EBMT European Society for Blood and Marrow Transplantation

Lymphoma- Med A-new drugs and treatments

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Lisbon, 19/03/2018

EBMT European Society for Blood and Marrow Transplantation

Disclosures: Roche, Gilead

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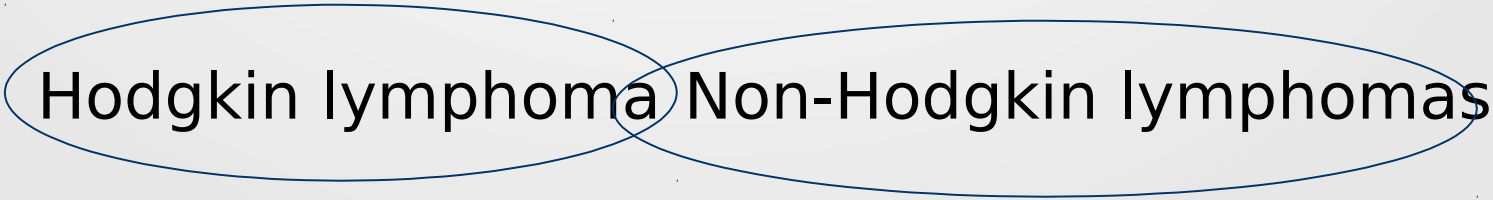
Outline

- Lymphoma- what is it?
  - Classification
  - Why does it matter
- Most frequent types of lymphoma
  - DLBCL
  - FL
  - HL
- Treatments
- New drugs
  - PI3 inhibitors
  - Bruton tyrosine kinase inhibitors (BTKi)
  - Checkpoint inhibitors
  - BCL-2 antagonists
  - New monoclonal antibodies (MoAb)

Definition of lymphoma

HETEROGENOUS group of malignant neoplasms arising in the reticuloendothelial and lymphoid system.

Hodgkin lymphoma	Non-Hodgkin lymphomas



Classification of lymphomas

- Non-Hodgkin lymphomas
  - B-cell lymphomas
  - T-cell lymphomas
- Hodgkin lymphoma

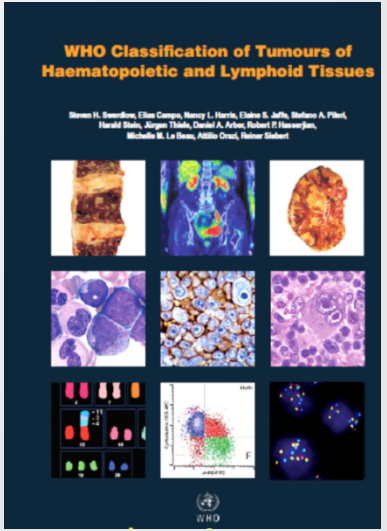
From REAL to WHO

A Revised European-American Classification of Lymphoid Neoplasms: A Proposal From the International Lymphoma Study Group

By Nancy Lee Harris, Elaine S. Jaffe, Harald Stein, Peter M. Banks, John K.C. Chan, Michael L. Cleary, Georges Delsol, Christine De Wolf-Peeters, Brunangelo Falini, Kevin C. Gatter, Thomas M. Grogan, Peter G. Isaacson, Daniel M. Knowles, David Y. Mason, Hans-Konrad Muller-Hermelink, Stefano A. Pileri, Miguel A. Piris, Elisabeth Ralfkiaer, and Roger A. Warnke

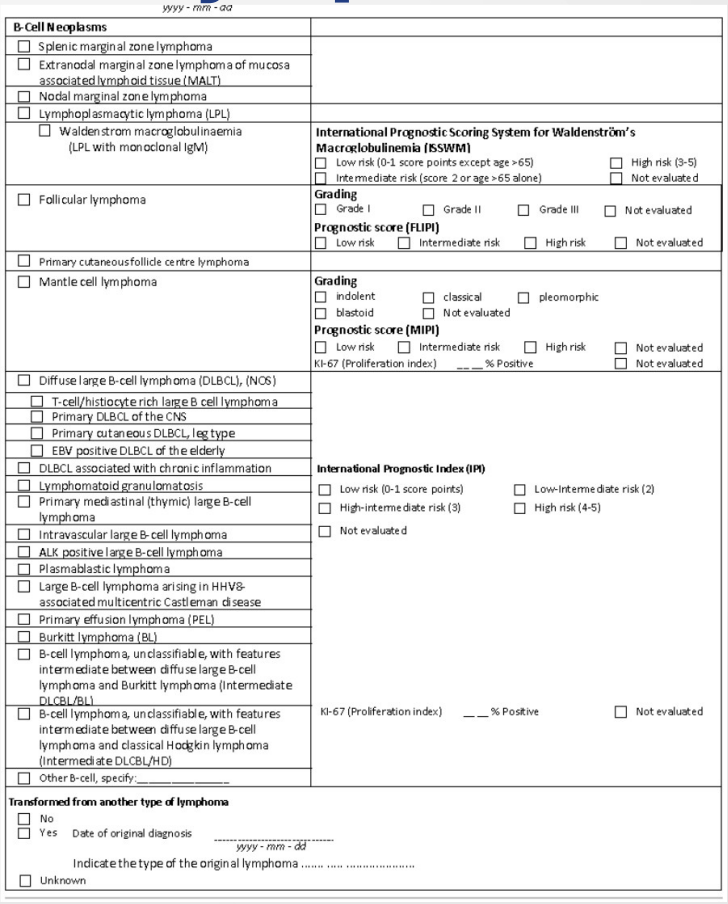
Clinico-pathological entities defined by

- Morphology
- Immunology
- Genetics
- Molecular
- Clinical



Classification of lymphoma and MED-A

From WHO 2008!!



yyyy - mm - aa

B-Cell Neoplasms	
☐ Splenic marginal zone lymphoma	
☐ Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT)	
☐ Nodal marginal zone lymphoma	
☐ Lymphoplasmacytic lymphoma (LPL)	
☐ Waldenstrom macroglobulinaemia (LPL with monoclonal IgM)	**International Prognostic Scoring System for Waldenström's Macroglobulinemia (ISSWM)** ☐ Low risk (0-1 score points except age >65) ☐ High risk (3-5) ☐ Intermediate risk (score 2 or age >65 alone) ☐ Not evaluated
☐ Follicular lymphoma	**Grading** ☐ Grade I ☐ Grade II ☐ Grade III ☐ Not evaluated **Prognostic score (FLIPI)** ☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated
☐ Primary cutaneous follicle centre lymphoma	
☐ Mantle cell lymphoma	**Grading** ☐ indolent ☐ classical ☐ pleomorphic ☐ blastoid ☐ Not evaluated **Prognostic score (MIPI)** ☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated KI-67 (Proliferation index) __ __ % Positive ☐ Not evaluated
☐ 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	**International Prognostic Index (IPI)**
☐ Lymphomatoid granulomatosis	☐ Low risk (0-1 score points) ☐ Low-Intermediate risk (2)
☐ Primary mediastinal (thymic) large B-cell lymphoma	☐ High-intermediate risk (3) ☐ High risk (4-5)
☐ Intravascular large B-cell lymphoma	☐ Not evaluated
☐ ALK positive large B-cell lymphoma	
☐ Plasmablastic lymphoma	
☐ Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease	
☐ Primary effusion lymphoma (PEL)	
☐ Burkitt lymphoma (BL)	
☐ B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (Intermediate DLCBL/BL)	
☐ B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (Intermediate DLCBL/HD)	KI-67 (Proliferation index) __ __ % Positive ☐ Not evaluated
☐ Other B-cell, specify:_____	

Transformed from another type of lymphoma

☐ No
☐ Yes Date of original diagnosis ..... (yyyy - mm - dd)
Indicate the type of the original lymphoma ....
☐ Unknown

Classification of lymphoma and MED-A

	Abnormality	Absent	Present	FISH used	Not Evaluated
Mantle cell lymphoma or Waldenstrom macroglobulinaemia	del 17p	☐	☐	☐ No ☐ Yes	☐
BL or "Intermediate DLCBL/Burkitt Lymphoma"	t(2;8)	☐	☐		☐
	t(8;14)	☐	☐		☐
	t(8;22)	☐	☐		☐
	t(14;18)	☐	☐		☐
	myc rearrangement	☒	☐		☐
	BCL-2 rearrangement	☒	☐		☐
	BCL-6 rearrangement	☐	☐		☐

High-grade lymphoma with *MYC* and *BCL-2* rearrangement

WHO 2016-Lymphoma classification B-

Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
*Large B-cell lymphoma with IRF4 rearrangement**
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia*

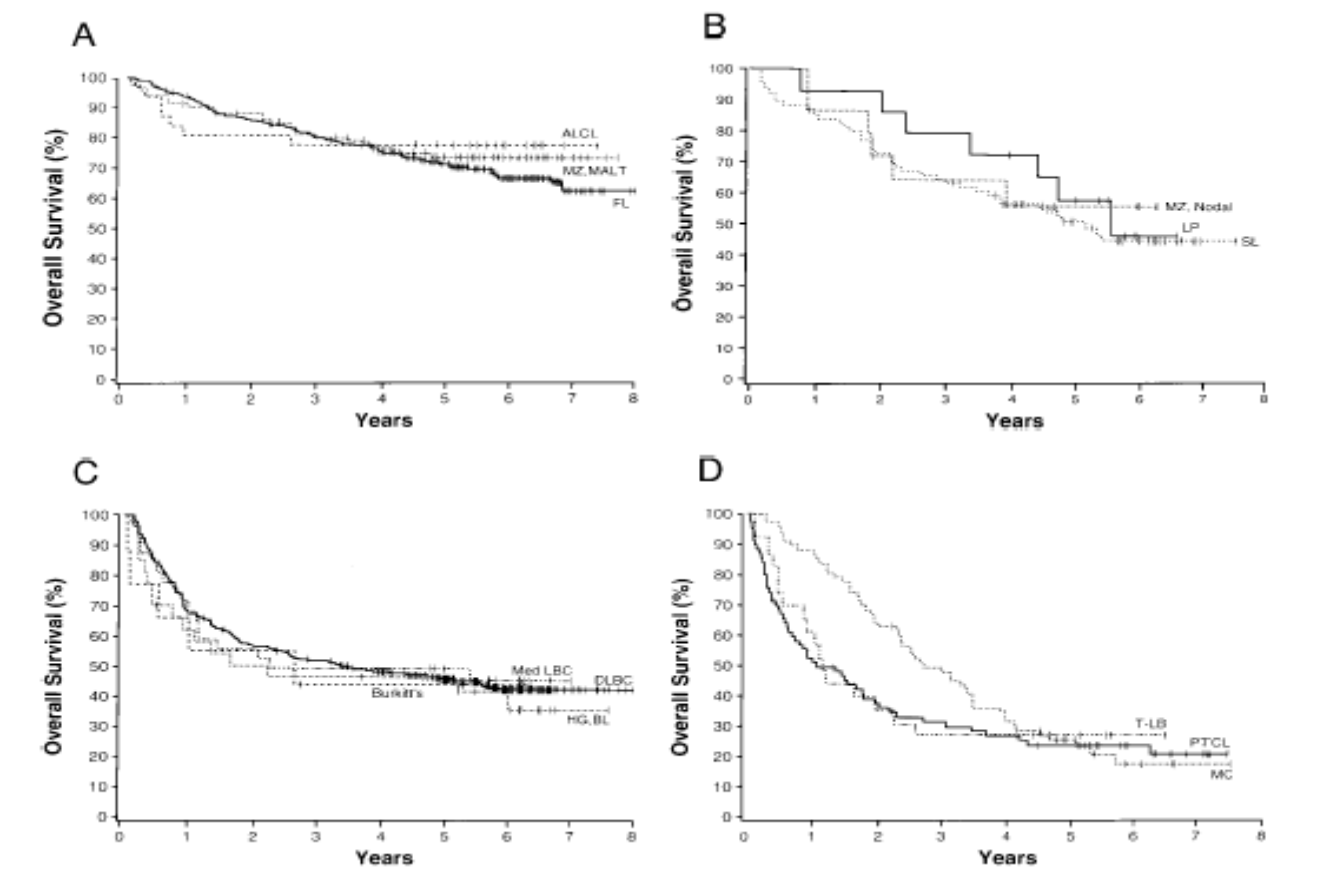
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV^+ DLBCL, NOS*
*EBV^+ mucocutaneous ulcer**
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK^+ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
*$HHV8^+$ DLBCL, NOS**
Burkitt lymphoma
*Burkitt-like lymphoma with 11q aberration**
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

WHO 2016-Lymphoma classification T-NHL and HL

Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK *
*Breast implant–associated anaplastic large-cell lymphoma**

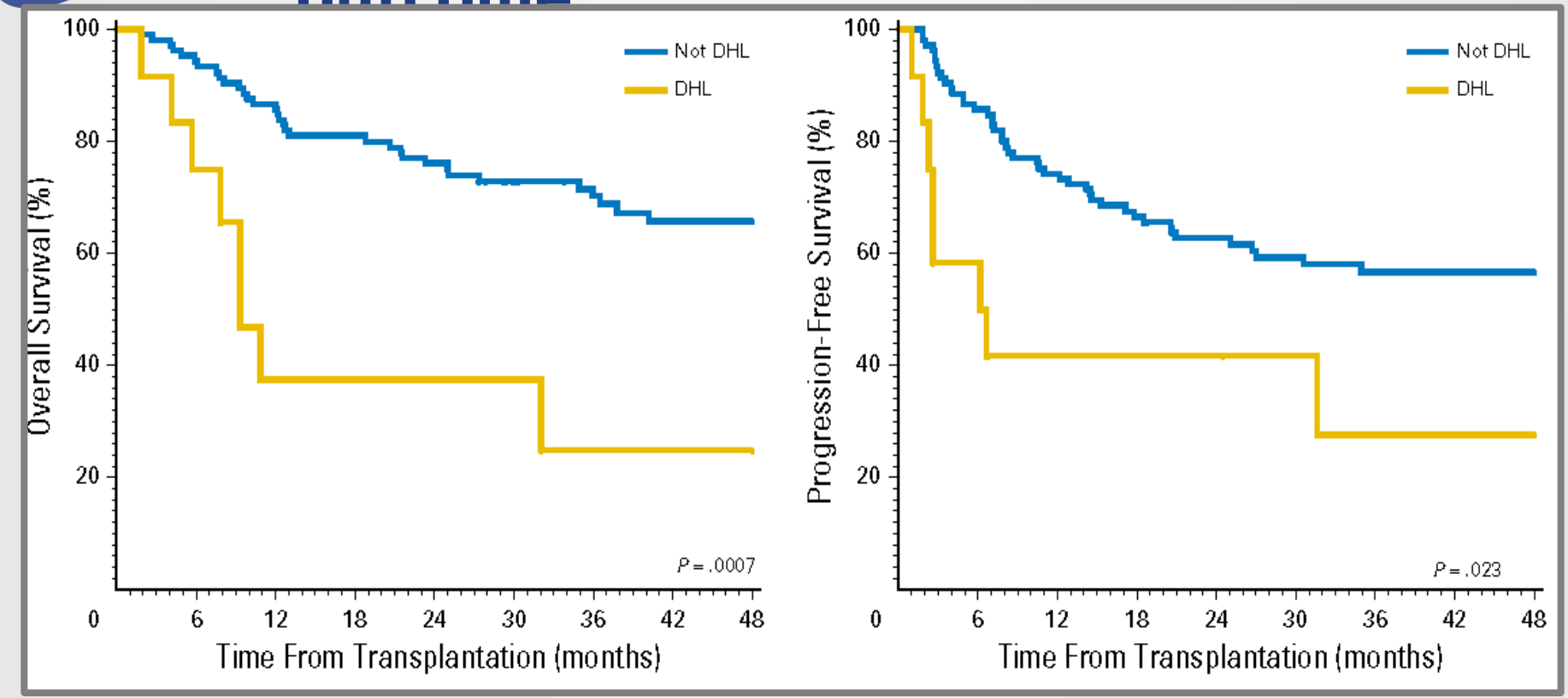
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
Classical Hodgkin lymphoma PTLD
Histiocytic and dendritic cell neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease*

Overall survival in patients with



NHL Classification Project, 199

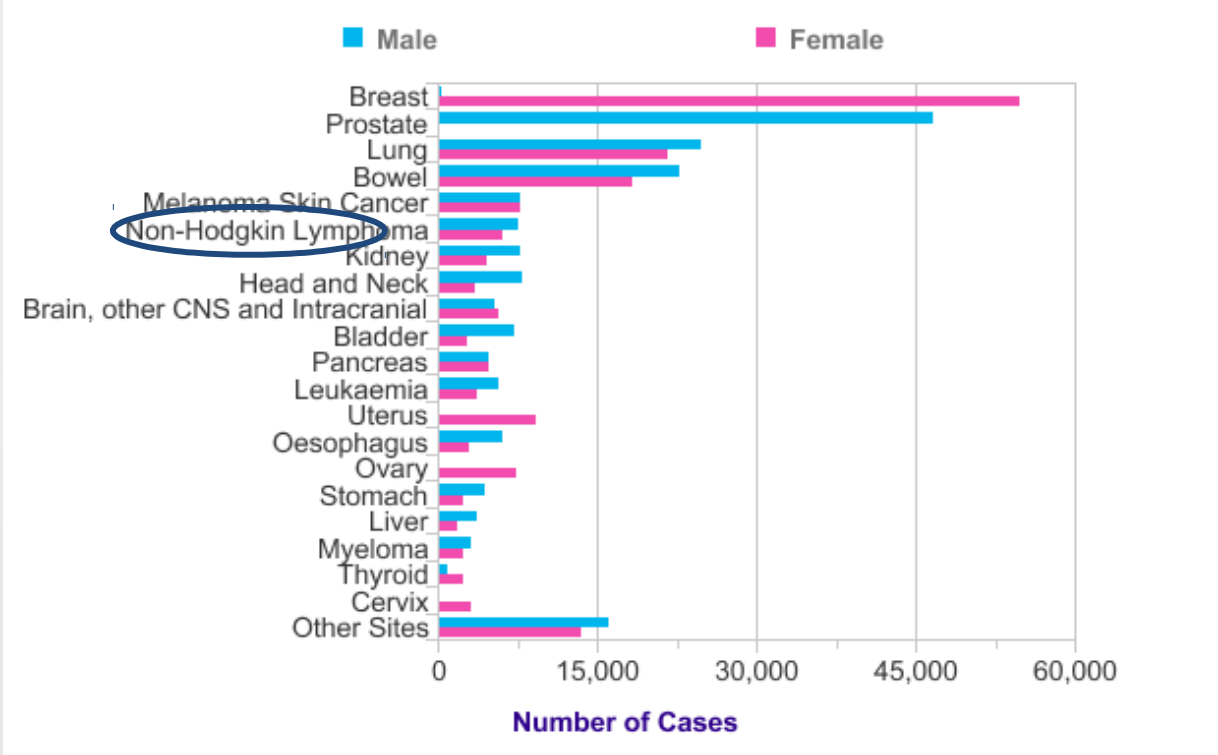
Impact of molecular abnormalities on outcome



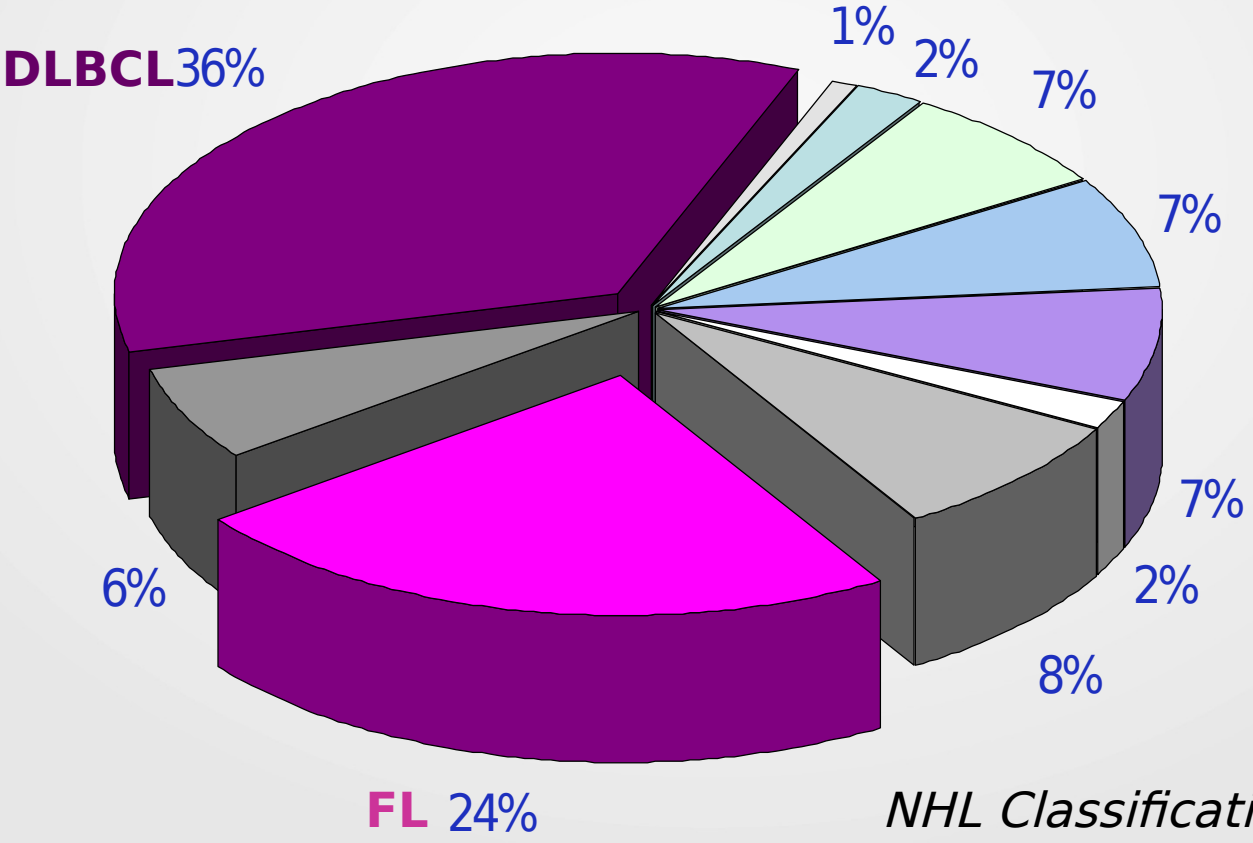
Herrera et al, J Clin Oncol, 2017

Non Hodgkin lymphoma

- Median age at diagnosis: 65 yrs
- >13,000 new cases/year in UK



Frequency of subtypes of NHL



NHL Classification Project, 1997

Diffuse large B cell lymphoma: clinical characteristics

- Median age: 60-70 years
- Advanced stage: 50-60%
- BM involvement: 15-20%
- Primary extranodal: 20-30%

How bad is DLBCL?

ADVANCED DIFFUSE HISTIOCYTIC LYMPHOMA, A POTENTIALLY CURABLE DISEASE

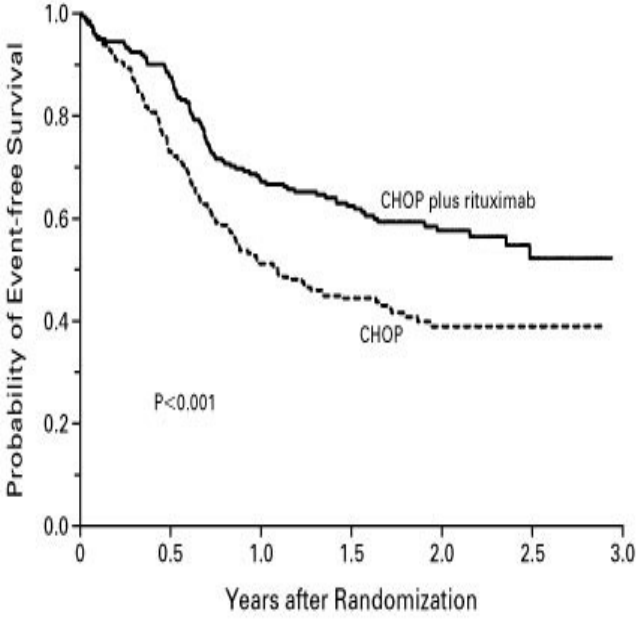
RESULTS WITH COMBINATION CHEMOTHERAPY

VINCENT T. DEVITA, JR. GEORGE P. CANELLOS
BRUCE CHABNER PHILIP SCHEIN *
SUSAN P. HUBBARD ROBERT C. YOUNG

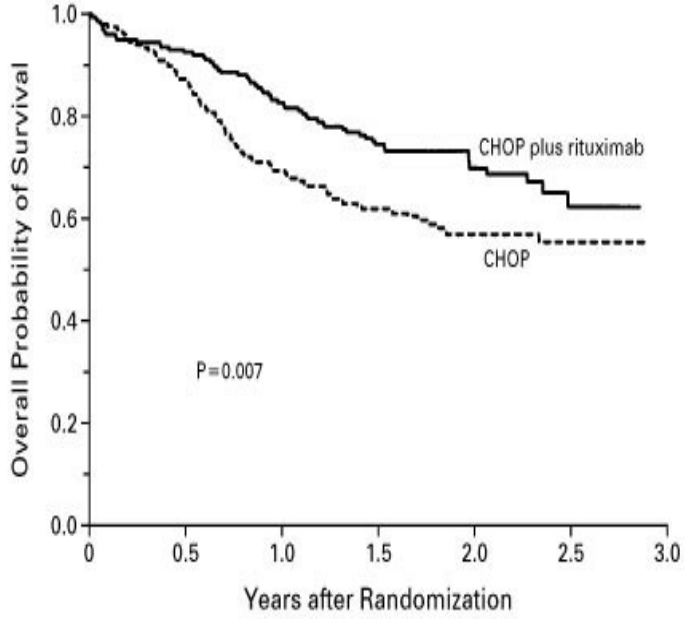
Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014, U.S.A.

Lancet, February 1, 1975

Treatment of DLBCL



No. at Risk						
CHOP plus rituximab	202	177	137	108	63	19
CHOP	197	144	101	72	42	17

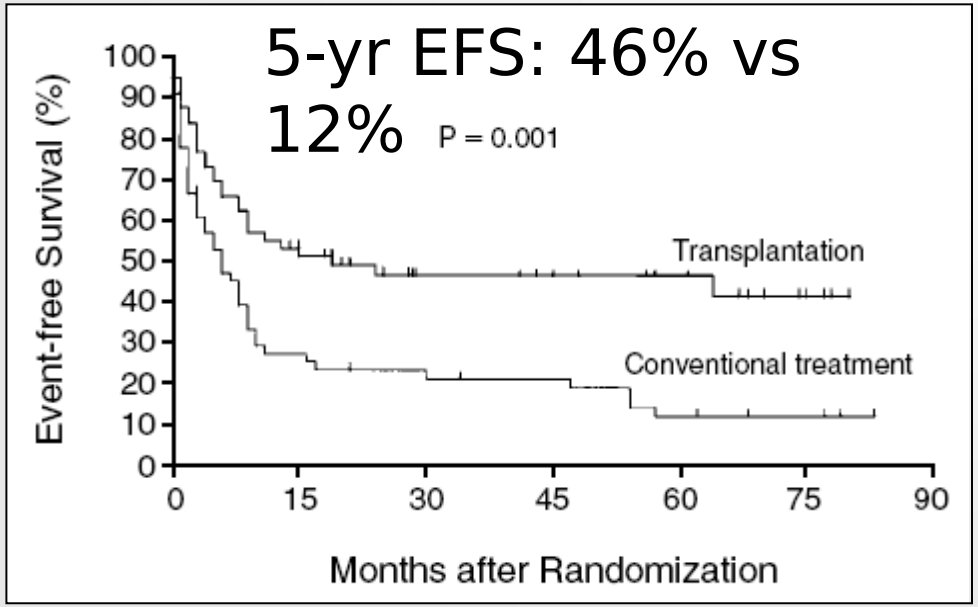


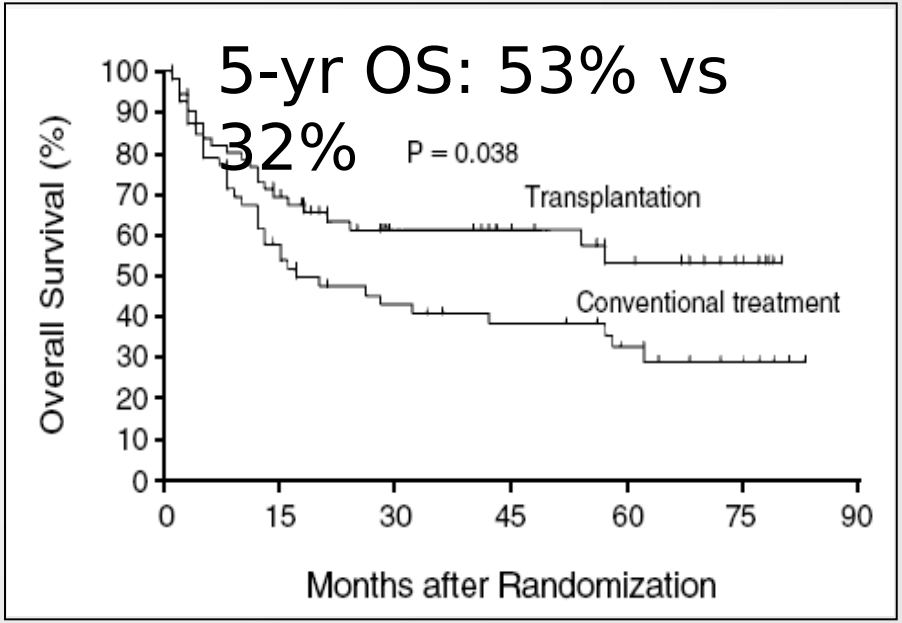
No. at Risk						
CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

Coiffier et al, New Engl J Med, 2002

Role of HDT-ASCR in DLBCL

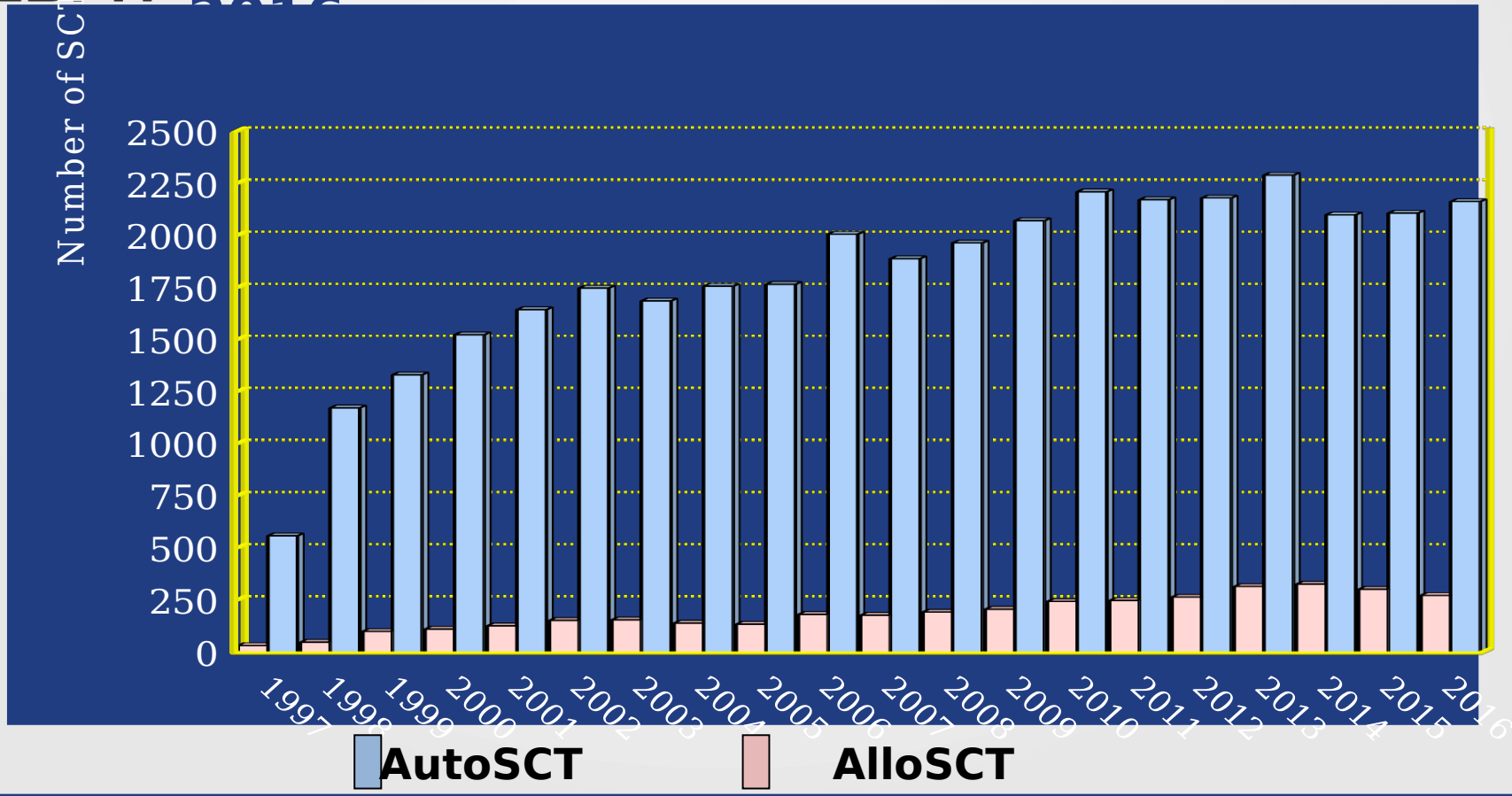
The PARMA trial for relapsed/resistant DLBCL: chemotherapy vs HDT-ASCR





Philip et al, N Engl J Med, 1995

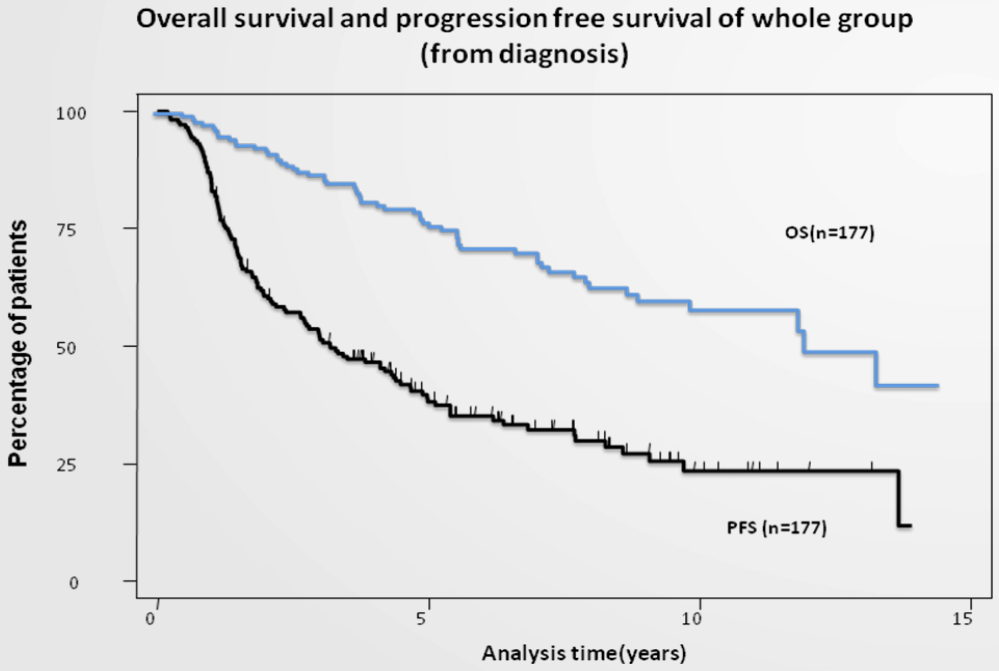
Lymphoma Registry: SCT for DLBCL 1997-2016



Follicular lymphoma: clinical characteristics

- Median age: 50-60 yrs
- Good performance status
- Advanced stage: 80%
- BM infiltration: 60%

Follicular lymphoma



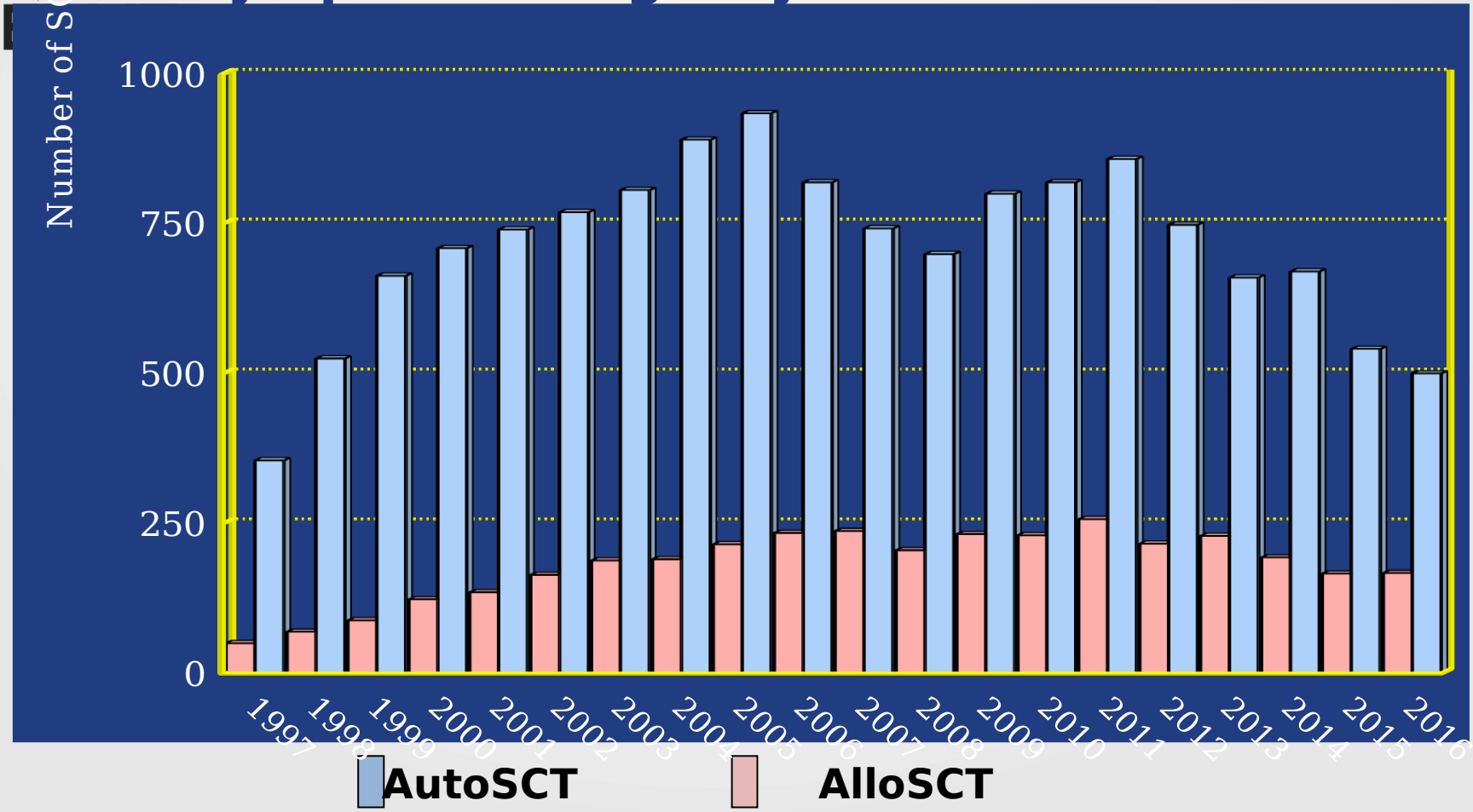
- Long survival
- Multiple relapses
- Risk of histological transformation
- Incurable (with conventional treatment)

Barts 1997-2007

FL: treatment options

	Morbility	*Mortality*	*Symptomatic improvement*	*Response rate*	*Prolonged response*
Expectant management	**0**	**0**	**0**	**+**	**0/+**
Monotherapy	**+**	**+**	**++**	**++**	**+**
Combination chemotherapy	**++**	**+**	**+++**	**+++**	**++**
Rituximab	**+**	**0**	**++**	**++**	**+**
Radio-MoAb	**+**	**+**	**+++**	**+++**	**++**
Rituximab + PQT	**++**	**+**	**+++**	**+++**	**+++**
AutoSCT	**+++**	**++**	**+++**	**+++**	**+++**
AlloSCT	**++++**	**+++**	**+++**	**+++**	**+++**

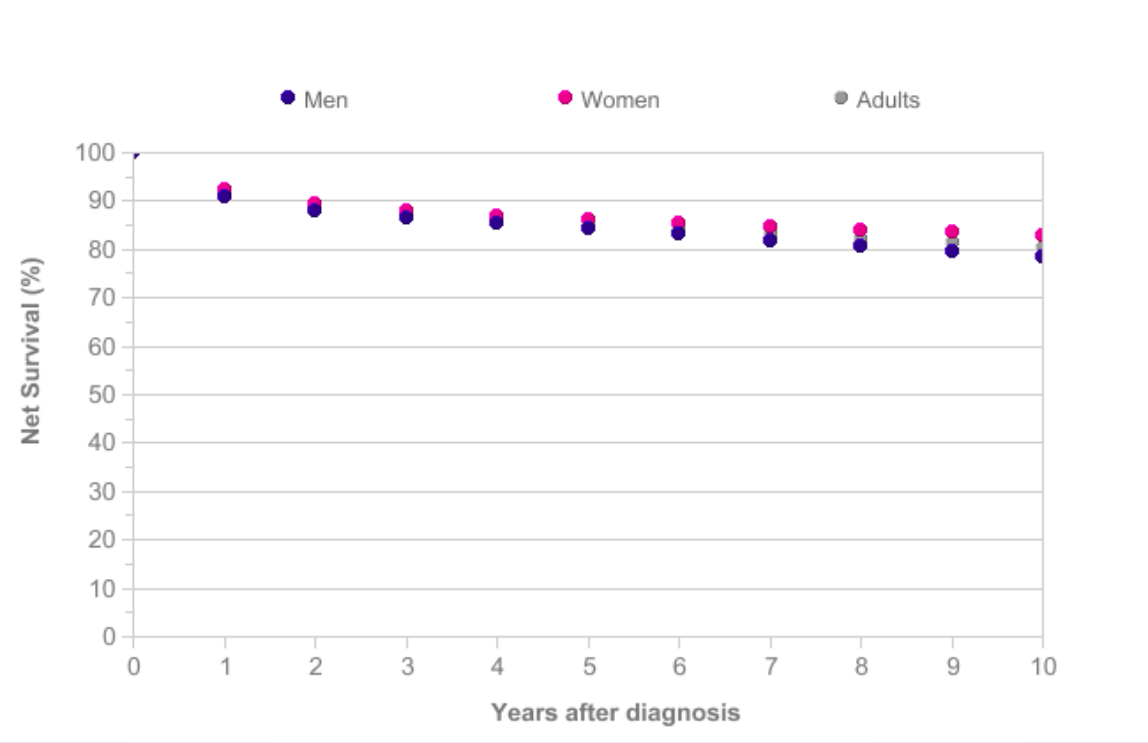
Lymphoma Registry: SCT for FL 1997-2016



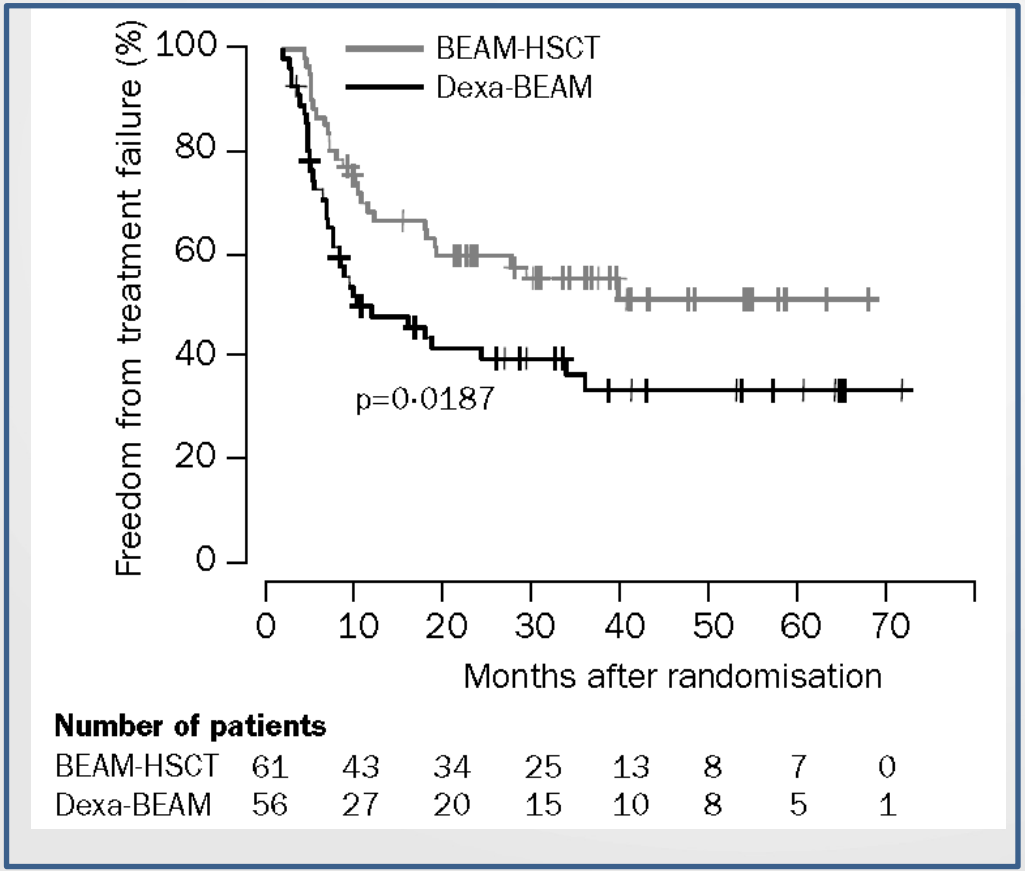
Hodgkin lymphoma

- ~1500 new cases every year in the UK
  ~ Incidence: 3/100,000/year
- Bimodal age distribution: 15-34 yrs, > 60 yrs
- Male/female ratio: 1.4:1

Survival of adult patients with l...

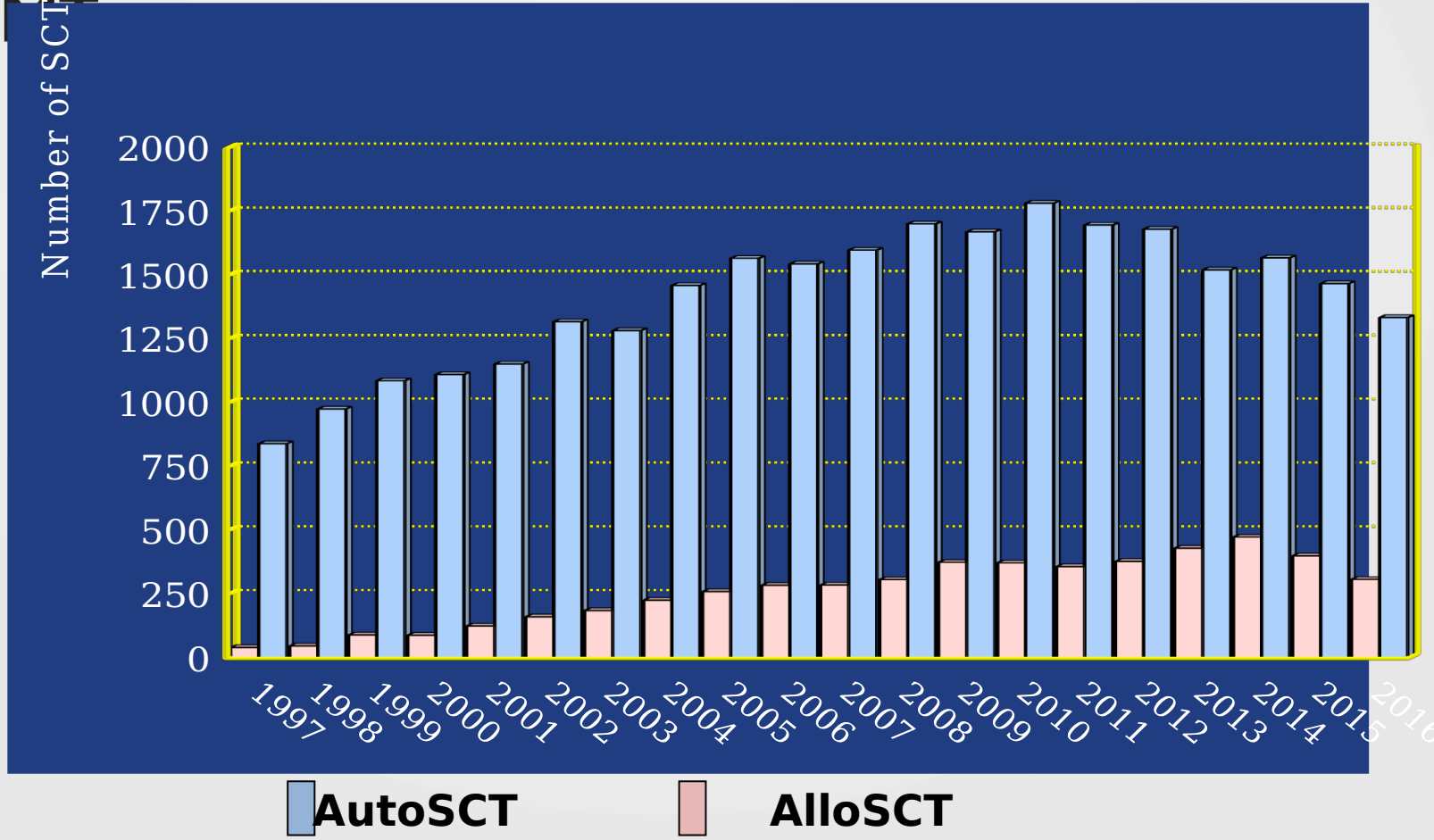


Is there a 2nd chance?



Schmitz et al, Lancet, 200

Lymphoma Registry: SCT for HL 1997-2016

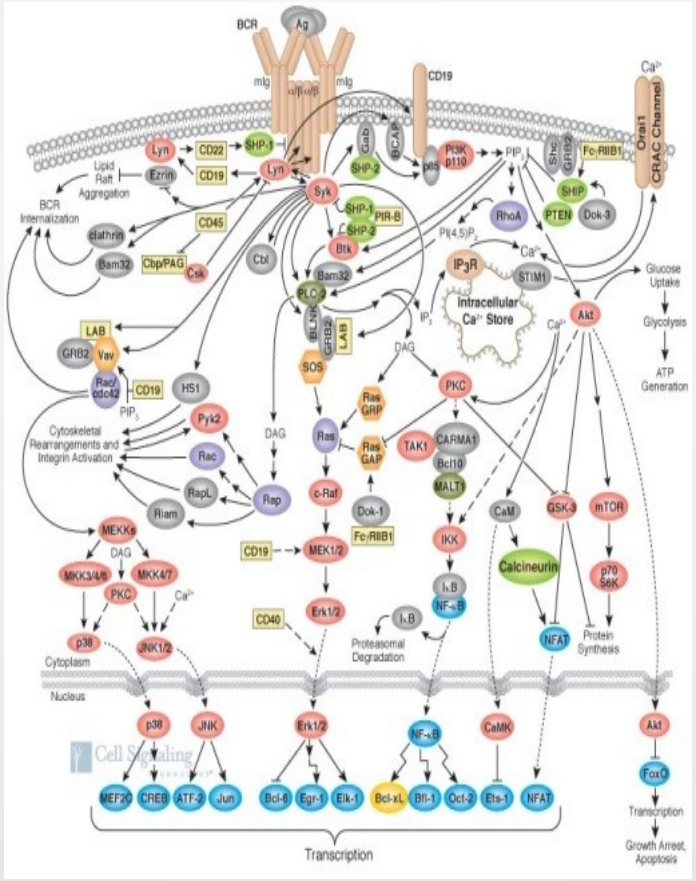


Treatment options for patients with lymphoma

- Radiotherapy
- Single agent chemotherapy
- Combination chemotherapy
- Stem cell transplant (autologous, allogeneic -sibling, MUD, RIC-)

- Immunotherapy (monoclonal antibodies, CAR-T cells...)
- Pathway inhibitors (targeted agents)

Pathways inhibitors



Families of new drugs

- PI3□inhibitors:
  - Idelalisib
  - Copanlisib
- Bruton tyrosine kinase inhibitors:
  - Ibrutinib
  - Acalabrutinib
- Checkpoint inhibitors:
  - Nivolumab
  - Pembrolizumab
- BCL-2 antagonists:
  - Venetoclax
- New monoclonal antibodies (MoAb)
  - Brentuximab vedotin
  - Obinutuzimab

FL

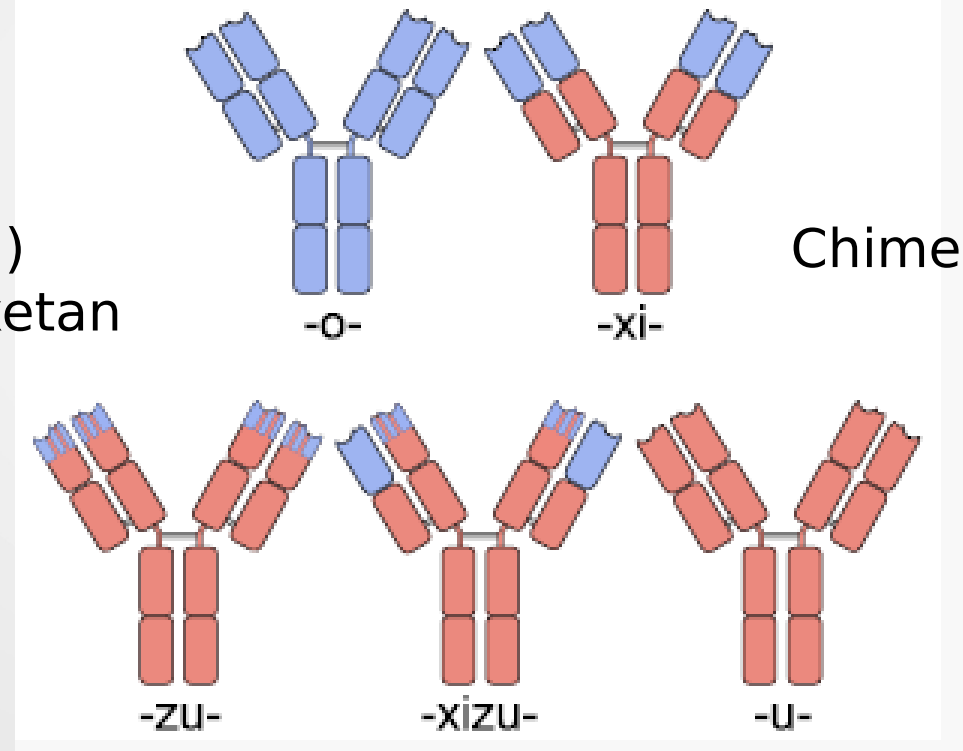
MCL,
CLL,
DLBCL

HL

FL

New monoclonal antibodies

Murine:
tositumOmab (B1)
ibritumOmab tiuxetan

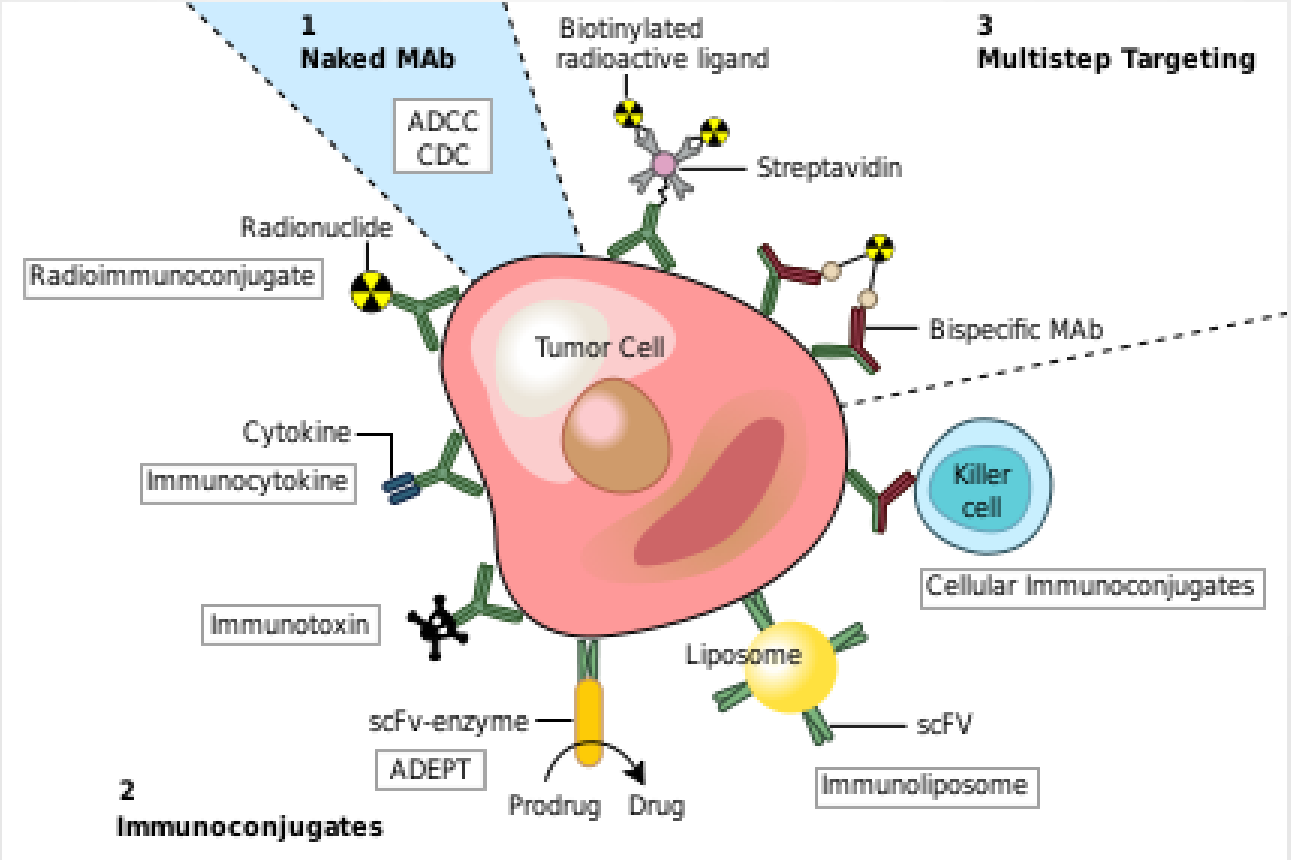


Chimeric: rituXImab

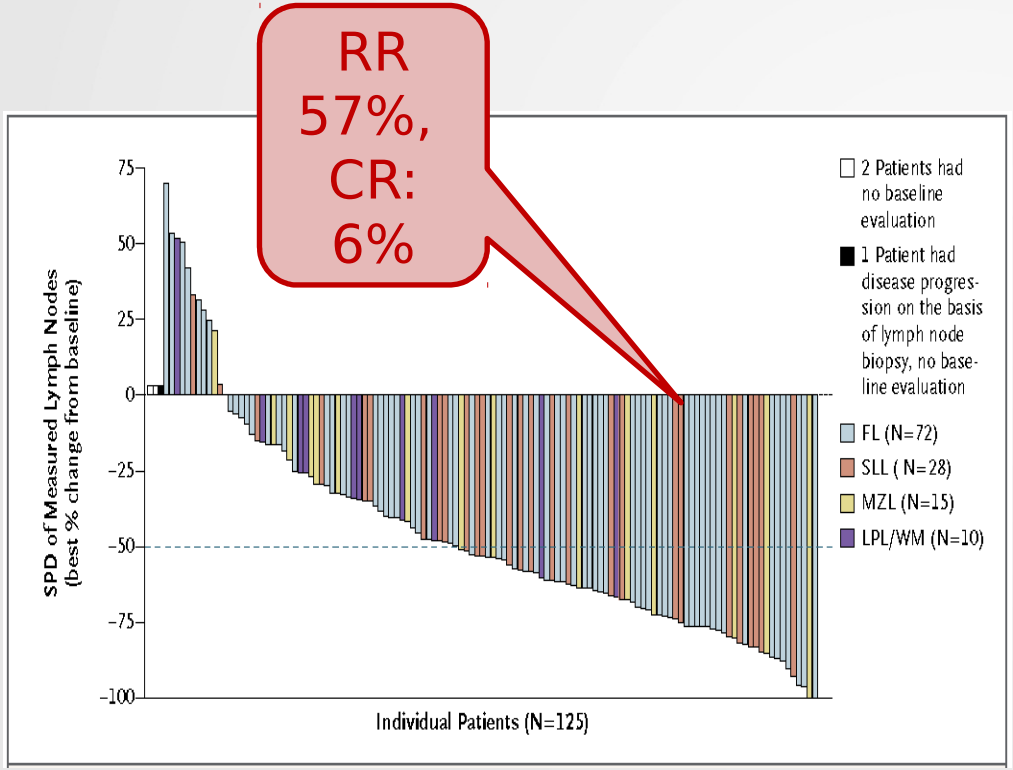
Humanised:
veltuZUmab (2nd generation)
obinutuZUmab: GA101 (3rd generation)

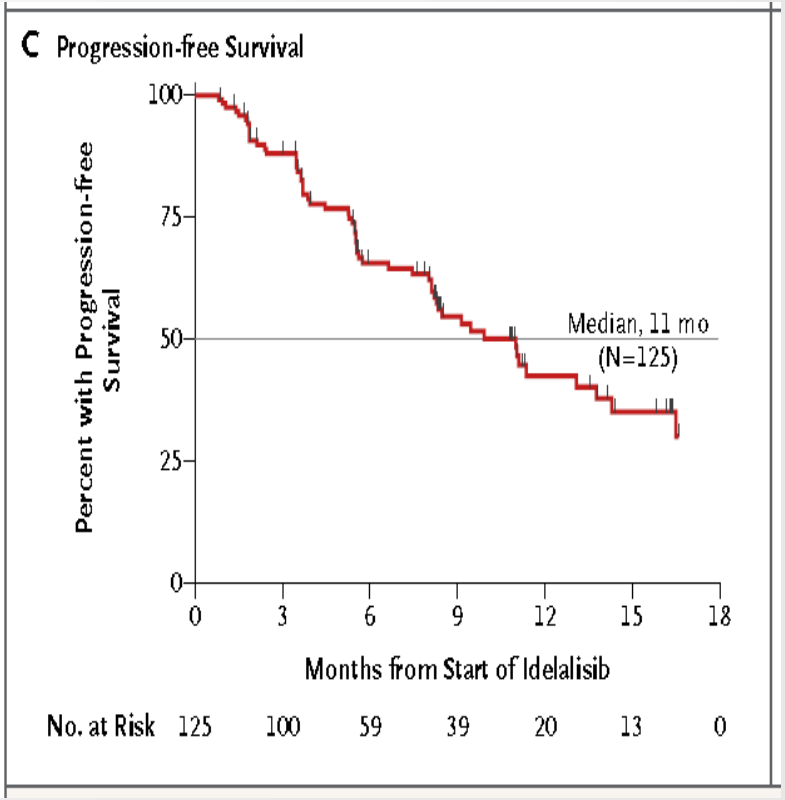
Human: ofatumUmab (2nd generatio

Types of monoclonal antibodies



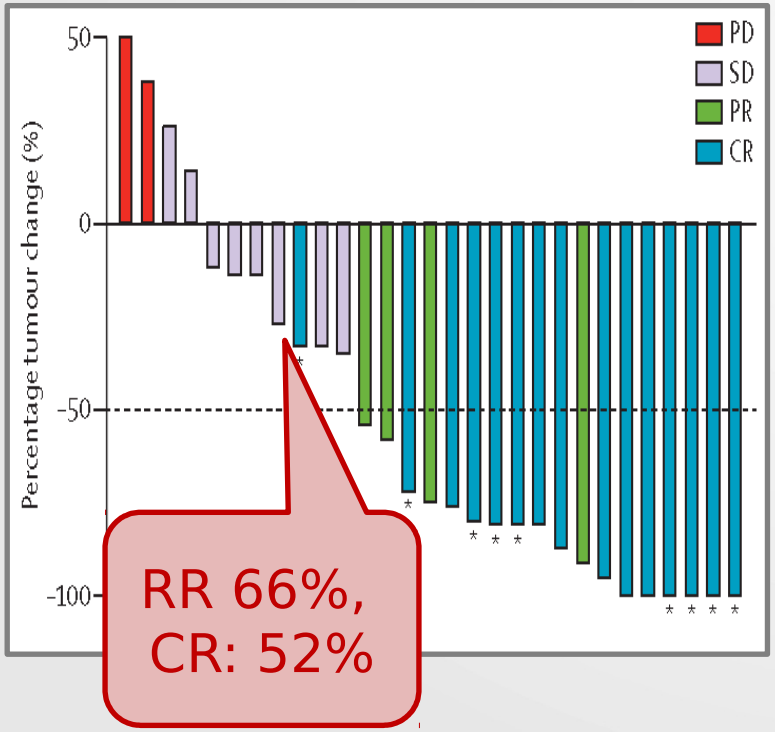
Idelalisib in R/R iNHL



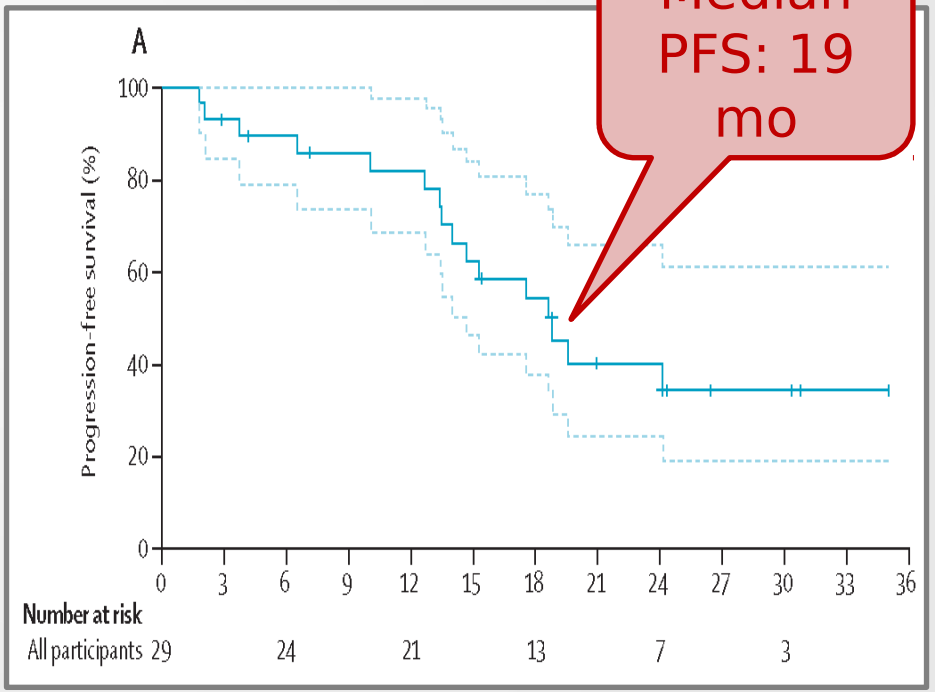


Gopal A et al, N Eng J Med, 2014

Checkpoint inhibitors + rituximab in 29 rFL



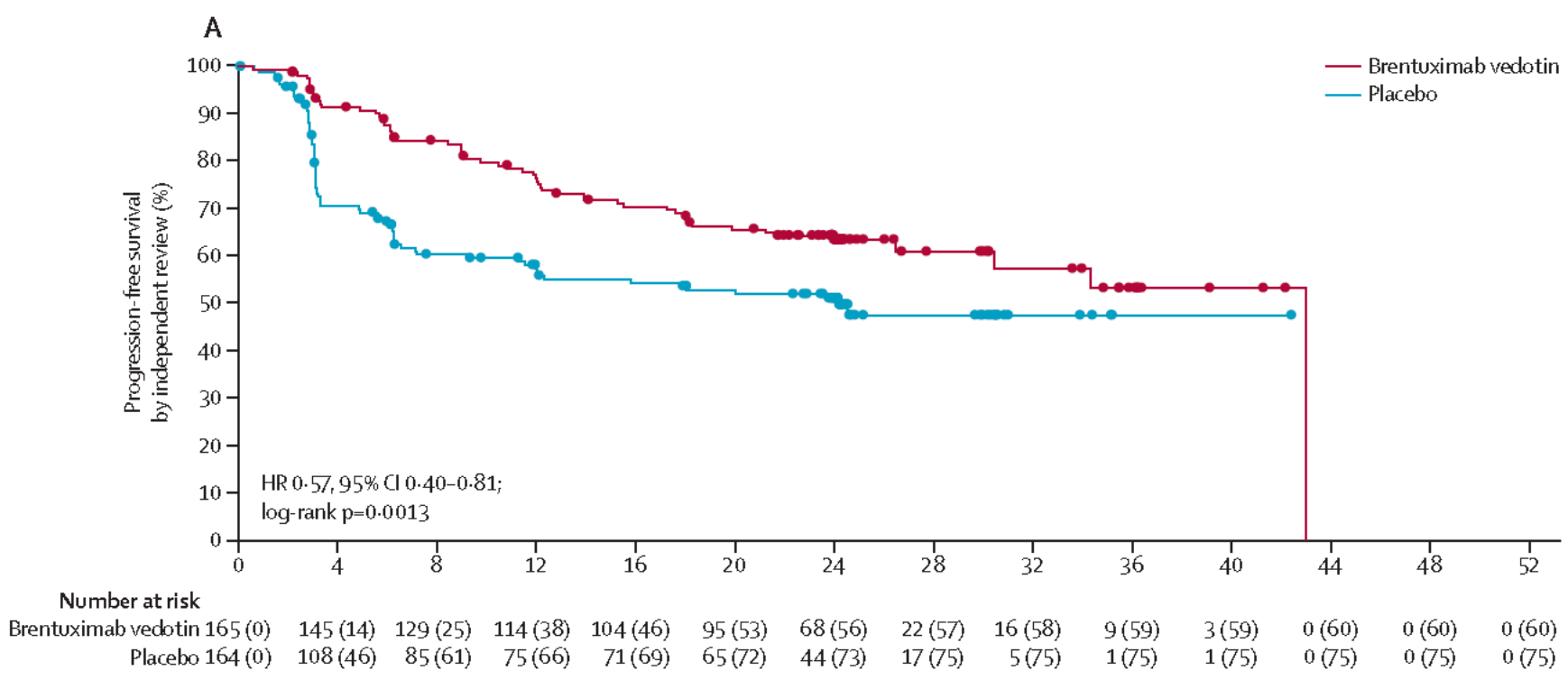
RR 66%, CR: 52%



Median PFS: 19 mo

Westin R et al, Lancet Oncol, 2014

Brentuximab vedotin post HDT-ASCR



Moskowitz CK et al, Lancet, 2015

New drugs and SCT

- Use of new drugs
  - As bridge to SCT
  - Relapse post SCT
  - Maintenance post SCT

- Concerns
  - Efficacy of SCT after new drugs
  - Toxicity of SCT after new drugs
  - (Diminish the role of SCT)

LWP studies involving new drugs

- 2013-N-02i Pwi prior to SCT
- 2013-N-02, 2016-R-01 PWI pre and post allo studies
- 2015-R-01A BV as bridge to SCT in ALCL
- 2015-R-01H BV as bridge to SCT in HL
- 2015-R-01H BV post allo in HL
- 2016-S-01 Checkpoint inhibitors pre/post alloHCT
- 2017-R-05 Ibru post ASCT MCL

MED-A and new drugs

Treatment pre-HSCT

Enter first day of treatment and mark all drugs from that date until conditioning

☐ No
☐ Yes Date of treatment ----------
yyyy - mm - dd

Drugs given

		Relapse/progression under this drug		
		Yes	No	Unknown
Antibodies:	☐ Alemtuzumab (MabCampath) (CD52)	☐	☐	☐
	☐ Brentuximab (Adcetris) (CD30)	☐	☐	☐
	☐ Obinutuzumab (Gyzeva) (CD20)	☐	☐	☐
	☐ Ofatumumab (Azerra) (CD20)	☐	☐	☐
	☐ Rituximab (Mabthera) (CD20)	☐	☐	☐
	☐ other antibody, specify_____	☐	☐	☐
Radioimmunotherapy:	☐ Bexxar (CD20) (radiolabelled MoAB)	☐	☐	☐
	☐ Zevalin (CD20) (radiolabelled MoAB)	☐	☐	☐
Specific inhibitors:	☐ ABT-199 (BCL2-Inhibitor)	☐	☐	☐
	☐ Crizotinib (ALK-Inhibitor)	☐	☐	☐
	☐ CC-292 (B cell receptor kinase inhibitor)	☐	☐	☐
	☐ Ibrutinib (B cell receptor kinase inhibitor)	☐	☐	☐
	☐ Idelalisib (B cell receptor kinase inhibitor)	☐	☐	☐
	☐ other inhibitor, specify_____	☐	☐	☐
Other:	☐ Bortezomib (Velcade)			
	☐ Lenalidomide (Revlimid)			
	☐ Other, specify _____			

Conclusions

- New insights into the biology of lymphoma
  - New entities
  - Sub-types with worse prognosis
  - New drugs

- Main focus of research: relationship between new drugs and SCT

EBMT European Society for Blood and Marrow Transplantation

Thank you!

@LymphomaWP_EBMT