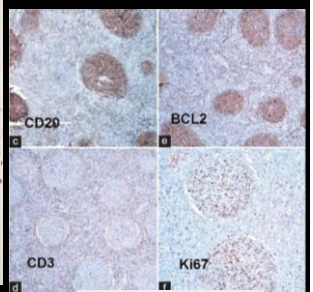
PET scan



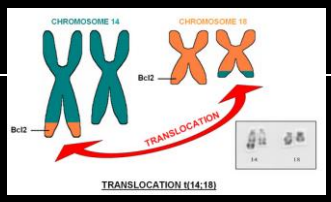
LN biopsy



Histopathology



Immunohistochemistry

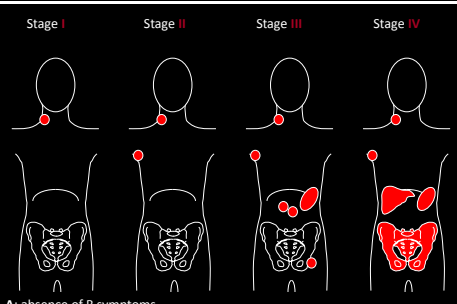


- Final diagnosis: Follicular lymphoma grade 1-2
- Treatment: Watchful expectancy

Lymphoma Biology

- Aggressive NHL
  - short natural history (patients die within months if untreated)
  - disease of rapid cellular proliferation, cured with intensive combination chemotherapy regimens
- Indolent NHL
  - relatively good prognosis, long natural history (patients can live for many years untreated)
  - disease of slow cellular accumulation, not curable

Ann Arbor Staging of lymphoma



A: absence of B symptoms
B: fever, night sweats, weight loss

Three common lymphomas

- Follicular lymphoma
- Diffuse large B-cell lymphoma
- Hodgkin lymphoma

Follicular lymphoma

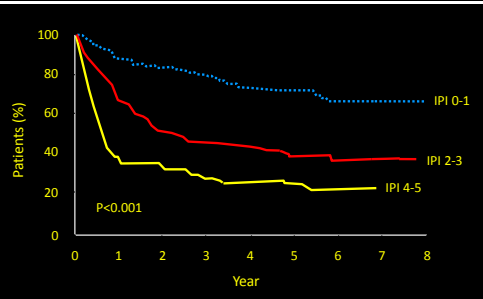
- most common type of “indolent” lymphoma
- usually widespread at presentation
- often asymptomatic
- not curable (some exceptions)
- associated with BCL-2 gene rearrangement [t(14;18)]
- cell of origin: germinal center B-cell

- defer treatment if asymptomatic (“watch-and-wait”)
- several chemotherapy options if symptomatic
- median survival: years
- despite “indolent” label, morbidity and mortality can be considerable
- transformation to aggressive lymphoma can occur

Diffuse large B-cell lymphoma

- most common type of "aggressive" lymphoma
- usually symptomatic
- extranodal involvement is common
- cell of origin: germinal center B-cell or activated B-cell
- treatment should be offered- R-CHOP is the standard
- curable in ~ 40%

Diffuse Large B-Cell Lymphoma (DLCL): OS



Adapted from Armitage. J Clin Oncol. 1998;16:2780.

Strategies tested to improve the clinical outcome of DLBCL patients

Modality investigated	Improvement in response rate	Improvement in PFS or OS
Dose Dense R-CHOP14 vs. R-CHOP-21 LNH03-6B GELA study	No	No
Increase number of cycles R-CHOP x 6 vs. R-CHOP x 8 (RICOVER study)	No	No
High dose chemotherapy and autologous stem cell support (HDC0ASCS) in first remission for high risk DLBCL (Stiff et al., JCO 2011, #8011)	No	Favor in PFS at 2-years (69% vs. 56%, P=0.005). Study included CHOP and R-CHOP treated patients
Increasing intensity regimen without HDC-ASCT R-CHOP vs. R-Mega-CHOP	No	No
Rituximab Maintenance (ECOG 4494 and CORAL studies)	No	No

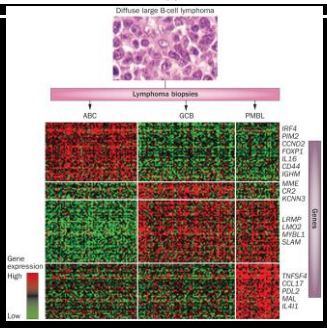
Current areas of research in aggressive B-cell lymphoma

1) Predicting patients that are less likely to respond to rituximab-CHOP in the front-line setting

2) The identification of key-regulatory pathways present in relapsed/refractory DLBCL

3) Can the targeting those pathways translate into clinical benefit?

Gene-expression profiling subdivides morphologically indistinguishable DLBCL tumors into three distinct cell-of-origin (COO) subtypes



Roschewski, M. et al. Nat. Rev. Clin. Oncol.2014; 11:11-23

Distinct subtypes of DLBCL

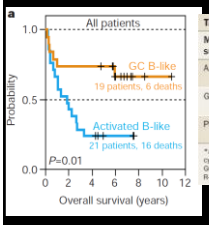


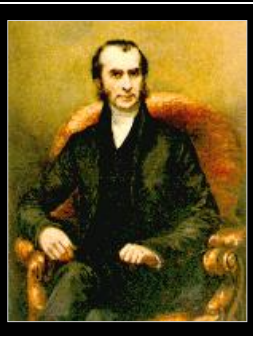
Table 2 | PFS and overall survival for each DLBCL molecular subtype

Molecular subtype	Regimen	3-year PFS rate	3-year overall survival rate	Reference
ABC DLBCL	R-CHOP	40%	Approximately 45%	Lenz *et al.* (2008)[29]
GCB DLBCL	R-CHOP	74%	Approximately 80%	Lenz *et al.* (2008)[29]
PMBL	DA-EPOCH-R	100%*	97%*	Dunleavy *et al.* (2013)[58]

*At 5 years. Abbreviations: ABC, activated B-cell; DA-EPOCH-R, dose-adjusted etoposide, doxorubicin and cyclophosphamide with vincristine, prednisone and rituximab; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell; PFS, progression-free survival; PMBL, primary mediastinal B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

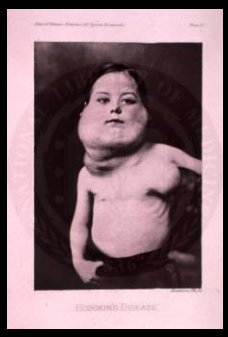
Alizadeh et al. Noture 2000. 403(6769): 503-11
Roschewski, M. et al. Nat. Rev. Clin. Oncol.2014; 11:11-23

Hodgkin lymphoma



Thomas Hodgkin
(1798-1866)

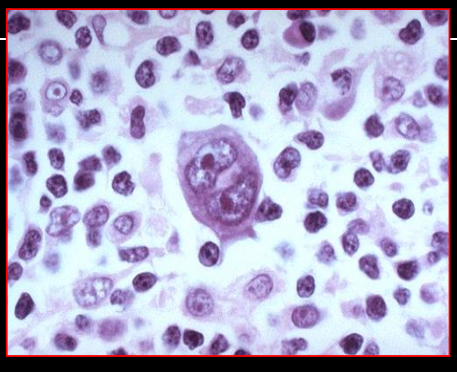
Classical Hodgkin Lymphoma



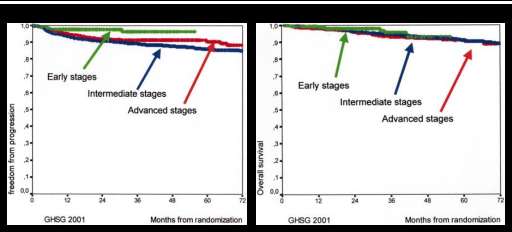
Hodgkin lymphoma

- cell of origin: germinal centre B-cell
- Reed-Sternberg cells (or RS variants) in the affected tissues
- most cells in affected lymph node are polyclonal reactive lymphoid cells, not neoplastic cells
- Standard therapy: ABVD

Reed-Sternberg cell

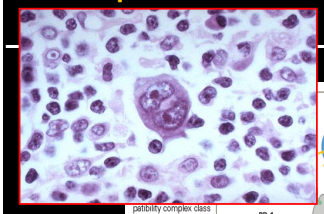


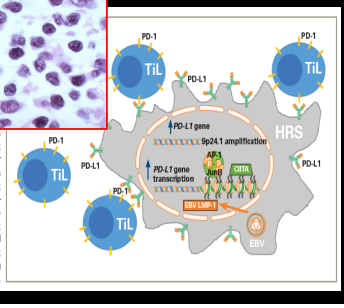
Clinical outcome of HL patients based on risk category



Kaplan Meyer curves for freedom from progression (FFP)/Overall survival and for early (HD7, arm B, 289 patients), intermediate (HD8, 1138 patients), and advanced (HD9, arm C, 466 patients) Hodgkin's lymphoma patients according to the experience of the German Hodgkin's Lymphoma Study Group (GHSG)

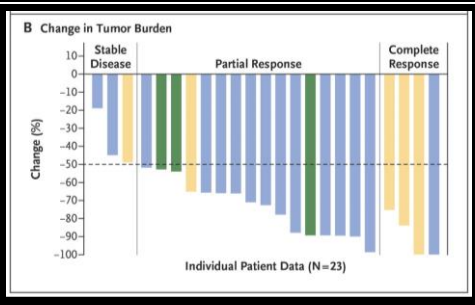
Checkpoint inhibition in HL





patibility complex class II transcription factor; EBV = Epstein-Barr virus; HRS = Hodgkin and Reed-Sternberg; LMP-1 = latent membrane protein 1; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; TiL = tumor-infiltrating lymphocyte.

Bench to bedside….nivolumab in HL



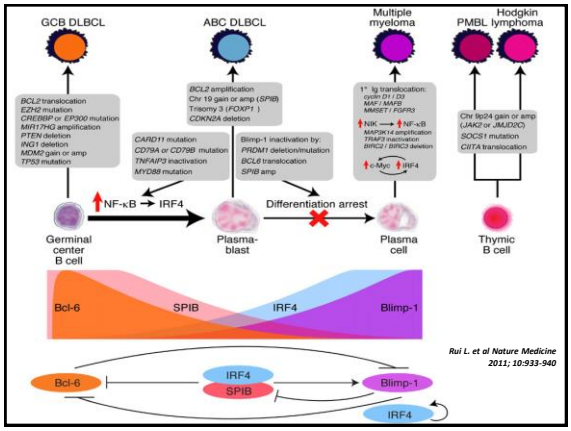
Ansell et al. NEJM 2015; 372: 311-318

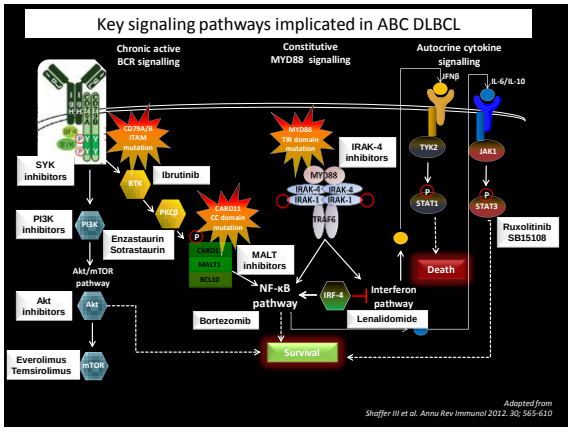
A practical way to think of lymphoma

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

LOOKING AHEAD: Precision medicine

- Recent advances in preclinical research have resulted in a better understanding of the molecular pathogenesis of lymphomas
- Discover pathways involved in their development and progression
- Several new agents have been developed that specifically inhibit the components of these pathways and which are now in clinical evaluation for lymphomas





Oncogenic mechanisms and potential targets in DLBCL subtypes

Table 1 | Oncogenic mechanisms and potential targets in DLBCL subtypes

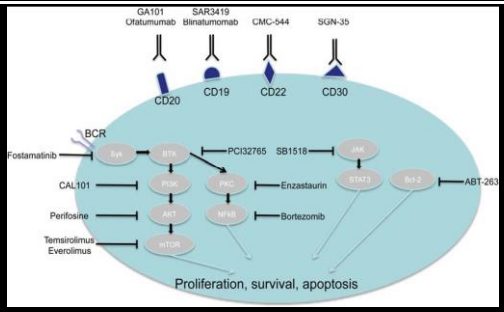
DLBCL subtype	Cell of origin	Oncogenic mechanisms	Potential targets
GCB	Germinal centre B-cell	*BCL2* translocation*	BCL6
		EZH2 mutations‡	EZH2
		PTEN deletions§	PI3K/Akt
		Loss of PTEN expression	
ABC	Post-germinal centre B-cell	NF-κB activation‖	BCR
		CARD11 mutations	CBM complex
		MYD88 mutations	IRAK-4
		CD79B mutations	JAK–STAT
		A20 deletions	
PMBL	Post-thymic B-cell	NF-κB activation¶	JAK–STAT
		9p24 amplification¶	PD-1#
		REL amplification	
		JAK2 mutations	
		CIITA translocations#	

Roschewski, M. et al. Nat. Rev. Clin. Oncol.2014; 11:11-23

New monoclonal antibodies

- Advances in monoclonal antibody (mAb) technology have allowed the production of a high number of new mAbs directed against antigens present on the surface of lymphoma cells
- Based on the cell surface antigens they recognize, mAbs can be divided into those directed against :
  - B-cell lineage specific antigens (e.g. CD20, CD19, CD22, CD23, CD37)
  - Other superficial antigens (not B-cell specific, e.g. CD40, CD80, CD30)

New antibodies and targets

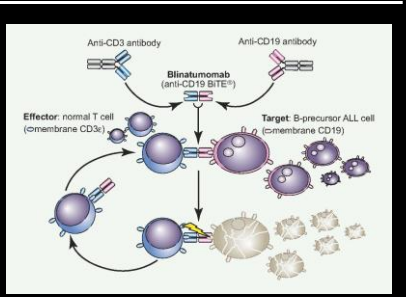


Blinatumomab- BiTE

CD19 is a B-cell specific antigen that has been targeted for the treatment of lymphomas

Blinatumomab, a bispecific T-cell engager antibody, is composed of a single-chain bi-specific antibody targeting both CD19 and CD3

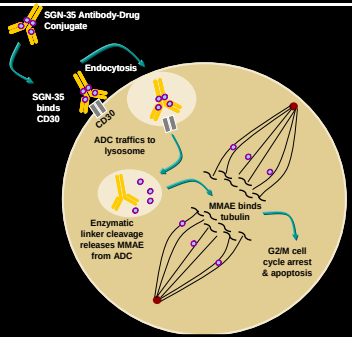
Bringing cytotoxic CD3-positive T cells in the proximity of the malignant CD19-positive lymphoma cells to be killed



Antibody-drug conjugate

- CD22 is expressed in 60%–90% of B-cell NHLs, and represents an excellent target for therapy with antibody drug conjugates (ADCs)
- Inotuzumab ozogamicin (CMC-544), a CD22 mAb conjugated with the potent chemotherapy agent calicheamicin, resulted in substantial single-agent activity in both indolent and aggressive NHL
- CMC-544 has entered clinical evaluation in combination with rituximab, with salvage chemotherapy regimens and more recently with other targeted agents
- Brentuximab vedotin (SGN35) is an anti-CD30 ADC , already approved

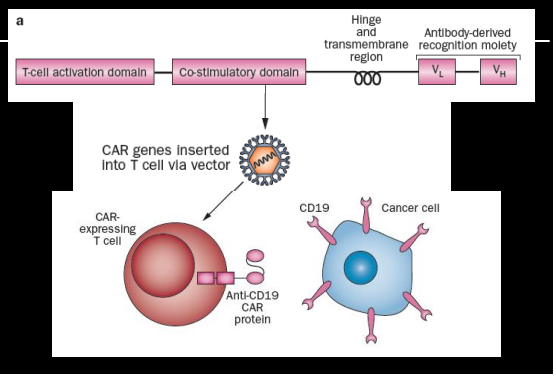
Antibody drug conjugate

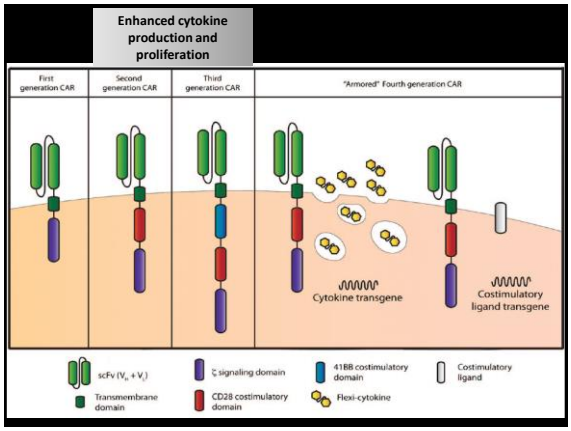


Small molecules in clinical development

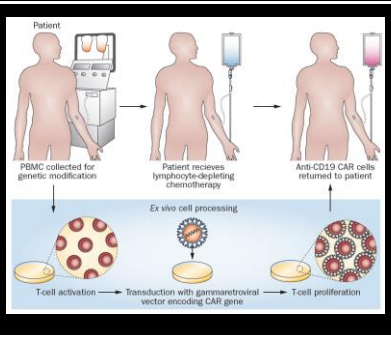
- The PI3K/akt/mTOR pathway: important in several cellular processes including cell proliferation, survival, growth and motility
  - mTOR inhibitors: Temsirolimus and everolimus
  - PI3K: The isoform δ (PI3Kδ) has been linked to the development of lymphomas. CAL101
- Histone deacetylase inhibitors: Histone deacetylation is an epigenetic mechanism associated with gene silencing in both haematological and solid tumors. Vorinostat, romidepsin, panobinostat and mocetinostat

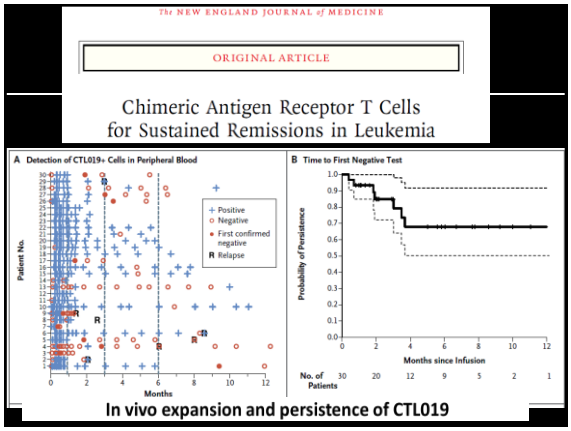
What are Chimeric antigen receptors?



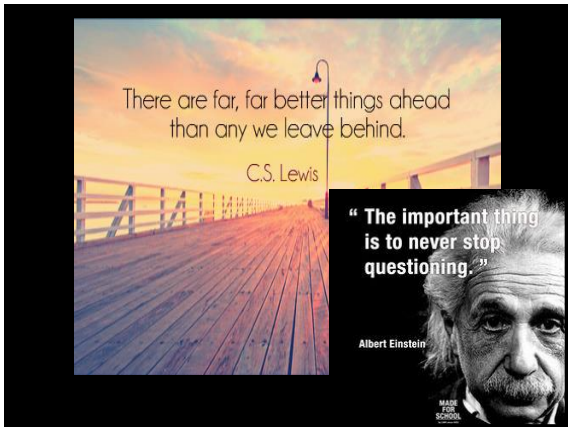


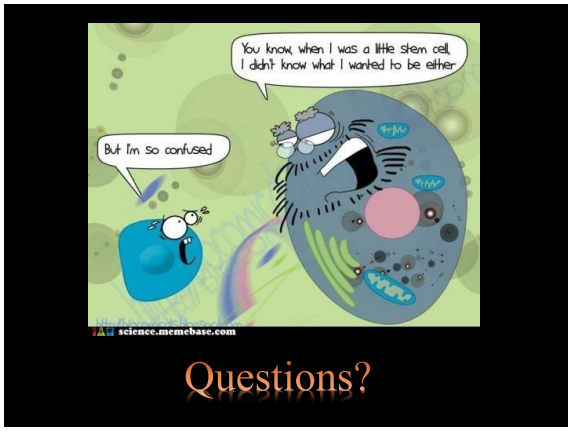
Chimeric Antigen Receptor (CAR) T-Cell Therapy





In vivo expansion and persistence of CTL019





Questions?