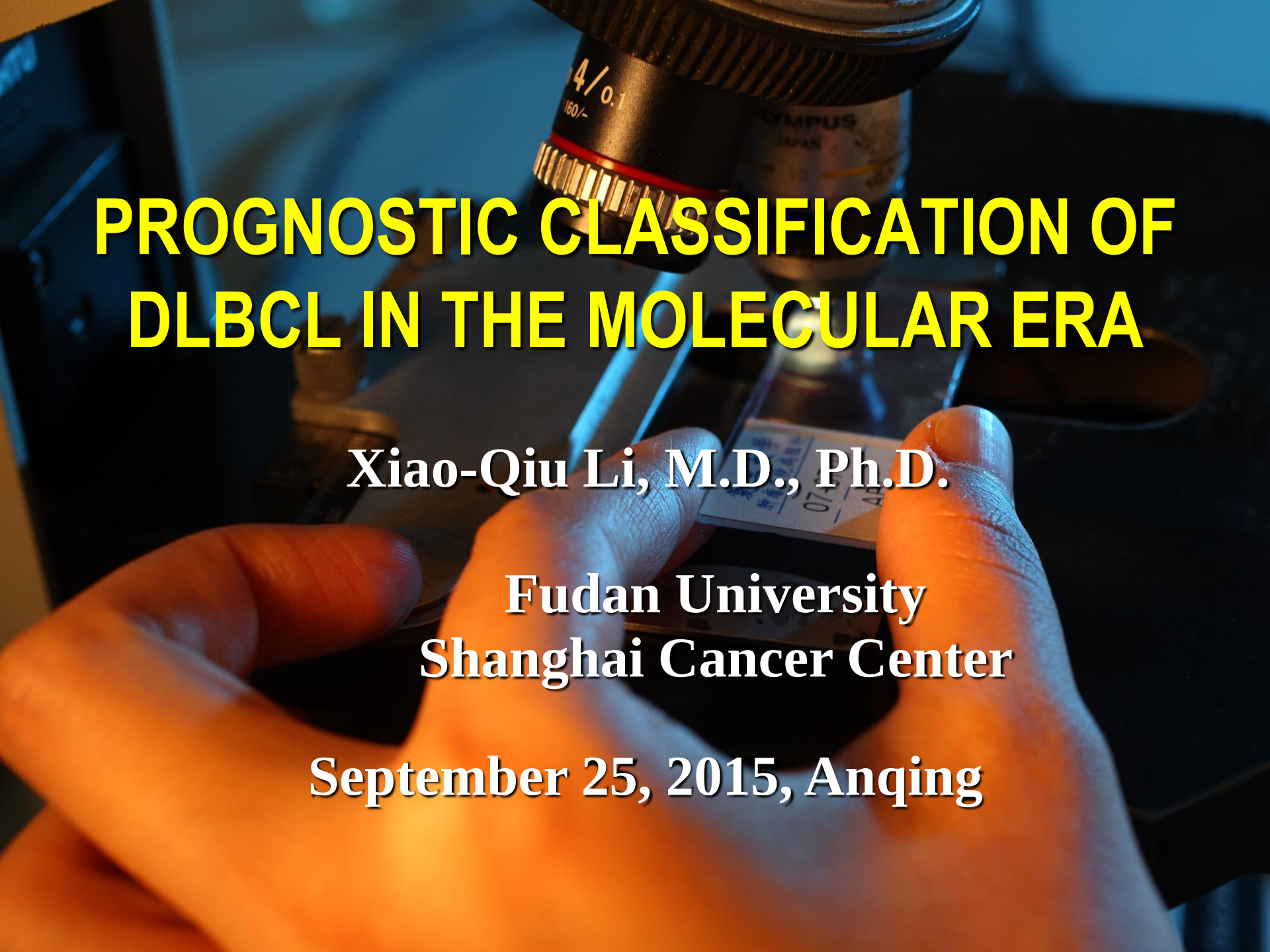

PROGNOSTIC CLASSIFICATION OF DLBCL IN THE MOLECULAR ERA

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Fudan University
Shanghai Cancer Center

September 25, 2015, Anqing

·论著·

中国淋巴瘤亚型分布:国内多中心性病例 10 002 例分析

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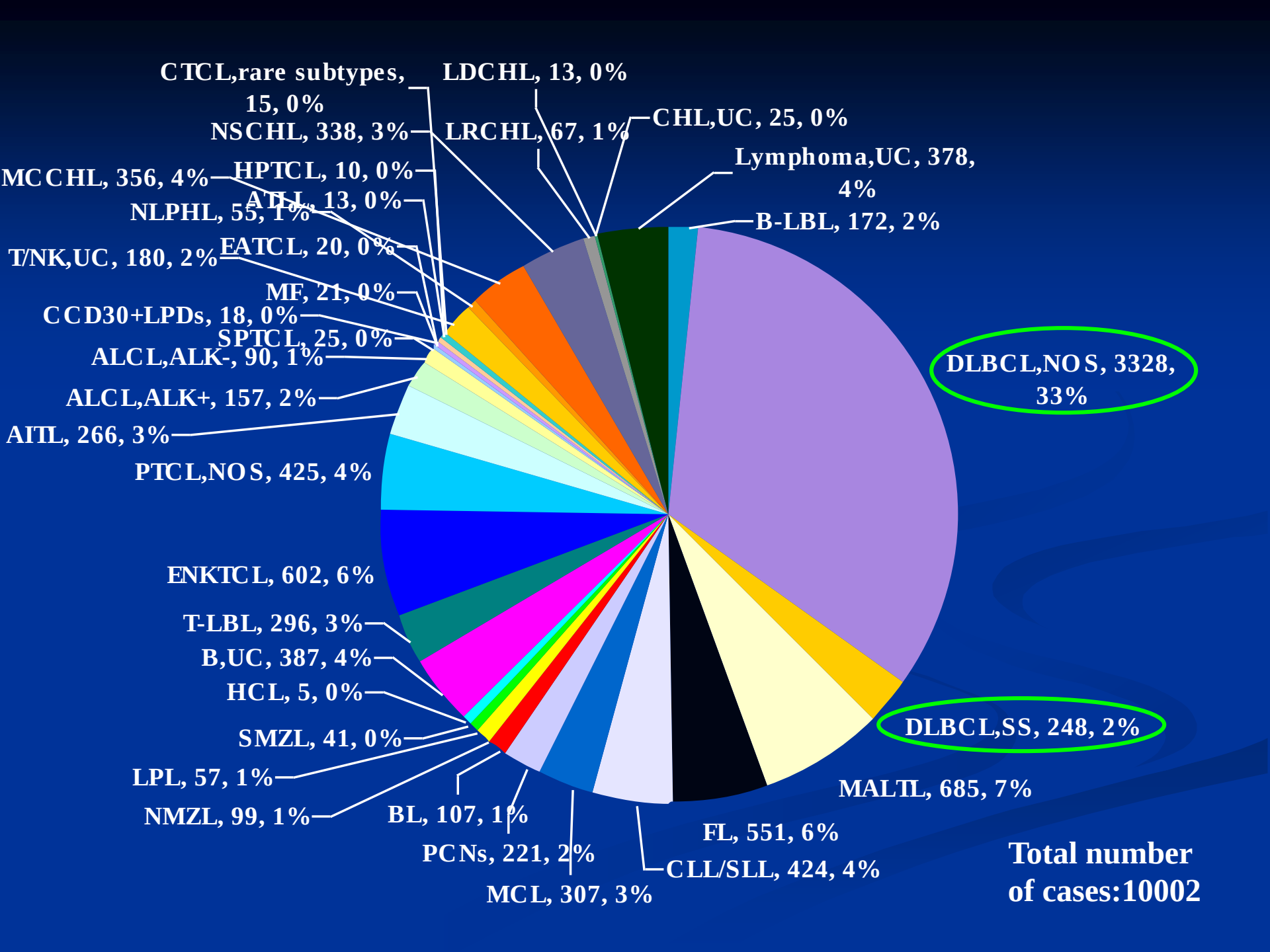
2. 四川大学华西医学院病理学系 华西医院病理科,成都 610041;
3. 北京大学医学中心病理学系,北京 100191;
4. 首都医科大学附属北京友谊医院病理科,北京 100050)

[摘要] **目的**:采用国内多中心性合作,回顾性分析 10 002 例淋巴瘤病例的临床和病理资料,以探讨我国淋巴瘤流行病学特点。**方法**:组织全国范围内的合作研究,选择来自 24 家有代表性的医学机构的 10 002 例淋巴瘤病例,复习其病理切片和临床资料,并作总结分析。**结果**:10 002 例淋巴瘤患者中,男性 6188 例,女性 3814 例,男女比为 1.6:1,中位年龄 54 岁;活检标本取自结外部位相较淋巴结活检略为多见,结内与结外病变比例为 1:1.2。我国人群最常见的淋巴瘤瘤类型是弥漫性大 B 细胞淋巴瘤(非特指性淋巴瘤占 33.27%),滤泡性淋巴瘤较西方人群相对少见,而 T 细胞及 NK 细胞淋巴瘤在我国人群相对多见(占所有淋巴瘤的 21.38%),霍奇金淋巴瘤占所有淋巴瘤的构成比为 8.54%,且最常见的亚型为混合细胞型和结节硬化型。**结论**:我国淋巴瘤亚型分布有其独特特征。

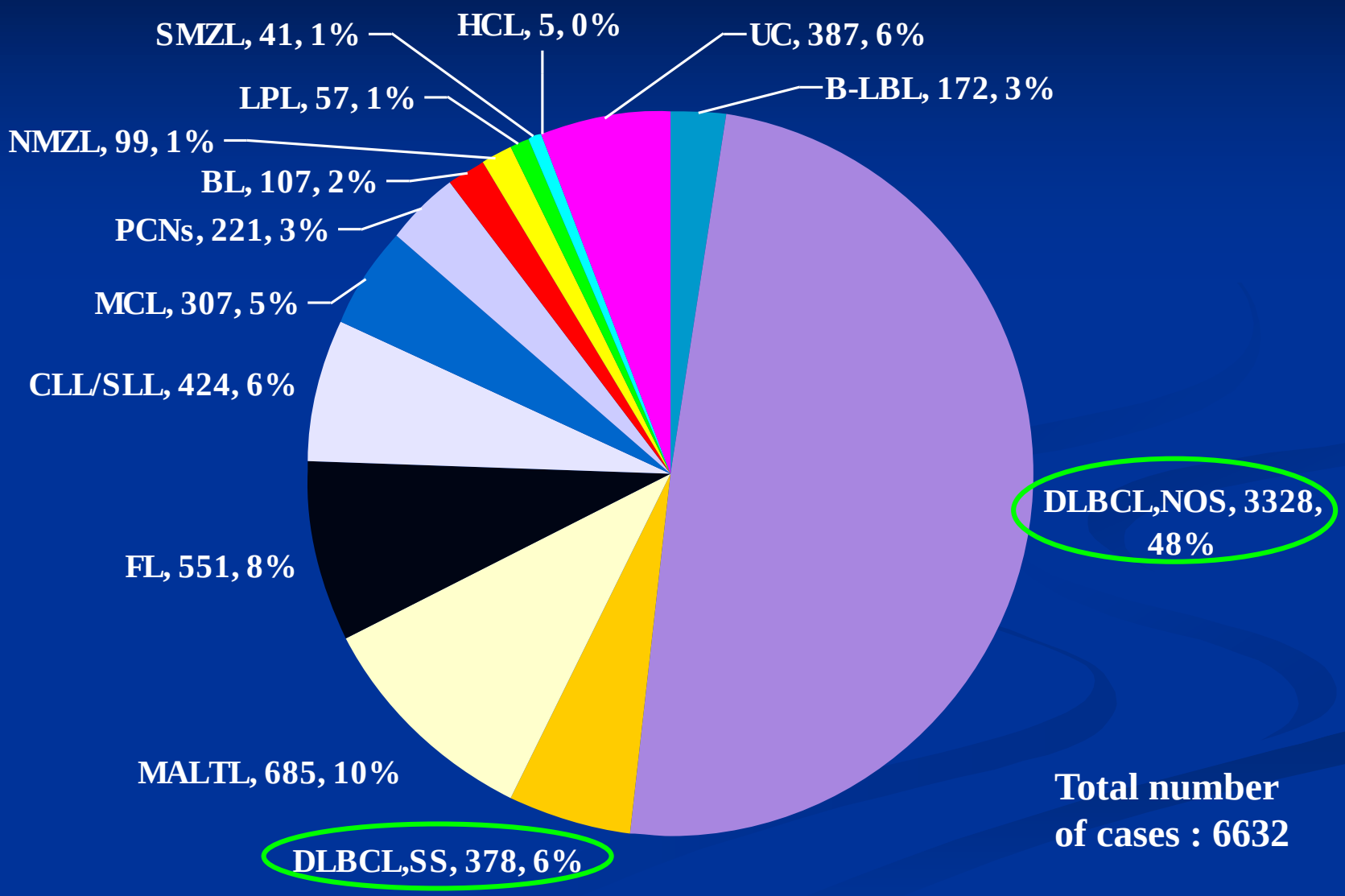
关键词:淋巴瘤; 流行病学; 亚型分布

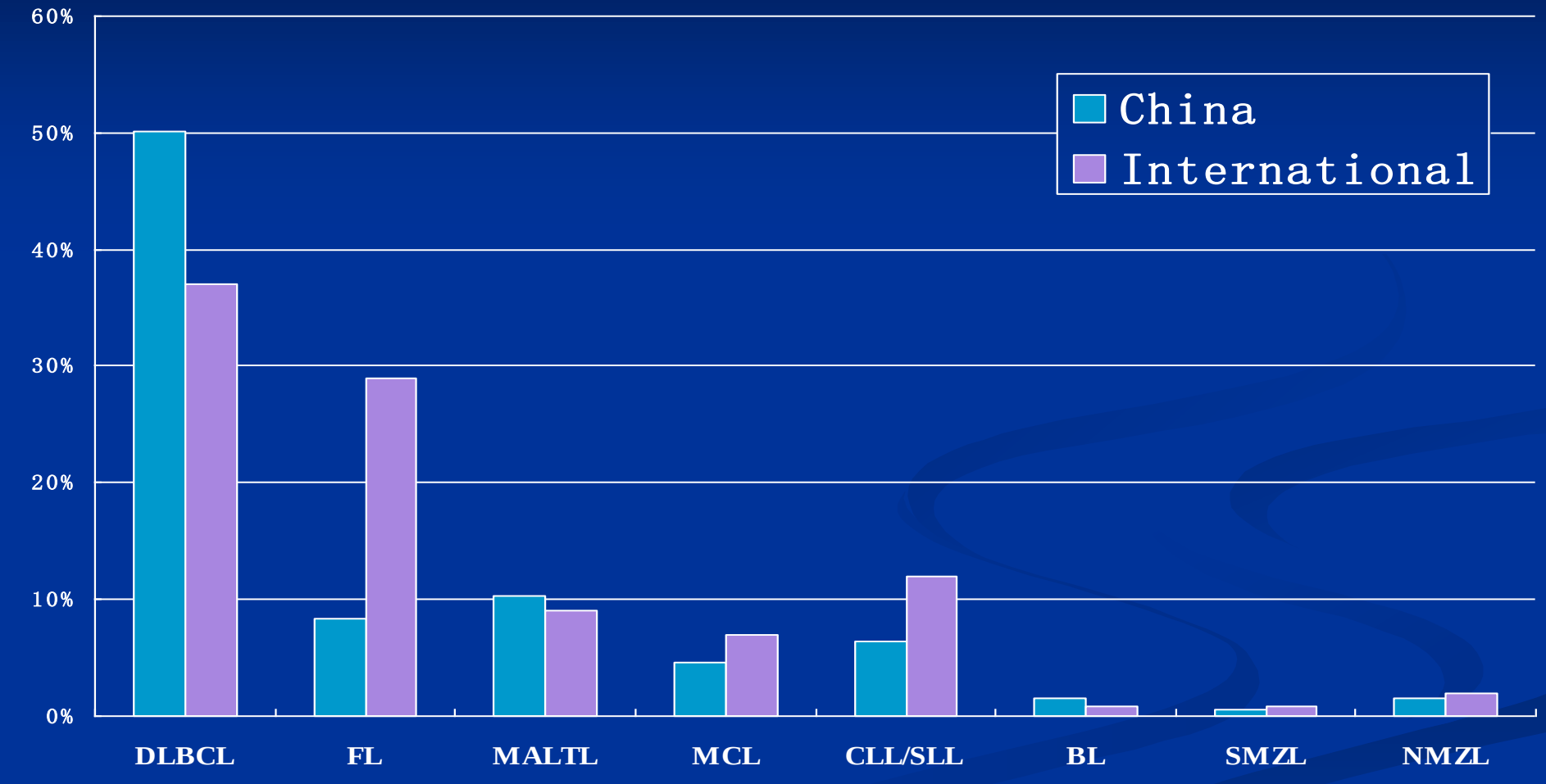
中图分类号:R733.1 **文献标识码**:A **文章编号**:1671-2870(2012)02-0000-00

DOI:10.3969/j.issn.1671-2870.2012.02.000

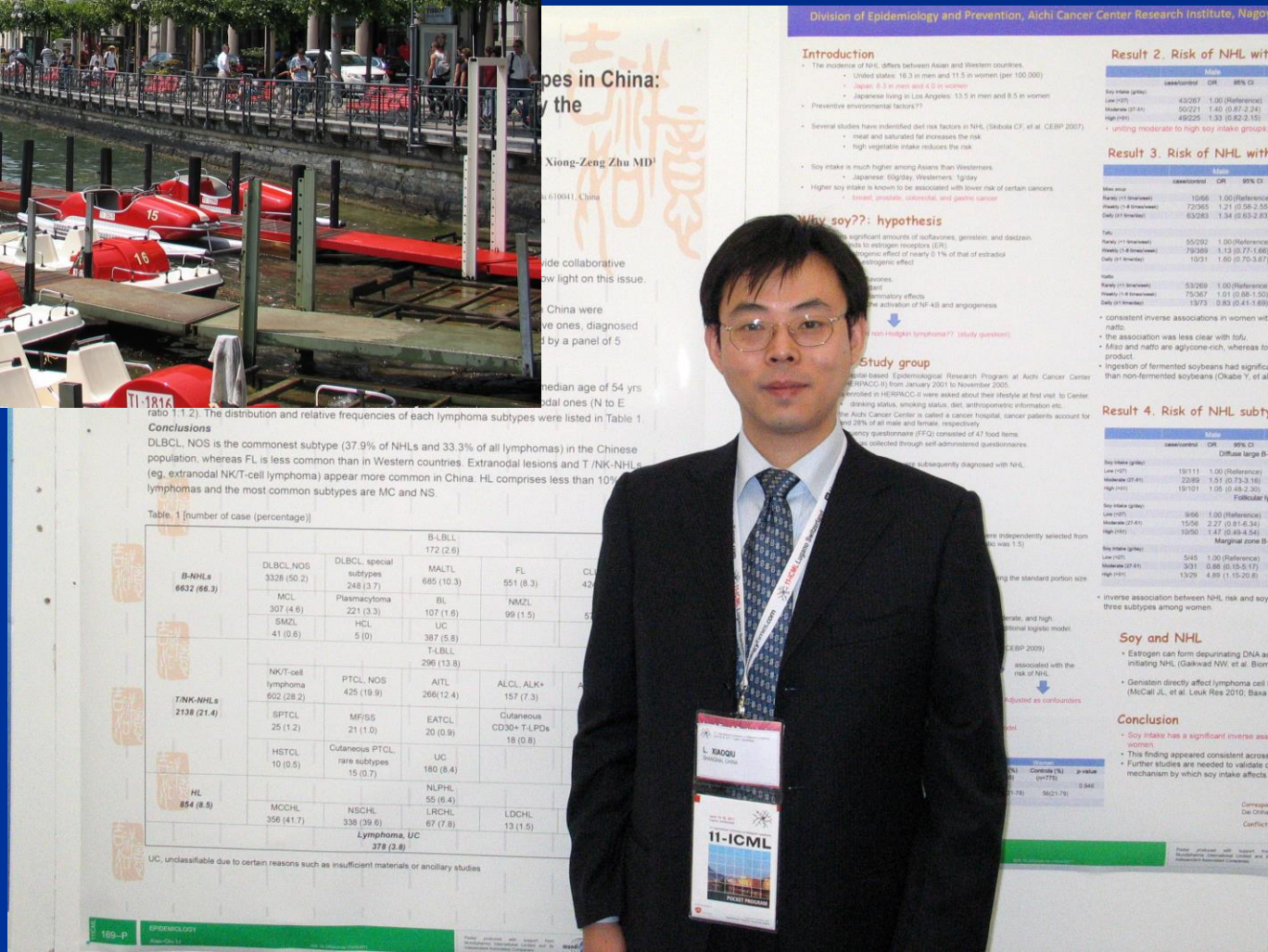

CTCL,rare subtypes, 15, 0%
LDCHL, 13, 0%
NSCHL, 338, 3%
LRCHL, 67, 1%
CHL,UC, 25, 0%
MCCHL, 356, 4%
HPTCL, 10, 0%
Lymphoma,UC, 378, 4%
NLPHL, 55, 1%
ATLL, 13, 0%
B-LBL, 172, 2%
T/NK,UC, 180, 2%
EATCL, 20, 0%
MF, 21, 0%
CCD30+LPDs, 18, 0%
SPTCL, 25, 0%
ALCL,ALK-, 90, 1%
DLBCL,NOS, 3328, 33%
ALCL,ALK+, 157, 2%
AITL, 266, 3%
PTCL,NOS, 425, 4%
ENKTCL, 602, 6%
T-LBL, 296, 3%
B,UC, 387, 4%
HCL, 5, 0%
DLBCL,SS, 248, 2%
SMZL, 41, 0%
LPL, 57, 1%
MALTL, 685, 7%
NMZL, 99, 1%
BL, 107, 1%
FL, 551, 6%
PCNs, 221, 2%
CLL/SLL, 424, 4%
MCL, 307, 3%
Total number of cases:10002

The relative frequencies of B-NHL subtypes





The international data is based on "*Blood 1997; 89: 3909-18*"



Li XQ, et al.
Ann Oncol 2011;
22(suppl 4): iv 141

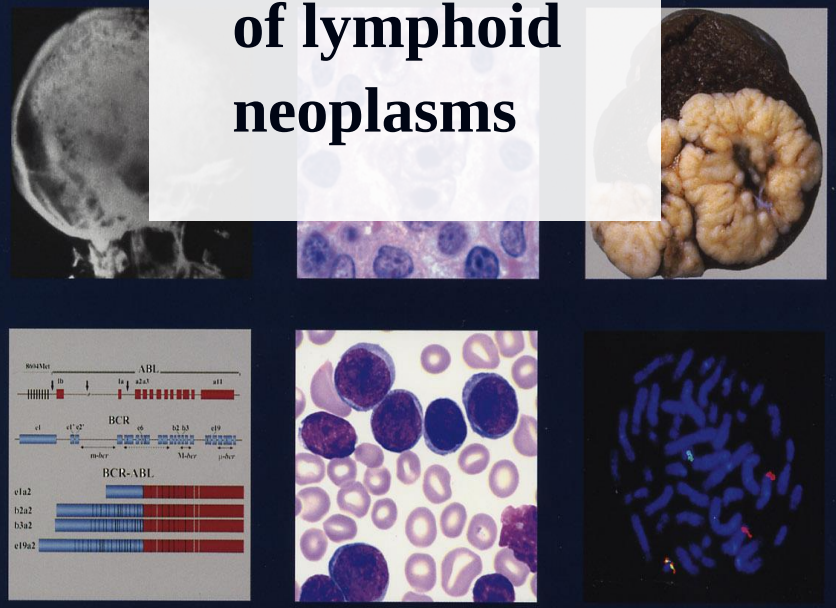
World Health Organization Classification of Tumours

Pathology & Genetics

Tumours of Haematopoietic and Lymphoid Tissues

Edited by Elaine S. Jaffe, Nancy Lee Harris, Harald Stein, James W. Vardiman

- 351 pages
- ~37 categories of lymphoid neoplasms

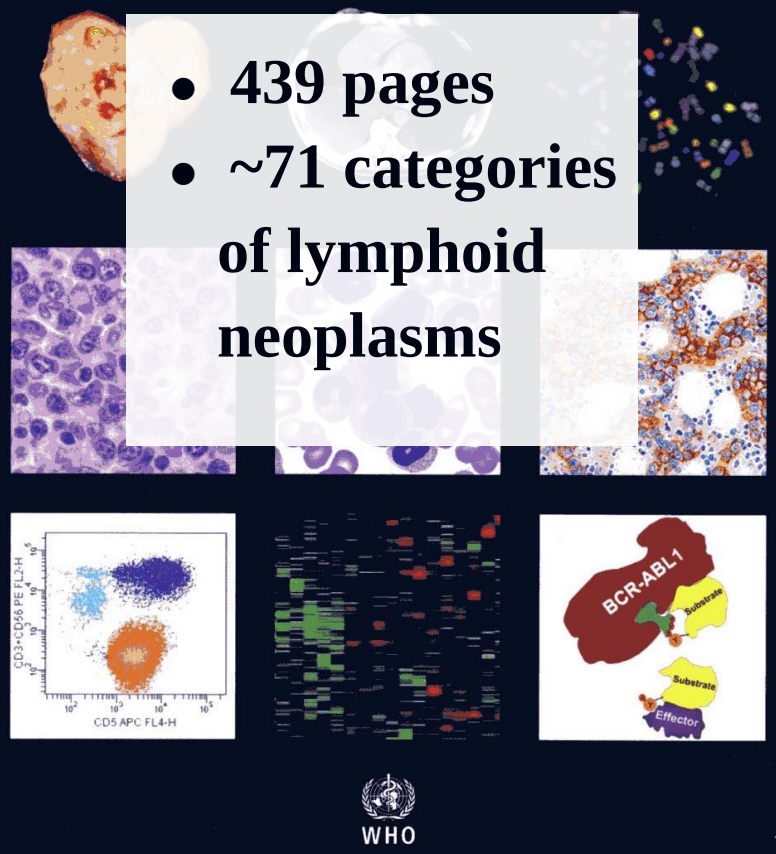


WHO 3rd Edition, 2001

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Edited by Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jürgen Thiele, James W. Vardiman

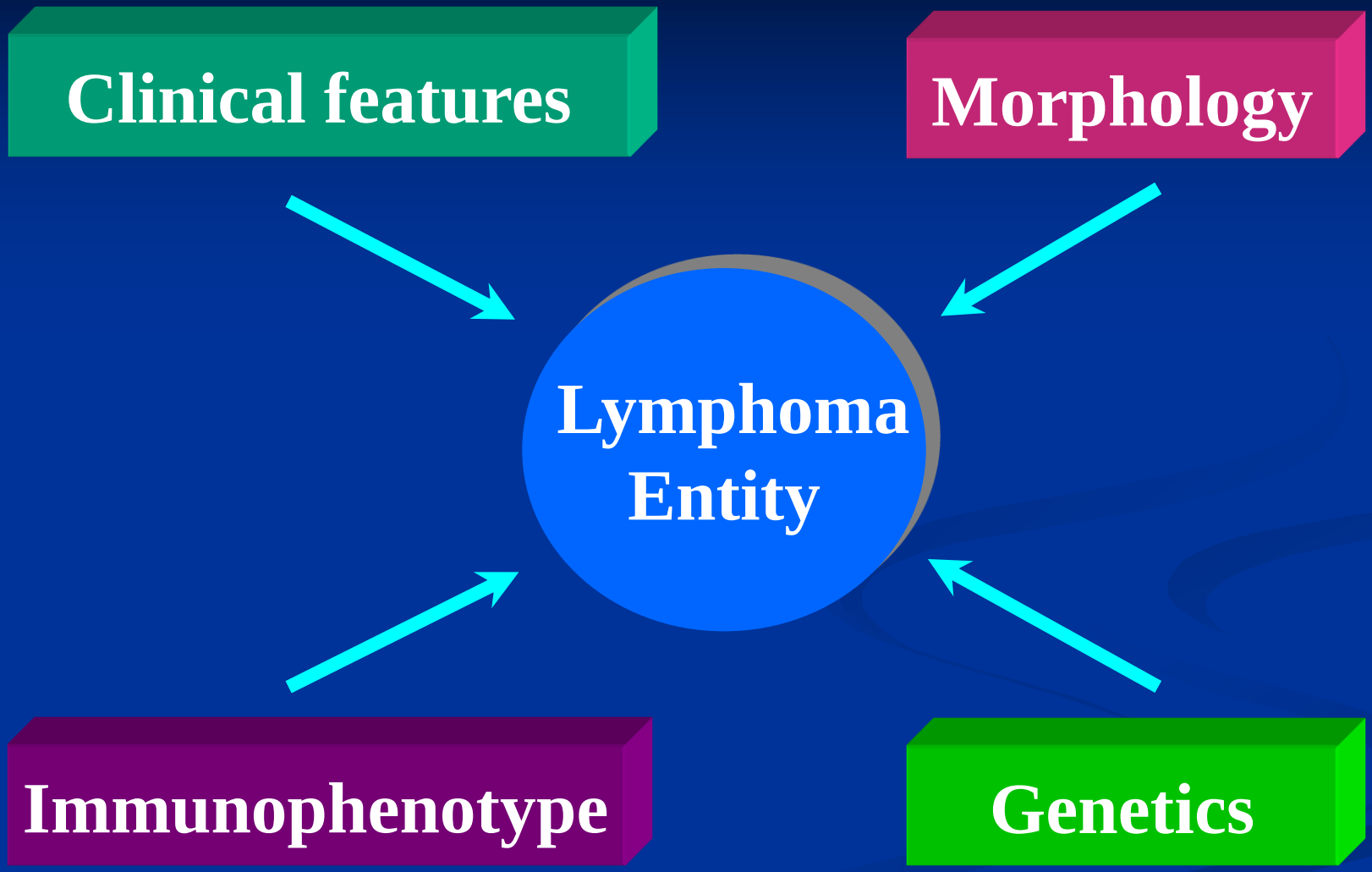
- 439 pages
- ~71 categories of lymphoid neoplasms



WHO 4th Edition, 2008

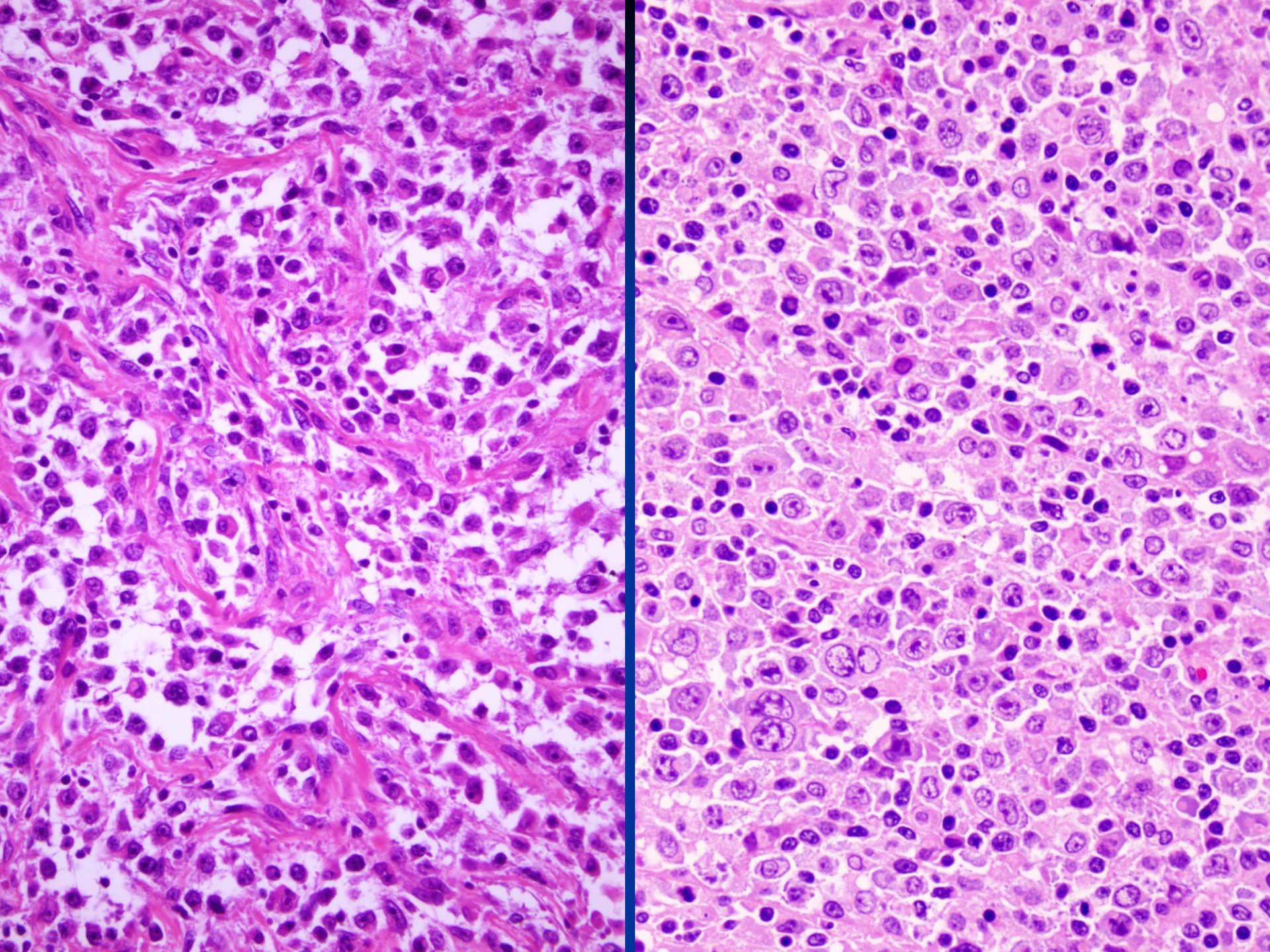
DLBCL: Split into many more entities

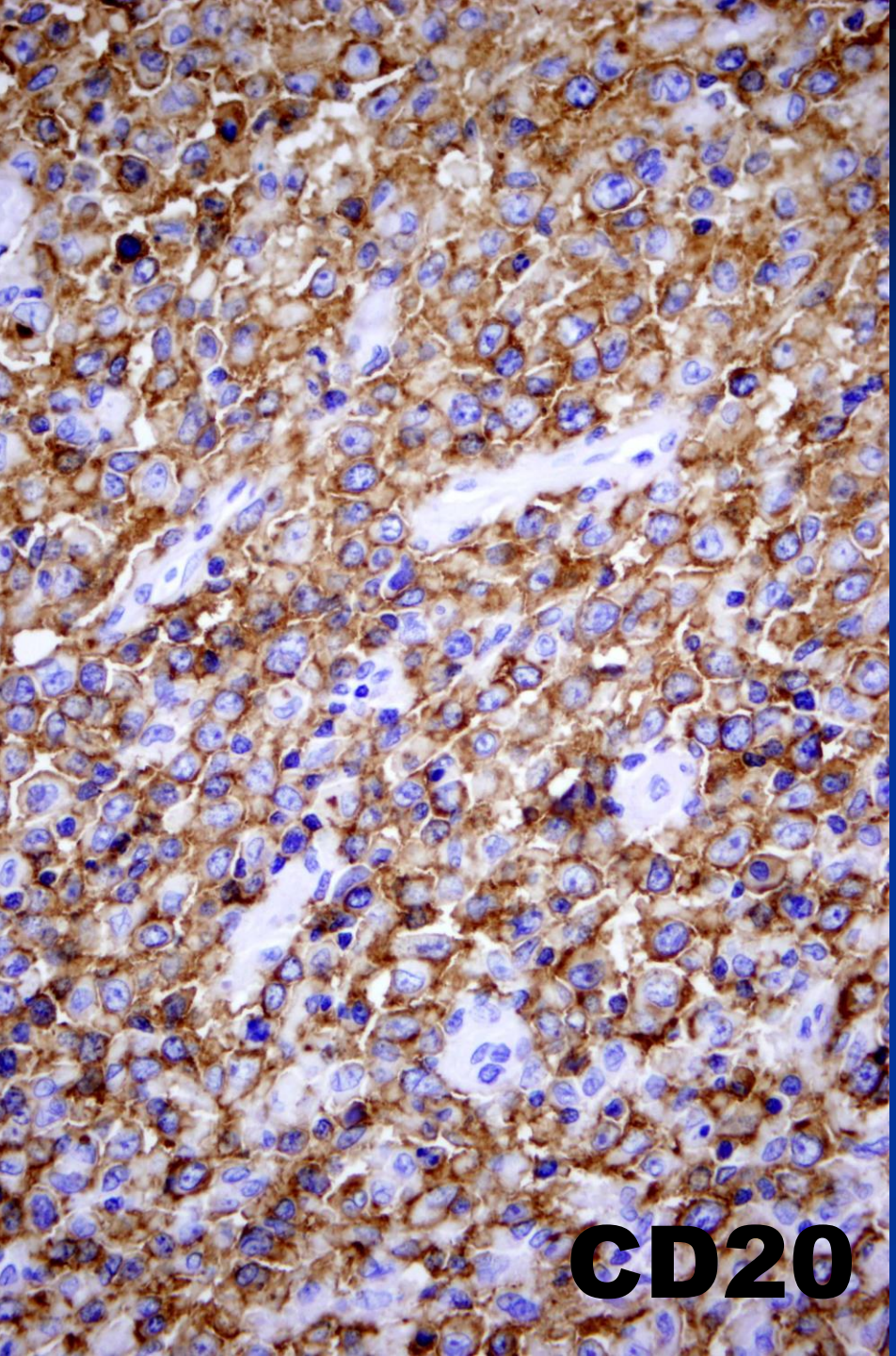
- **Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS)**
- **Diffuse large B-cell lymphoma subtypes**
  - **T-cell/histiocyte-rich large B-cell lymphoma**
  - **Primary DLBCL of the CNS**
  - **Primary cutaneous DLBCL, leg type**
  - **EBV-positive DLBCL of the elderly**
  - **Primary mediastinal (thymic) large B-cell lymphoma**
  - **Intravascular large B-cell lymphoma**
  - **DLBCL associated with chronic inflammation *(EBV)***
  - **Lymphomatoid granulomatosis *(EBV)***
  - **ALK-positive large B-cell lymphoma**
  - **Plasmablastic lymphoma *(HIV&EBV)***
  - **Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease**
  - **Primary effusion lymphoma (*HIV&EBV, HHV8*)**
- **Borderline cases**
  - **B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL**
  - **B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical HL**

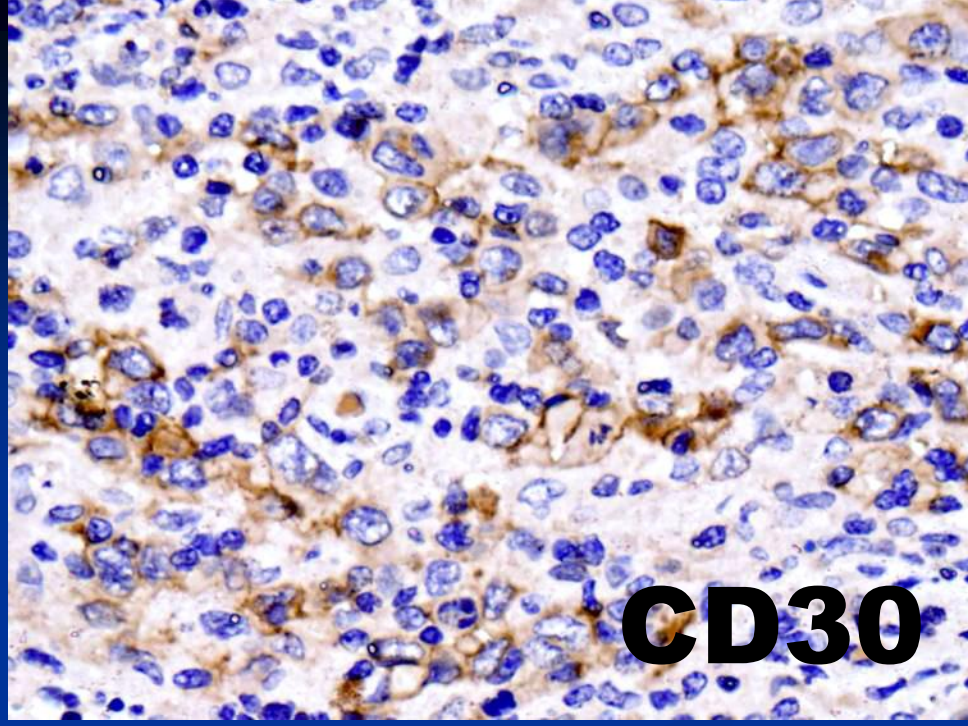

Clinical features
Morphology
Lymphoma Entity
Immunophenotype
Genetics

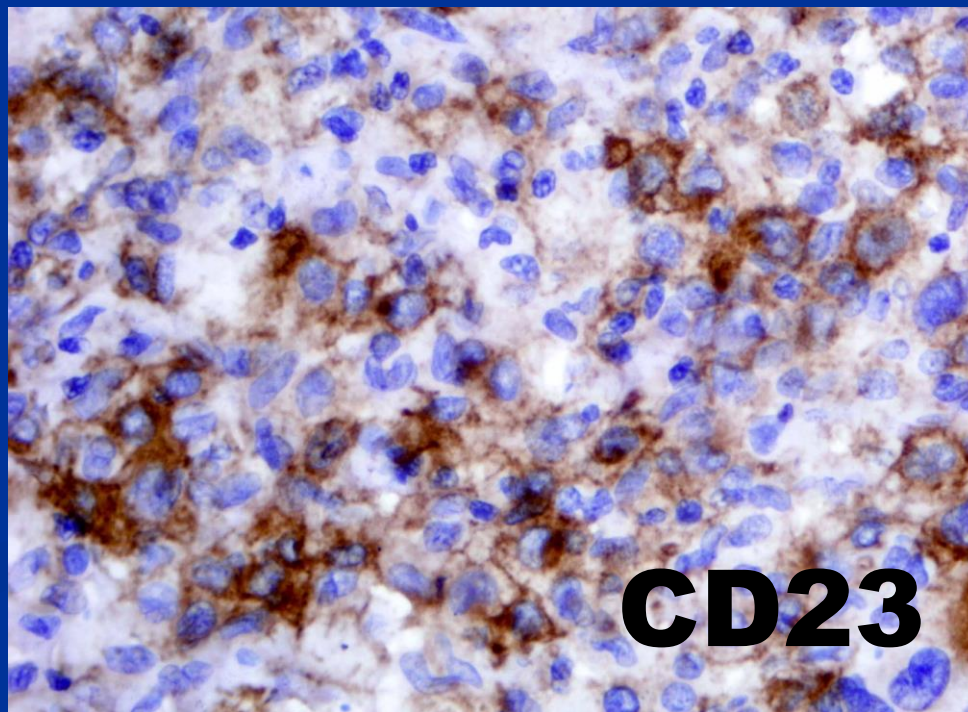
Primary mediastinal large B-cell lymphoma (PMBL)

- 2-4% of NHLs, young female predominance (M:F 1:2)
- Localized anterosuperior mediastinal mass, bulky disease and superior vena cava syndrome, invasion of adjacent structures, absence of lymph node and BM involvement
- Compartmentalizing alveolar fibrosis commonly seen, medium-sized to large tumour cells with abundant pale cytoplasm and round/oval nuclei, pleomorphic /multilobated (HRS-like) cells can be seen
- Phenotype: CD20+, CD79a+, Ig-, CD30+/-, CD15-, MUM1+/-, CD23+/-, MAL+/-, P63+/-



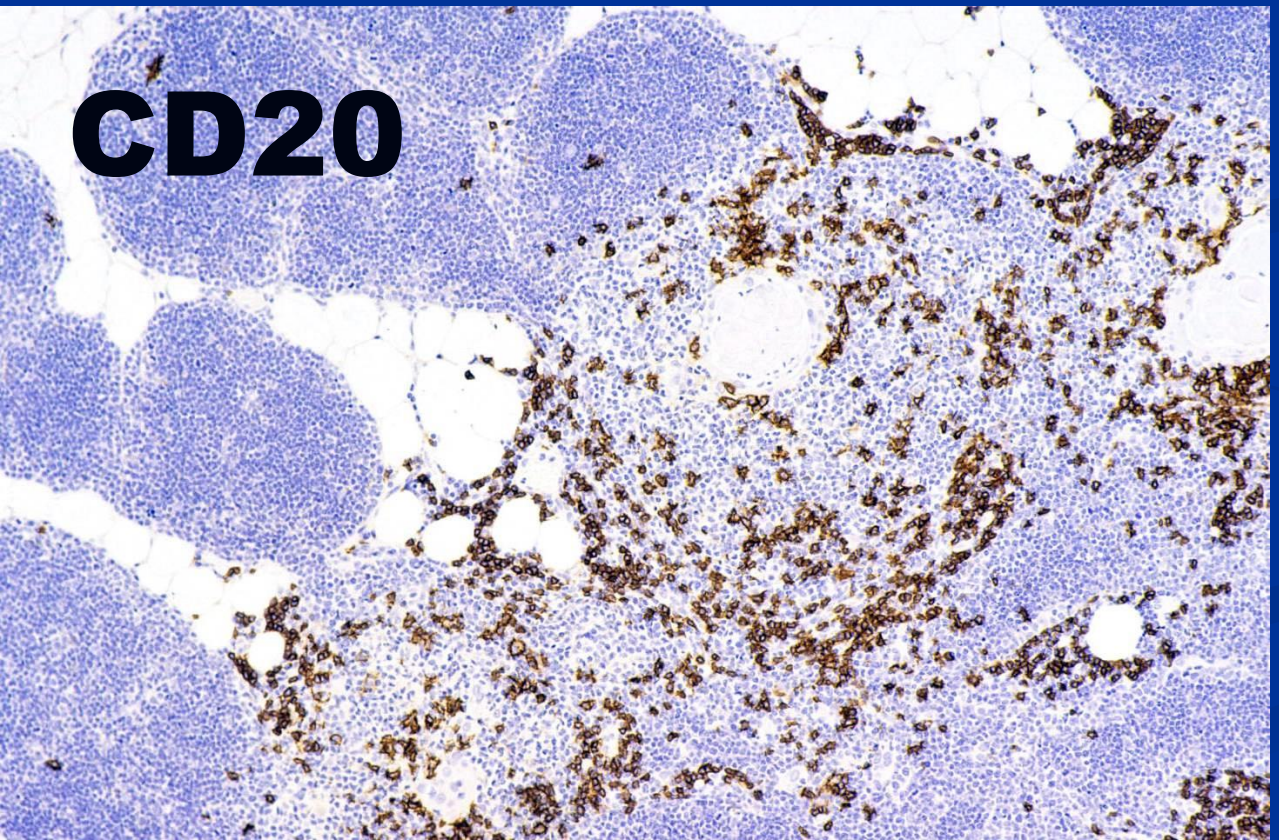

CD20

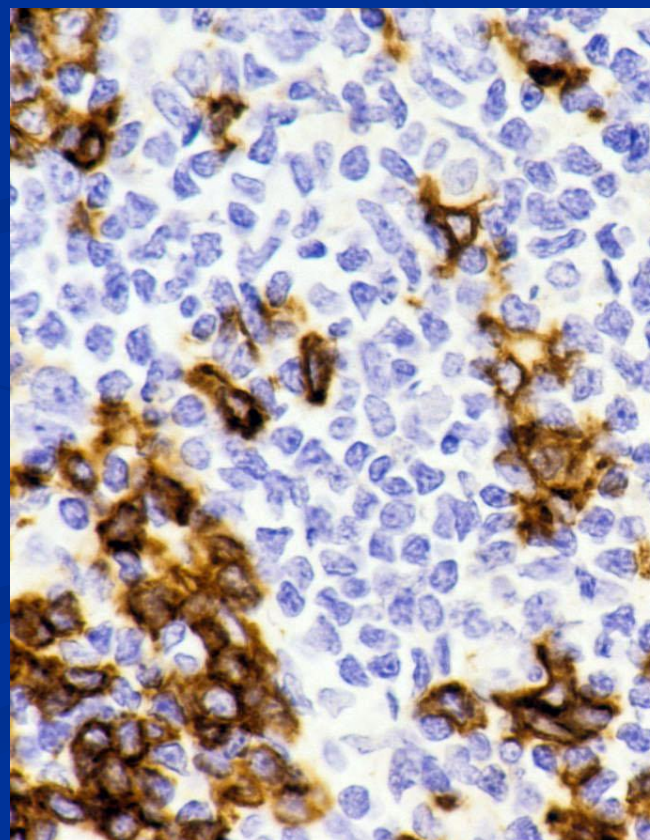

CD30


CD23

Primary mediastinal large B-cell lymphoma (PMBL)

- Proposed normal counterpart: thymic B lymphocyte (often with an asteroid morphology)

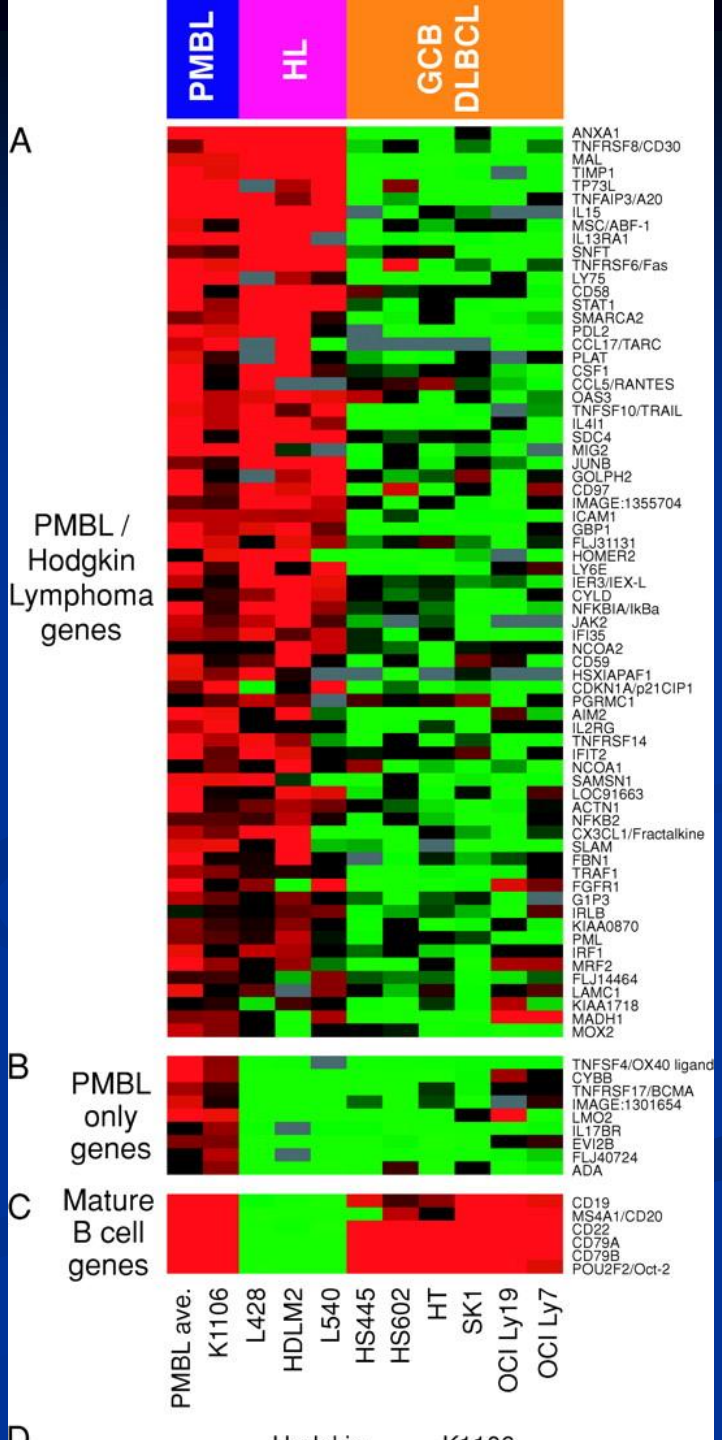




PMBL: Gene expression profiling

GEP studies show greater similarity to classical Hodgkin lymphoma than conventional DLBCL!

Rosenwald A, et al. J Exp Med 2003
Savage KJ, et al. Blood 2003

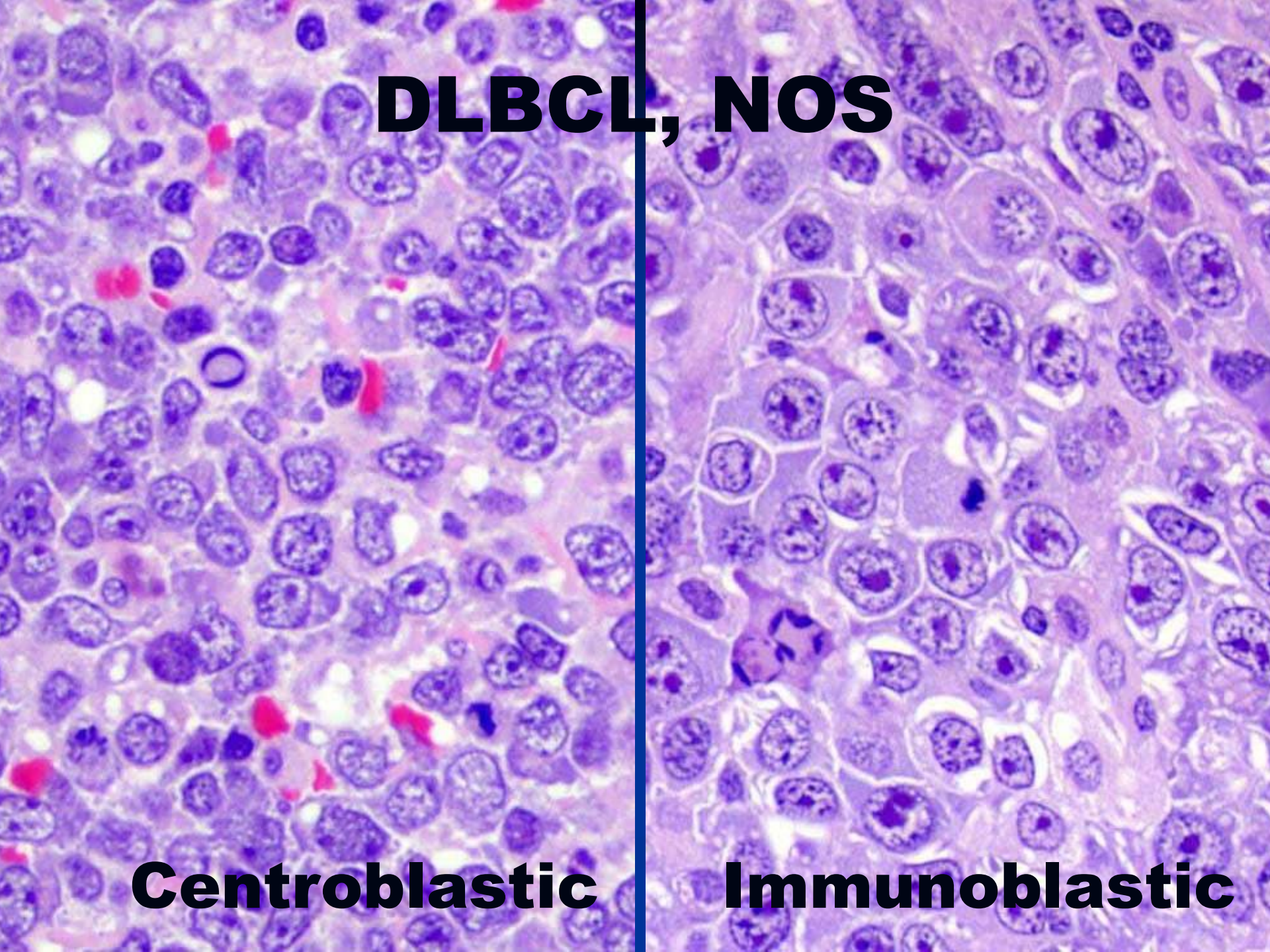


Remarkable clinical and genetic heterogeneity of DLBCL, NOS

Are there better ways to delineate entities within this waste-basket category?

WHO classification (4th edition) of DLBCL, NOS

- **Common morphologic variants**
  - **Centroblastic**
  - **Immunoblastic**
  - **Anaplastic**
- **Rare morphologic variants**
- **Molecular subgroups**
  - **Germinal centre B-cell like (GCB)**
  - **Activated B-cell like (ABC)**
- **Immunohistochemical subgroups**
  - **CD5-positive DLBCL**
  - **Germinal centre B-cell like (GCB)**
  - **Non-germinal centre B-cell like (non-GCB)**

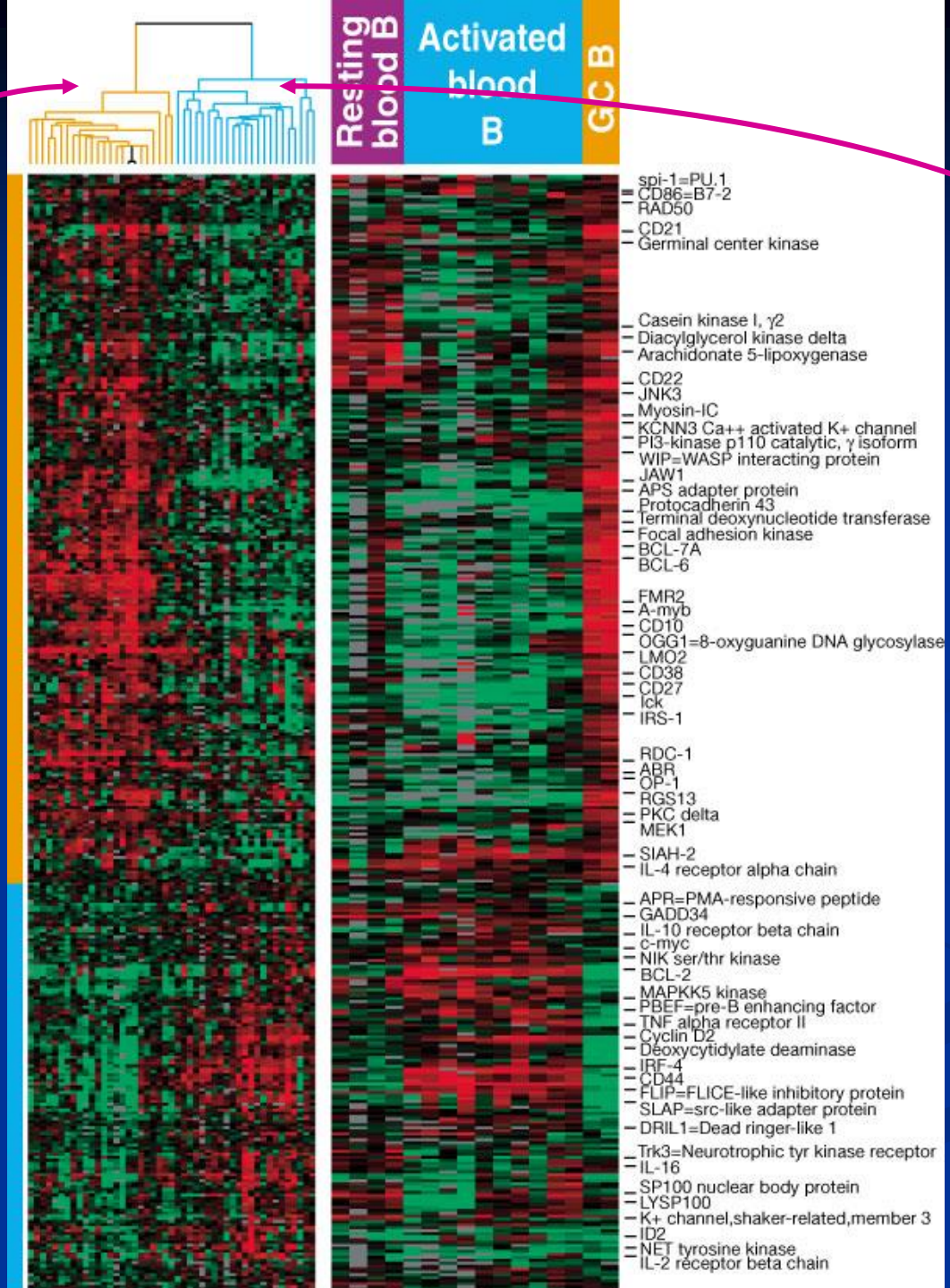

DLBCL, NOS
Centroblastic
Immunoblastic

Distinct types of DLBCL identified by GEP

- **Analysis of gene expression profiles (signatures) of DLBCL reveals two subgroups:**
  - **Germinal center B-like**
  - **Activated B-cell-like**

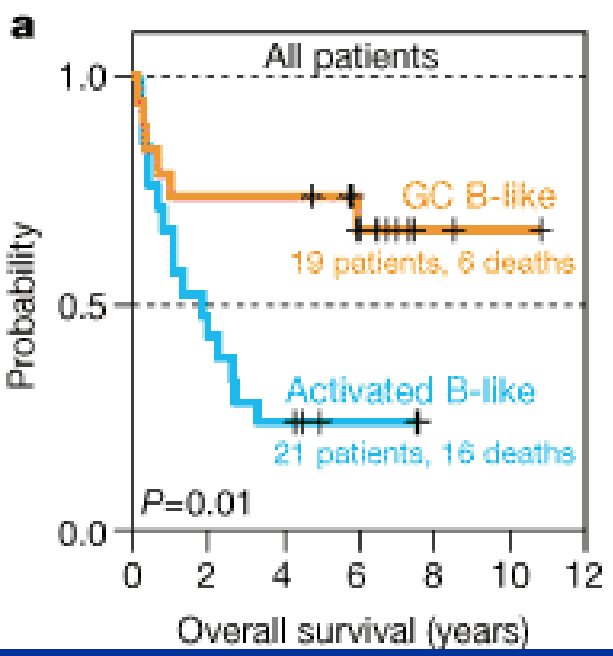
Alizadeh, et al.
Nature 2000; 403: 503-11

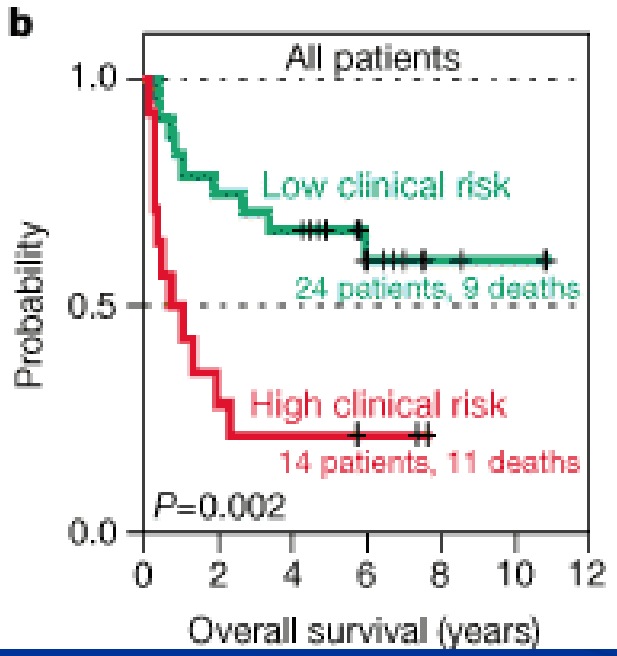
Germinal center B cell-like

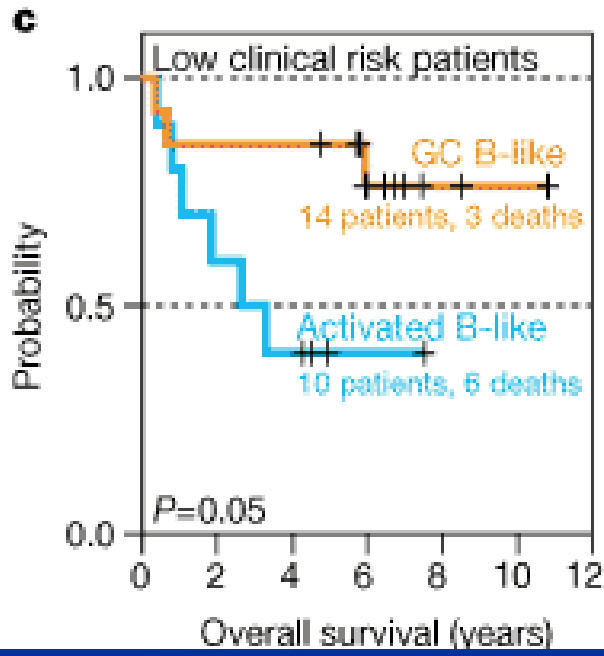


Activated B cell-like

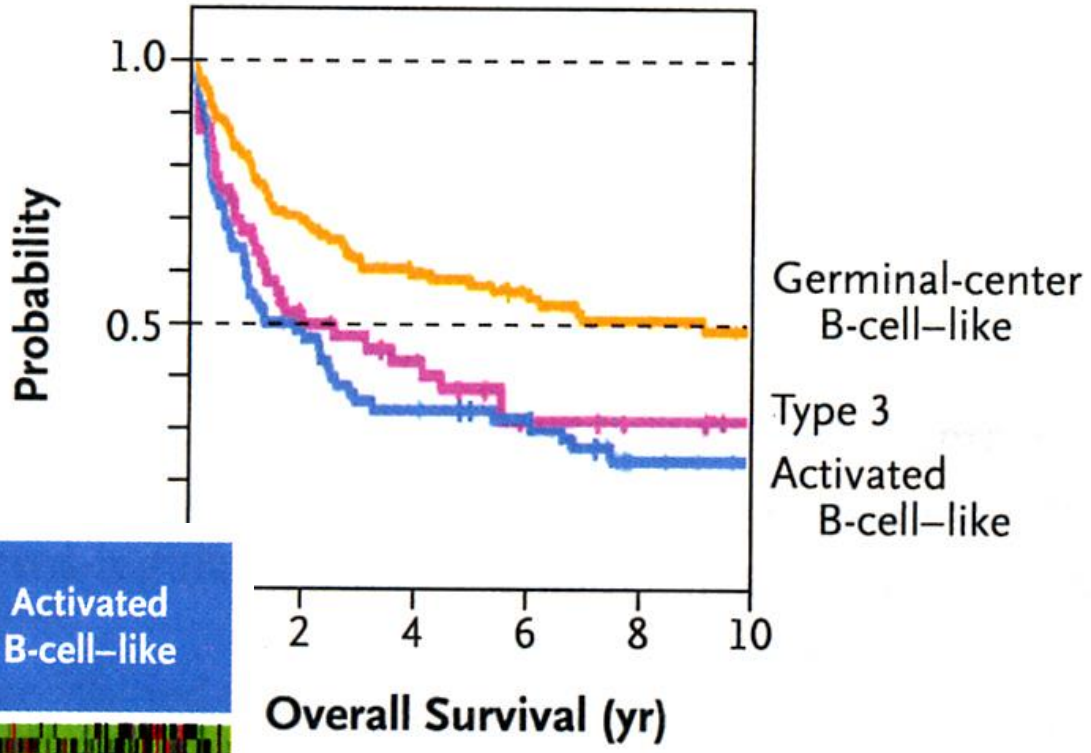
5-yr OS 76% vs 16%

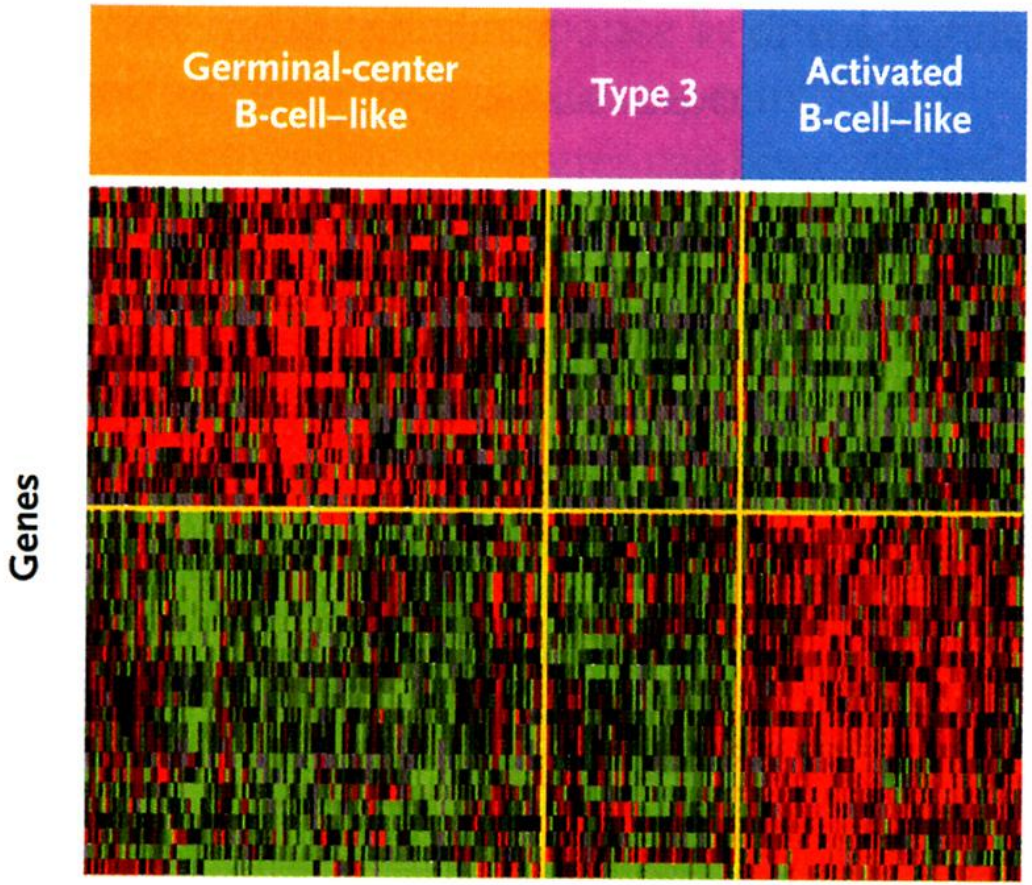






Prognostic significance of this division is maintained even if IPI is taken into consideration

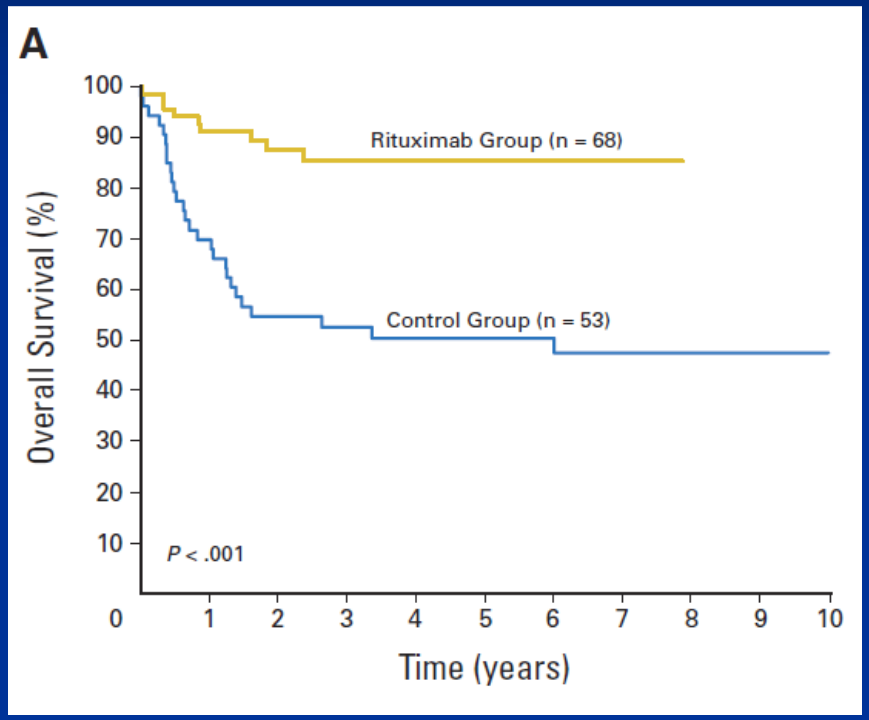


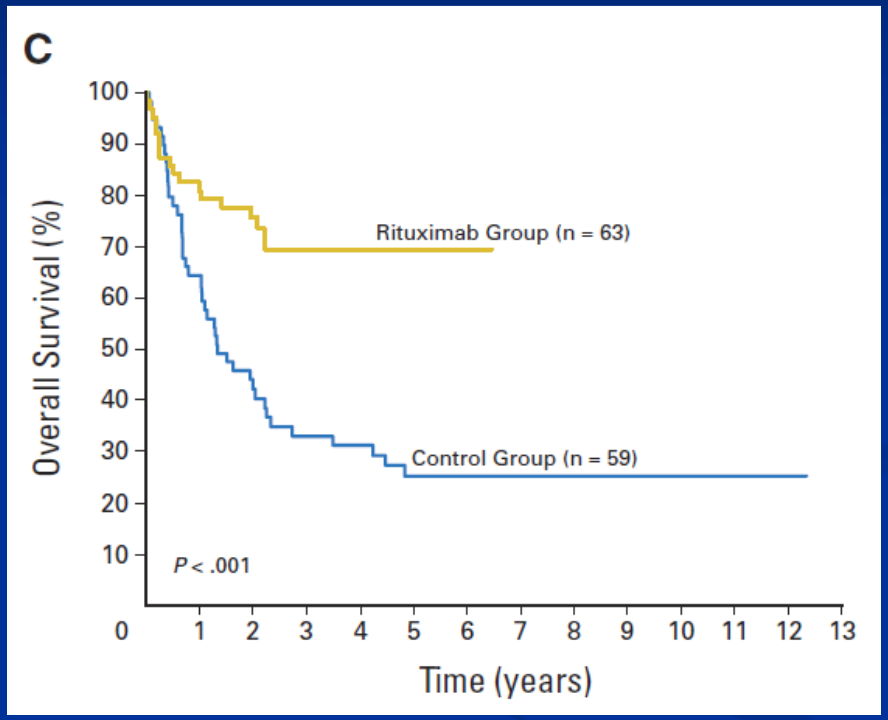


GCB v.s. ABC

Rosenwald A, et al. N Engl J Med 2002; 346(25): 1937-47

Both GCB and non-GCB DLBCL benefit from the R-CHOP treatment





GCB	R-CHOP	CHOP	*P* value
3 yr OS	85%	52%	< 0.001

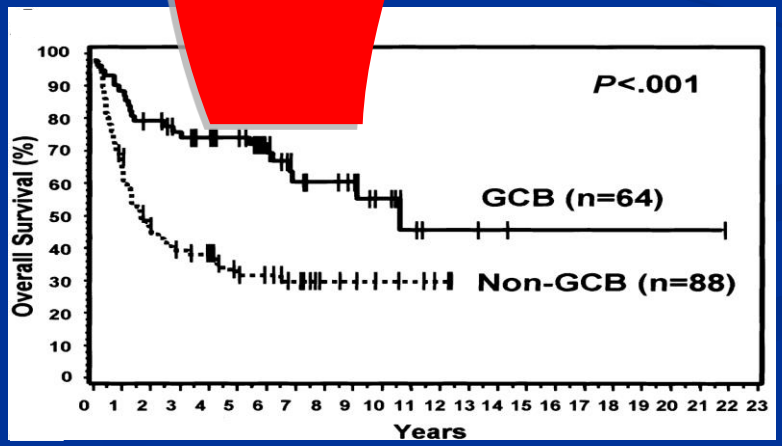
non-GCB	R-CHOP	CHOP	*P* value
3 yr OS	69%	33%	< 0.001

Fu K, et al. J Clin Oncol 2008; 26: 4587

Immunostain algorithm for subgrouping DLBCL

Hans Classifier

Choi Classifier



Immunoblastic morphology but not the immunohistochemical GCB/nonGCB classifier predicts outcome in diffuse large B-cell lymphoma in the RICOVER-60 trial of the DSHNHL

German Ott,[1,2] Marita Ziepert,[3] Wolfram Klapper,[4] Heike Horn,[2] Monika Szczepanowski,[4] Heinz-Wolfram Bernd,[5] Christoph Thorns,[5] Alfred C. Feller,[5] Dido Lenze,[6] Michael Hummel,[6] Harald Stein,[6] Hans-Konrad Müller-Hermelink,[1] Matthias Frank,[7] Martin-Leo Hansmann,[7] Thomas F. E. Barth,[8] Peter Möller,[8] Sergio Cogliatti,[9] Michael Pfreundschuh,[10] Norbert Schmitz,[11] Lorenz Trümper,[12] Markus Loeffler,[3] and Andreas Rosenwald[1]

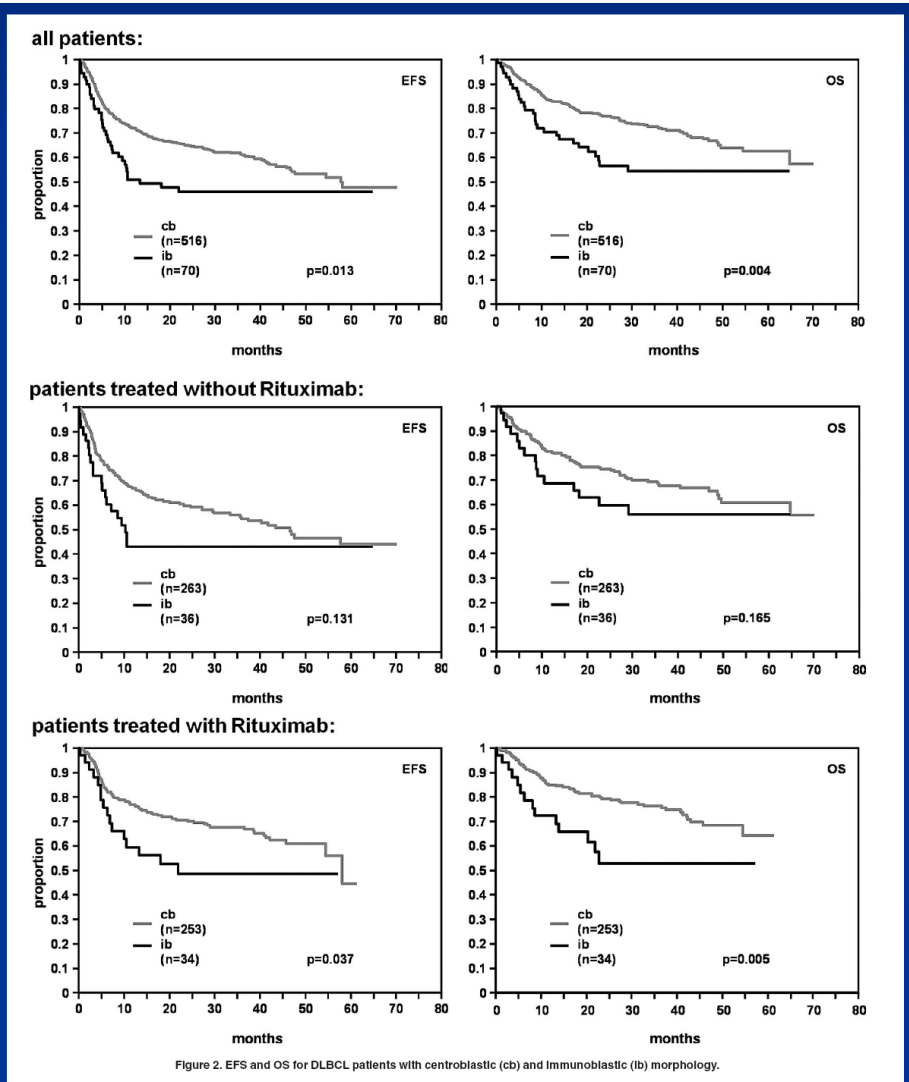
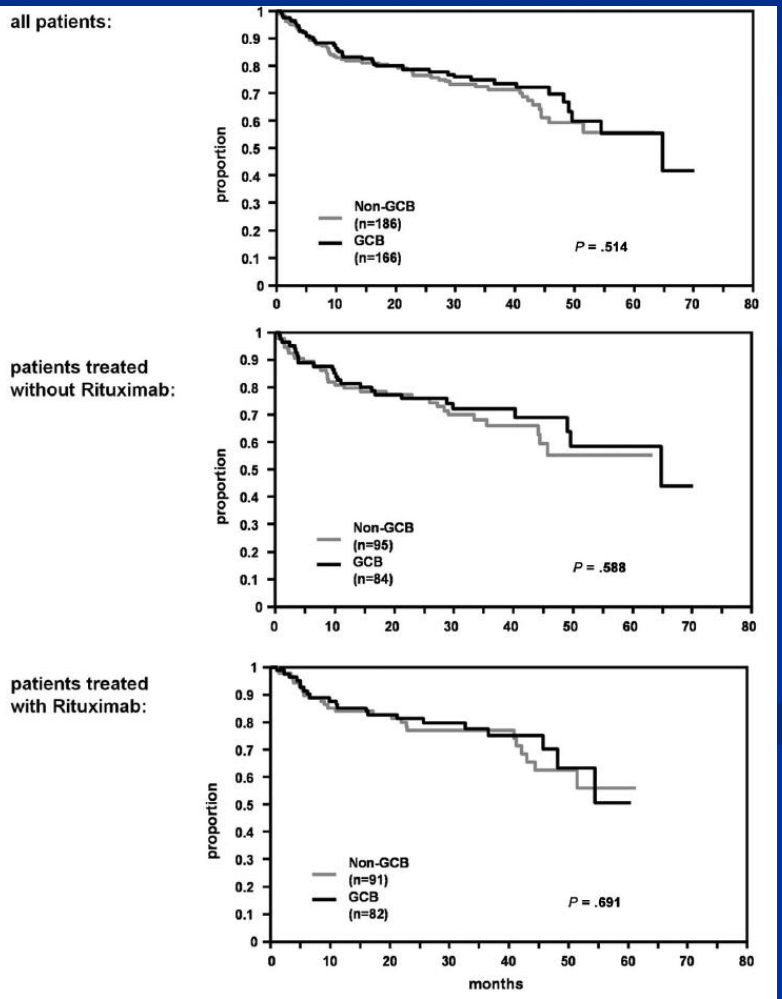


Figure 2. EFS and OS for DLBCL patients with centroblastic (cb) and immunoblastic (ib) morphology.

(*Blood*. 2010;116(23):4916-4925)



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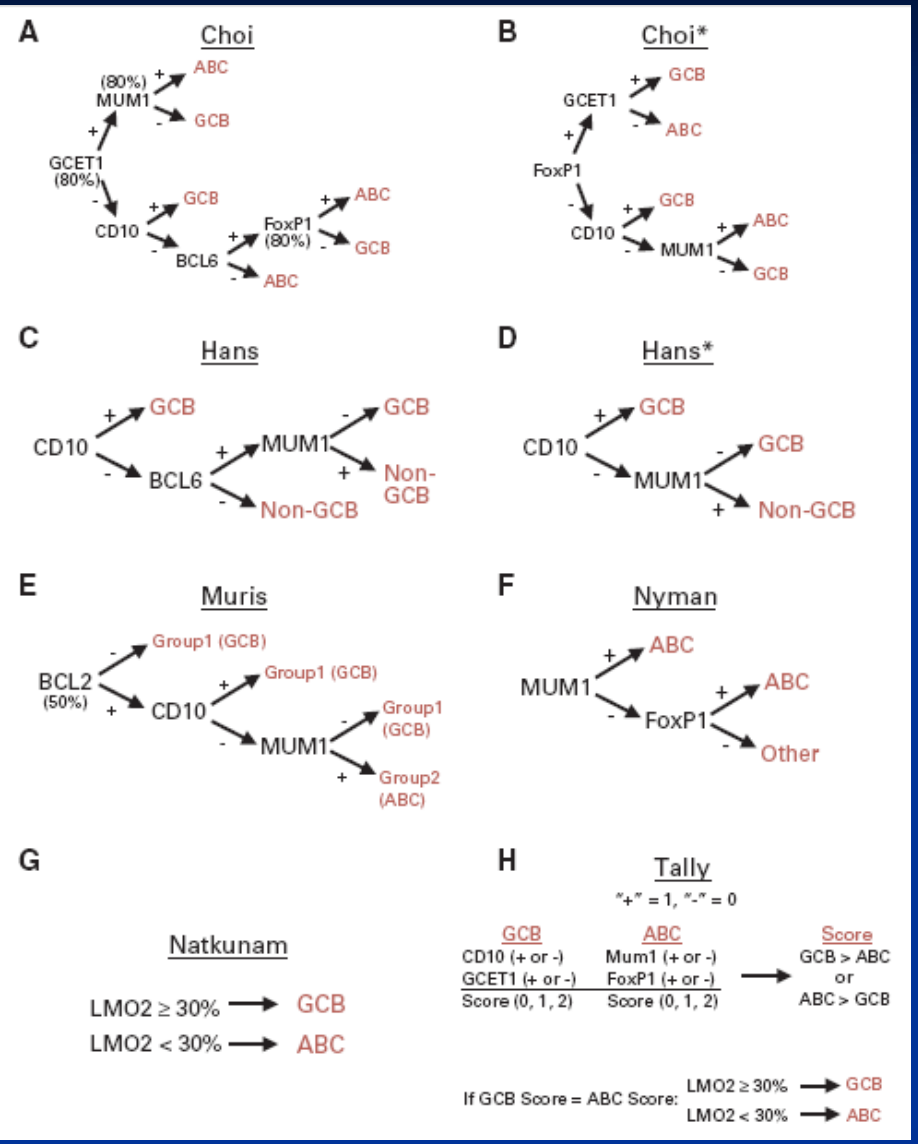
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Immunohistochemical Methods for Predicting Cell of Origin and Survival in Patients With Diffuse Large B-Cell Lymphoma Treated With Rituximab

Paul N. Meyer, Kai Fu, Timothy C. Greiner, Lynette M. Smith, Jan Delabie, Randy D. Gascoyne, German Ott, Andreas Rosenwald, Rita M. Braziel, Elias Campo, Julie M. Vose, Georg Lenz, Louis M. Staudt, Wing C. Chan, and Dennis D. Weisenburger


A
Choi
(80%)
MUM1
ABC
GCB
GCET1
(80%)
CD10
GCB
FoxP1
(80%)
ABC
GCB
BCL6
ABC
B
Choi*
GCET1
GCB
ABC
FoxP1
CD10
GCB
MUM1
ABC
GCB
C
Hans
CD10
GCB
BCL6
MUM1
GCB
Non-
GCB
Non-GCB
D
Hans*
CD10
GCB
MUM1
GCB
Non-GCB
E
Muris
BCL2
(50%)
Group1 (GCB)
CD10
Group1 (GCB)
MUM1
Group1
(GCB)
Group2
(ABC)
F
Nyman
MUM1
ABC
FoxP1
ABC
Other
G
Natkunam
LMO2 ≥ 30% → GCB
LMO2 < 30% → ABC
H
Tally
"+" = 1, "-" = 0
GCB
CD10 (+ or -)
GCET1 (+ or -)
Score (0, 1, 2)
ABC
Mum1 (+ or -)
FoxP1 (+ or -)
Score (0, 1, 2)
Score
GCB > ABC
or
ABC > GCB
If GCB Score = ABC Score:
LMO2 ≥ 30% → GCB
LMO2 < 30% → ABC

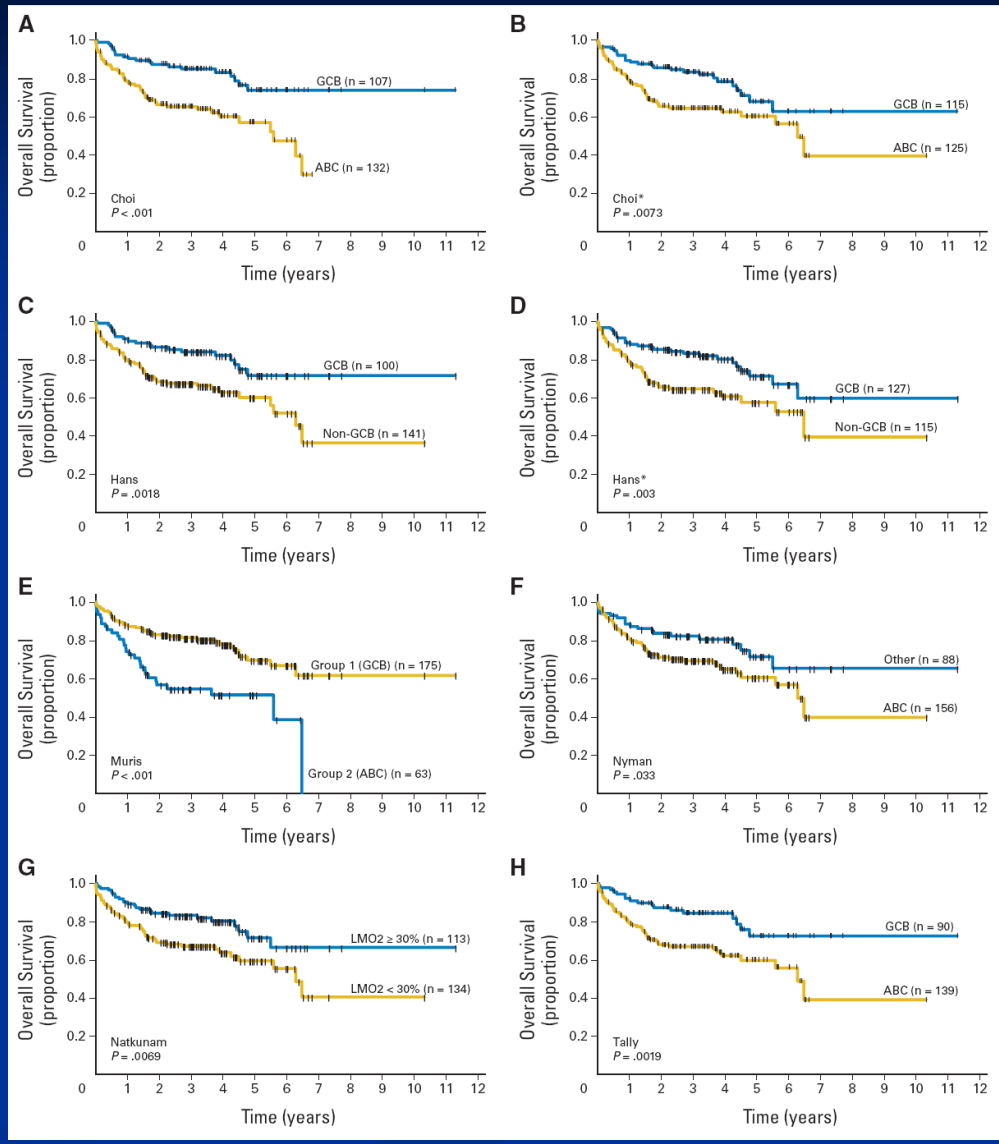

A
Overall Survival (proportion)
GCB (n = 107)
ABC (n = 132)
Choi
P < .001
Time (years)
B
GCB (n = 115)
ABC (n = 125)
Choi*
P = .0073
C
GCB (n = 100)
Non-GCB (n = 141)
Hans
P = .0018
D
GCB (n = 127)
Non-GCB (n = 115)
Hans*
P = .003
E
Group 1 (GCB) (n = 175)
Group 2 (ABC) (n = 63)
Muris
P < .001
F
Other (n = 88)
ABC (n = 156)
Nyman
P = .033
G
LMO2 ≥ 30% (n = 113)
LMO2 < 30% (n = 134)
Natkunam
P = .0069
H
GCB (n = 90)
ABC (n = 139)
Tally
P = .0019

Table 2. Results for Each Algorithm Adjusted for IPI

Algorithm and IPT	No.	Conc (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Survival (n)	EFS		OS	
								HR	95% CI	HR	95% CI
Choi											
GCB	83	87	85	89	89	85	78	2.5	1.5 to 4.3	2.4	1.3 to 4.4
ABC	86						86				
Choi*											
GCB	83	87	85	89	89	85	84	2.3	1.4 to 3.9	1.9	1.1 to 3.4
ABC	87						81				
Hans											
GCB	79	86	82	90	90	82	75	2.5	1.5 to 4.3	2.2	1.2 to 4.0
ABC	90						89				
Hans*											
GCB	93	87	90	83	85	88	91	2.3	1.4 to 3.9	2.0	1.1 to 4.5
ABC	78						75				
Muris											
GCB	122	77	99	54	69	98	125	3.4	2.0 to 5.8	3.2	1.8 to 5.6
ABC	45						38				
Nyman											
GCB	62	81	67	95	94	73	62	1.7	1.0 to 3.0	1.6	0.9 to 2.9
ABC	108						105				
Natkunam											
GCB	84	74	74	74	76	73	85	2.2	1.3 to 3.6	1.9	1.1 to 3.5
ABC	86						84				
Tally											
GCB	76	93	86	99	99	87	69	2.5	1.4 to 4.4	2.2	1.2 to 4.1
ABC	94						87				

NOTE. The hazard ratio of GCB or its equivalent is set to 1 for each algorithm. Of the total number of patients analyzed, 130 have algorithm data, IPI data, and gene expression profile data determined by microarray analysis. Of those 130 patients, 122 have data for all algorithms, two patients are missing one algorithm, and an additional two patients are missing two algorithms.

Abbreviations: IPI, International Prognostic Index; IPT, immunophenotype determined by the algorithm; Conc, concordance; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; EFS, event-free survival; HR, hazard ratio; OS, overall survival; GCB, germinal center B-cell type; ABC, activated B-cell type; Choi*, modified Choi algorithm; Hans*, modified Hans algorithm.

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Comprehensive gene expression profiling and immunohistochemical studies support application of immunophenotypic algorithm for molecular subtype classification in diffuse large B-cell lymphoma: A report from the International DLBCL Rituximab-CHOP Consortium Program Study

Carlo Visco[1,2], **Yan Li**[3], **Zijun Y. Xu-Monette**[1], **Roberto N. Miranda**[1], **Tina M. Green**[4], **Yong Li**[5], **Alexander Tzankov**[6], **Wei Wen**[3], **Wei-min Liu**[3], **Brad S. Kahl**[7], **Emanuele S. G. d'Amore**[2], **Santiago Montes-Moreno**[8], **Karen Dybkær**[9], **April Chiu**[10], **Wayne Tam**[11], **Attilio Orazi**[11], **Youli Zu**[12], **Govind Bhagat**[13], **Jane N. Winter**[14], **Huan-You Wang**[15], **Stacey O'Neill**[16], **Cherie H. Dunphy**[16], **Eric D. Hsi**[17], **X. Frank Zhao**[18], **Ronald S. Go**[19], **William W. L. Choi**[20], **Fan Zhou**[21], **Magdalena Czader**[22], **Jiefeng Tong**[23], **Xiaoying Zhao**[23], **J. Han van Krieken**[24], **Qing Huang**[25], **Weiyun Ai**[26], **Joan Etzell**[26], **Maurilio Ponzoni**[27], **Andres J. M. Ferreri**[27], **Miguel A. Piris**[8], **Michael B. Møller**[4], **Carlos E. Bueso-Ramos**[1], **L. Jeffrey Medeiros**[1], **Lin Wu**[3], and **Ken H. Young**[1,¶]

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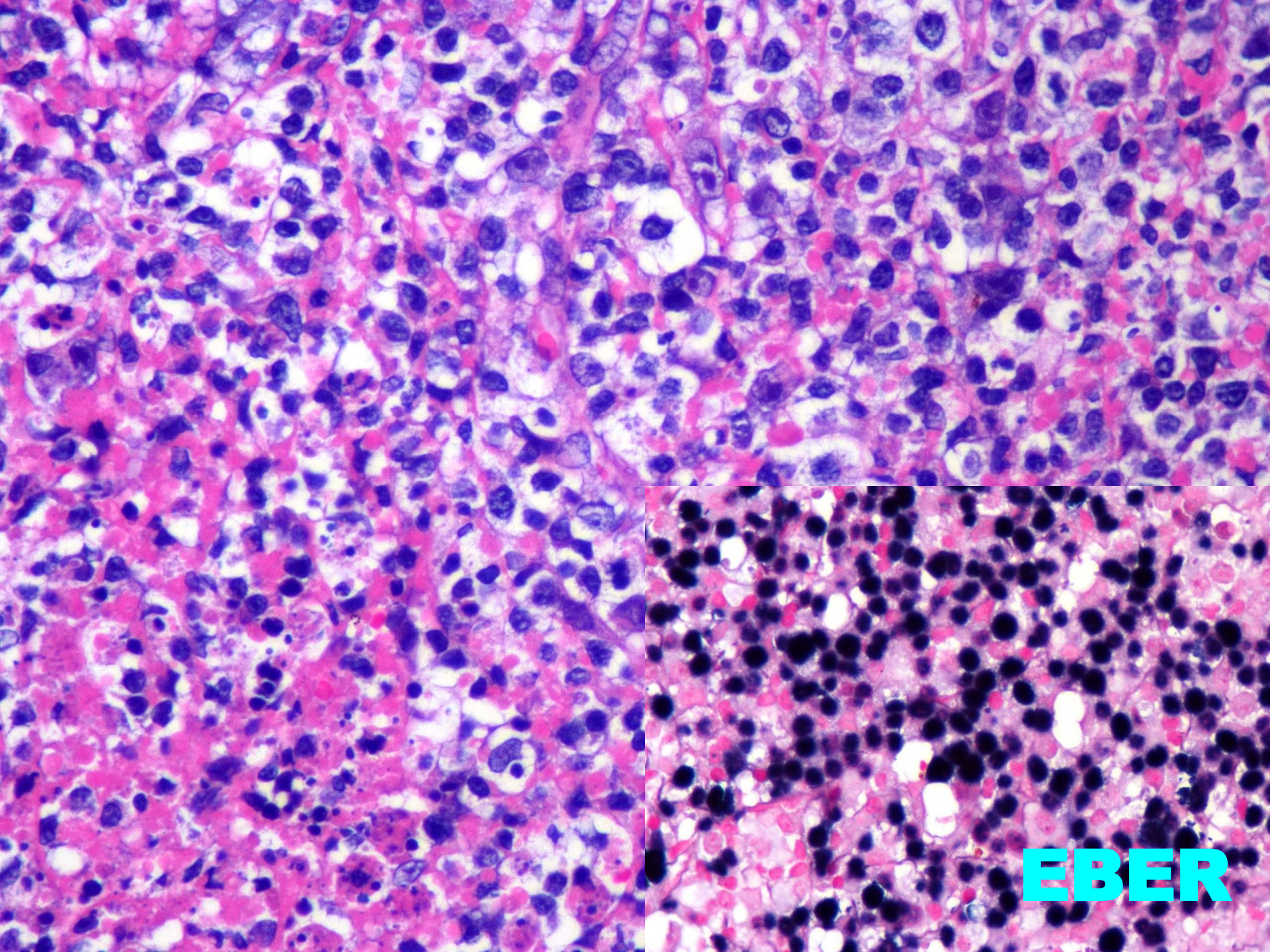
DLBCL: 2016 WHO Classification

- **Diffuse large B-cell lymphoma, NOS (GCB, ABC, others)**
- **Diffuse large B-cell lymphoma subtypes**
  - **T-cell/histiocyte-rich large B-cell lymphoma**
  - **Primary DLBCL of the CNS**
  - **Primary cutaneous DLBCL, leg type**
  - **EBV-positive DLBCL**
  - **Primary mediastinal (thymic) large B-cell lymphoma**
  - **Intravascular large B-cell lymphoma**
  - **DLBCL associated with chronic inflammation**
  - **Lymphomatoid granulomatosis**
  - **ALK-positive large B-cell lymphoma**
  - **Plasmablastic lymphoma**
  - **Multicentric Castleman disease**
  - **Primary effusion lymphoma**
- **Borderline cases**
  - **B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (modified definition)**
  - **B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical HL**

EBV+ DLBCL of the elderly

- > 50 yrs (may occur in younger adults), without any known immunodeficiency, other well defined EBV-associated disorders should be excluded
- Accounts for 8-10% of DLBCL, median age 71 yr, M:F ratio 1.4:1
- 70% of patients present with extranodal disease
- Architecture effaced, polymorphous and large cell lymphoma subtypes, HRS-like cells, geographical necrosis
- CD20+, CD79a+, PAX5+, may show plasmablastic differentiation; EBER+, LMP1+, EBNA2-/+, CD30+/-
- Aggressive course, with a median survival of 24 mons


EBER

Annals of Oncology 26: 548–555, 2015
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EBV-positive diffuse large B-cell lymphoma in young adults: is this a distinct disease entity?

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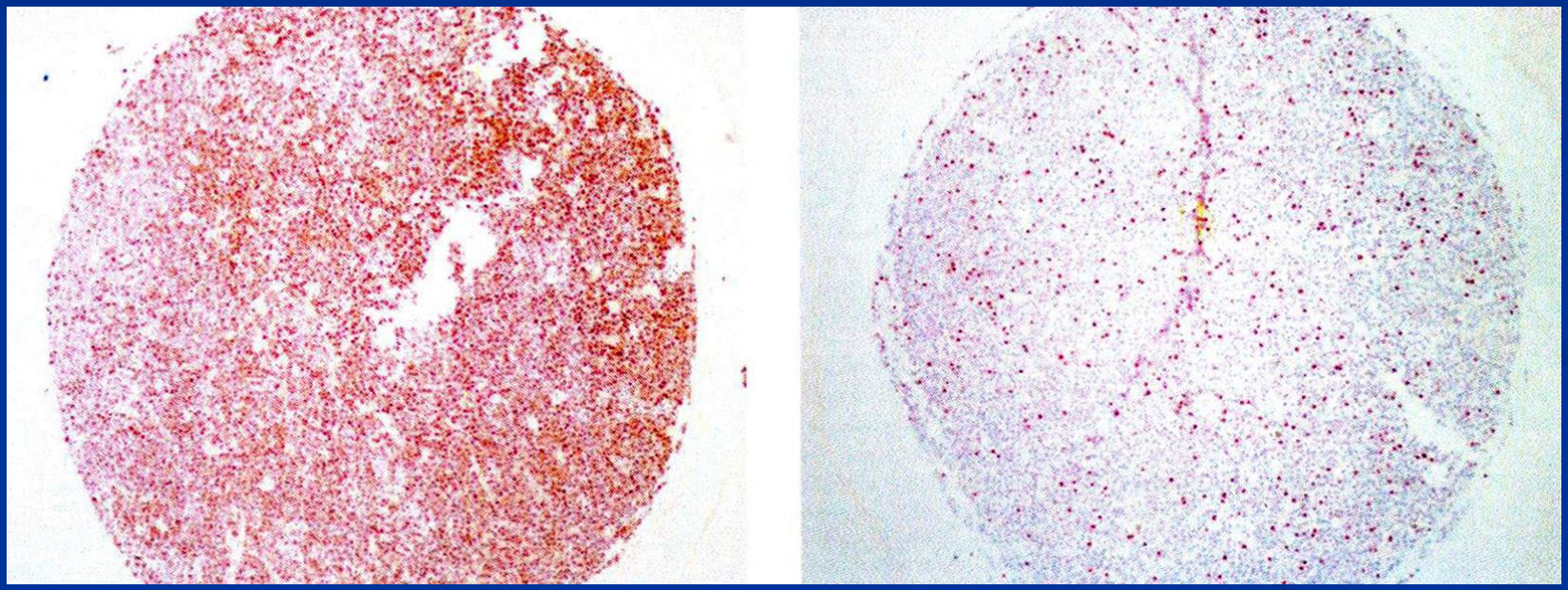
Background: Epstein–Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL) of the elderly is defined only in adults older than 50 years. However, EBV-positive DLBCL can affect younger patients. We investigated the prevalence, clinical characteristics and survival outcomes of EBV-positive DLBCL in young adults.

Patients and methods: We analyzed patients with *de novo* DLBCL who were registered in the Samsung Medical Center (SMC) retrospective lymphoma cohort and prospective SMC Lymphoma Cohort Study I (ClinicalTrials.gov: NCT00822731).

Results: A total of 571 cases were included in the analysis. The prevalence of EBV positivity was 6.7% (13/195) and 9.3% (35/376) in the young group (≤50 years) and in the elderly group (>50 years), respectively. EBV status was closely associated with unique unfavorable clinical characteristics [older age, more advanced stage, two or more sites of extranodal involvement, higher International Prognostic Index (IPI), and age-adjusted IPI risk] only in the elderly group. Poor prognostic impact of EBV positivity on overall survival was observed only in the elderly group [hazard ratio (HR) 2.86; 95% confidence interval (CI) 1.83–4.47; $P < 0.001$], but not in the young group (HR 1.17; 95% CI 0.35–3.89; $P = 0.801$).

Conclusion: A substantial proportion of EBV-positive DLBCL of the elderly can occur in young adults. EBV positivity of DLBCL in young adults was not associated with unfavorable clinical characteristics or worse outcomes. We suggest that EBV-positive DLBCL should not be confined only in the elderly and 'EBV-positive DLBCL in young adults' needs to be considered as a clinically distinct disease entity.

EBV+ DLBCL: The cut-off of EBV+ tumor cells?



The proportion of EBER+ tumor cells varies considerably in individual cases

Correlation of EBV status and clinicopathologic characteristics in 195 DLBCLs

No. of cases (%)		EBER+ tumor cells of any %			EBER+ tumor cells > 20%			EBER+ tumor cells > 50%		
		EBV+	EBV-	*P* value	EBV+	EBV-	*P* value	EBV+	EBV-	*P* value
	Total	27 (13.9)	168 (86.1)		22 (10.3)	173 (89.7)		17 (8.7)	178 (91.3)	
Age	Mean (yrs)	57	55.7		58.3	55.5		59.1	55.5	
	≤50 yrs	8 (29.6)	51 (30.4)	0.568	6 (27.3)	53 (30.6)	0.480	5 (31.2)	54 (30.2)	0.554
	>50 yrs	19 (70.4)	117 (69.6)		16 (72.7)	120 (69.4)		11 (68.8)	125 (69.8)	
Sex	Male	19 (70.4)	97 (57.7)	0.151	16 (72.7)	100 (57.8)	0.132	11 (68.8)	105 (58.7)	0.305
	Female	8 (29.6)	71 (42.3)		6 (27.3)	73 (42.2)		5 (31.2)	74 (41.3)	
Sites	Extranodal	1 (3.7)	28 (16.7)	0.060	1 (4.5)	28 (16.2)	0.125	1 (6.2)	28 (15.6)	0.276
	Nodal	26 (96.3)	140 (83.3)		21 (95.5)	145 (83.8)		15 (93.8)	151 (84.4)	
Stage	I/II	11 (40.7)	104 (64.2)	0.019	9 (40.9)	106 (63.5)	0.037	7 (43.8)	108 (62.4)	0.117
	III/IV	16 (59.3)	58 (35.8)		13 (59.1)	61 (36.5)		9 (56.2)	65 (37.6)	
LDH	Normal	7 (25.9)	83 (52.9)	0.008	5 (22.7)	85 (52.5)	0.007	5 (31.2)	85 (50.6)	0.111
	Increased	20 (74.1)	74 (47.1)		17 (77.3)	77 (47.5)		11 (68.8)	83 (49.4)	
ECOG	0	2 (8.3)	58 (42.0)	0.007	2 (10.5)	58 (40.6)	0.039	1 (7.1)	59 (39.9)	0.050
	1	19 (79.2)	70 (50.7)		15 (78.9)	74 (51.7)		11 (78.6)	78 (52.7)	
	≥2	3 (12.5)	10 (7.2)		2 (10.5)	11 (7.7)		2 (14.3)	11 (7.4)	
Extra-nodal	≤1 site	21 (80.8)	140 (87.5)	0.256	18 (85.7)	143 (86.7)	0.561	14 (93.3)	147 (86.0)	0.371
	> 1 site	5 (19.2)	20 (12.5)		3 (14.3)	22 (13.3)		1 (6.7)	24 (14.0)	
IPI	0-2	16 (64.0)	116 (81.1)	0.053	14 (66.7)	118 (80.3)	0.129	12 (75.0)	120 (78.9)	0.461
	3-5	9 (36.0)	27 (18.9)		7 (33.3)	29 (19.7)		4 (25.0)	32 (21.1)	

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Correlation of EBV status and clinicopathologic characteristics in 195 DLBCLs

No. of cases (%)		EBER+ tumor cells of any %			EBER+ tumor cells > 20%			EBER+ tumor cells > 50%		
		EBV+	EBV-	*P* value	EBV+	EBV-	*P* value	EBV+	EBV-	*P* value
Hans	GCB-like	7 (25.9)	56 (33.3)	0.299	5 (22.7)	58 (33.5)	0.221	3 (18.8)	60 (33.5)	0.177
	non-GCB-like	20 (74.1)	112 (66.7)		17 (77.3)	115 (66.5)		13 (81.2)	119 (66.5)	
Muris	GCB-like	14 (51.9)	117 (69.6)	0.056	12 (54.5)	119 (68.8)	0.137	9 (56.2)	122 (68.2)	0.240
	non-GCB-like	13 (48.1)	51 (30.4)		10 (45.5)	54 (31.2)		7 (43.8)	57 (31.8)	
CD10	+	6 (22.2)	32 (19.0)	0.435	5 (22.7)	33 (19.1)	0.434	3 (18.8)	35 (19.6)	0.620
	-	21 (77.8)	136 (81.0)		17 (77.3)	140 (80.9)		13 (81.2)	144 (80.4)	
BCL6	+	7 (25.9)	102 (60.7)	0.001	5 (22.7)	104 (60.1)	0.001	4 (25.0)	105 (58.7)	0.010
	-	20 (74.1)	66 (39.3)		17 (77.3)	69 (39.9)		12 (75.0)	74 (41.3)	
MUM1	+	8 (29.6)	95 (56.5)	0.008	6 (27.3)	97 (56.1)	0.010	4 (25.0)	99 (55.3)	0.019
	-	19 (70.4)	73 (43.5)		16 (72.7)	76 (43.9)		12 (75.0)	80 (44.7)	
BCL2	+	12 (44.4)	109 (64.9)	0.036	9 (40.9)	112 (64.7)	0.028	7 (43.8)	114 (63.7)	0.097
	-	15 (55.6)	59 (35.1)		13 (59.1)	61 (35.3)		9 (56.2)	65 (36.3)	
Ki-67	≤ 50%	5 (18.5)	25 (14.9)	0.403	4 (18.2)	26 (15.0)	0.448	3 (18.8)	152 (84.9)	0.460
	> 50%	22 (81.5)	143 (85.1)		18 (81.8)	147 (85.0)		13 (81.2)	27 (15.1)	
Treatment	CHOP-like	15 (60.0)	83 (55.3)	0.416	14 (70.0)	84 (54.2)	0.135	8 (57.1)	90 (55.9)	0.579
	RCHOP-like	10 (40.0)	67 (44.7)		6 (30.0)	71 (45.8)		6 (42.9)	71 (44.1)	
DFS				< 0.001			< 0.001			0.038
OS				< 0.001			< 0.001			0.008

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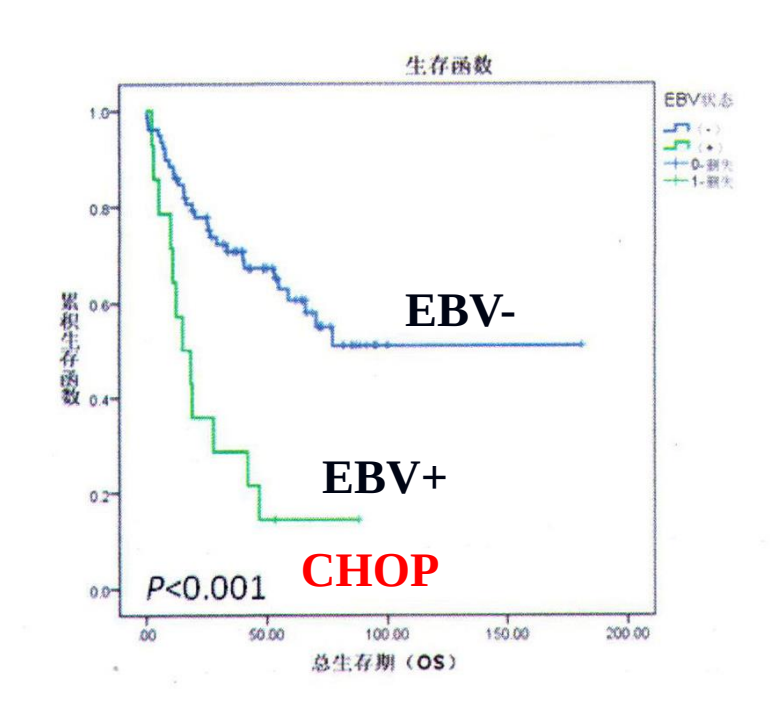
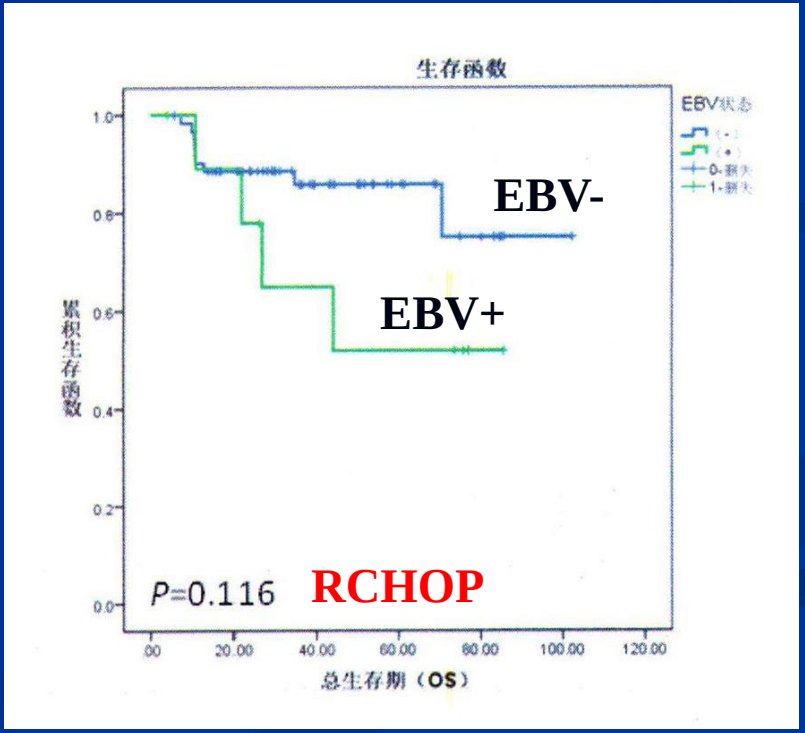
Survival of EBV+ DLBCLs with different therapeutic regimens

	CHOP			RCHOP		
	Case No.	DFS	OS	Case No.	DFS	OS
EBV+	14	< 0.001	< 0.001	10	< 0.001	< 0.001
EBV-	79			62		





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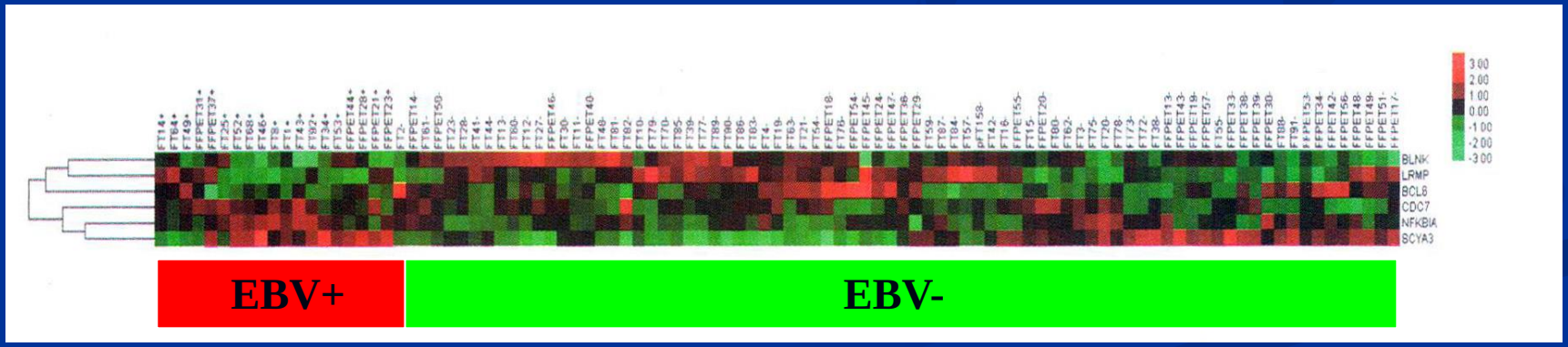
EBV+ DLBCL-related differential genes

Gene symbol	*P* value	FDR	Geom mean of intensities in EBV+	Geom mean of intensities in EBV-	Fold-change
BLNK	0.0003381	0.0159	592.5	1214.82	0.49
NFKBIA	0.0025516	0.06	BLNK	1887.96	1.35
BCL6	0.0248577	0.273	575.13	927.76	0.62
LRMP	0.0250088	0.273	653.37	1091.59	0.6
CDC7	0.0346789	0.273	273.26	212.11	1.29
SCYA3	0.0349144	0.273	265.89	166.43	1.6



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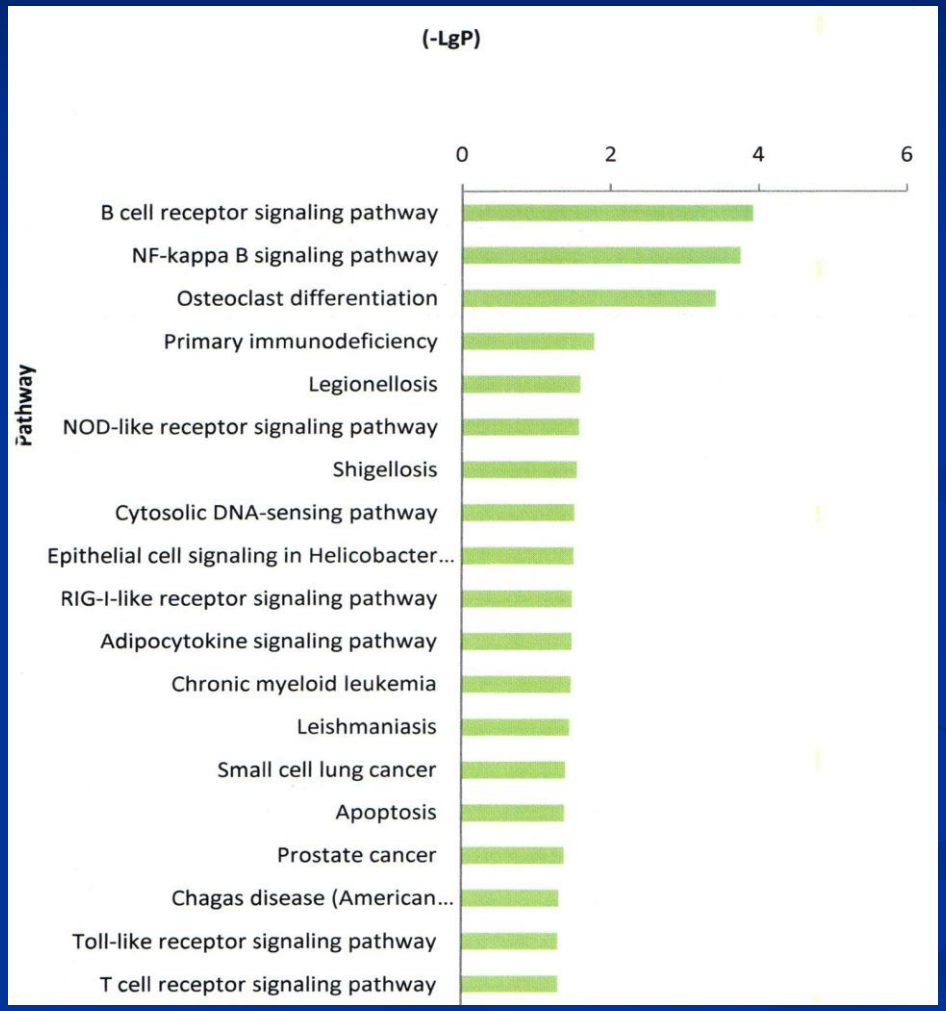
Possible signaling pathways involved in EBV+ DLBCLs



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Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response

Stefano Monti, Kerry J. Savage, Jeffery L. Kutok, Friedrich Feuerhake, Paul Kurtin, Martin Mihm, Bingyan Wu, Laura Pasqualucci, Donna Neuberg, Ricardo C. T. Aguiar, Paola Dal Cin, Christine Ladd, Geraldine S. Pinkus, Gilles Salles, Nancy Lee Harris, Riccardo Dalla-Favera, Thomas M. Habermann, Jon C. Aster, Todd R. Golub, and Margaret A. Shipp

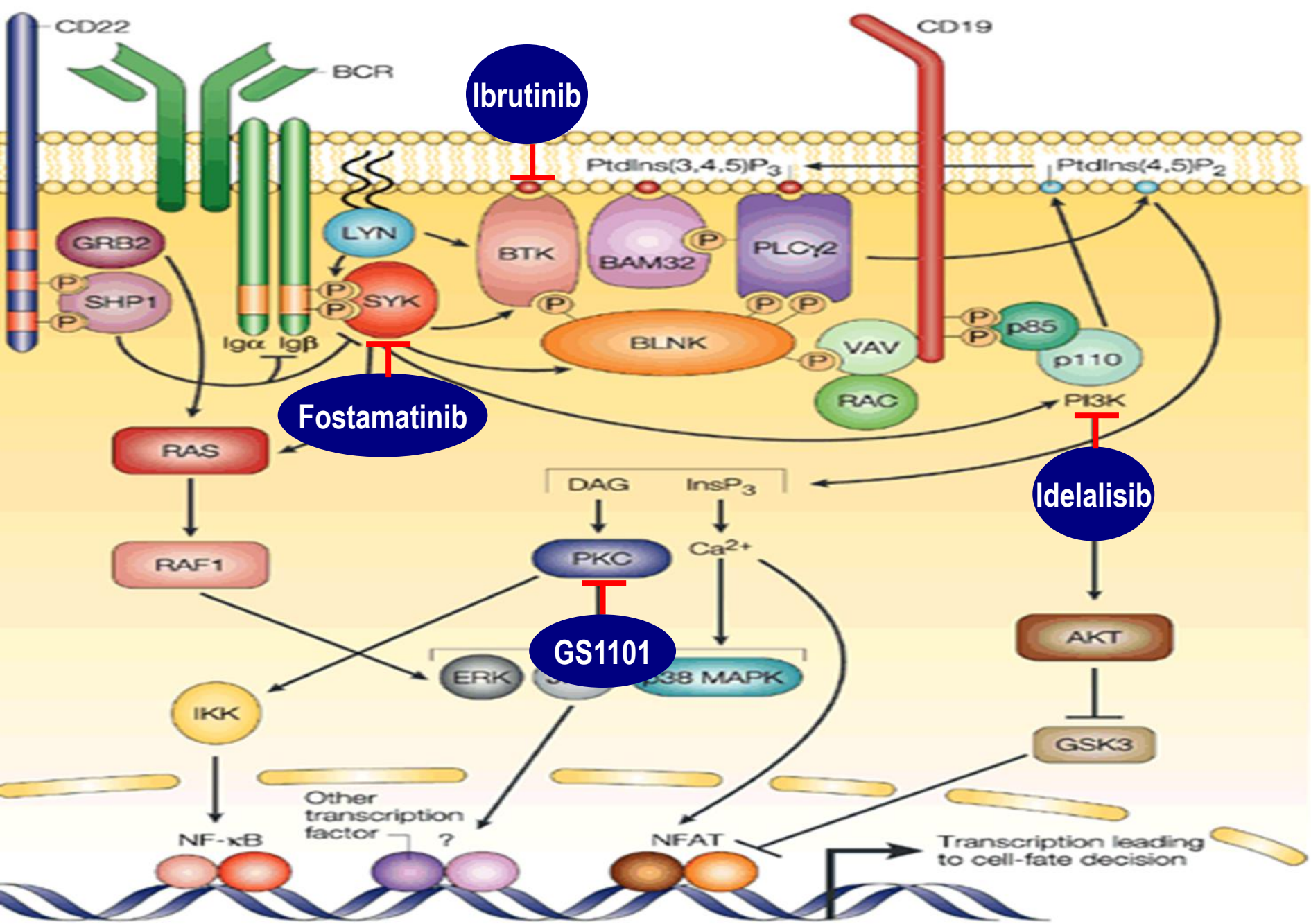
DLBCL. There were 3 discrete subsets of DLBCL—"oxidative phosphorylation," "B-cell receptor/proliferation," and "host response" (HR)—identified characterized us-

(Blood. 2005;105:1851-1861)

COO	Consensus clusters: OxPhos	BCR/Prolif.	HR	CTOT
ABC	9	18	8	35
GCB	23	41	15	79
Other	18	18	26	62
RTOT	50	77	49	176

Figure 4. Relationship of consensus clusters to cell-of-origin (COO) signature.

- **OxPhos: Enriched in genes involved in oxidative phosphorylation, mitochondrial function, and electron transport chain; higher levels of *BCL2* family members**
- **BCR/proliferation: Has more abundant expression of cell-cycle regulatory genes (CDK2, MCM family members, etc.); increased expression of DNA repair genes (PMS2, H2AX, PTIP, P53); higher levels of BCR signaling cascade components (CD19, Ig, CD79a, SYK, BLK) and B-cell-related transcription factors (PAX5, OBF-1, E2A, BCL6, STAT6, MYC)**
- **HR: Enriched for markers of T-cell-mediated immune response and classical complement pathway; increased expression of an overlapping set of inflammatory mediators and connective tissue components**
- **The three consensus clusters have similar 5-yr-survivals, suggesting the clusters may be more useful for identifying potential pathogenetic mechanisms and cluster-specific therapeutic targets than predicting responses to combination CT**



Nature Reviews | Immunology

Loss of B-cell Receptor Expression Defines a Subset of Diffuse Large B-cell Lymphoma Characterized by Silent BCR/PI3K/AKT Signaling and a Germinal Center Phenotype Displaying Low-risk Clinicopathologic Features

Wei-Ge Wang, MD,† Wen-Li Cui, MD, PhD,*†‡ Lei Wang, MD, PhD,*† Fen Zhu, MD,§ Xiao-Chun Wan, MD,*† Bo Ping, MD, PhD,*† Xiao-Yan Zhou, MD, PhD,*† and Xiao-Qiu Li, MD, PhD*†*

Abstract: B-cell receptor (BCR) signaling is crucial for the survival of normal and neoplastic B cells, and inhibitors targeting BCR signaling pathways have shown promising therapeutic outcomes for patients with B-cell lymphomas. In the current study, we analyzed de novo diffuse large B-cell lymphoma without BCR expression (DLBCL, BCR$^-$) in 25 cases to determine the BCR/phosphatidylinositol-3-kinase/AKT (BCR/PI3K/AKT) signaling status, clinicopathologic features, and underlying causes leading to the loss of BCR. On the basis of clinical features, 15 (60%) DLBCL, BCR$^-$ patients were classified into the low-risk group, and 18 (86%) experienced complete remission. Morphologically and immunopheno-

PI3K/AKT pathway were expressed at low levels in DLBCL, BCR$^-$ tissue. In vitro validation revealed that in DLBCL, BCR$^-$ cell lines, the BCR/PI3K/AKT pathway did not respond to BCR stimulation or inhibition. Our findings suggest that DLBCL, BCR$^-$ was characterized by a silent BCR/PI3K/AKT pathway, germinal center phenotype, and low risk and may not be a candidate for BCR-targeted therapies.

Key Words: diffuse large B-cell lymphoma, B-cell receptor, clinicopathologic features, PI3K, AKT

(*Am J Surg Pathol* 2015;39:902–911)

Metabolic Signatures Uncover Distinct Targets in Molecular Subsets of Diffuse Large B Cell Lymphoma

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[10]These authors contributed equally to this work

Cancer Cell *22*, 547–560, October 16, 2012

SUMMARY

Molecular signatures have identified several subsets of diffuse large B cell lymphoma (DLBCL) and rational targets within the B cell receptor (BCR) signaling axis. The OxPhos-DLBCL subset, which harbors the signature of genes involved in mitochondrial metabolism, is insensitive to inhibition of BCR survival signaling but is functionally undefined. We show that, compared with BCR-DLBCLs, OxPhos-DLBCLs display enhanced mitochondrial energy transduction, greater incorporation of nutrient-derived carbons into the tricarboxylic acid cycle, and increased glutathione levels. Moreover, perturbation of the fatty acid oxidation program and glutathione synthesis proved selectively toxic to this tumor subset. Our analysis provides evidence for distinct metabolic fingerprints and associated survival mechanisms in DLBCL and may have therapeutic implications.

DLBCL carrying *MYC* abnormalities

- ***MYC*** **gene (8q24.21) play important roles in the regulation of cell differentiation, cell cycle, apoptosis, adhesion, and angiogenesis**
- ***MYC*** **abnormalities may be involved in the pathogenesis of some aggressive B-cell lymphomas**
  - **Predominantly gene rearrangement associated with chromosomal translocation, with occasional gene amplification**
  - **Comprising BL, DLBCL and BLU, with features intermediate between DLBCL and BL**
- **DLBCL carrying** ***MYC*** **abnormalities has been reported to be associated with a worse clinical outcome**

DLBCL with *MYC* rearrangement: Incidence and clinicopathologic characteristics

表 1-4 含有 *MYC* 基因重排的 DLBCL 的临床病理学特征

临床病理学特征	DLBCL,MYC+ n(%) n=17(9.3%)	DLBCL,MYC- n(%) n=165	*p* 值
临床参数			
中位年龄[范围]，岁	58 [22-86]	59 [23-86]	0.856
男	7(41)	87(52)	0.448
女	10(59)	78(48)	
IPI 0-2	7(41)	119(72)	**0.008**
IPI 3-5	10(59)	46(28)	
大块病灶（直径>10cm）	3(17)	29(18)	1
使用 RCHOP 方案	5（36）	55（38）	1
使用 CHOP 方案	9（64）	89（62）	
免疫表型			
GCB	11(65)	89(54)	0.452
non-GCB	6(35)	76(46)	
Ki-67 中位值[范围]	80[50-95]	82.5[40-100]	0.895

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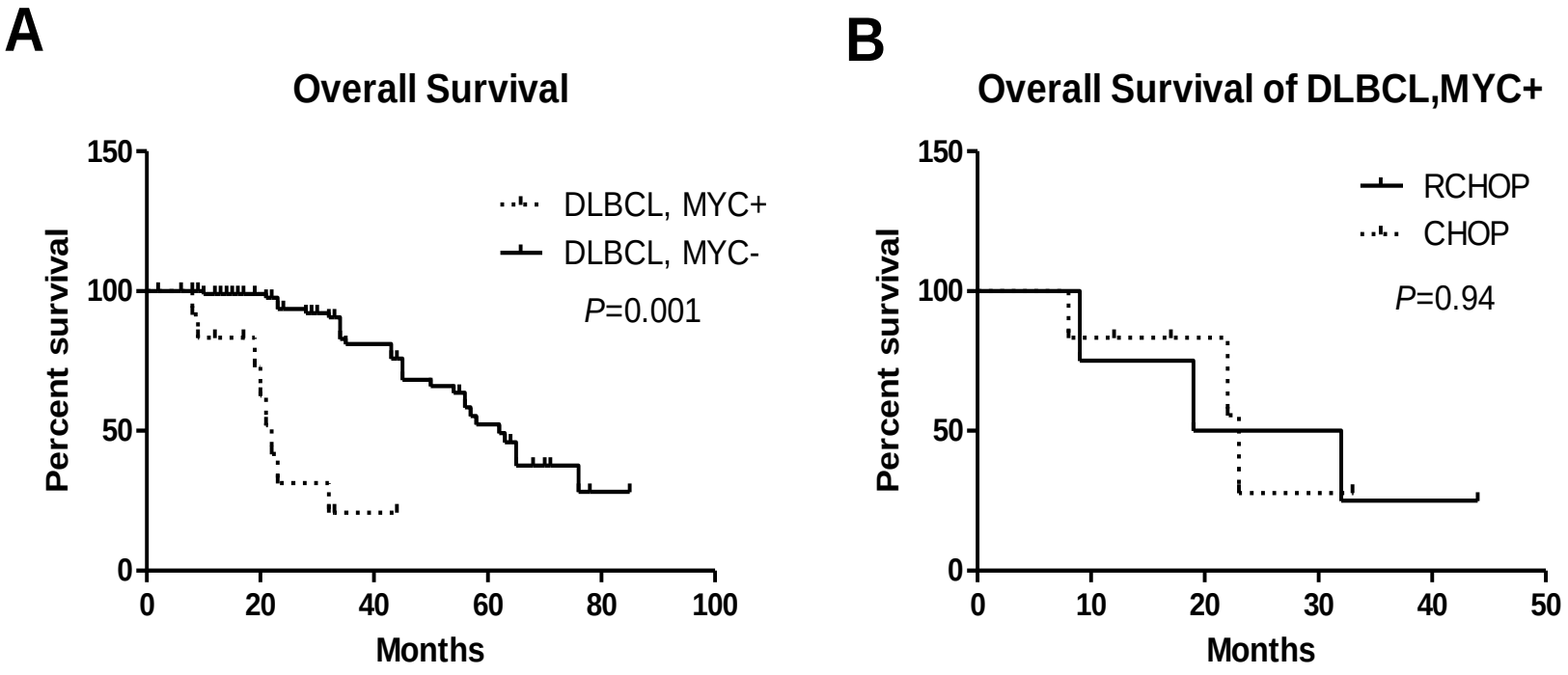
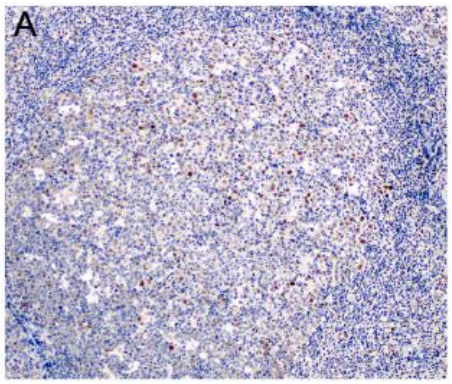
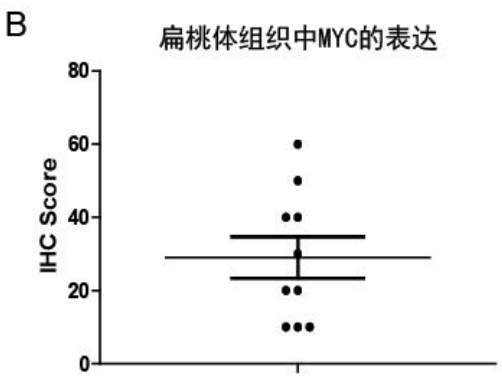
Prognostic impact of *MYC* rearrangement in DLBCL

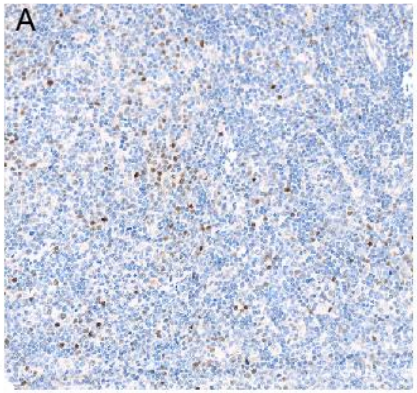


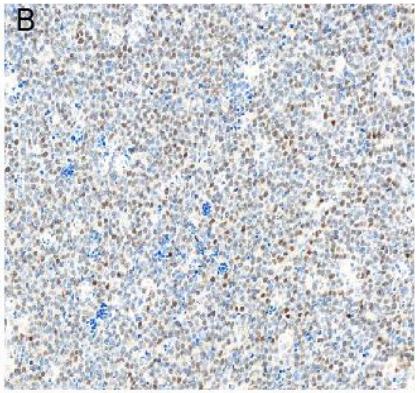
Wang WG, et al. Unpublished data from FUSCC

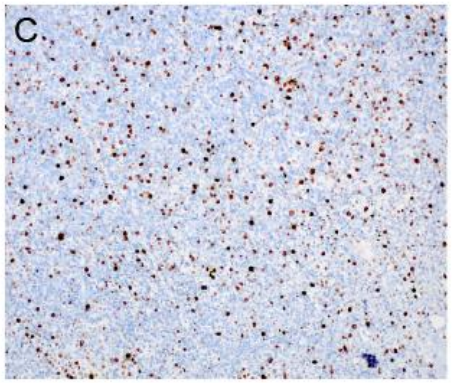
Expression of MYC protein in DLBCL

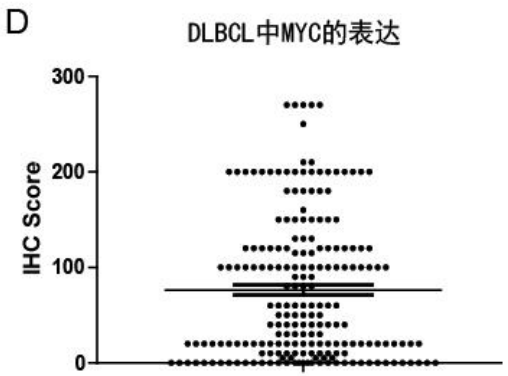


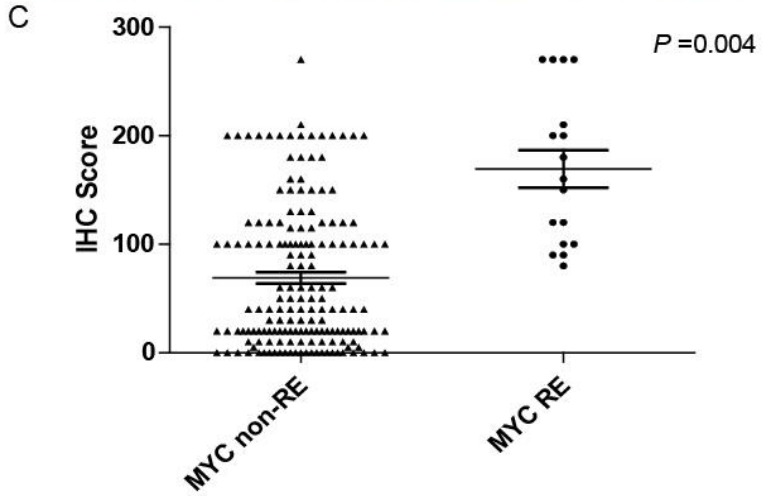












Wang WG, Li XQ, et al. Unpublished data from FUSCC

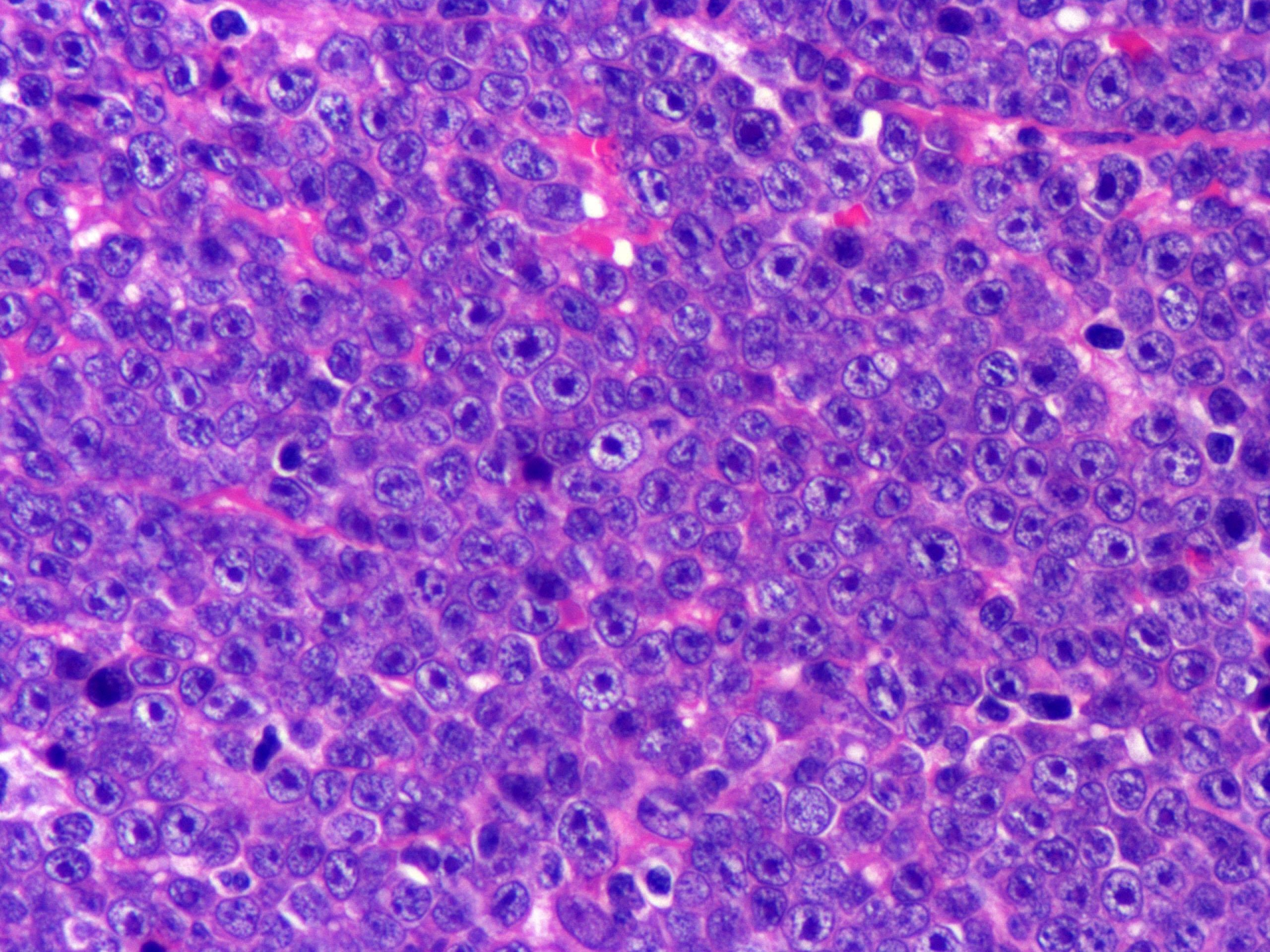
Double-hit B-cell lymphoma (DHL)

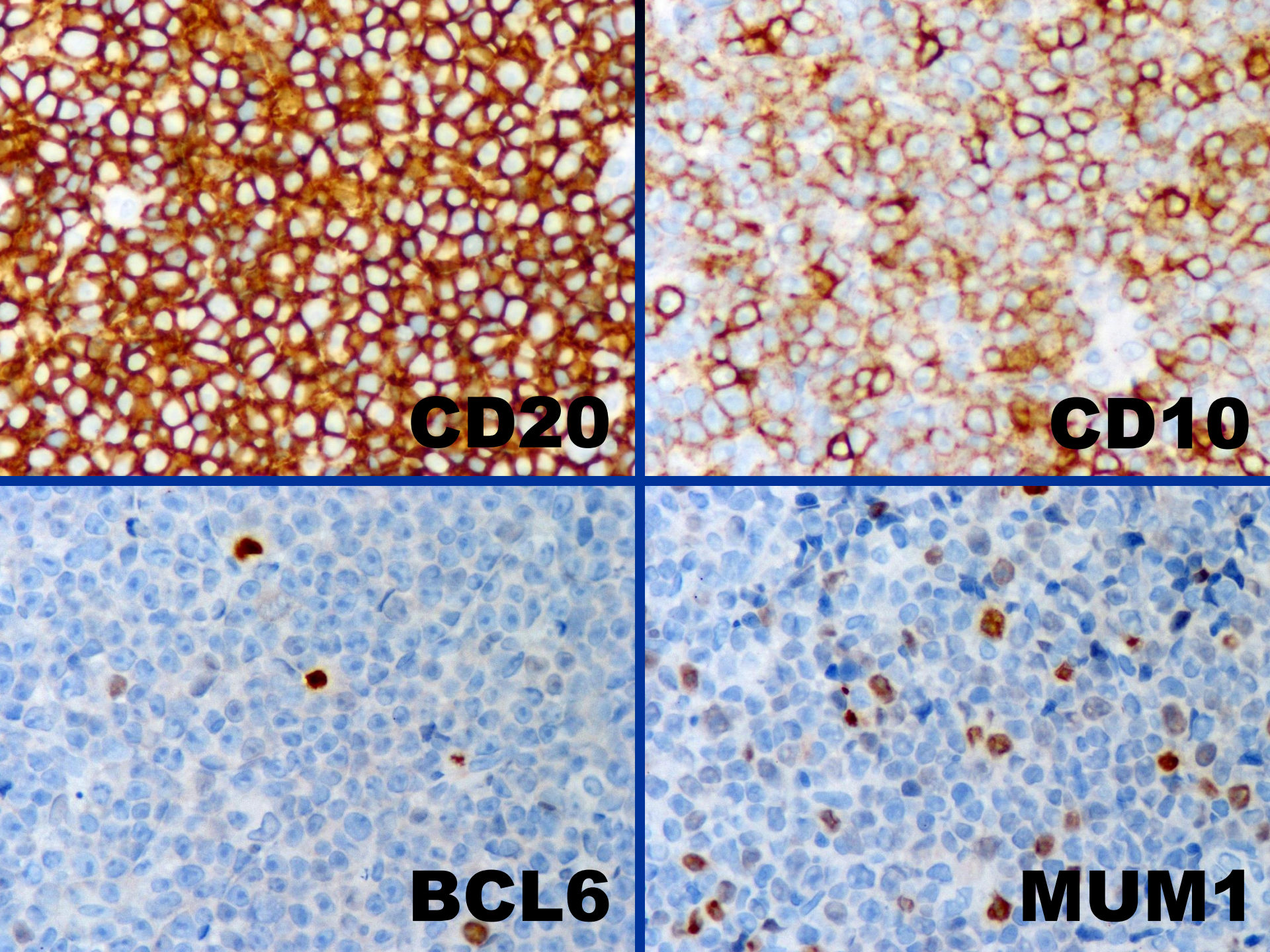
- **Refers to a B-cell lymphoma with 8q24/*MYC* rearrangements in combination with a translocation involving another gene (e.g., *BCL2*, *BCL3*, *BCL6*)**
- **The most common form is *MYC*/*BCL2* DHL**
  - **Morphologically resemble conventional DLBCL or BLU, with features intermediate between DLBCL and BL**
  - **GCB phenotype, high proliferation rate, complex karyotype**
  - **Aggressive clinical course, poor prognosis**
- **The spectrum of *MYC*/*BCL2* DHL has been recently broadened to include those have concurrent *MYC* and *BCL2* cytogenetic abnormalities other than translocations**
- **A subset of DLBCL overexpressing MYC and BCL2 show overlap with *MYC*/*BCL2* DHL, but are not equivalent**

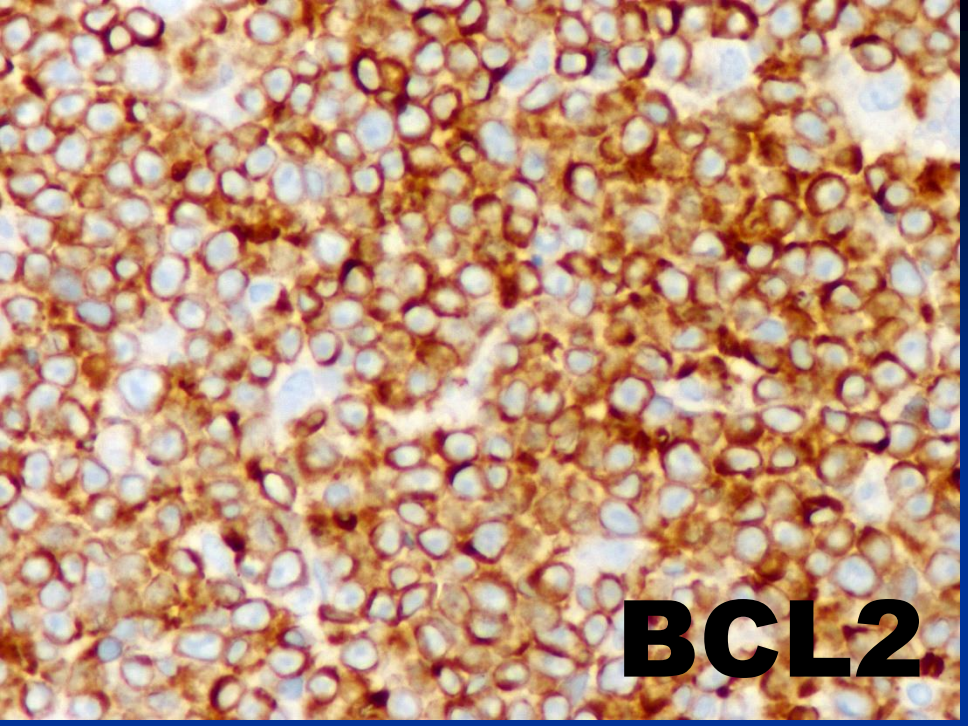
Classification of DHLs

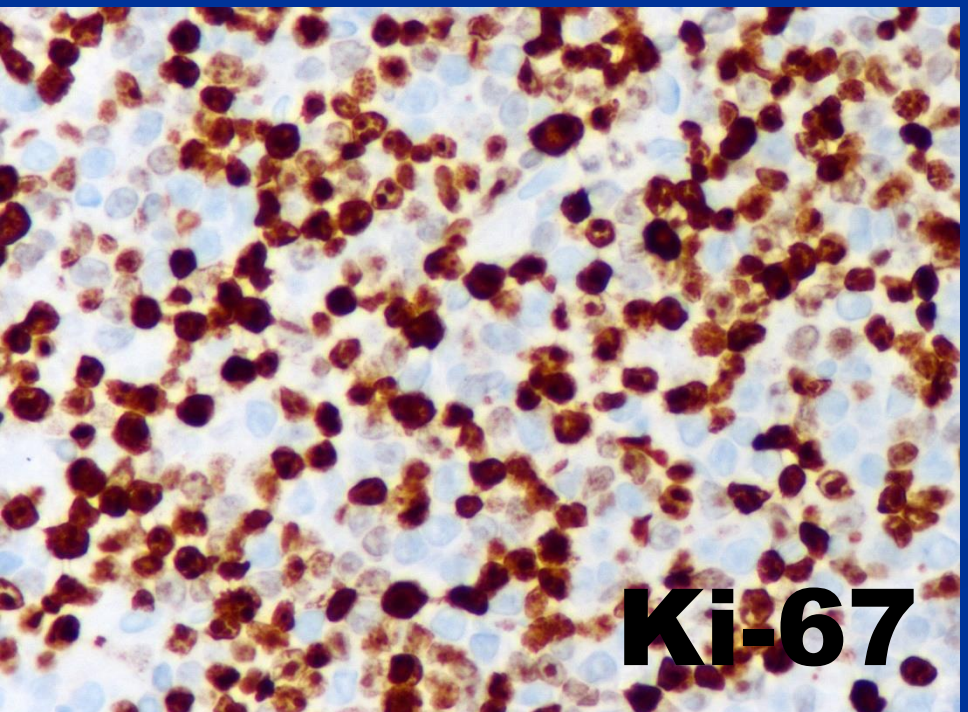
DH lymphomas	N	Percentage of all 326 DH cases
BCL2$^+$/*MYC*$^+$	203	62
BCL6$^+$/*MYC*$^+$	26	8
BCL2$^+$/*BCL6*$^+$/MYC$^+$	53	16
CCND1$^+$/*MYC*$^+$	34	10
BCL3$^+$/*MYC*$^+$	5	2
9p13$^+$/*MYC*$^+$	4	1
BCL3$^+$/9p13$^+$/*MYC*$^+$ TH	1	0
Total DH and TH cases	326	100
MYC only		
Burkitt lymphoma	205	
Other lymphomas	158	
Total	689	

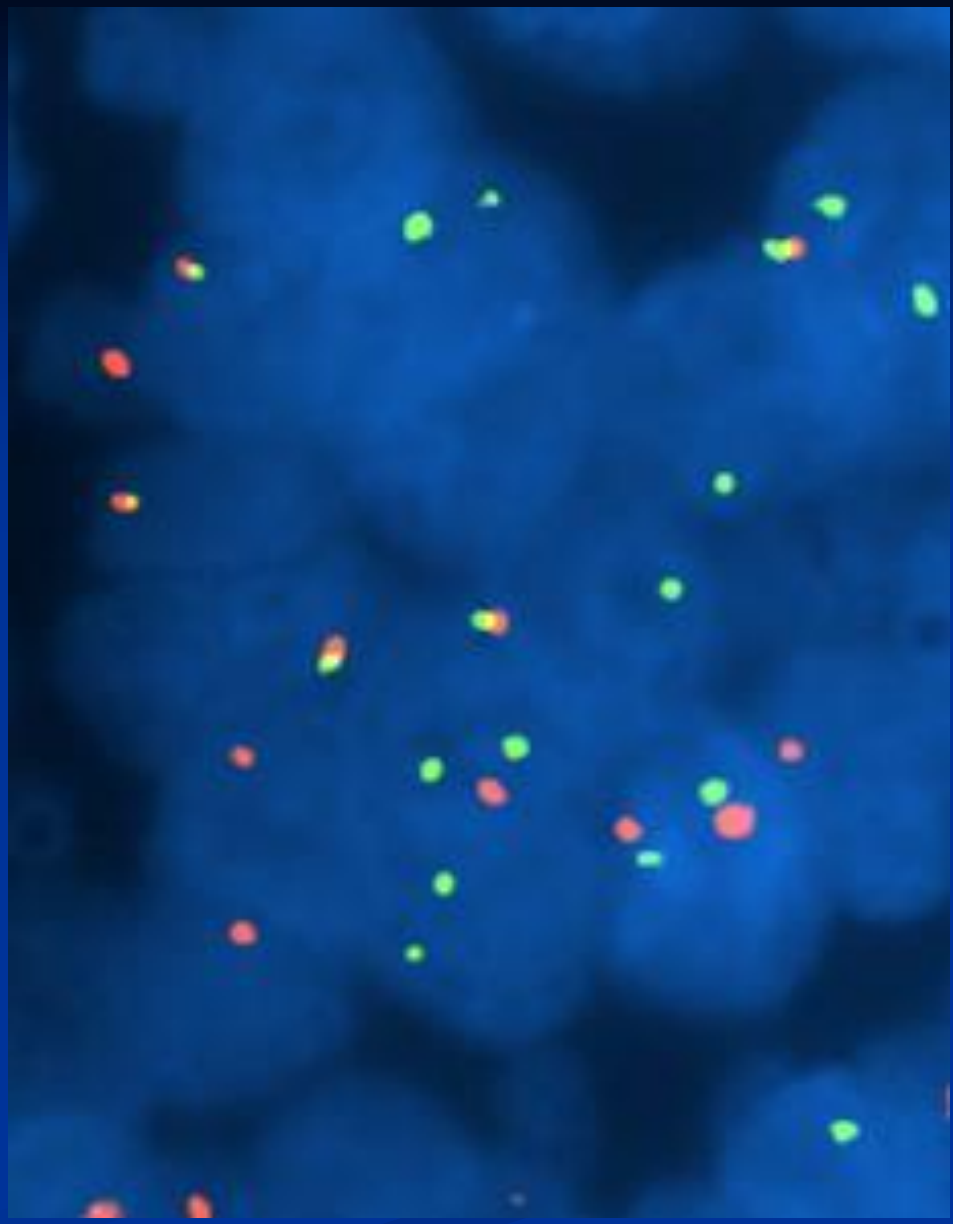
Aukema SM, et al. Blood 2011; 117: 2319



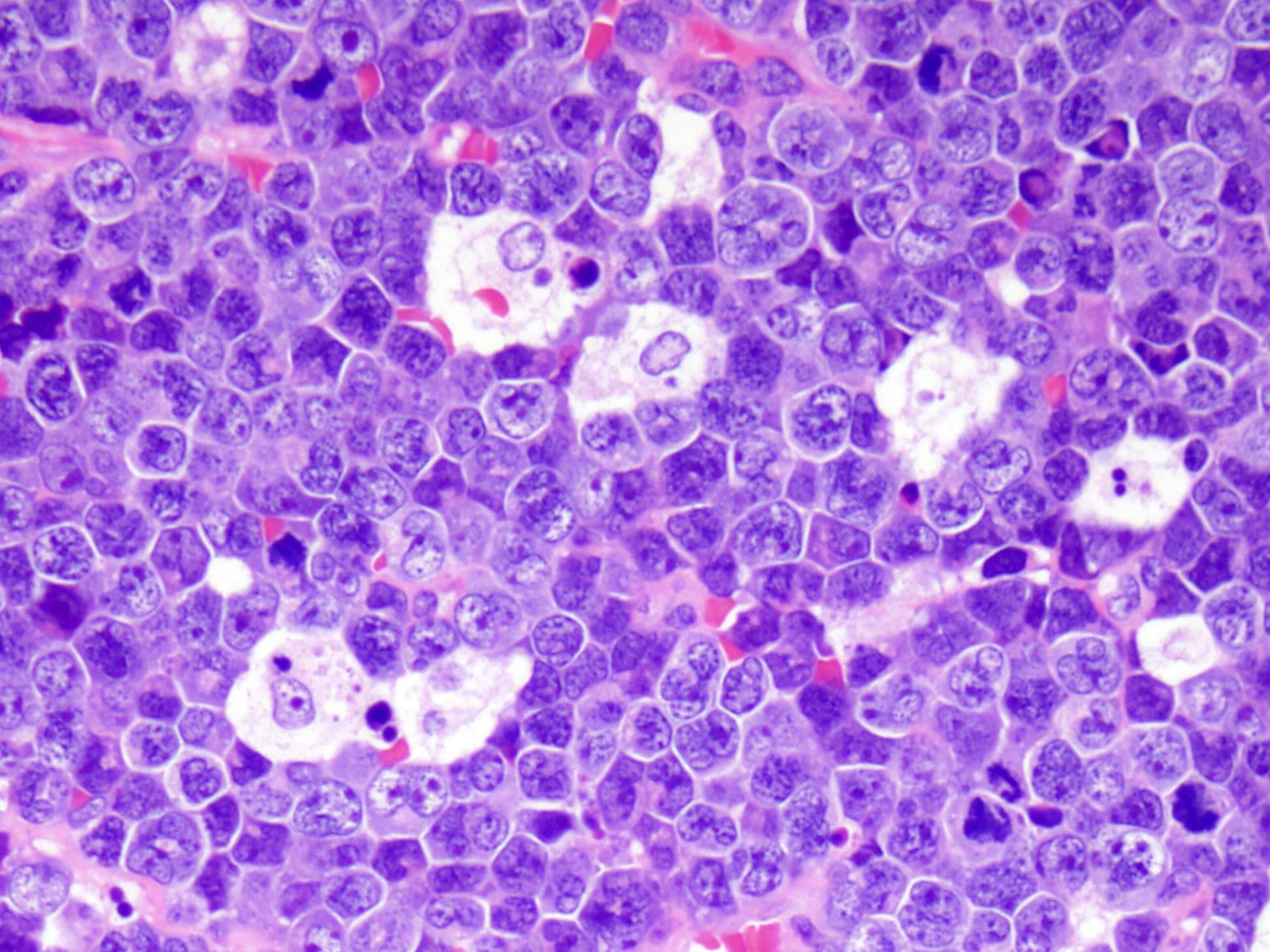

CD20
CD10
BCL6
MUM1

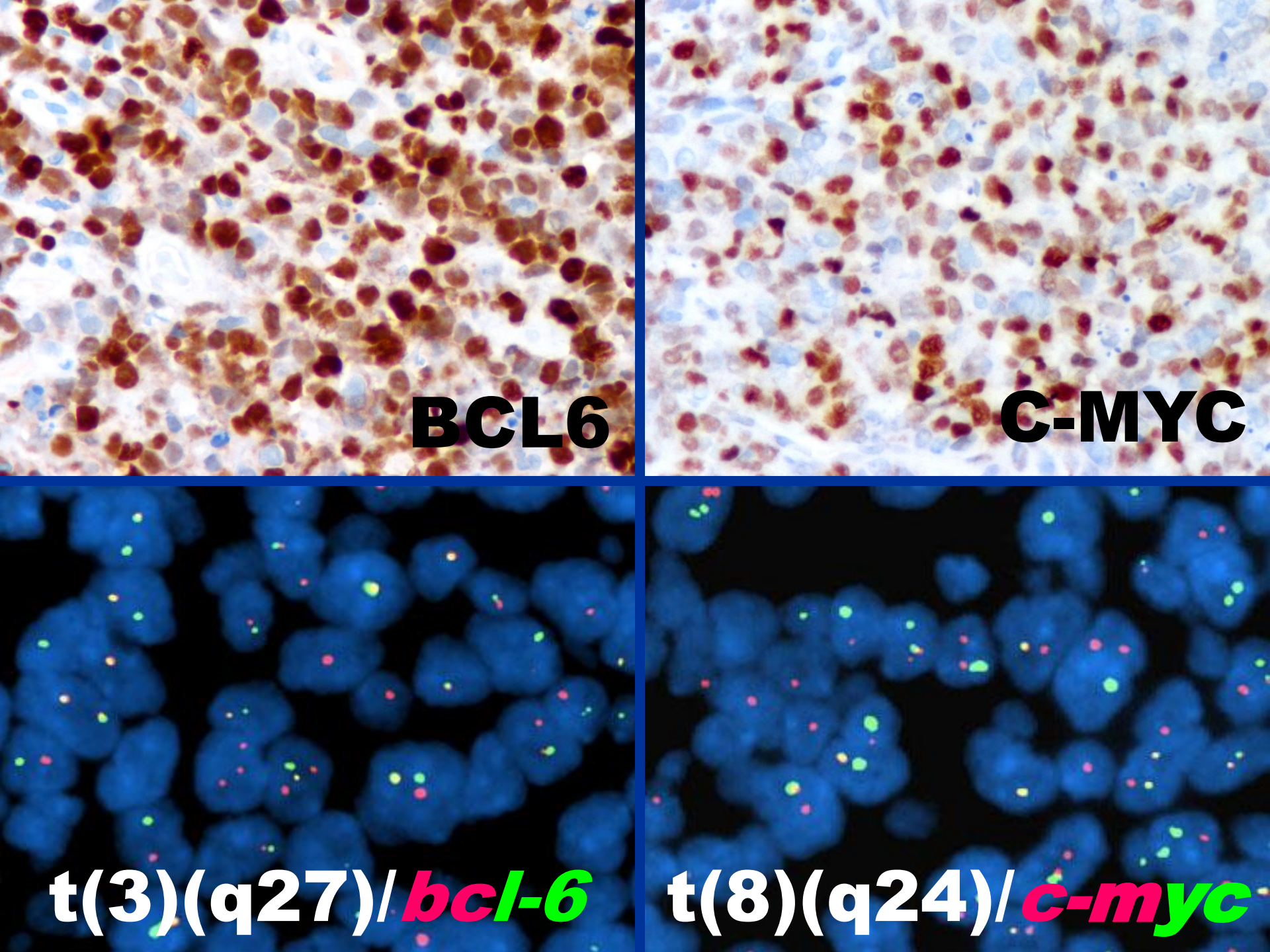






t(8)(q24)/c-myc




BCL6
C-MYC
t(3)(q27)/bcl-6
t(8)(q24)/c-myc

DHL: *BCL6+/MYC+* v.s. *BCL2+/MYC+*

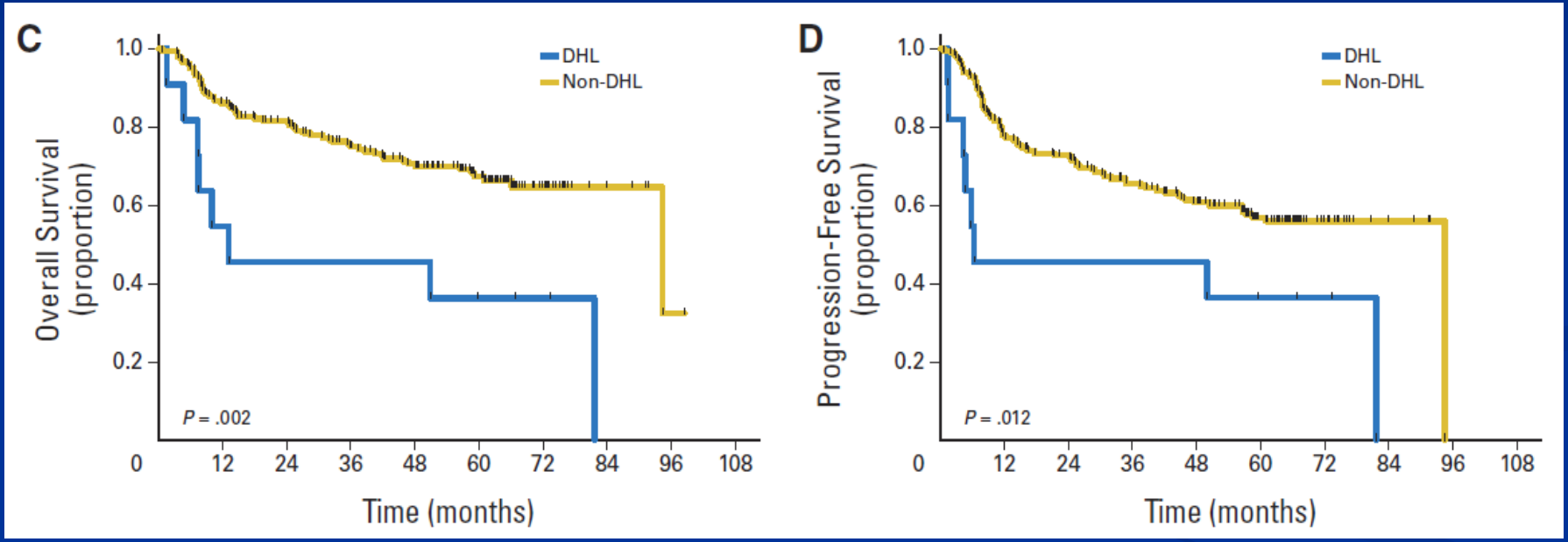
	BCL6+/MYC+ (%)	*BCL2+/MYC+* (%)	*P*
CD20+	14/14 (100)	117/119 (98)	NS
CD10+	7/11 (64)	143/159 (90)	0.03
BCL6+	6/7 (86)	68/83 (82)	NS
BCL2+	2/9 (22)	130/142 (92)	<0.0001
IRF4/MUM1+	3/4 (75)	12/67 (18)	0.03
GCB-type	6/7 (86)	143/159 (90)	NS
IG/MYC trans.	9/14 (64)	101/142 (71)	NS

Pillai RK, et al. Am J Surg Pathol 2013; 37: 323

Immunohistochemical DHLs

- **Johnson NA, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.** ***J Clin Oncol 2012; 30(28): 3452-9***
- **Green TM, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.** ***J Clin Oncol 2012; 30(28): 3460-7***

Prognostic significance of IDHLs

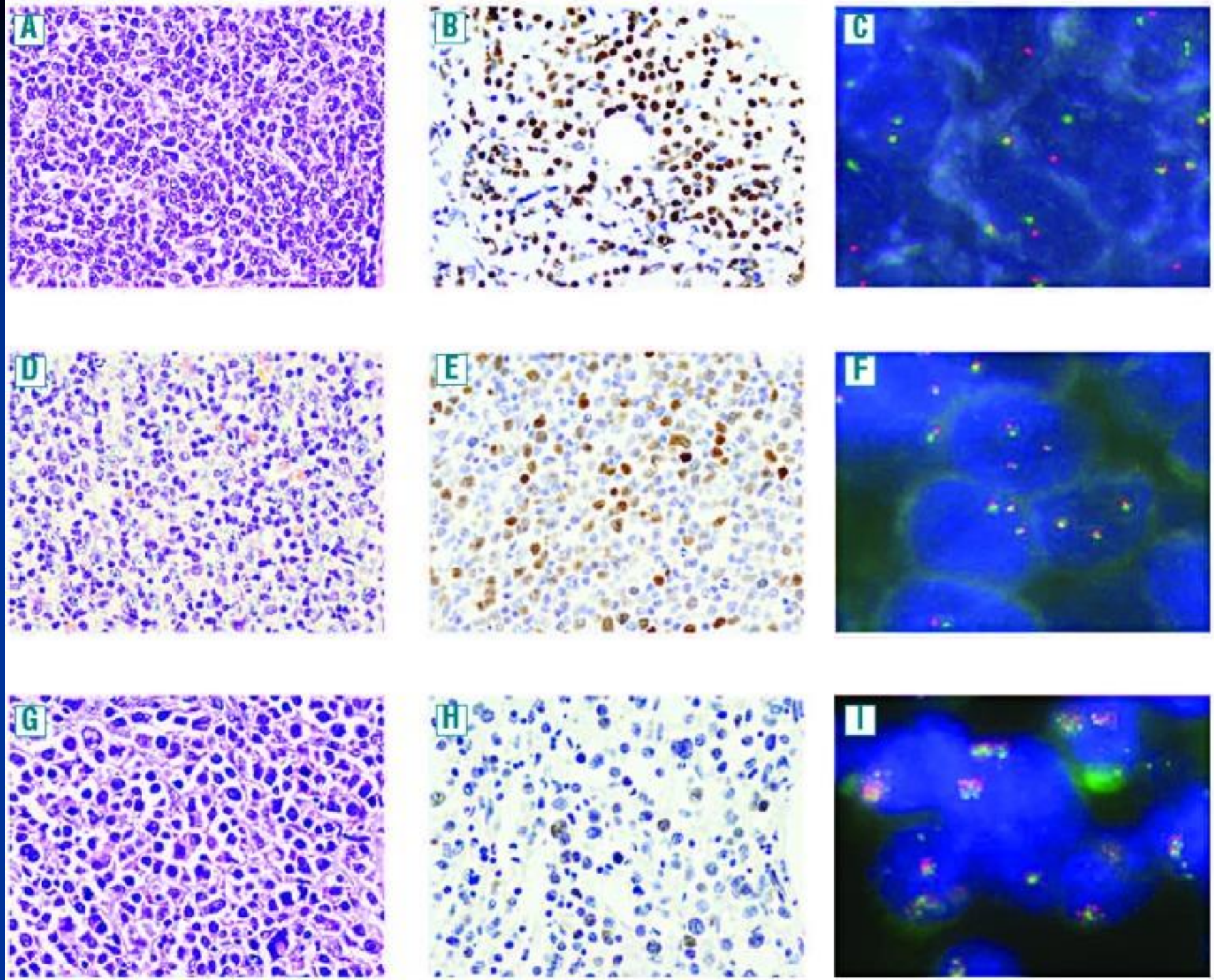


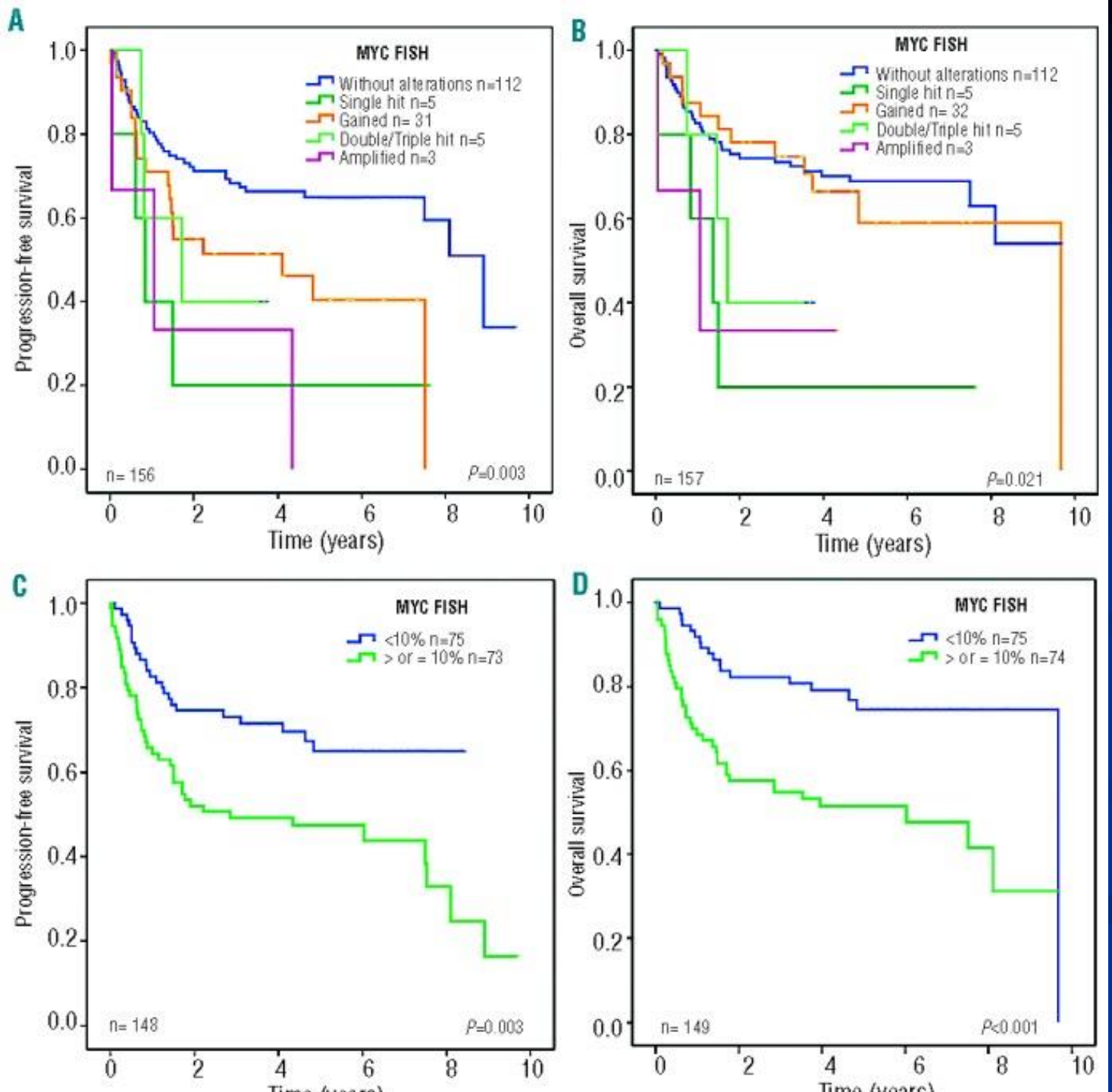
Green TM, et al. J Clin Oncol 2012; 30: 3460

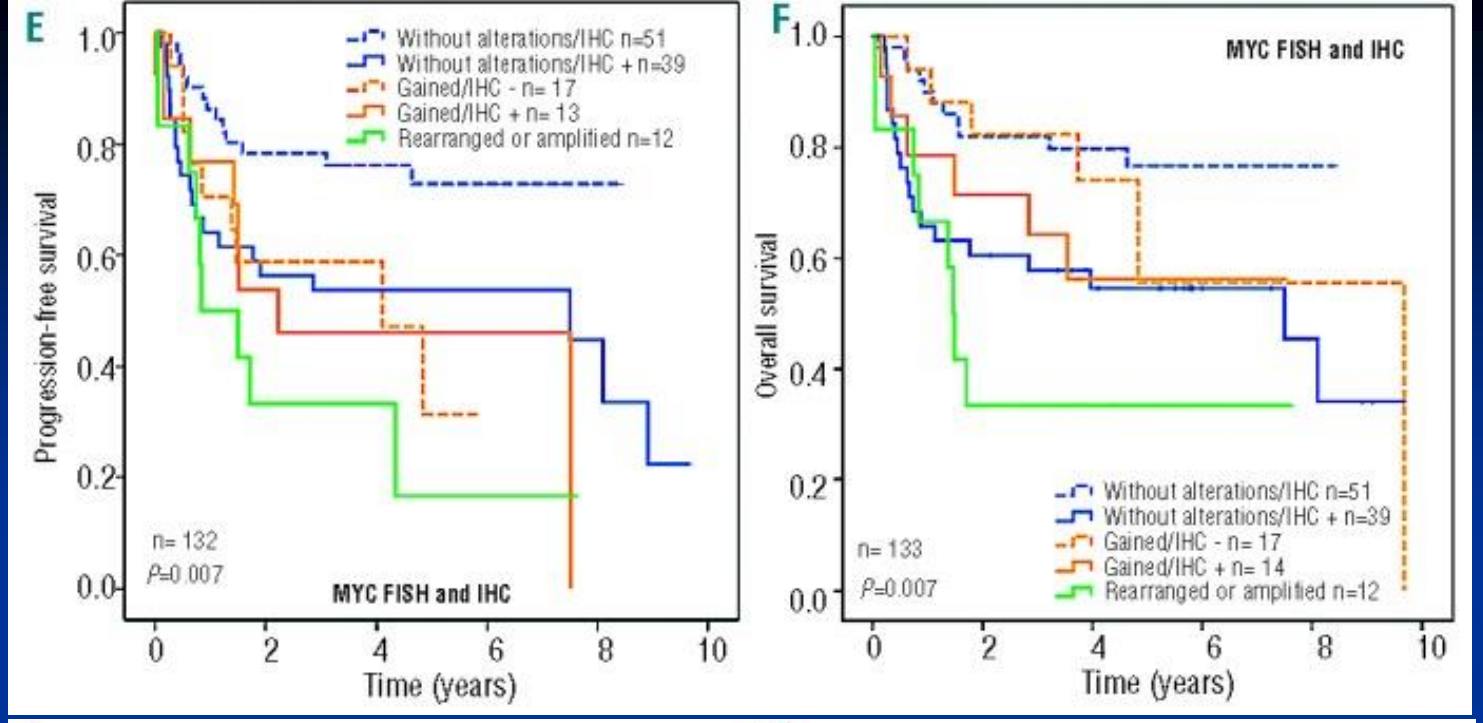
MYC protein expression and genetic alterations have prognostic impact in patients with diffuse large B-cell lymphoma treated with immunochemotherapy

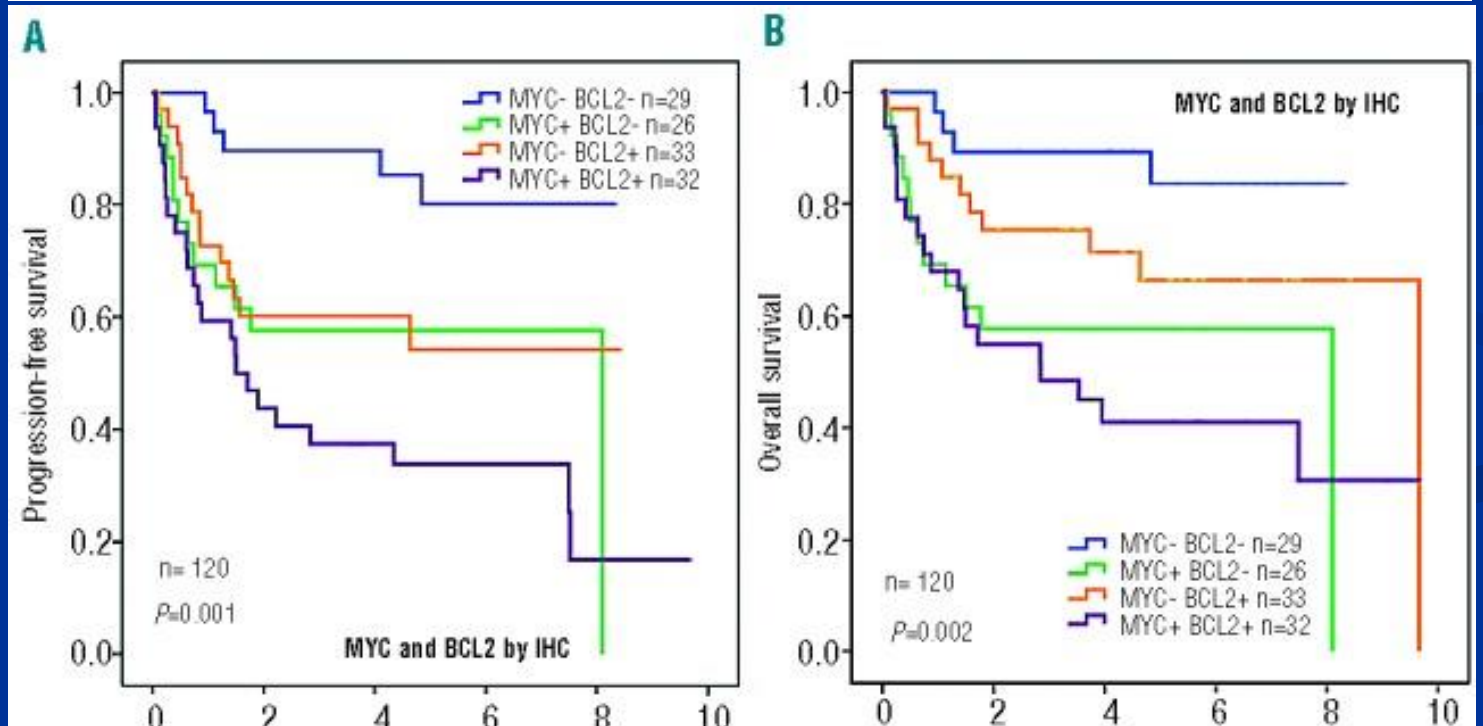
Valera A, et al. Haematologica 2013; 98(10): 1554-62

- ***MYC*** **rearrangement as the sole abnormality (*MYC* single-hit) in 3% of cases, *MYC* and concurrent *BCL2* and/or *BCL6* rearrangements (*MYC* double/triple-hit) in 4%, *MYC* amplifications in 2% and *MYC* gains in 19%**
- ***MYC*** **single-hit, *MYC* double/triple-hit and *MYC* amplifications, but not *MYC* gains or other gene rearrangements, were associated with unfavorable PFS and OS**
- **MYC protein expression captured the unfavorable prognosis of *MYC* translocations/amplifications and identified an additional subset of patients without gene alterations but with similar poor prognosis**
- **Patients with tumors expressing both MYC/BCL2 had the worst prognosis, whereas those with double-negative tumors had the best outcome**
- **High MYC expression was associated with shorter overall survival irrespectively of the IPI and BCL2 expression**


A
B
C
D
E
F
G
H
I


A
MYC FISH
Without alterations n=112
Single hit n=5
Gained n= 31
Double/Triple hit n=5
Amplified n=3
Progression-free survival
n= 156
P=0.003
Time (years)
B
MYC FISH
Without alterations n=112
Single hit n=5
Gained n= 32
Double/Triple hit n=5
Amplified n=3
Overall survival
n= 157
P=0.021
Time (years)
C
MYC FISH
<10% n=75
> or = 10% n=73
Progression-free survival
n= 148
P=0.003
D
MYC FISH
<10% n=75
> or = 10% n=74
Overall survival
n= 149
P<0.001


E
Progression-free survival
Time (years)
Without alterations/IHC n=51
Without alterations/IHC + n=39
Gained/IHC - n= 17
Gained/IHC + n= 13
Rearranged or amplified n=12
n= 132
P=0.007
MYC FISH and IHC
F
Overall survival
Time (years)
MYC FISH and IHC
Without alterations/IHC n=51
Without alterations/IHC + n=39
Gained/IHC - n= 17
Gained/IHC + n= 14
Rearranged or amplified n=12
n= 133
P=0.007


A
Progression-free survival
MYC- BCL2- n=29
MYC+ BCL2- n=26
MYC- BCL2+ n=33
MYC+ BCL2+ n=32
n= 120
P=0.001
MYC and BCL2 by IHC
B
Overall survival
MYC and BCL2 by IHC
MYC- BCL2- n=29
MYC+ BCL2- n=26
MYC- BCL2+ n=33
MYC+ BCL2+ n=32
n= 120
P=0.002

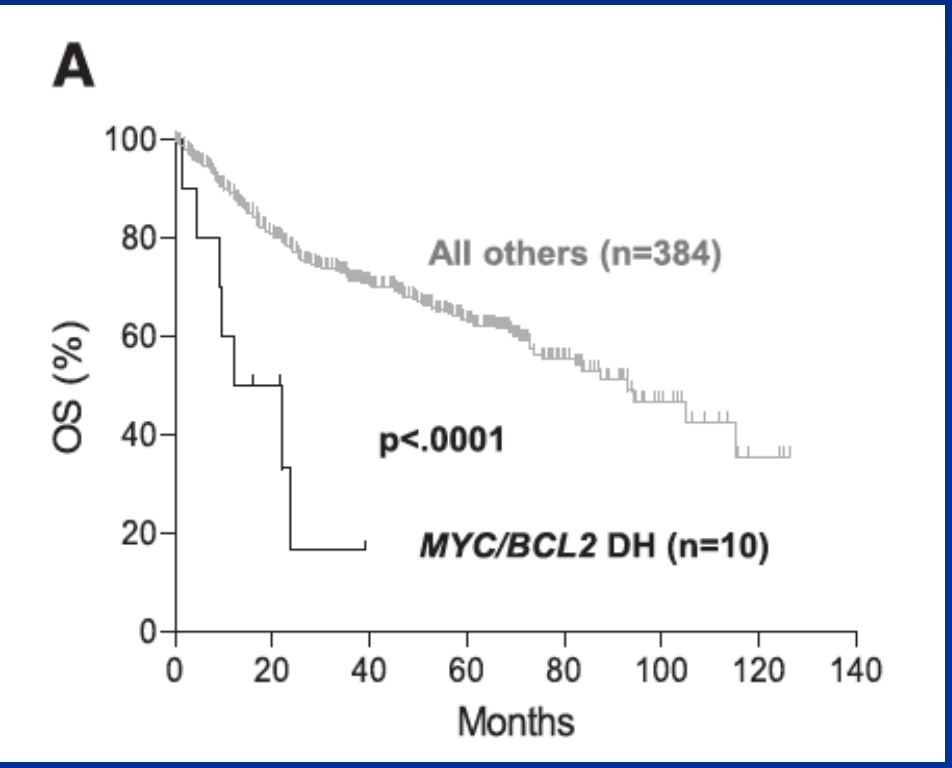
MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program

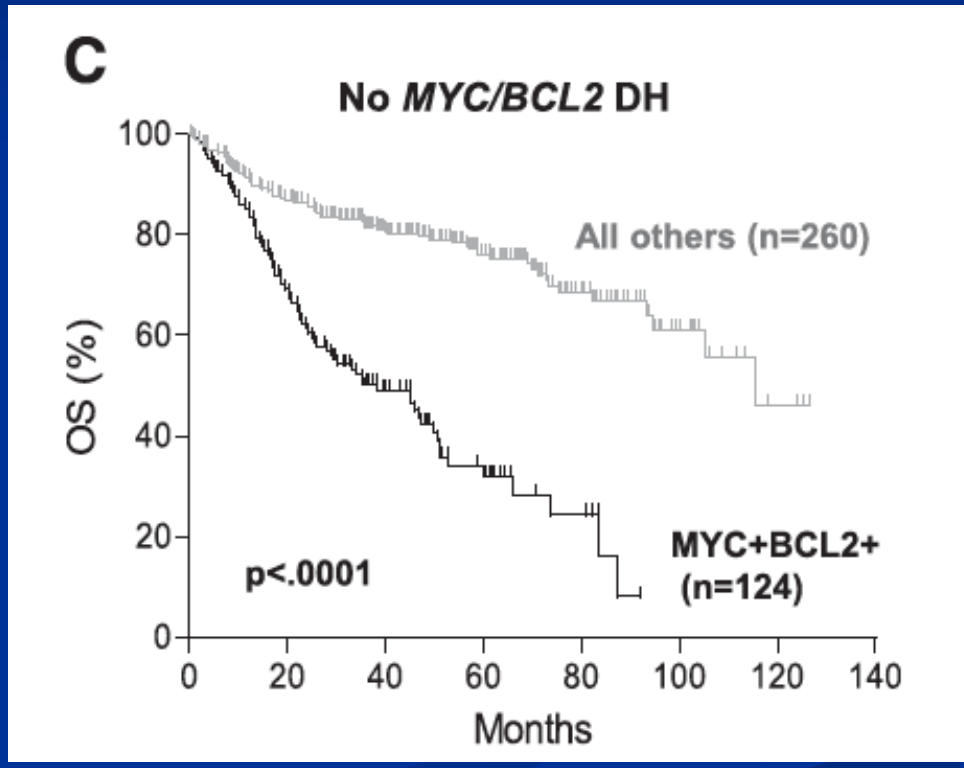
Shimin Hu,[1] Zijun Y. Xu-Monette,[1] Alexander Tzankov,[2] Tina Green,[3] Lin Wu,[4] Aarthi Balasubramanyam,[4] Wei-min Liu,[4] Carlo Visco,[5] Yong Li,[6] Roberto N. Miranda,[1] Santiago Montes-Moreno,[7] Karen Dybkaer,[8] April Chiu,[9] Attilio Orazi,[10] Youli Zu,[11] Govind Bhagat,[12] Kristy L. Richards,[13] Eric D. Hsi,[14] William W. L. Choi,[15] Xiaoying Zhao,[16] J. Han van Krieken,[17] Qin Huang,[18] Jooryung Huh,[19] Weiyun Ai,[20] Maurilio Ponzoni,[21] Andrés J. M. Ferreri,[21] Fan Zhou,[22] Graham W. Slack,[23] Randy D. Gascoyne,[23] Meifeng Tu,[24] Daina Variakojis,[25] Weina Chen,[26] Ronald S. Go,[27] Miguel A. Piris,[7] Michael B. Møller,[3] L. Jeffrey Medeiros,[1] and Ken H. Young[1]

[1]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]University Hospital, Basel, Switzerland; [3]Odense University Hospital, Odense, Denmark; [4]Roche Molecular Systems, Pleasanton, CA; [5]San Bortolo Hospital, Vicenza, Italy; [6]University of Louisville, Louisville, KY; [7]Hospital Universitario Marques de Valdecilla, Santander, Spain; [8]Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark; [9]Memorial Sloan-Kettering Cancer Center, New York, NY; [10]Weill Medical College of Cornell University, New York, NY; [11]The Methodist Hospital, Houston, TX; [12]Columbia University Medical Center and New York Presbyterian Hospital, New York, NY; [13]University of North Carolina School of Medicine, Chapel Hill, NC; [14]Cleveland Clinic, Cleveland, OH; [15]Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China; [16]Zhejiang University School of Medicine, Second University Hospital, Hangzhou, China; [17]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; [18]City of Hope National Medical Center, Duarte, CA; [19]Asan Medical Center, College of Medicine, Ulsan University, Seoul, Korea; [20]School of Medicine, University of California San Francisco, San Francisco, CA; [21]San Raffaele H. Scientific Institute, Milan, Italy; [22]Southwest Washington Medical Center, Vancouver, WA; [23]BC Cancer Agency and BC Cancer Research Centre, Vancouver, British Columbia, Canada; [24]Peking University School of Oncology, Beijing Cancer Hospital, Beijing, China; [25]Feinberg School of Medicine, Northwestern University, Chicago, IL; [26]Ameripath/Quest Diagnostics, Dallas, TX; and [27]Gundersen Lutheran Health System, La Crosse, WI

proteins, those involving matrix deposition/remodeling and cell adhesion, and upregulation of proliferation-associated genes. We conclude that MYC/BCL2 coexpression in DLBCL is associated with an aggressive clinical course, is more common in the ABC subtype, and contributes to the overall inferior prognosis of patients with ABC-DLBCL. In conclusion, the data suggest that MYC/BCL2 coexpression, rather than cell-of-origin classification, is a better predictor of prognosis in patients with DLBCL treated with R-CHOP.
(*Blood*. 2013;121(20):4021-4031)

MYC/BCL2 coexpression in DLBCL: A common event with a poor prognosis





Hu S, et al. Blood 2013; 121: 4021-31

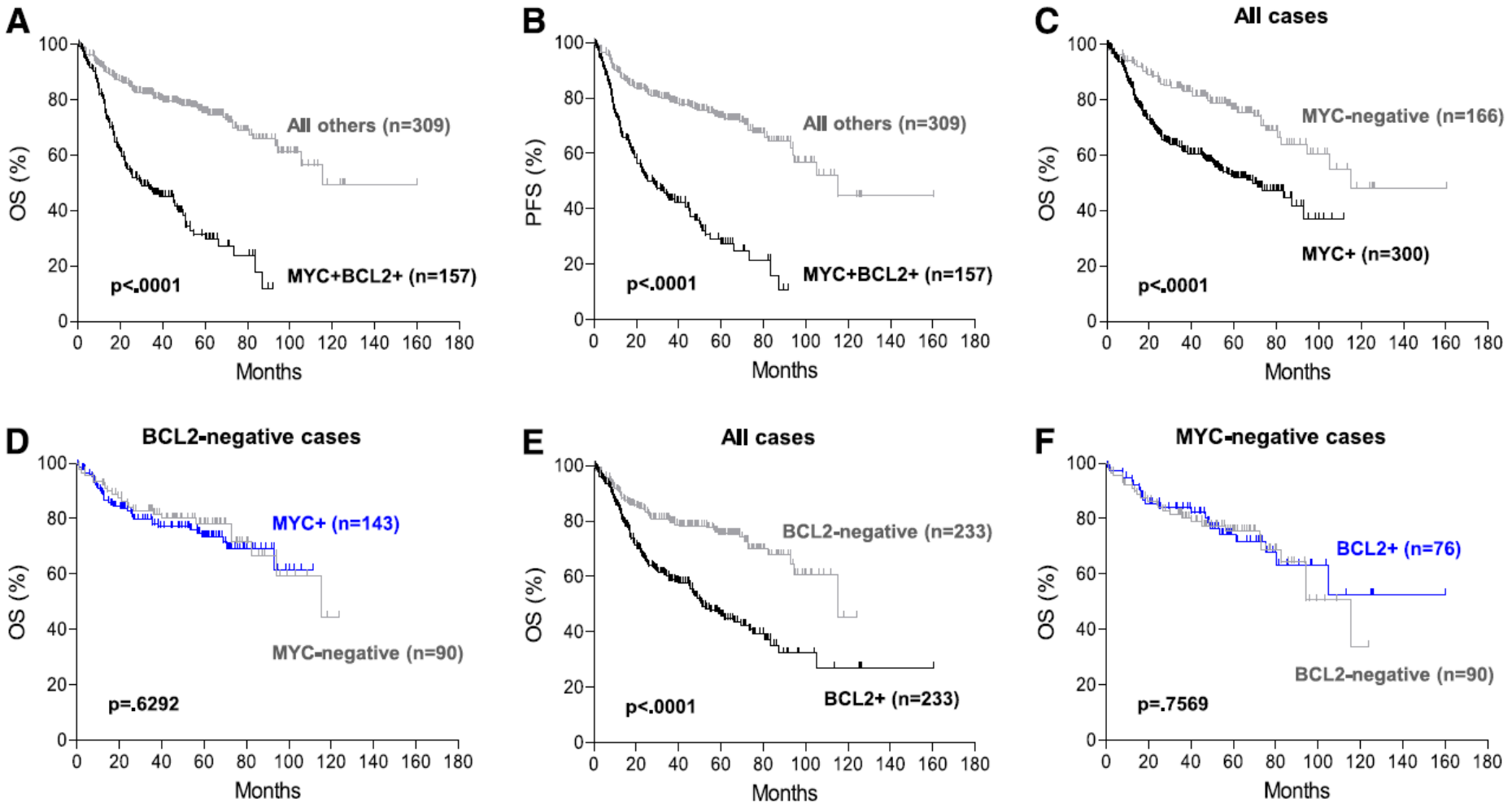


Figure 1. Prognostic impact of MYC/BCL2 coexpression in DLBCL. (A-B) OS (A) and PFS (B) of patients with DLBCL with MYC/BCL2 coexpression (MYC^+BCL2^+) in the training set. (C-D) OS of patients with MYC^+ DLBCL in the presence (C) or absence (D) of BCL2 coexpression in the training set. (E-F) OS of patients with $BCL2^+$ DLBCL in the presence (E) or absence (F) of MYC coexpression in the training set.

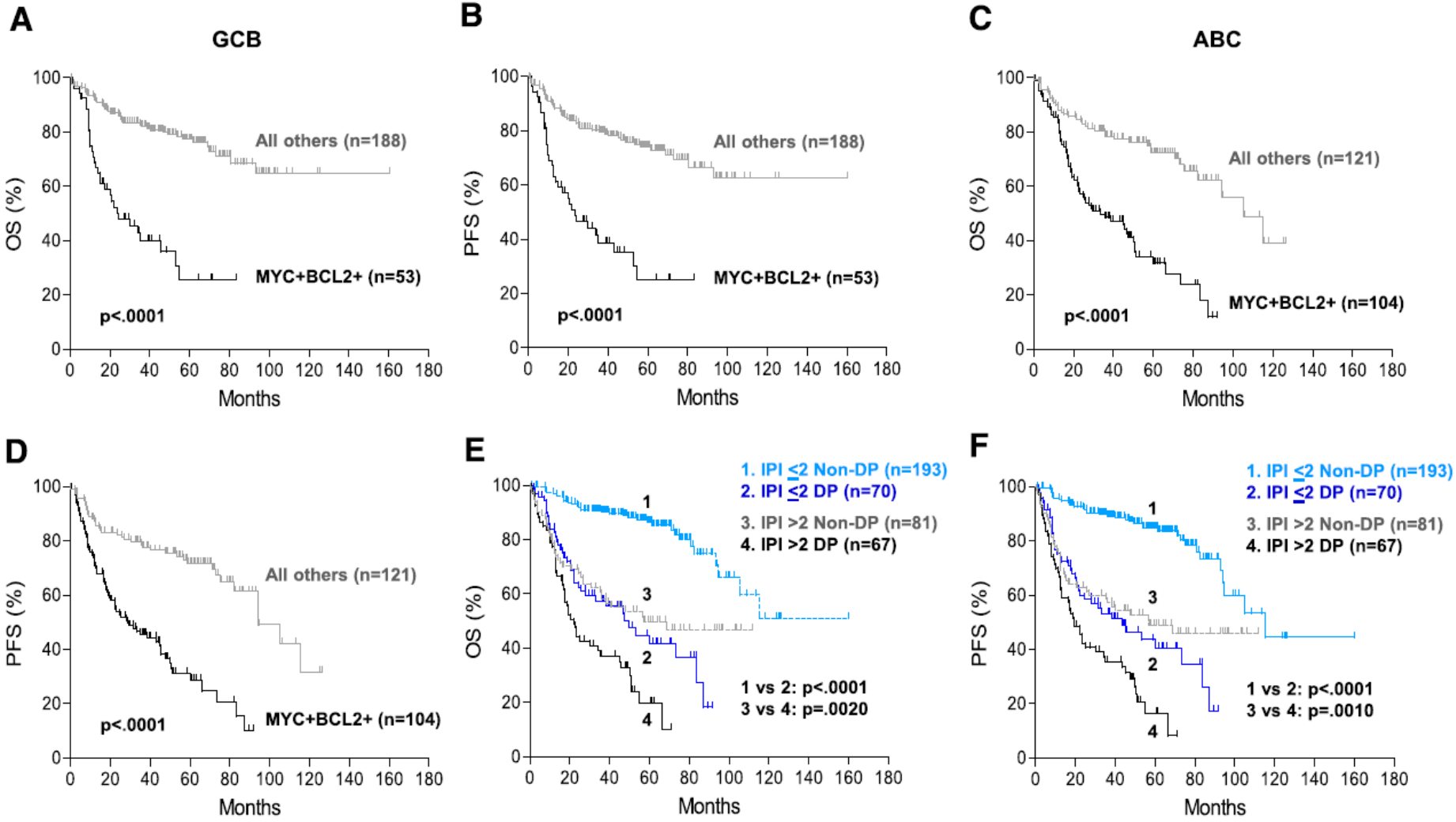
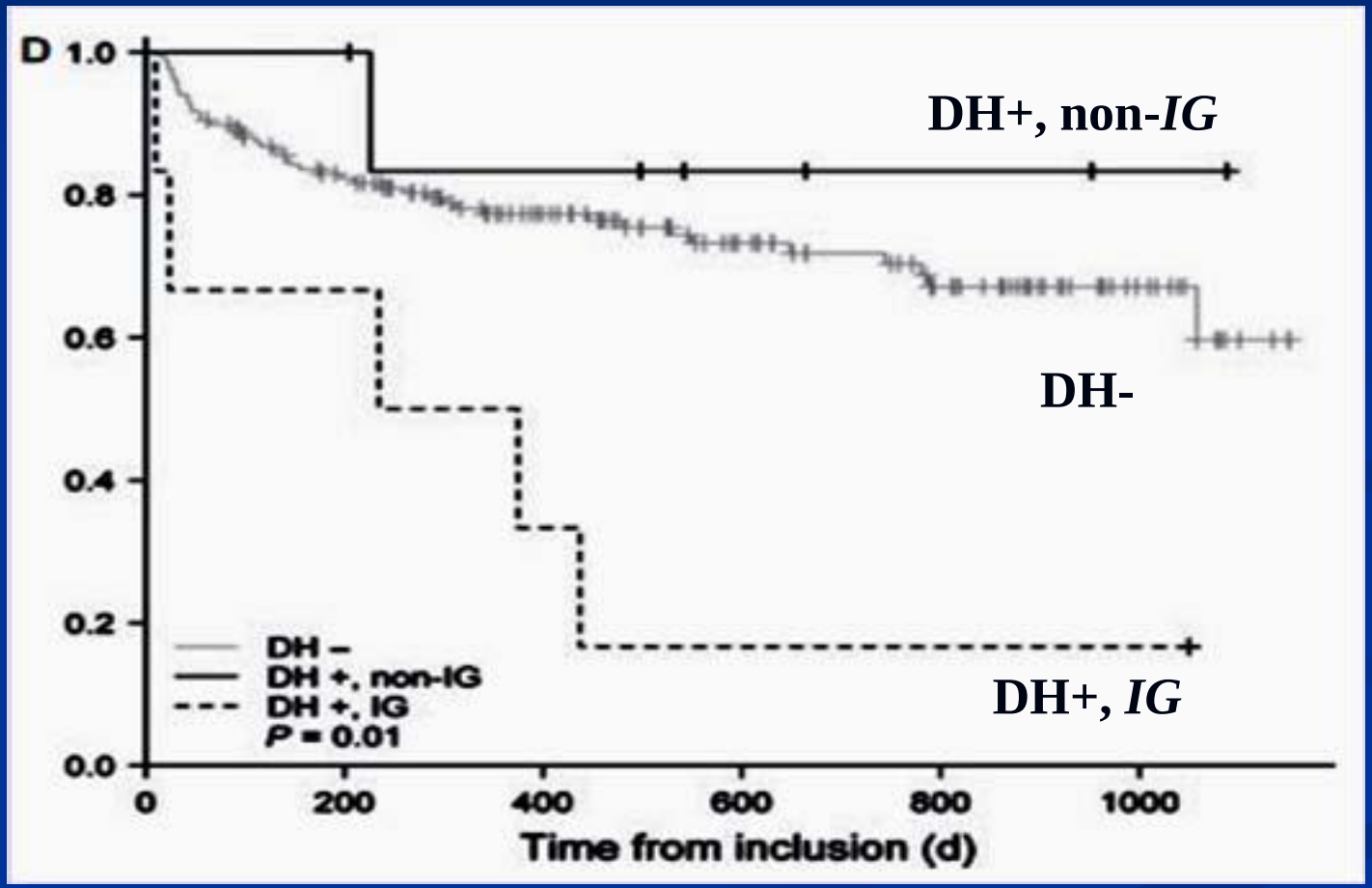


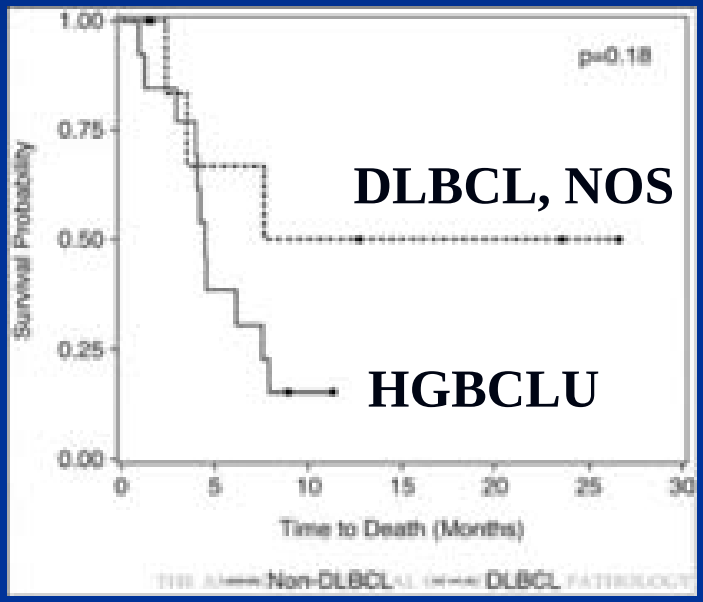
Figure 2. Prognostic impact of MYC/BCL2 coexpression in DLBCL risk-stratified according to clinicopathologic parameters. (A-B) OS (A) and PFS (B) of patients with MYC^+BCL2^+ DLBCL of the GCB subtype in the training set. (C-D) OS (C) and PFS (D) of patients with MYC^+BCL2^+ DLBCL of the ABC subtype in the training set. (E-F) OS (E) and PFS (F) of patients with MYC^+BCL2^+ DLBCL risk-stratified according to IPI risk scores in the training set. DP, MYC/BCL2 double-positive; Non-DP, non–double positive.

MYC translocation partner gene determines survival in DLBCL

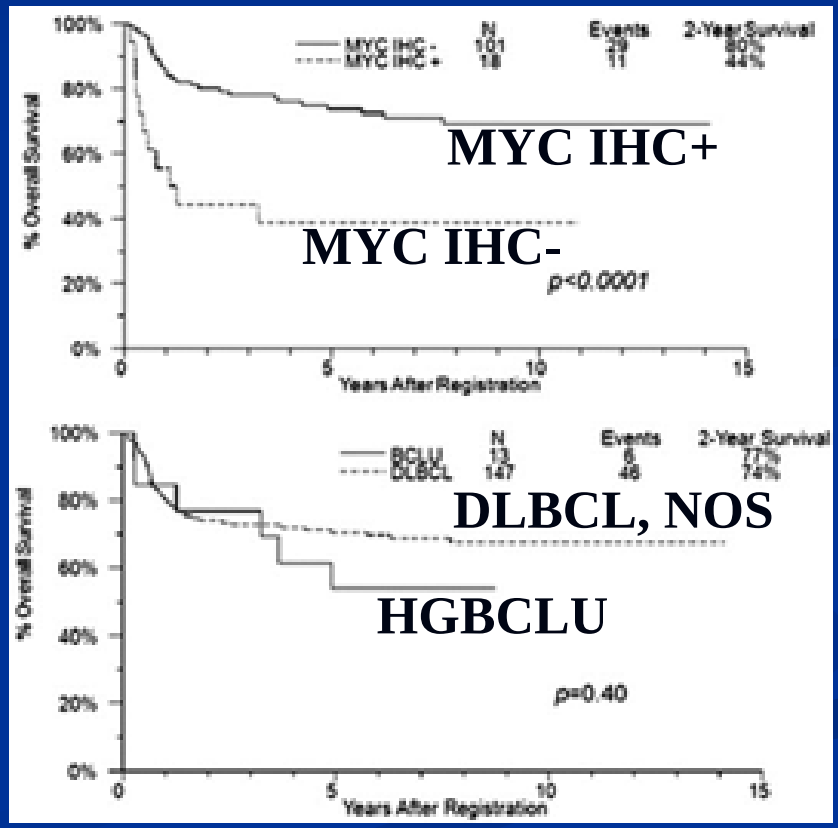


Pedersen, et al. Eur J Haematol 2014

DHL: Does histologic subtype (DLBCL,NOS v.s. HGBCLU) have prognostic relevance?



Snuderl, et al. Am J Surg Pathol 2010

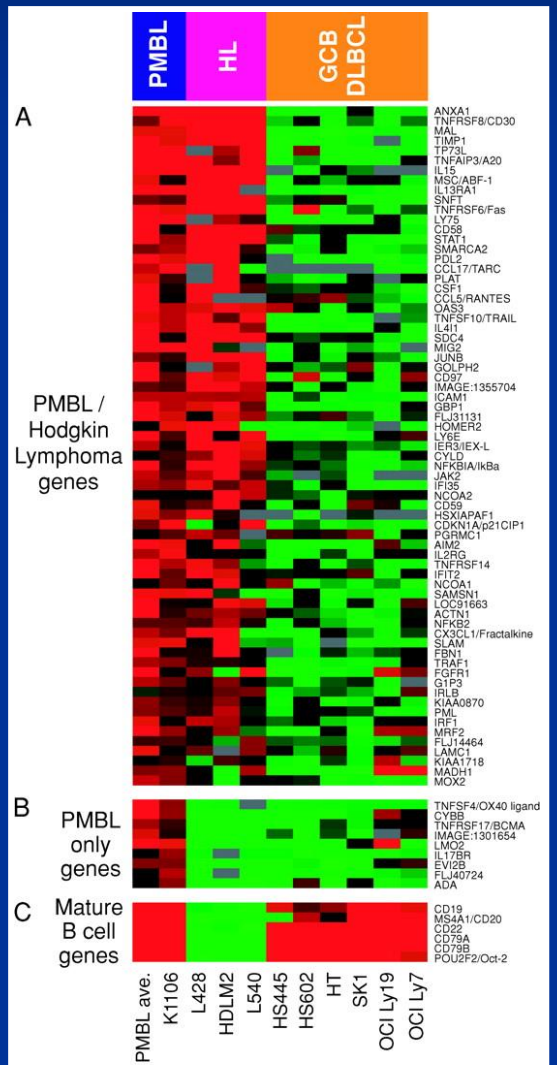


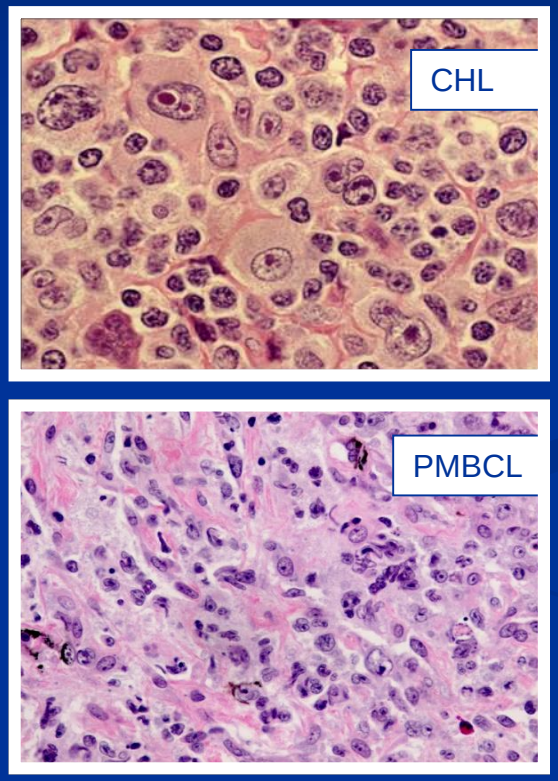
Cook, et al. Am J Surg Pathol 2014

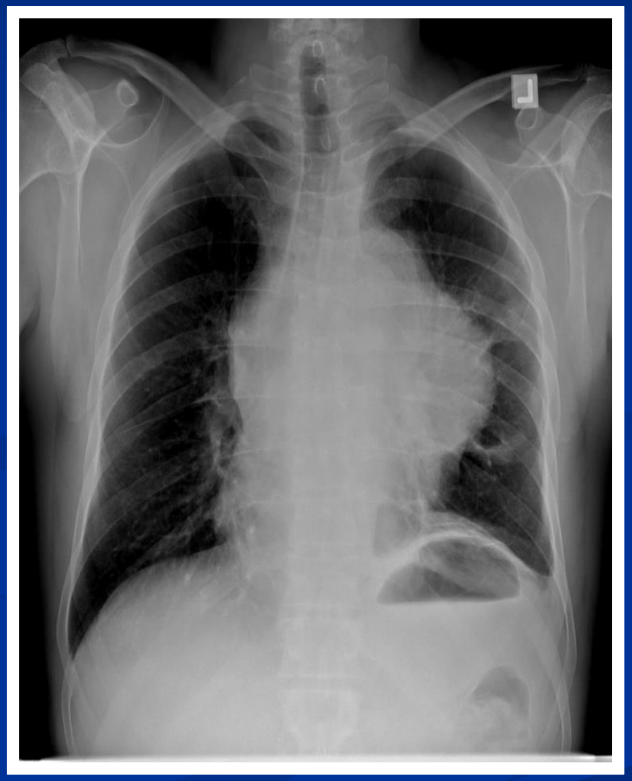
WHO proposal for DHL v.s. HGBCLU

- **DHL should be unified in a single category so that they can be further studied in clinical trials**
- **For cases with DH, can be labeled as "high-grade B-cell lymphoma, with translocations involving *MYC* and *BCL2* (or variant forms)" , and optional to further designate as DLBCL, NOS or Burkitt-like in morphology in comments**
- **For cases without DH, just use the terminology "High grade B-cell lymphoma, NOS"**

Clinical, morphological, immunophenotypic and biological overlap between CHL and PMBL





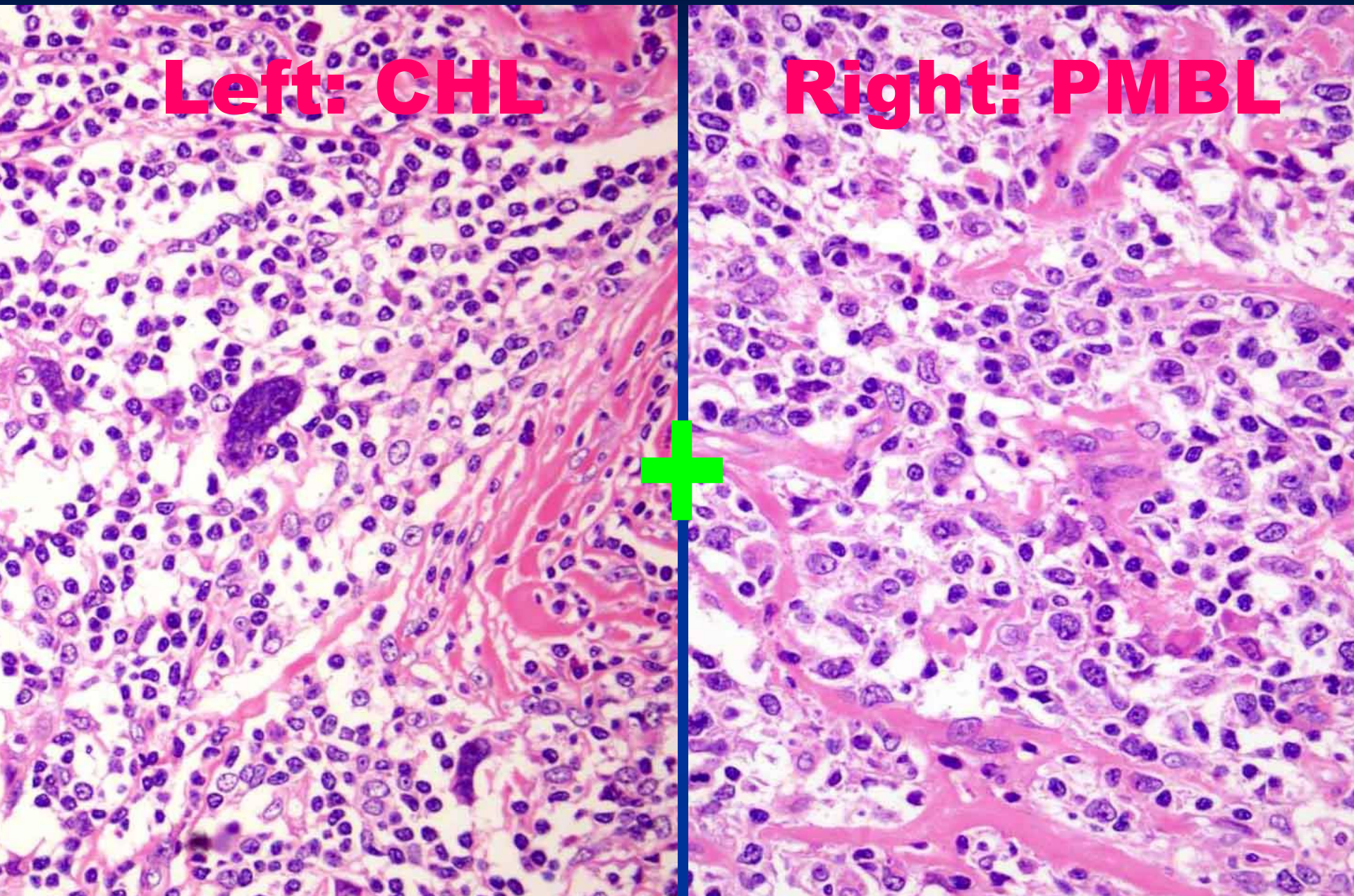


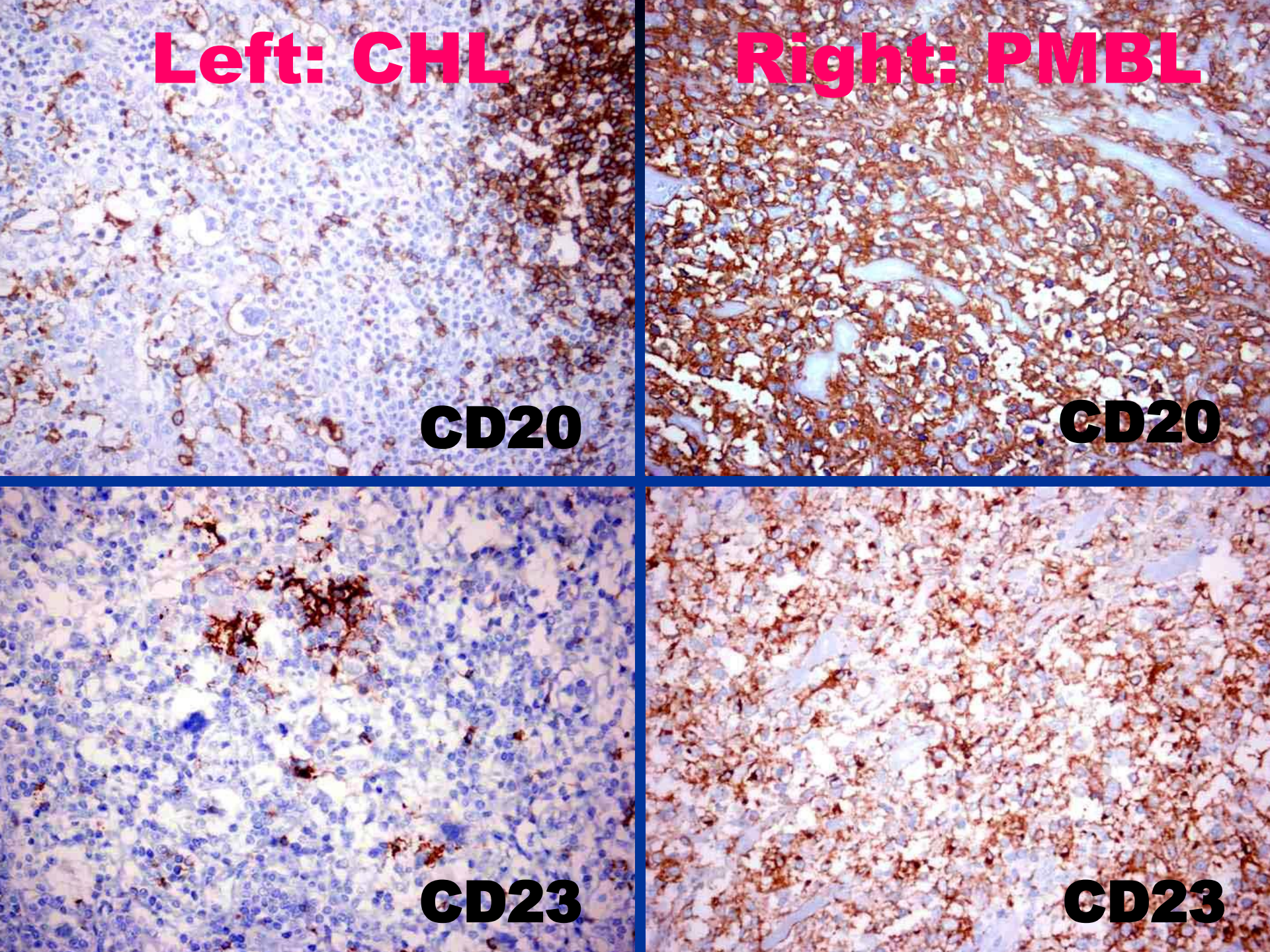
Rosenwald et al, J Exp Med 2003; 198: 851-62
Savage et al, Blood 2003; 102: 3871-9

No wonder there are:

- Composite tumors of classical Hodgkin lymphoma + PMBL (synchronous or metachronous)
- B-cell lymphomas with features intermediate between DLBCL and classical Hodgkin lymphoma (grey zone lymphoma, GZL)

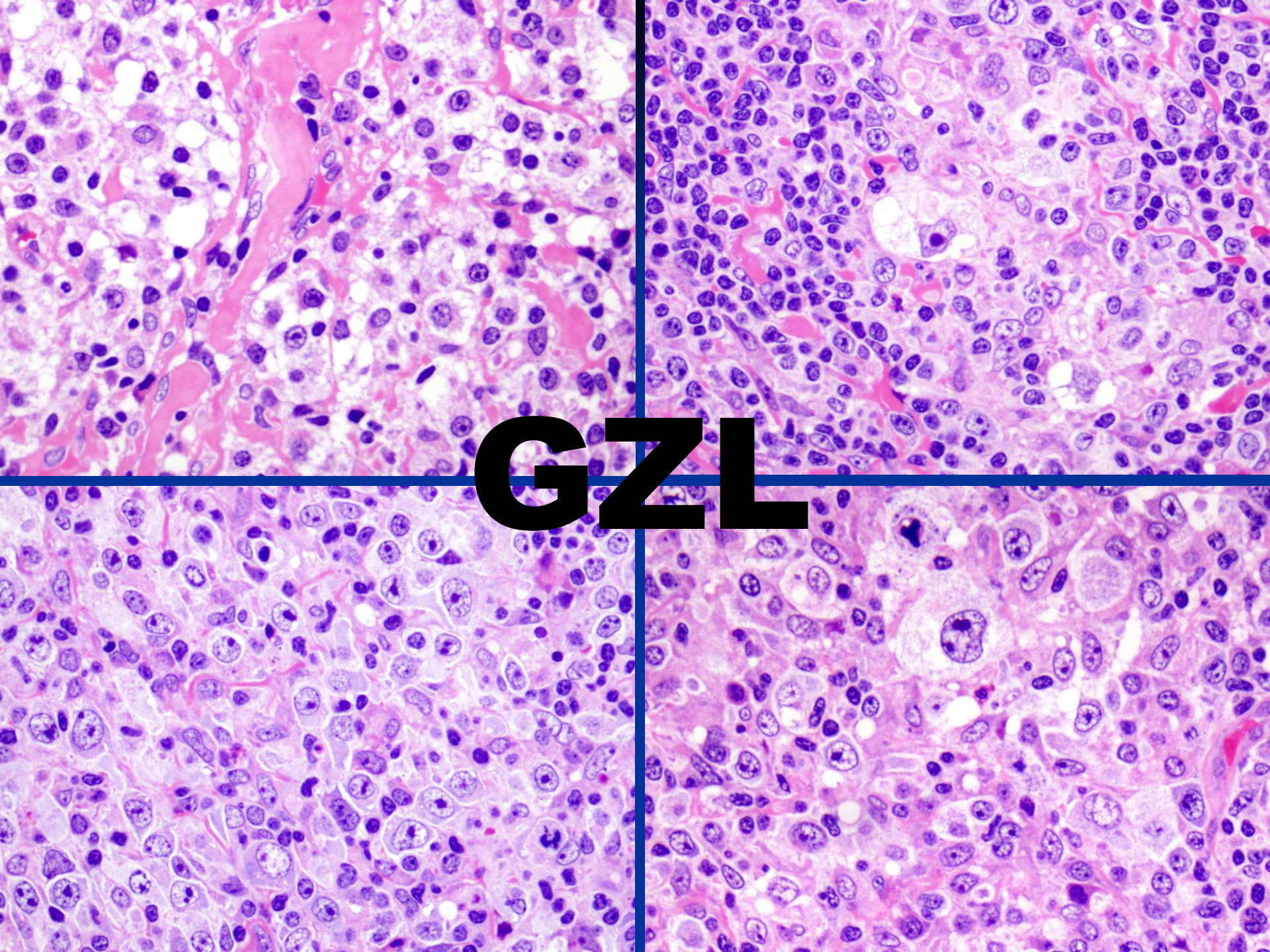
30-yr-old male, mediastinal mass

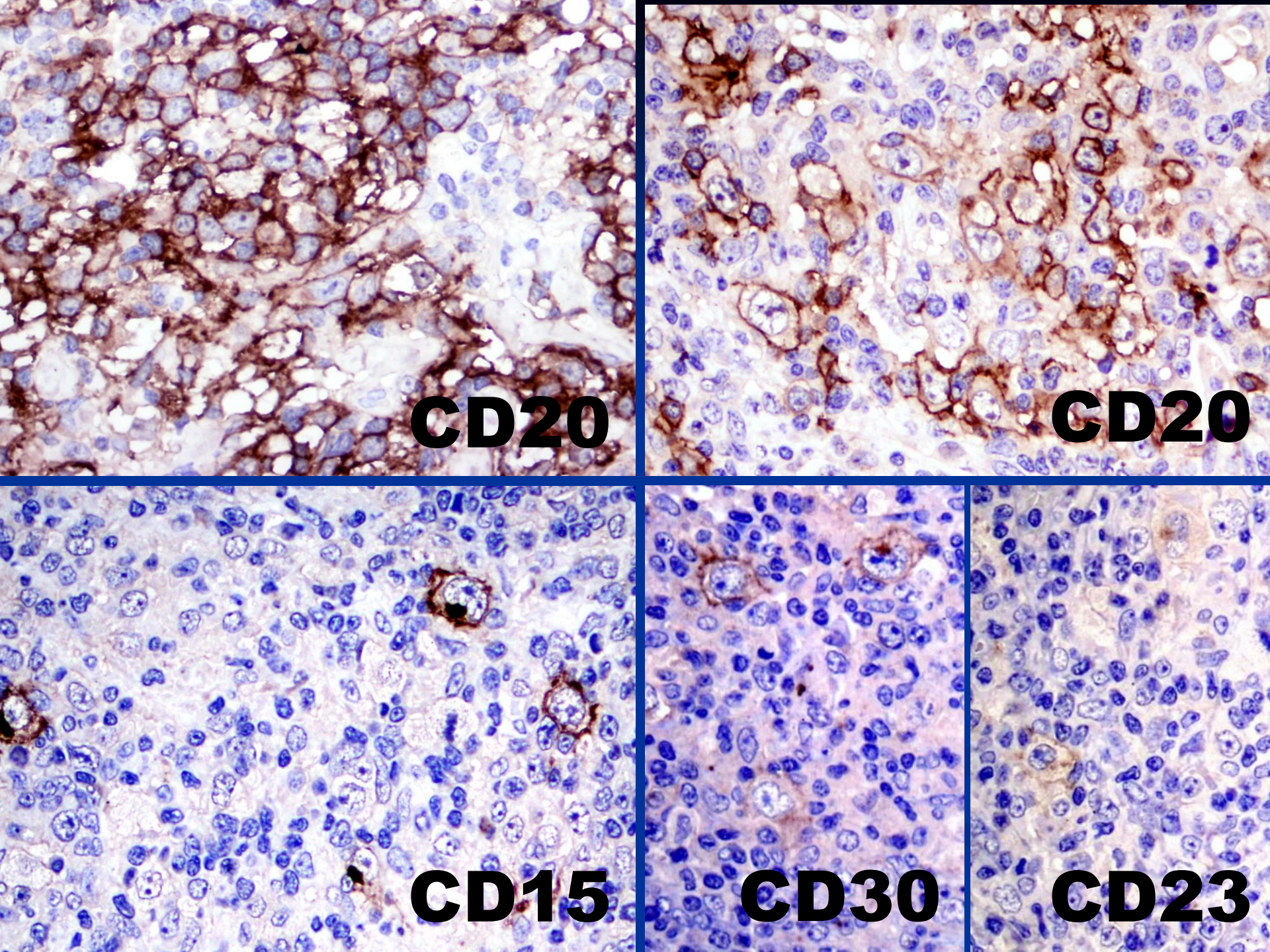


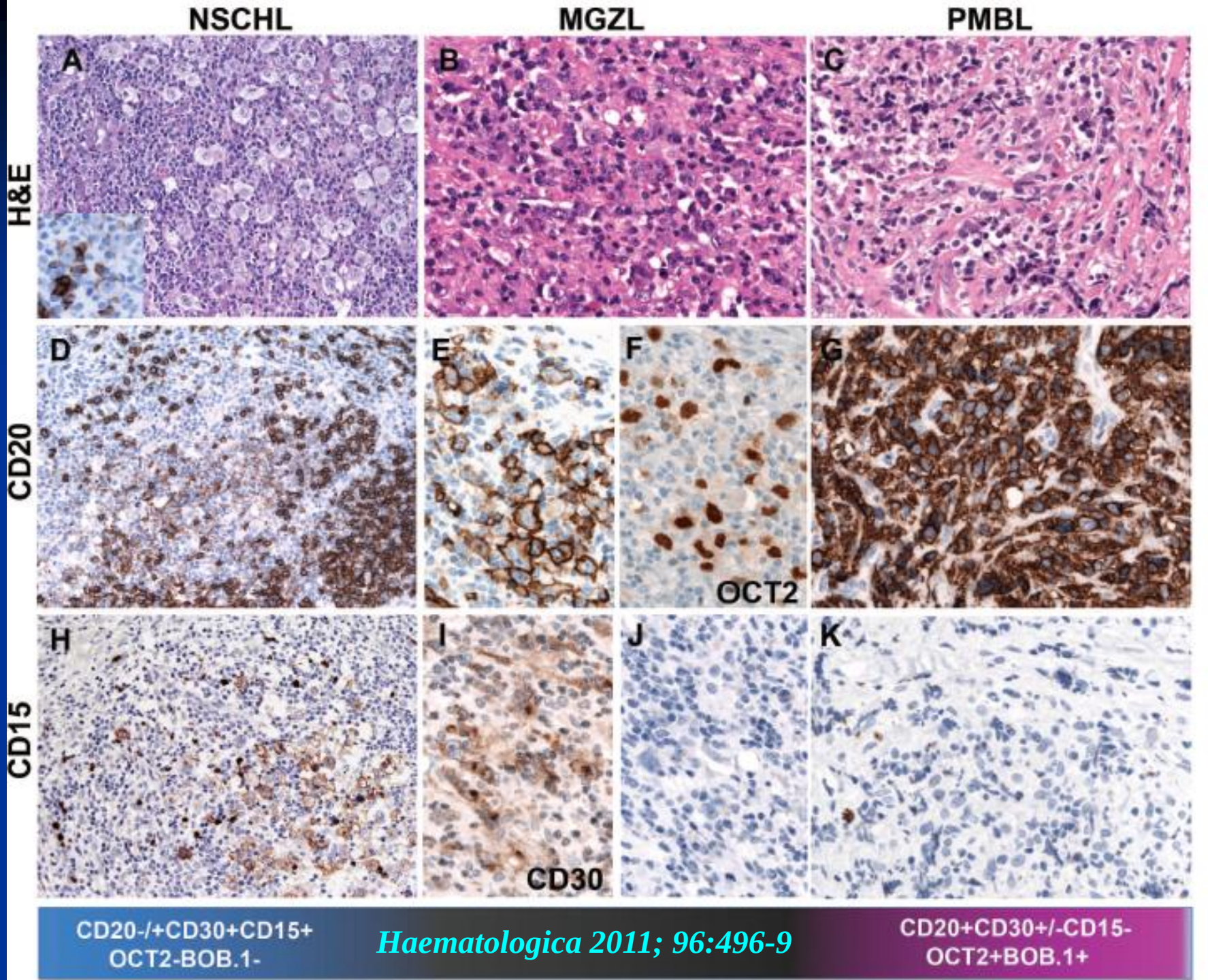

Left: CHL
CD20
Right: PMBL
CD20
CD23
CD23

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and CHL

- **Definition:**
  A B lineage lymphoma with overlapping clinical, morphological, and/or immunophenotypic features between CHL and PMBL (GZL)
- **Clinical features:**
  Young men, large mediastinal mass, aggressive and fails to respond to the therapeutic regimens effective in CHL or PMBL
- **Morphology:**
  Sheets of pleomorphic large cells, (H/RS-like), variable sclerosis and fibrous bands, a sparse inflammatory infiltrate, frequent necrosis
- **Immunophenotype:**
  CD45+, CD30+, PAX5+, CD20+/-, CD79a+/-, CD15+/-, CD10-, BCL6-/+


GZL


CD20
CD20
CD15
CD30
CD23


NSCHL
MGZL
PMBL
H&E
CD20
CD15
A
B
C
D
E
F
G
H
I
J
K
OCT2
CD30
CD20-/+CD30+CD15+
OCT2-BOB.1-
Haematologica 2011; 96:496-9
CD20+CD30+/-CD15-
OCT2+BOB.1+

·论著·人体病理学·

具有弥漫性大 B 细胞淋巴瘤和经典型霍奇金淋巴瘤中间特点的灰区淋巴瘤 16 例临床病理特征分析

王磊　王维格　李小秋　郭晔　朱雄增

【摘要】 **目的**　探讨具有弥漫性大 B 细胞淋巴瘤(DLBCL)和经典型霍奇金淋巴瘤(CHL)中间特点的灰区淋巴瘤的临床和病理特征,旨在深化对这类交界性 B 细胞肿瘤的认识。**方法**　回顾性分析 16 例典型病例的临床资料、组织学形态和免疫组织化学表型。**结果**　16 例患者男女比为 1.7∶1,平均年龄 40.2 岁。8 例表现为外周淋巴结病灶,5 例表现为纵隔受累。根据组织学形态和免疫表型特点将该组病变分为三种模式。模式 1:4 例,形态学上类似于 CHL,但肿瘤细胞 CD20 弥漫强阳性;模式 2:8 例,形态学上类似于 DLBCL,但肿瘤细胞异质性表达 CD20、PAX5,同时表达 CD30 和/或 CD15;模式 3:4 例,形态特点介于 CHL 和 DLBCL 之间,肿瘤细胞不同程度地表达 CD20、CD30 和 CD15。11 例受检病例中,6 例肿瘤细胞表达 EB 病毒潜伏膜蛋白 1。临床上,绝大多数患者对联合利妥昔单抗和 CHOP(R-CHOP)方案的免疫化疗不敏感。**结论**　通过描述三种常见的组织学模式,提出了具有 DLBCL 和 CHL 中间特点的灰区淋巴瘤的诊断标准。这类肿瘤外周型病变和纵隔病变的病理特点似有不同。目前对这组交界性肿瘤尚无有效治疗方法,患者预后较差。

【关键词】 淋巴瘤,大 B-细胞,弥漫性;　霍奇金病;　诊断,鉴别

表 1　16 例具有弥漫性大 B 细胞淋巴瘤(DLBCL)和经典型霍奇金淋巴瘤(CHL)中间特点的灰区淋巴瘤的临床表现

例序	年龄(岁)	性别	累犯部位				临床分期	治疗方案	治疗结果	临床结局
			纵隔	外周淋巴结	结外部位	骨髓				
1	74	女	NA	+(A)	胸腔	+	ⅣB	RCHOP + ESHAP	PD	死亡
2	50	男	−	+(C, SC)	−	−	ⅡB	CT + ASCT	CR	无病生存
3	16	男	−	+(A)	−	−	ⅠA	RCHOP + RT	CR	无病生存
4	15	男	−	+(A, C)	−	−	ⅡA	RCHOP	PR	带病生存
5	45	男	+	NA	NA	NA	NA	NA	NA	NA
6	30	男	NA	+(C)	NA	NA	NA	NA	NA	NA
7	29	女	−	+(C)	乳腺	−	ⅡA	CHOP + RT	CR	无病生存
8	41	男	−	+(C, I)	−	−	ⅢB	RCHOP	SD	带病生存
9	64	男	−	+(C, RP)	−	−	ⅢA	RCHOP	PD	死亡
10	42	男	+	+(I)	−	−	ⅡB	RCHOP	PR	带病生存
11	61	女	−	+(C, RP)	−	−	ⅢA	RCHOP + RT	SD	带病生存
12	22	女	+	+(SC)	−	−	ⅡB	RCHOP	PR	带病生存
13	26	男	+	+(C, SC)	−	−	ⅢB	CT + ASCT	CR	无病生存
14	27	女	+	+(SC, RP)	−	−	ⅢA	CHOP	PR	带病生存
15	30	男	NA	+(C)	NA	NA	NA	NA	NA	NA
16	71	女	−	+(I, RP)	−	−	ⅡA	CHOP + AVBD	PR	带病生存

注:NA:信息不详;A:腋窝;C:颈部;I:腹股沟;SC:锁骨上;RP:腹膜后;CT:化疗;ASCT:自体干细胞移植;RT:放疗;CR:完全缓解;PR:部分缓解;SD:疾病稳定;PD:病情进展

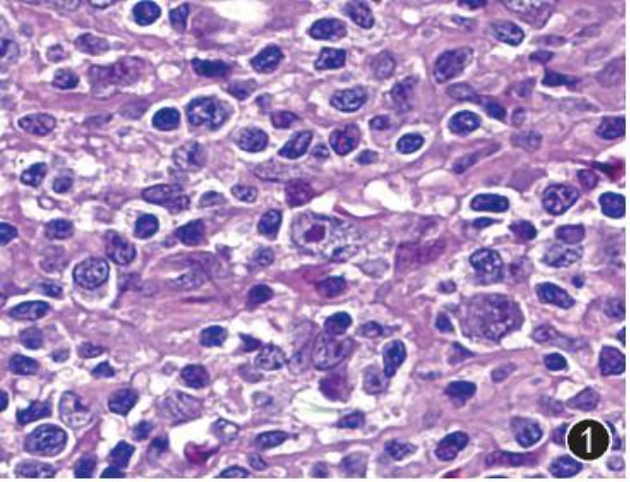
表 2　16 例具有 DLBCL 和 CHL 中间特点的灰区淋巴瘤的病理特征

例序	组织学形态				免疫表型						病理模式
	生长方式	肿瘤细胞	反应性细胞	坏死	CD45	CD20	PAX5	CD30	CD15	LMP1	
1	结节状	Ho, M, CB	L, E, H, PC	−	−	+	+	−	−	−	1
2	结节状	Ho, LA	L, E, H, PC	−	−	+	+	−	−	−	1
3	弥漫性	Ho, IB	L, E, H	−	ND	+	H +	H +	−	+	1
4	弥漫性	Ho, IB	L, E, H,	−	ND	+	+	F +	−	ND	1
5	结节状	A, Ho,	L, E, H	−	−	H +	H +	+	+	ND	2
6	结节状	IB, Ho	L, E	−	ND	H +	H +	+	+	ND	2
7	弥漫性	CC, Ho	L	−	−	H +	+	H +	H +	ND	2
8	弥漫性	CB, Ho, RS	L, E, H, PC	−	ND	−	H +	+	+	−	2
9	弥漫性	IB	L, E, H	+	ND	H +	H +	H +	H +	+	2
10	结节状	CB, Ho	L	+	−	H +	+	+	+	+	2
11	弥漫性	CC, CB, RS	L, E, H	−	−	+	+	+	F +	+	2
12	弥漫性	IB CB	L, H	−	ND	−	+	+	+	ND	2
13	结节状	CB, M	L, H	−	−	+	+	+	−	−	3
14	结节状	CC, CB	L, H	−	+	H +	H +	H +	H +	−	3
15	弥漫性	CB, Ho	L, PC	+	+	H +	−	+	F +	+	3
16	弥漫性	IB, Ho	L	−	ND	H +	H +	+	F +	+	3

注：Ho：霍奇金样细胞；M："干尸"细胞；CB：中心母细胞样细胞；LA：腔隙型霍奇金细胞；IB：免疫母细胞样细胞；A：间变性细胞；CC：胞浆透亮细胞；RS：RS 样细胞；L：淋巴细胞；E：嗜酸粒细胞；H：组织细胞；PC：浆细胞；ND：未检测

+：90% 以上的瘤细胞弥漫强阳性着色；H +：瘤细胞有强弱不等的抗原表达，且阳性细胞占所有瘤细胞的比例在 25% ~90% 之间；F +：10% ~25% 的肿瘤细胞强阳性或异质性阳性着色；−：无阳性肿瘤细胞或阳性瘤细胞比例少于 10%

模式 1：CHL 样形态，DLBCL 样表型；模式 2：DLBCL 样形态，CHL 样表型；模式 3：DLBCL 样和 CHL 样成分混合存在并相互移行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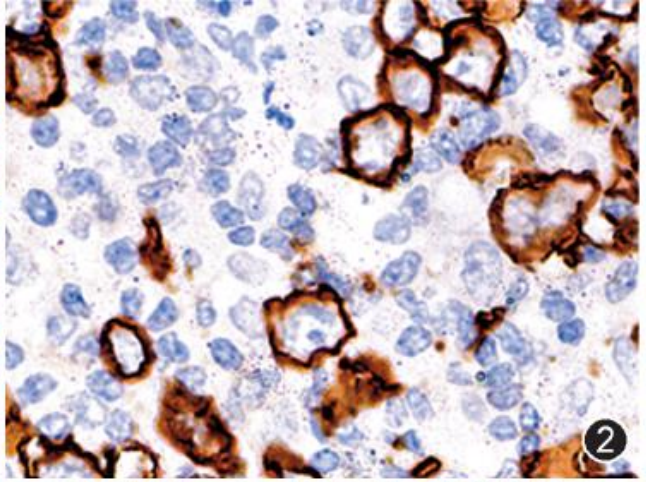
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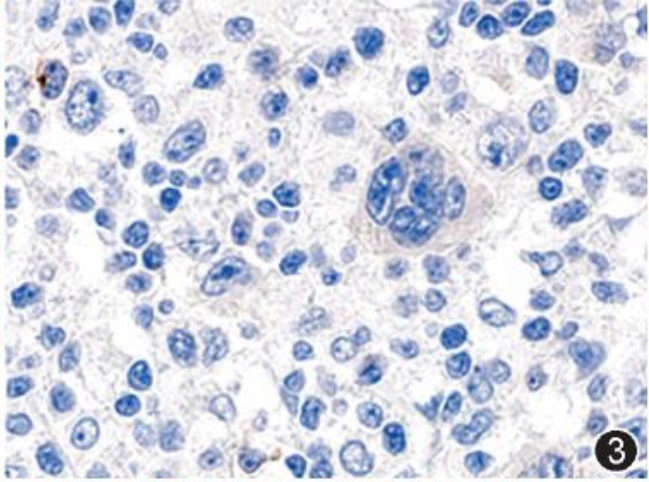
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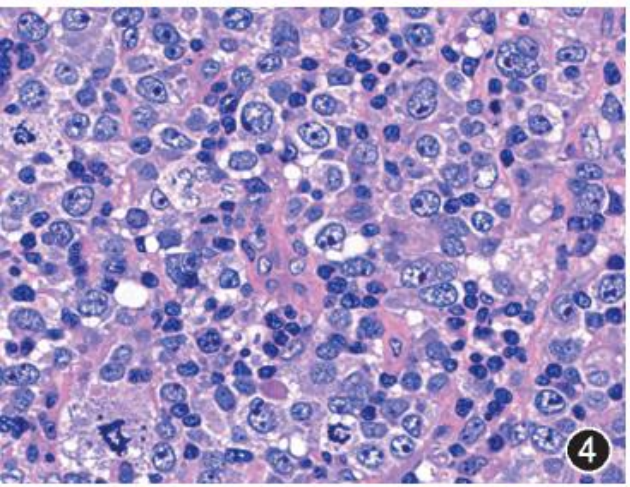
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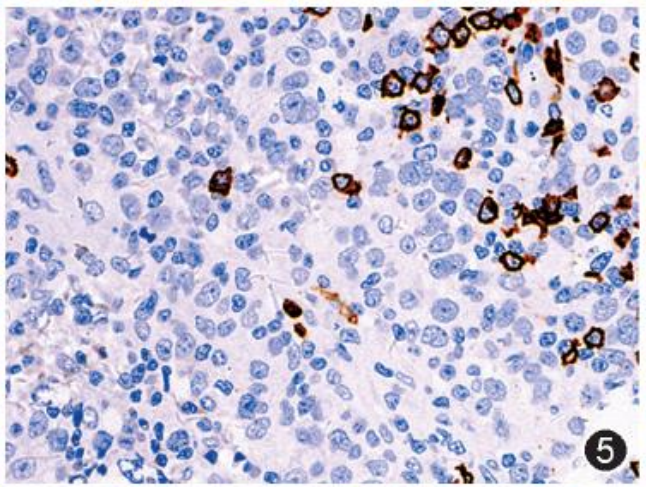
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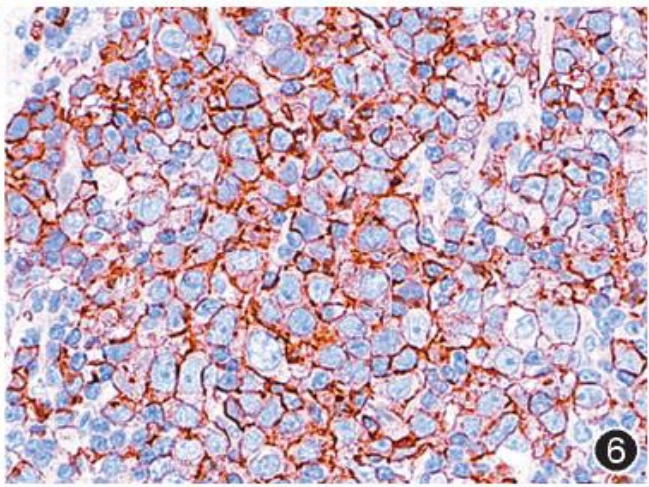
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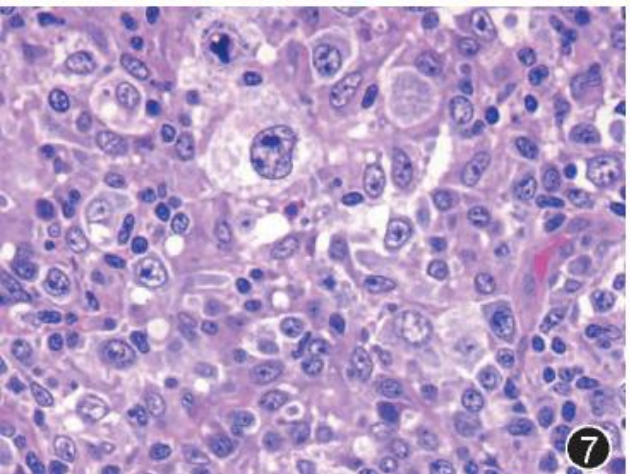
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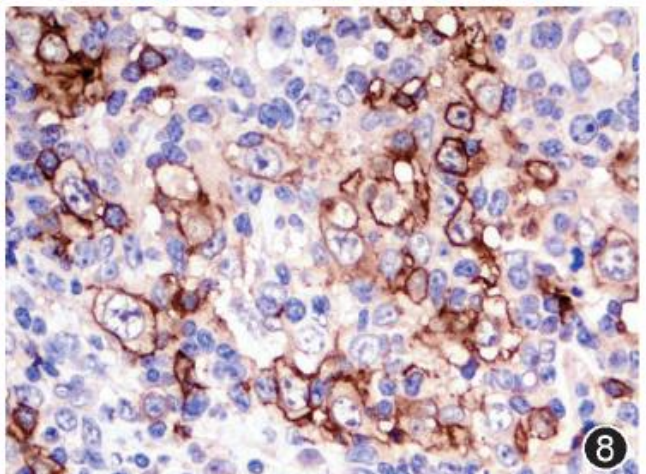
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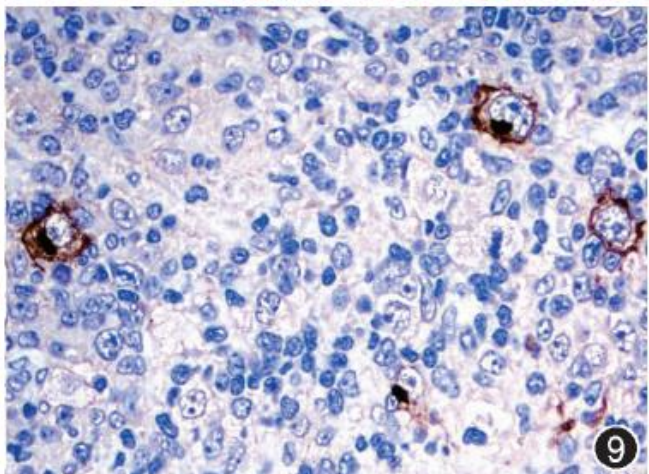
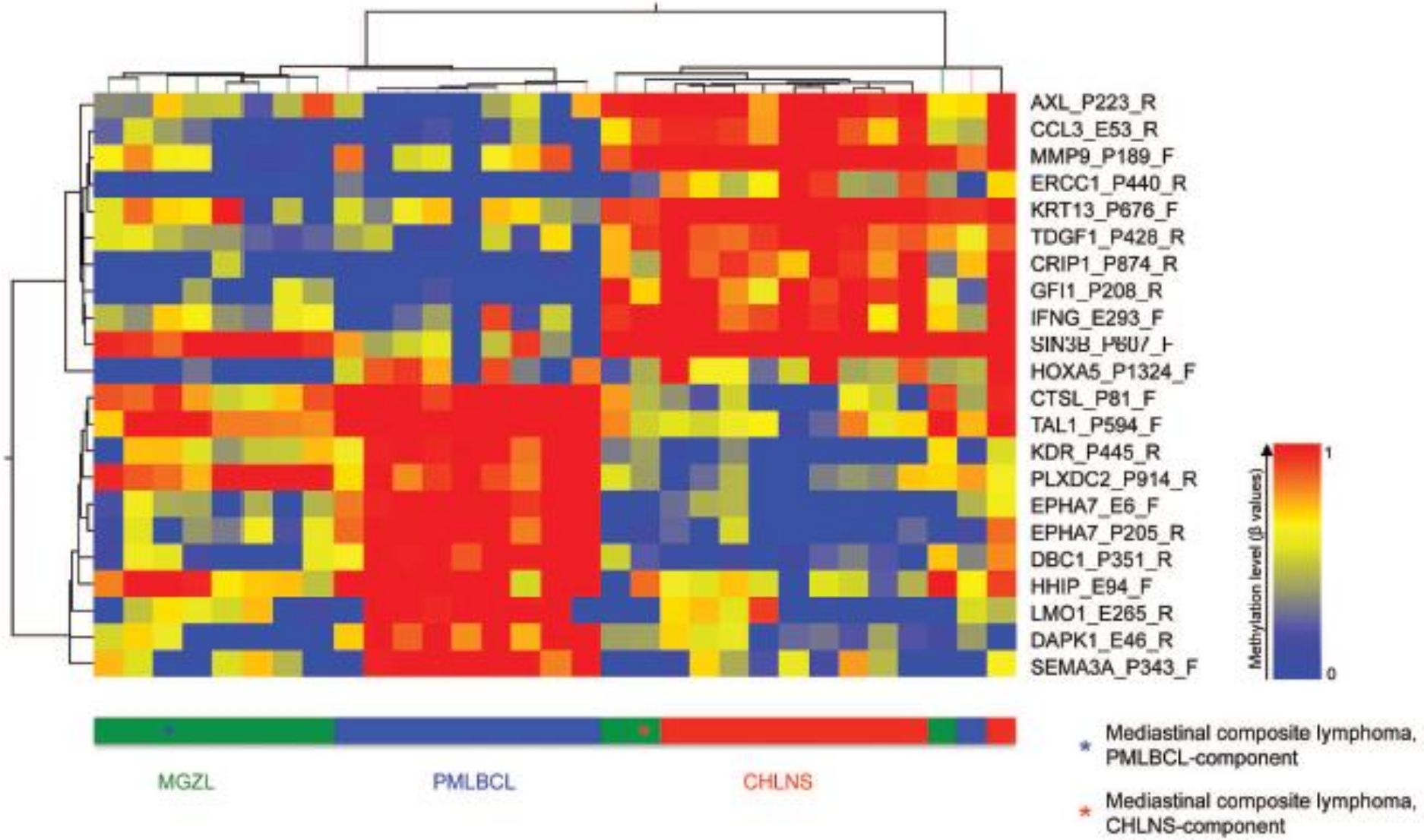

9

比较中央型和外周型病例，我们发现中央型病例通常患者更为年轻，但两组在患者性别、疾病分期、治疗结果等临床参数方面并无统计学差异。有趣的是，二者病理特征似乎不尽相同。例如，中央型病变更易见到纤维胶原组织增生和结节状分隔，更多呈现模式 2 和模式 3 型改变，且多数 EBV 阴性；而外周型病变则少有纤维胶原分隔，更多表现模式 2 和模式 1 型改变，且有相当部分病例与 EBV 相关。但由于病例数较少，上述差异并非均有统计学意义，可能还需更大样本研究才能得出结论。

GZL: What's new?

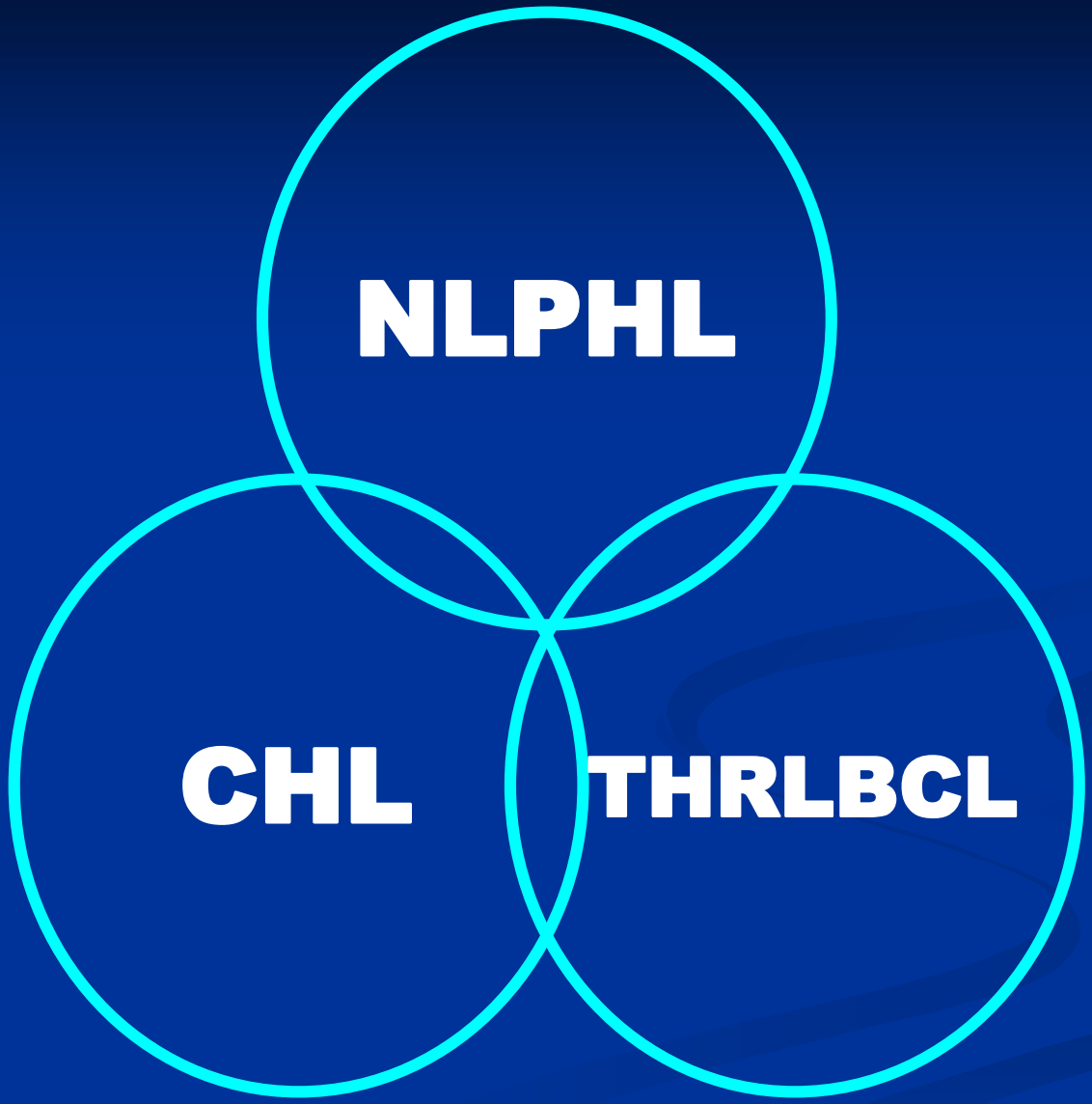
- PMBL and CHL share a common GEP signature
- The exact mechanisms responsible for the transformation of a B-cell to a HRS cell are not fully understood, but the down regulation of B-cell program in CHL may be responsible for the tumorigenesis, and these modifications may be controlled at the epigenetic level
- GZL differs from NSCHL and PMBL by differential methylation of selected CpG islands, thus, the epigenetic signature may serve as not only new diagnostic tools, but possible targets for future therapies

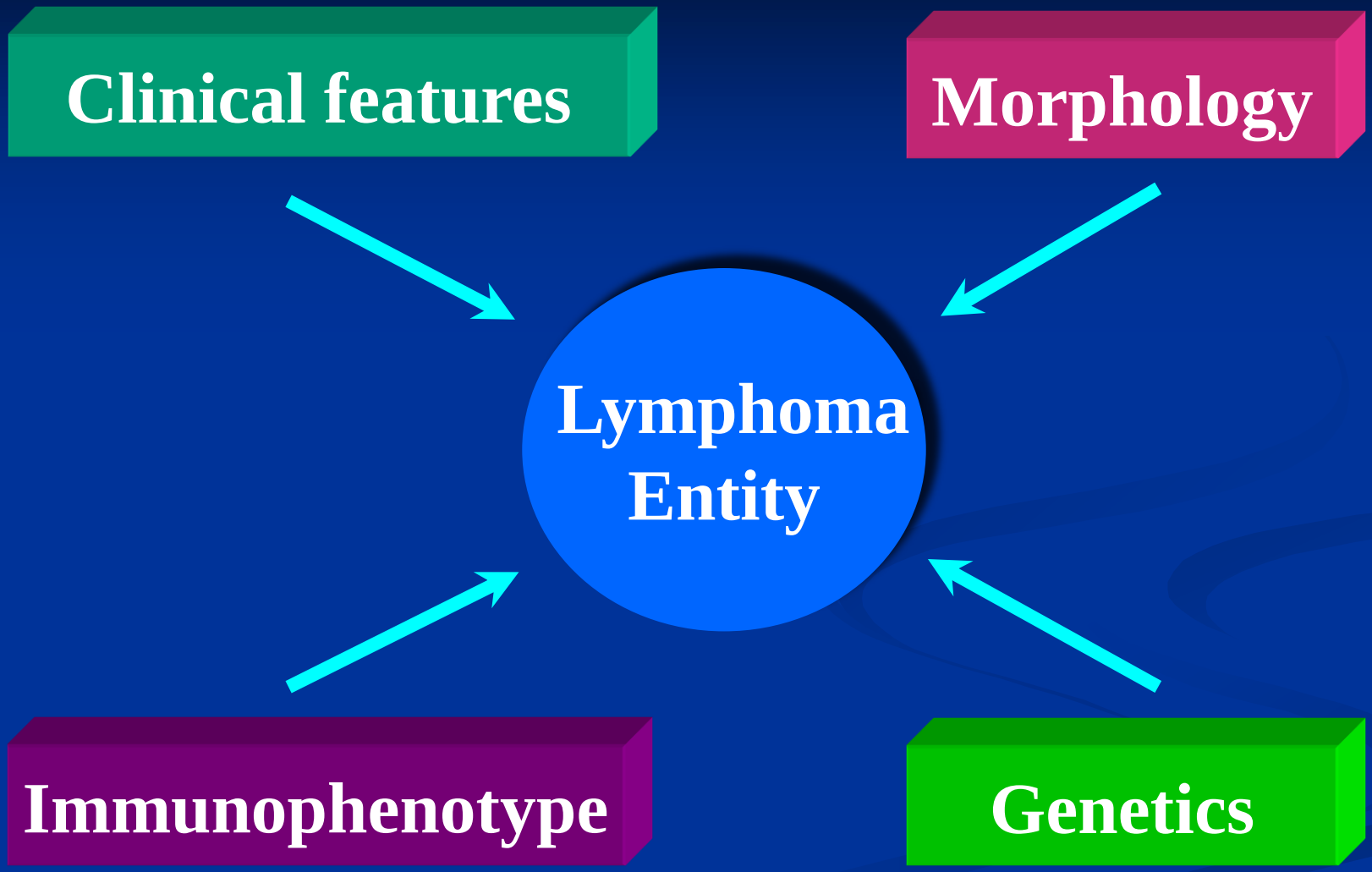
Identification of differentially methylation targets in NSCHL, PMBL, AND GZL



Haematologica 2011; 96: 558-65

Grey zone lymphomas include but are not restricted to the two examples listed in the 4th edition of WHO classification


NLPHL
CHL
THRLBCL


Clinical features
Morphology
Lymphoma Entity
Immunophenotype
Genetics

李小秋，主任医师、硕士生导师。现任复旦大学附属肿瘤医院病理科淋巴造血病理专科负责人。兼任中国抗癌协会淋巴瘤专业委员会常务委员暨病理学组副组长、中国抗癌协会淋巴瘤专业委员会青年学术委员会副主任委员、中华医学会病理学分会淋巴造血系统学组副组长、CSCO抗淋巴瘤联盟常务委员、中国抗癌协会血液肿瘤专业委员会血液病理工作组委员，中国抗癌协会肿瘤病理专业委员会青年委员、上海市抗癌协会淋巴瘤专业委员会副主任委员。现任《中华临床医师杂志》学术委员会委员、《诊断病理学杂志》、《白血病·淋巴瘤》编委、《中华病理学杂志》、《中国肿瘤临床》和《临床与实验病理学杂志》特邀审稿专家。现主要从事肿瘤病理诊断和研究工作，尤其擅长淋巴造血组织疾病病理，对于疑难病例和罕见病种的诊断和鉴别积累了丰富的经验。当前主要研究方向为弥漫性大B细胞淋巴瘤中B细胞受体信号途径以及*MYC*基因异常的调节机制及临床意义。曾负责或参与卫生部临床学科重点项目、国家自然科学基金、上海市科委基金资助的科研项目。迄今发表学术论文61篇(SCI论文20篇)。主译血液病理学专著1部，参编淋巴瘤及病理学专著5部。曾获“上海市科学技术成果奖”。培养硕士生5人，并参与指导博士生6人、硕士生4人。多次在国际学术会议以及全国性病理或淋巴瘤学术会议上作主题报告，并在若干国家级继续教育项目中担任教学工作。

淋巴瘤病理研究新进展

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［摘要］ 2008年版WHO淋巴瘤分类出版以来的数年中，淋巴瘤病理相关的知识又有所更新。对于B细胞非霍奇金淋巴瘤，人们较关注那些高度侵袭而又异质的亚型(例如：弥漫性大B细胞淋巴瘤)，并努力尝试在分子生物学基础之上建立起更好的分型方法。此外，人们对于如何正确理解并处理明显的恶性淋巴瘤以及那些并不具有明确恶性行为、克隆性淋巴组织增生性疾病之间的“边界性”病变的兴趣也日益增长。另一方面，有关T和NK(T/NK)细胞的亚群构成、细胞分化方面的研究进展以及新近认识到的外周T/NK细胞淋巴瘤中的遗传学异常和信号路径调节失常，也有助于我们更深入地了解这些肿瘤的生物学特性。临床惰性、克隆性T/NK细胞增生性病变、特别是发生于黏膜皮肤部位者，也愈发受到人们关注。这些新的知识进展会推动淋巴瘤分类不断向前演进。

［关键词］ 进展；淋巴瘤；B细胞；T和NK细胞；分类；侵袭性；惰性克隆性淋巴组织增生性疾病

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Thank you