Diffüz Büyük B Hücreli Lenfoma'da Genetik Temelli Tedavi

Yrd. Doç. Dr. Ömür Gökmen Sevindik

Fırat Üniversitesi Tıp Fakültesi Hematoloji Bilim Dalı

3. Hematolojik Onkoloji Kongresi, 2016, Kıbrıs

Sunum Planı

- Diffüz Büyük B Hücreli Lenfoma epidemiyoloji
- R-CHOP neden yetersiz?
- Hücre kökeni neden önemli, tespit edilebilir mi?
- Hücre kökeni dışında kötü gidişle ilişkili genetik alt gruplar var mı? (Double expressor, double hit)
- Hücre kökeni, double hit tedaviyi etkilemeli mi?
- Bunların ötesinde neleri hedefleyebiliriz?

Sunum öncesi sorular:

- Rutin pratiğinizde patoloji raporlarınız GCB veya non-GCB lenfoma ayrımı yapıyor mu?
  - Evet
  - Hayır

- Rutin pratiğinizde patoloji raporlarınız myc ve bcl2 ekspresyon durumunu içeriyor mu?
  - Evet
  - Hayır

- Double HIT lenfoma (doku fish) tespiti için ileri genetik yöntemler kullanıyor musunuz?
  - Evet
  - Hayır

- Hücre kökeni veya genetik özelliklerini bildiğiniz hastalarda tedavi seçiminiz değişiyor mu?
  - Evet
  - Hayır

Diffüz Büyük B Hücreli Lenfoma - Epidemiyoloji

- Diffüz Büyük B Hücreli Lenfoma en sık görülen Non-Hodgkin Lenfoma alt tipi, tüm NHL'lerin yaklaşık %25-35'ını oluşturuyor, yıllık insidans 7-4.9/100000, medyan tanı yaşı 64, erkeklerde hafif düzeyde daha sık, 5 yıllık OS %62 (kemik iliği tutulumu yoksa, %10 kemik iliği tutulumu varsa)

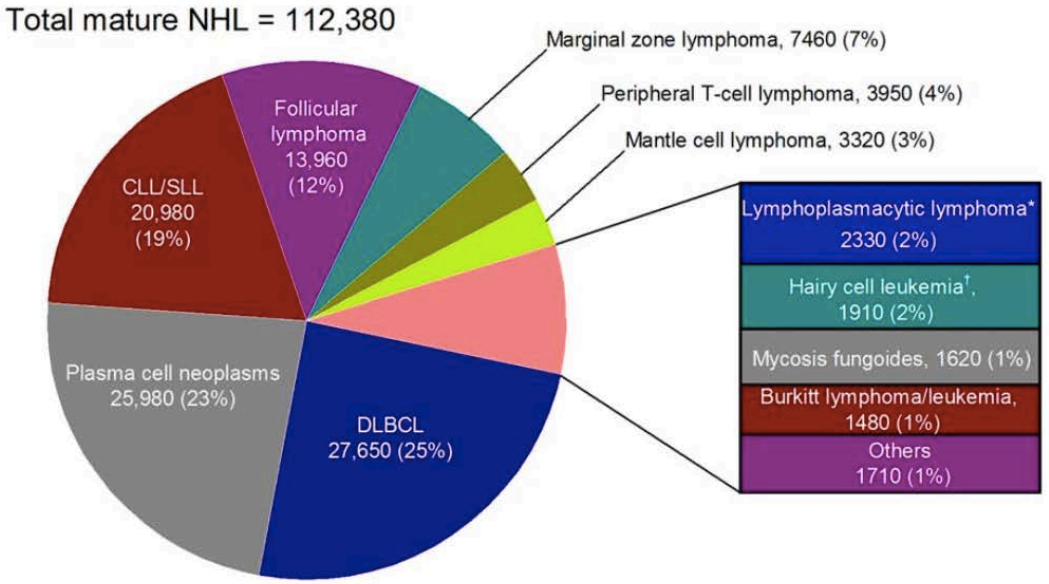
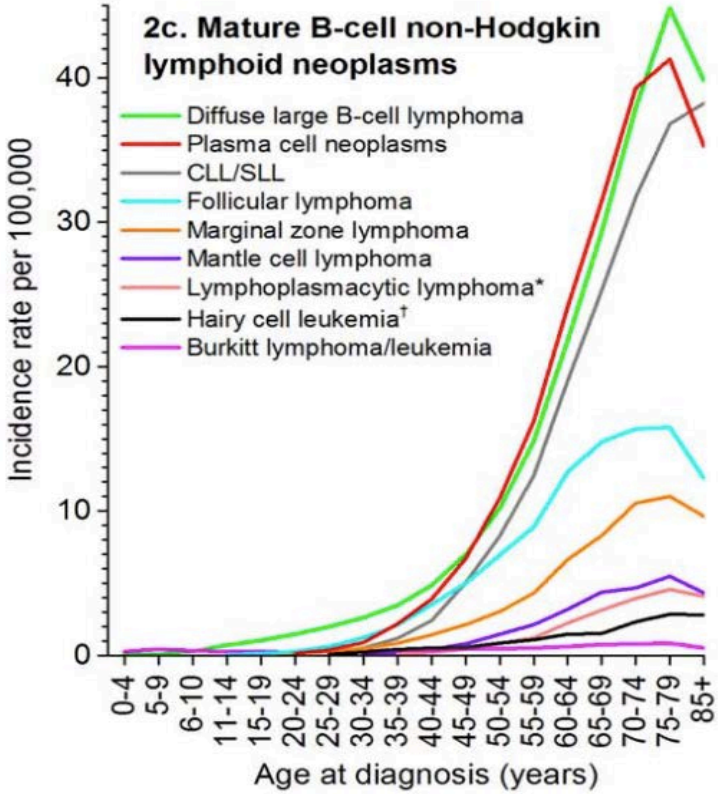
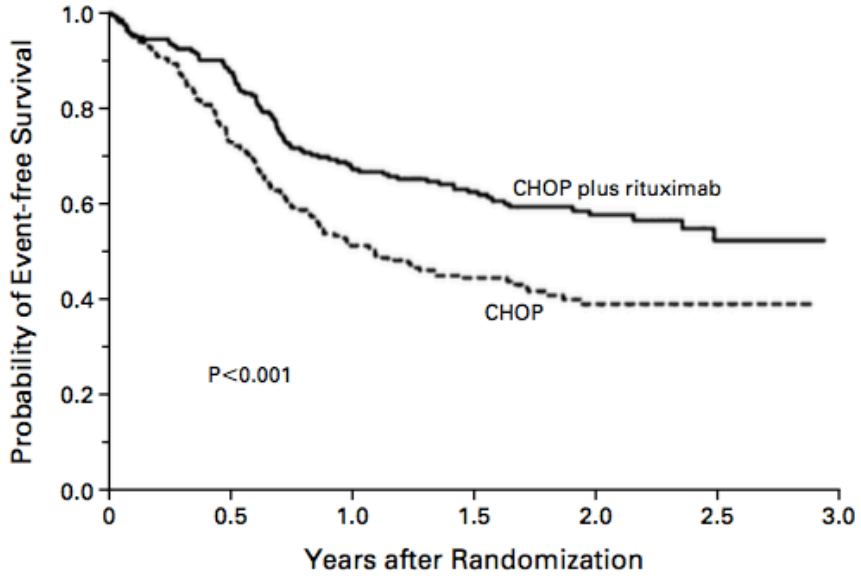


FIGURE 1. Estimated Cases and Distribution of Mature Non-Hodgkin Lymphoid Neoplasm Subtypes: United States, 2016.
CLL/SLL indicates chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma.
*Includes Waldenstrom macrolobulinemia.
†Includes Hairy cell leukemia variant.



CA CANCER J CLIN 2016 , SEER Database

R-CHOP neden yetersiz?



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

Figure 1. Event-free Survival among 399 Patients Assigned to Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) or with CHOP plus Rituximab.

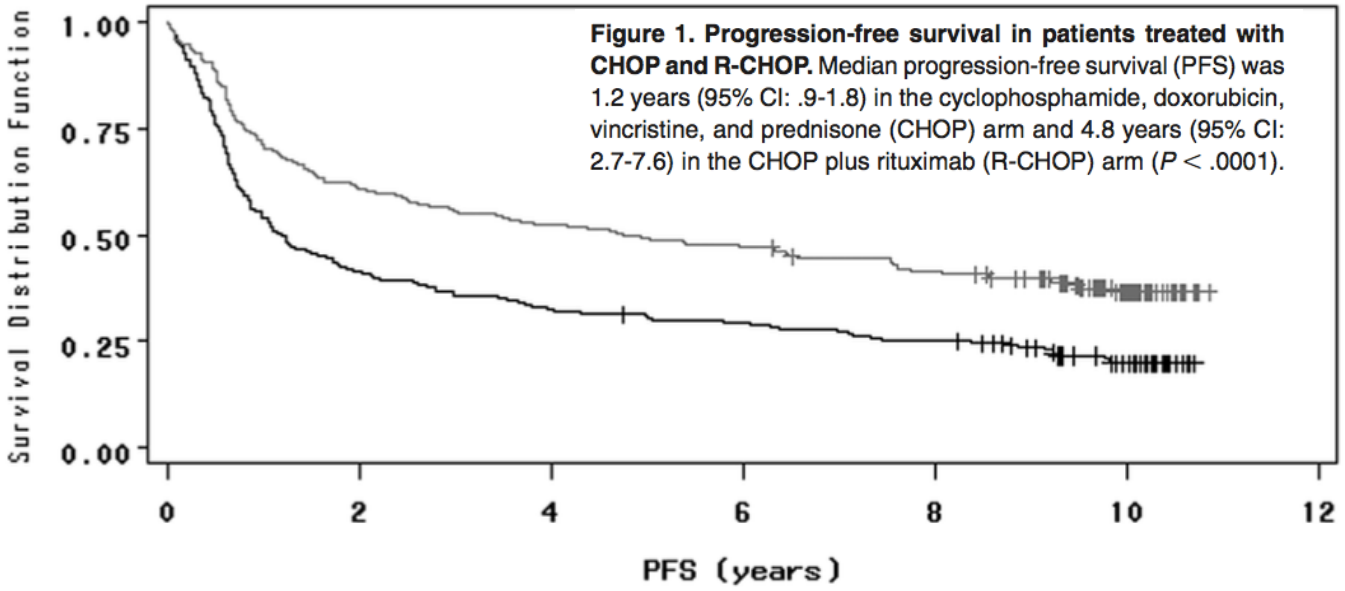


Figure 1. Progression-free survival in patients treated with CHOP and R-CHOP. Median progression-free survival (PFS) was 1.2 years (95% CI: .9-1.8) in the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) arm and 4.8 years (95% CI: 2.7-7.6) in the CHOP plus rituximab (R-CHOP) arm ($P < .0001$).

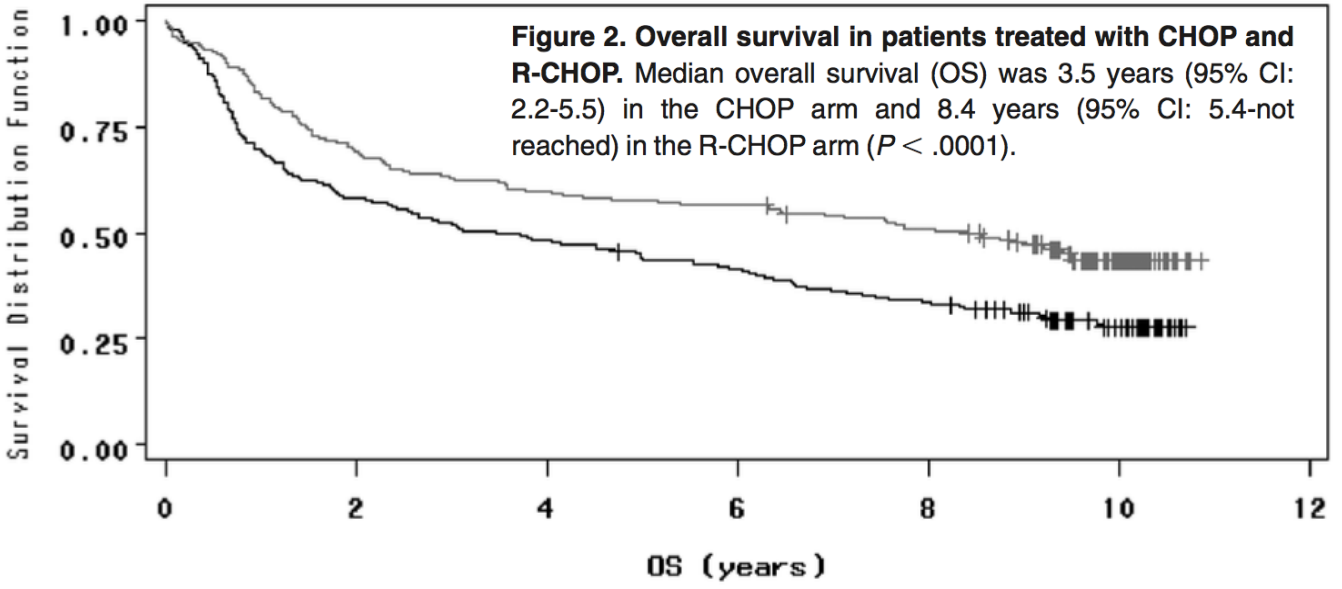
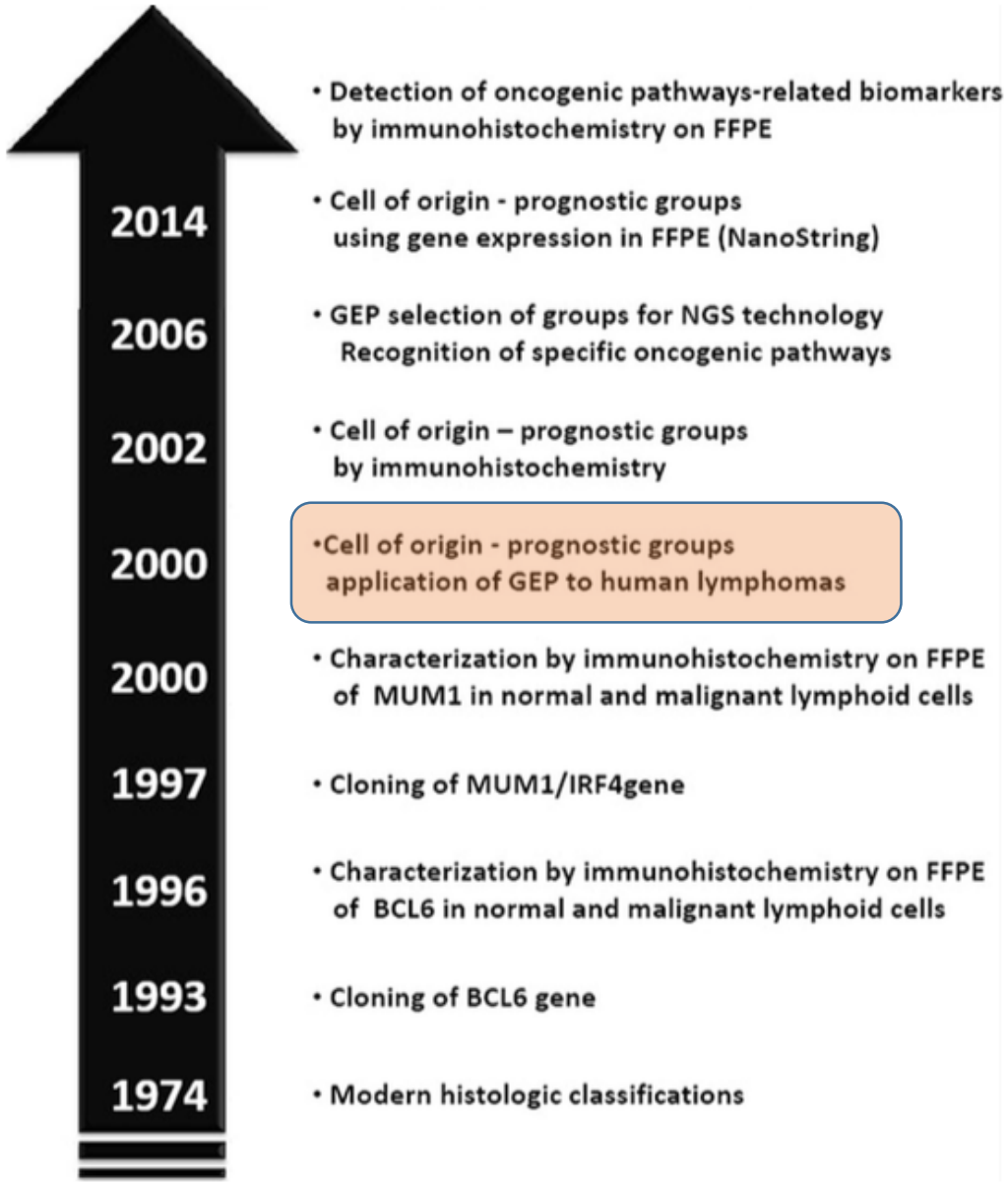


Figure 2. Overall survival in patients treated with CHOP and R-CHOP. Median overall survival (OS) was 3.5 years (95% CI: 2.2-5.5) in the CHOP arm and 8.4 years (95% CI: 5.4-not reached) in the R-CHOP arm ($P < .0001$).

Coiffier B et.al, Blood. 2010 Sep 23;116(12):2040-5

Author (trial/phase)	*N*	Treatment	Patient selection	PFS/EFS	OS
Coiffier et al. (GELA/III)	202	R-CHOP × 8 vs ×	Age 60-80 y	57% vs. 38% (2 y)	70% vs. 57% (2 y)
	197	CHOP × 8	Stage II-IV	35% vs. 20% (10 y)	43.5% vs. 28% (10 y)
Pfreundschuh et al.	413	R-CHOP-like* × 6 vs	Age 18-60 y	79% vs. 58% (3 y)	93% vs. 84% (3 y)
(MInT/III)	410	CHOP like* × 6	aaIPI 0 or 1	74% vs. 56% (6 y)	90% vs. 80% (6 y)
			Stage I(+bulk or II-IV)		
Pfreundschuh et al.	306	R-CHOP-14 × 6	Age 61-80 y	66.5% (3 y)	78% (3 y)
(RiCOVER-60/III)†	304	R-CHOP-14 × 8	Stage I-IV	63% (3 y)	72.5%(3 y)
	209	CHOP-14 × 6		47% (3 y)	68% (3 y)
	219	CHOP-14 × 8		53% (3 y)	66% (3 y)
Cunningham et al. (ASCO 2011)	540	R-CHOP-21 × 8	Age 61-80 y	81% vs. 83% (2 y)	81% vs. 83% (2 y)
(NCRI/III)	540	R-CHOP-14 × 6 + G-CSF			
Delarue et al. (ASCO 2012)	296	R-CHOP-21 × 8	Age 60-80 y	60% vs. 56% (3 y)	72% vs. 69% (3 y)
(LNH03-6B/III)	304	R-CHOP-14 × 6	aaIPI >1		
Recher et al. (LNH03-2B/III)	196	R-ACVBP	Age 18-59 y	87% vs. 73% (3 y)	92% vs. 89% (3 y)
	183	R-CHOP	aaIPI 1		
Wilson et al. (NCI/II)	72	DA-EPOCH-R	Age >18 y	79% (5 y)	80% (5 y)
			Stage II-IV		

Survival estimates shown for rituximab-containing regimens only and are rounded off where applicable to the nearest whole number.
*87% DLBCL; CHOP-like = CHOP-21 or CHOEP-21 in 92%; radiotherapy given to sites of bulk, extranodal disease (physician's discretion).
†80% DLBCL.
EFS = event free survival; G-CSF = granulocyte colony-stimulating factor; GELA = *Groupe d'Etude des Lymphomes de l'Adulte;*
PFS = progression-free survival; MInT = MabThera International Study Group; NCRI = British National Cancer Research Institute Study;
OS = overall survival; R = rituximab; RiCOVER-60 = rituximab with CHOP Over Age 60 Years; y = year.



Diffüz Büyük B Hücreli Lenfoma'da tarihsel evrim

Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling

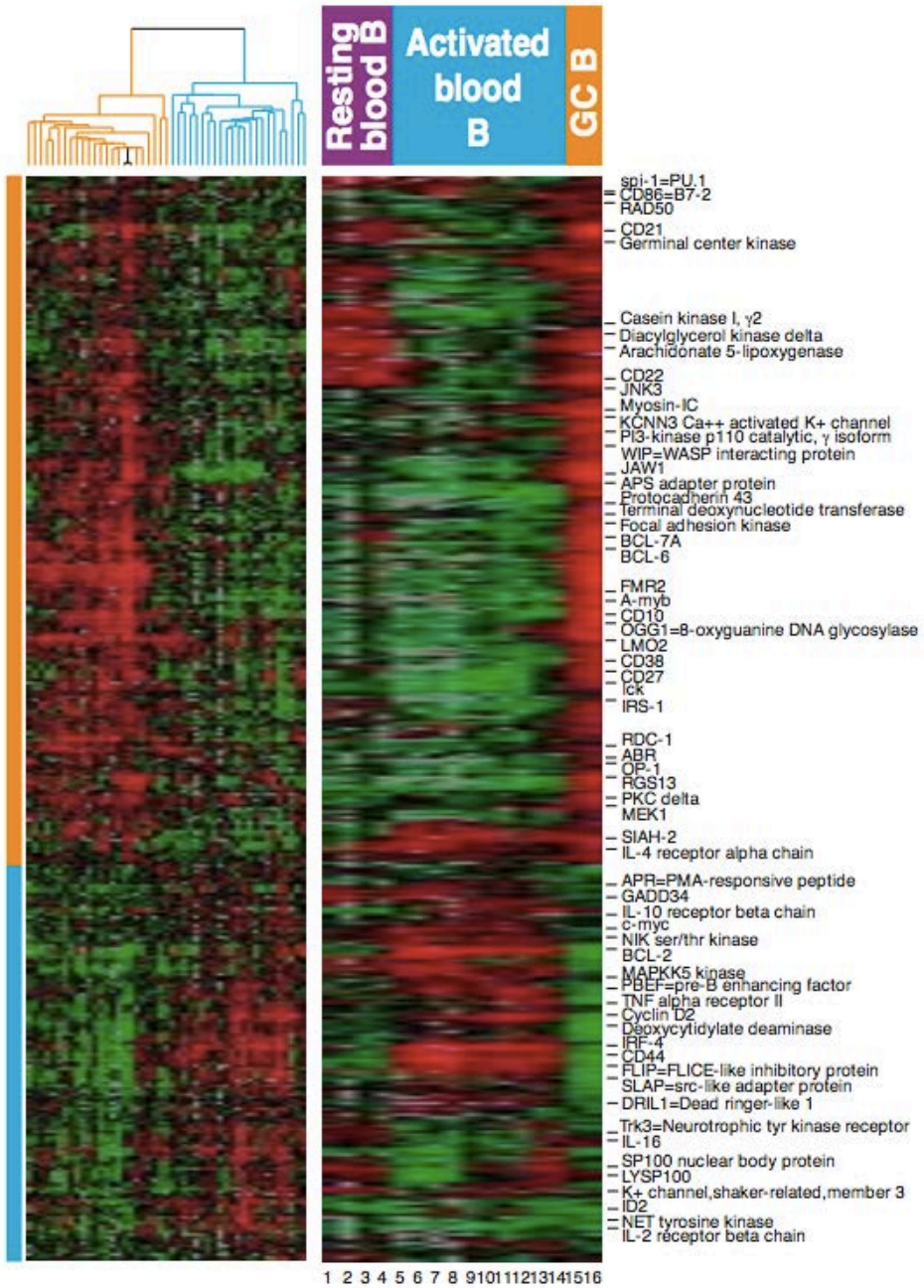
Ash A. Alizadeh[1,2], Michael B. Eisen[2,3,4], R. Eric Davis[5], Chi Ma[5], Izidore S. Lossos[6], Andreas Rosenwald[5], Jennifer C. Boldrick[1], Hajeer Sabet[5], Truc Tran[5], Xin Yu[5], John I. Powell[7], Liming Yang[7], Gerald E. Marti[8], Troy Moore[9], James Hudson Jr[9], Lisheng Lu[10], David B. Lewis[10], Robert Tibshirani[11], Gavin Sherlock[4], Wing C. Chan[12], Timothy C. Greiner[12], Dennis D. Weisenburger[12], James O. Armitage[13], Roger Warnke[14], Ronald Levy[6], Wyndham Wilson[15], Michael R. Grever[16], John C. Byrd[17], David Botstein[4], Patrick O. Brown[1,18] & Louis M. Staudt[5]

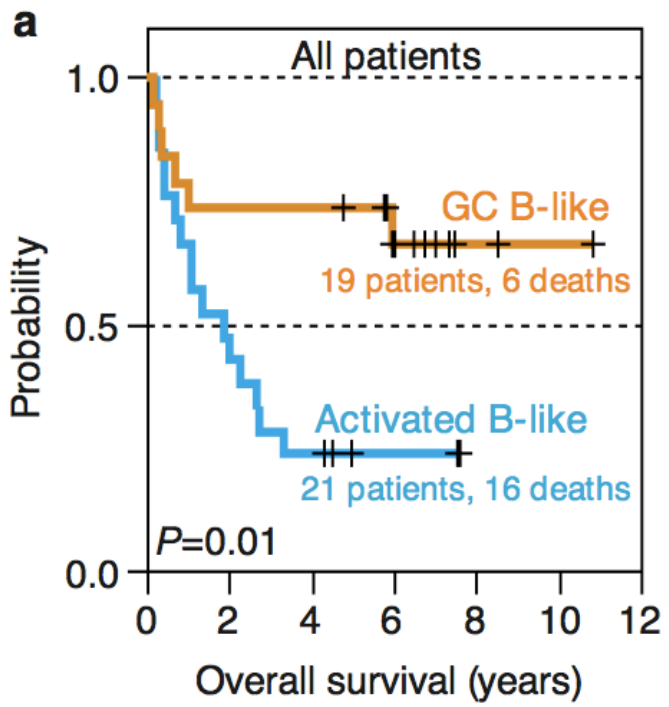
Departments of [1]Biochemistry, [3]Genetics, [14]Pathology, [6]Medicine, [10]Pediatrics and [11]Health Research & Policy and Statistics, and [18]Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, California 94305, USA
[5] Metabolism Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA
[7] Bioinformatics and Molecular Analysis Section, CBEL, CIT, NIH, Bethesda, Maryland 20892, USA
[8] CBER, FDA, Bethesda, Maryland 20892, USA
[9] Research Genetics, Huntsville, Alabama 35801, USA
Departments of [12]Pathology and Microbiology, and [13]Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska 68198, USA
[15] Medicine Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA
[16] Johns Hopkins Oncology Center, Johns Hopkins School of Medicine, Baltimore, Maryland 21287, USA
[17] Walter Reed Army Medical Center, Washington, DC 20307, USA
[2] These authors contributed equally to this work

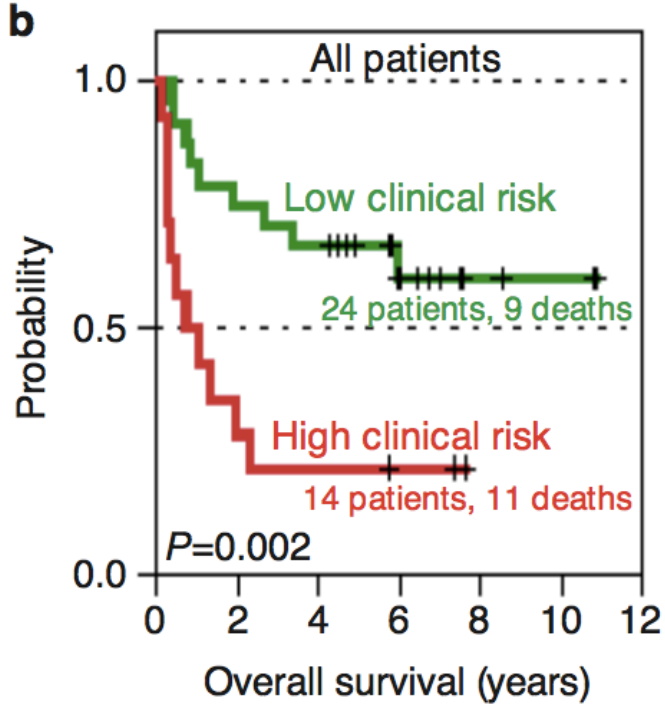
Erken ve dirençli nüksler, birincil dirençli hasta grupları ->
Acaba aynı hastalığı mı tedavi ediyoruz?

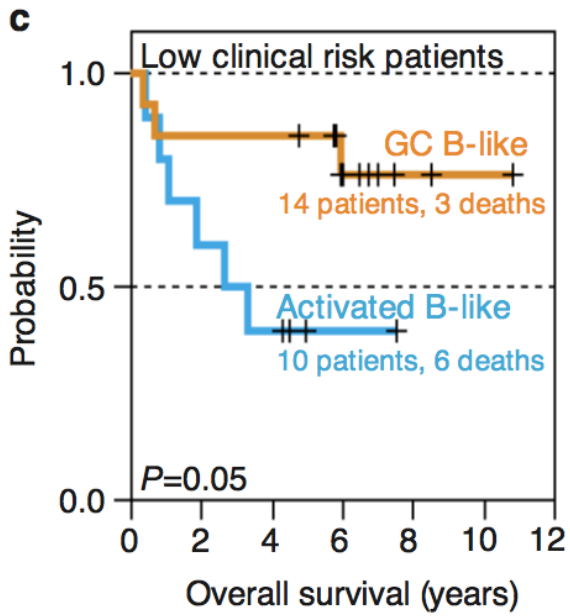
Diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin's lymphoma, is clinically heterogeneous: 40% of patients respond well to current therapy and have prolonged survival, whereas the remainder succumb to the disease. We proposed that this variability in natural history reflects unrecognized molecular heterogeneity in the tumours. Using DNA

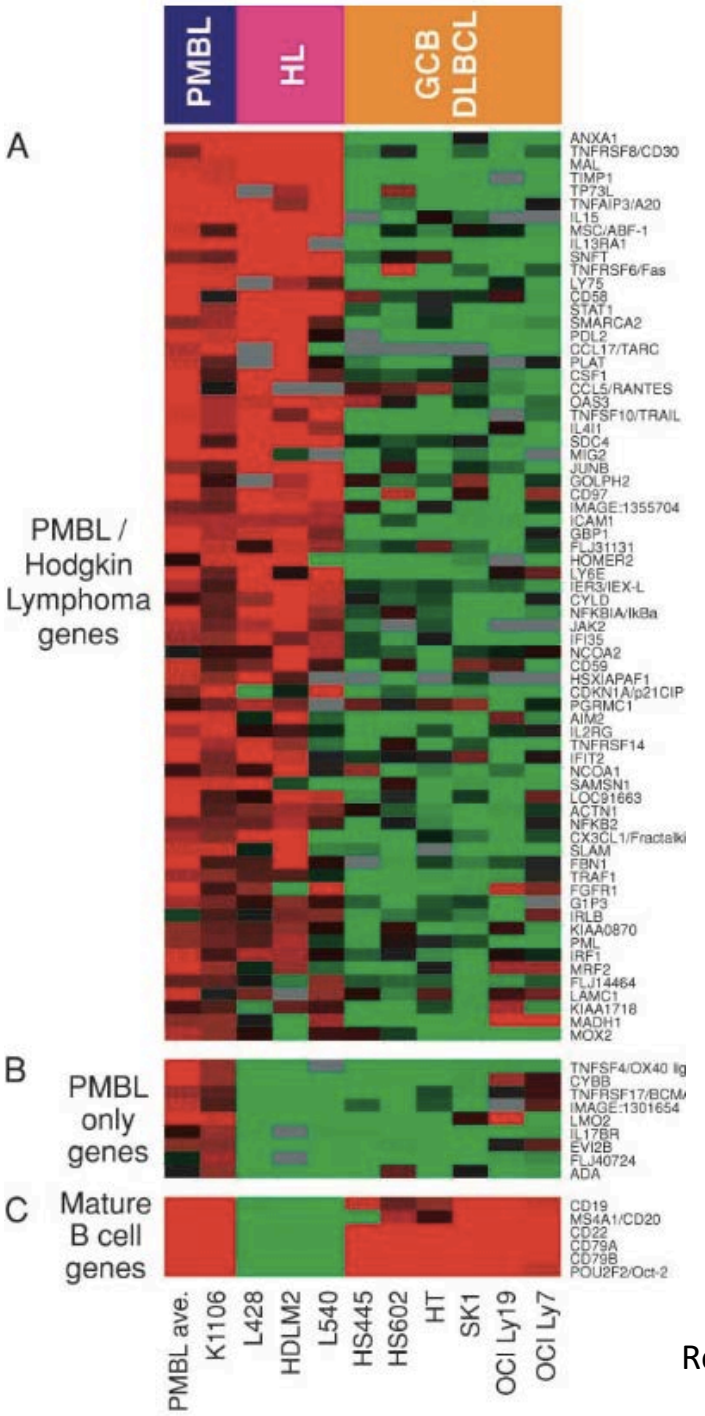
NATURE | VOL 403 | 3 FEBRUARY 2000

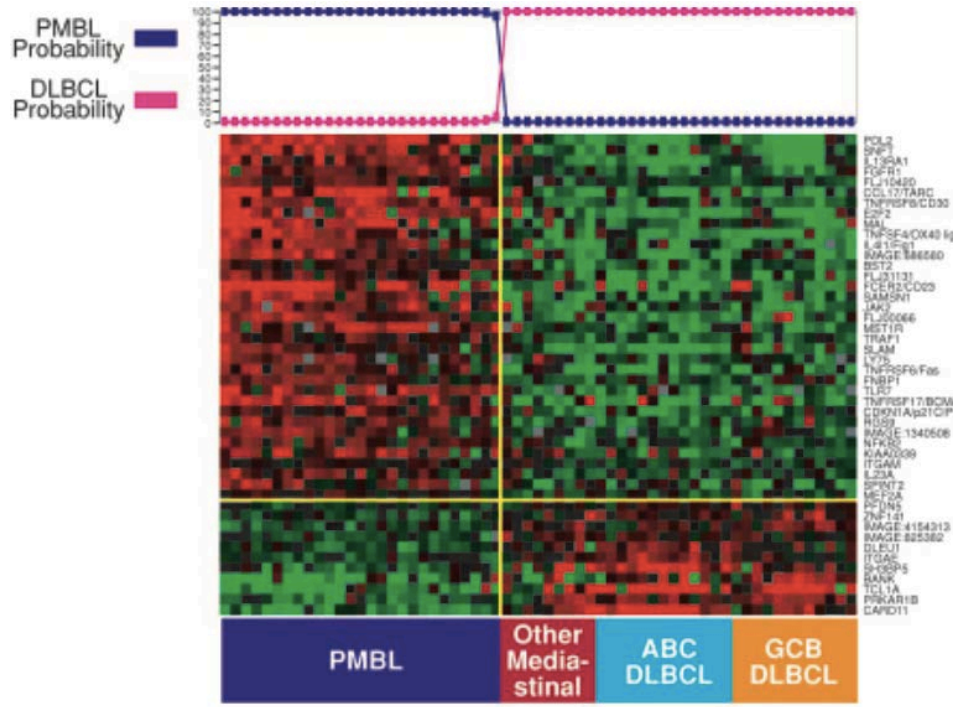

Resting blood B
Activated blood B
GC B
spi-1=PU.1
CD86=B7-2
RAD50
CD21
Germinal center kinase
Casein kinase I, γ2
Diacylglycerol kinase delta
Arachidonate 5-lipoxygenase
CD22
JNK3
Myosin-IC
KCNN3 Ca++ activated K+ channel
PI3-kinase p110 catalytic, γ isoform
WIP=WASP interacting protein
JAW1
APS adapter protein
Protocadherin 43
Terminal deoxynucleotide transferase
Focal adhesion kinase
BCL-7A
BCL-6
FMR2
A-myb
CD10
OGG1=8-oxyguanine DNA glycosylase
LMO2
CD38
CD27
Ick
IRS-1
RDC-1
ABR
OP-1
RGS13
PKC delta
MEK1
SIAH-2
IL-4 receptor alpha chain
APR=PMA-responsive peptide
GADD34
IL-10 receptor beta chain
c-myc
NIK ser/thr kinase
BCL-2
MAPKK5 kinase
PBEF=pre-B enhancing factor
TNF alpha receptor II
Cyclin D2
Deoxycytidylate deaminase
IRF-4
CD44
FLIP=FLICE-like inhibitory protein
SLAP=src-like adapter protein
DRIL1=Dead ringer-like 1
Trk3=Neurotrophic tyr kinase receptor
IL-16
SP100 nuclear body protein
LYSP100
K+ channel,shaker-related,member 3
ID2
NET tyrosine kinase
IL-2 receptor beta chain
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

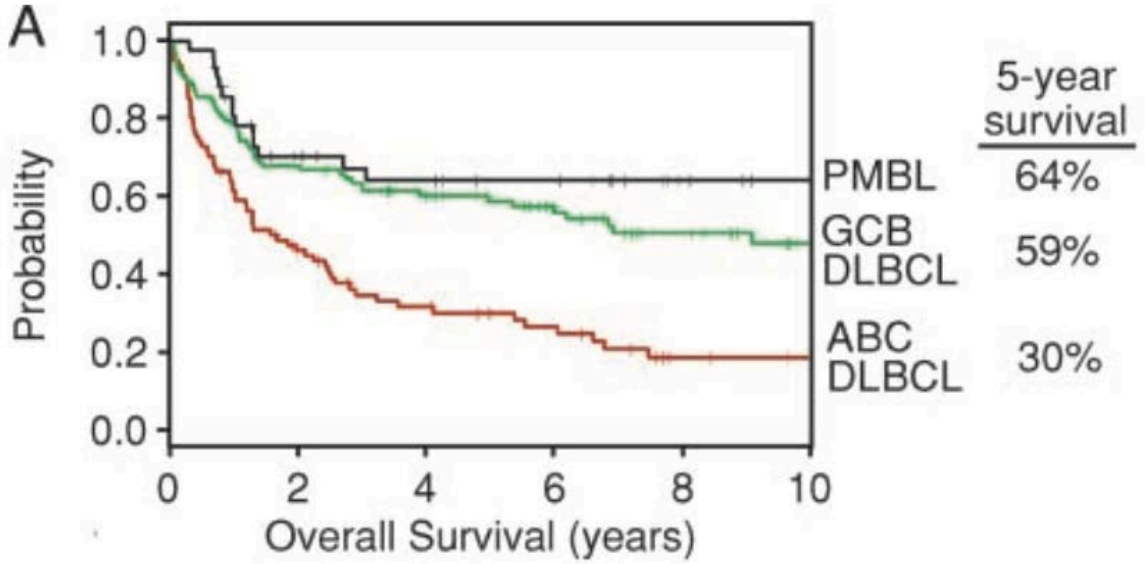

a
All patients
GC B-like
19 patients, 6 deaths
Activated B-like
21 patients, 16 deaths
P=0.01
Probability
1.0
0.5
0.0
0 2 4 6 8 10 12
Overall survival (years)


b
All patients
Low clinical risk
24 patients, 9 deaths
High clinical risk
14 patients, 11 deaths
P=0.002
Probability
1.0
0.5
0.0
0 2 4 6 8 10 12
Overall survival (years)

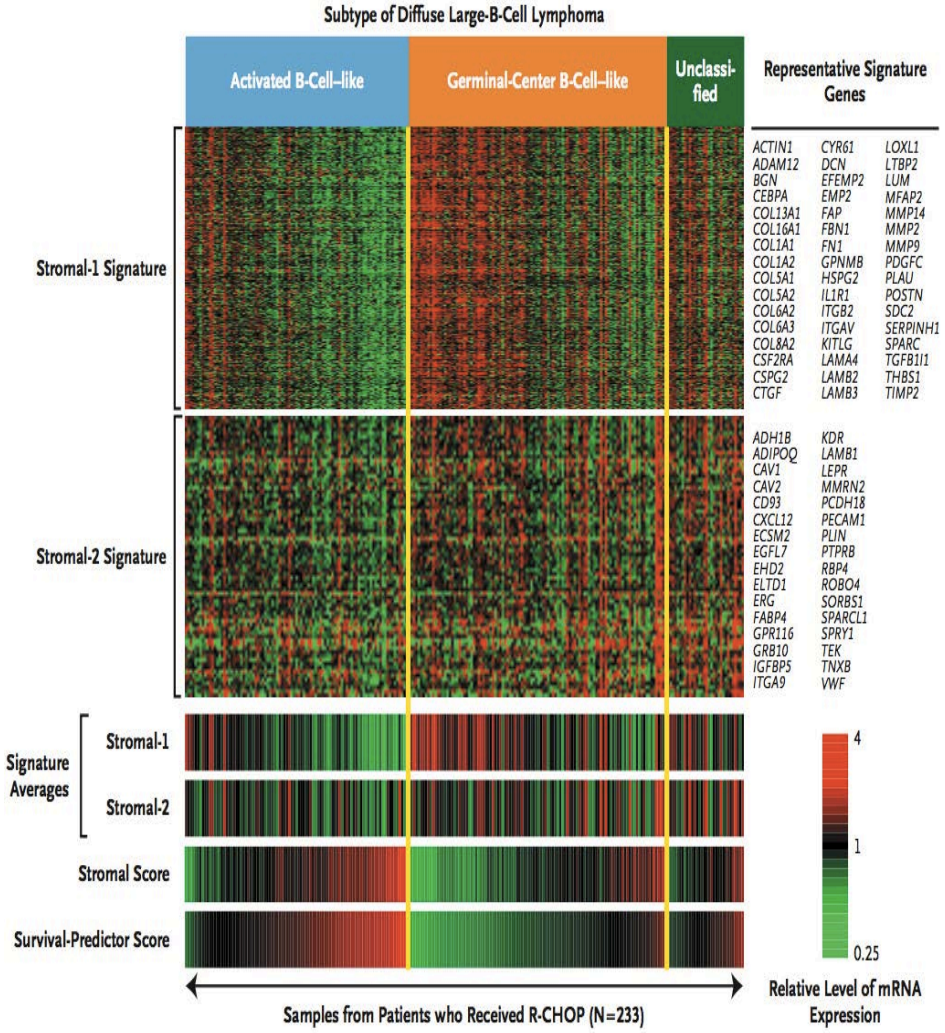

c
Low clinical risk patients
GC B-like
14 patients, 3 deaths
Activated B-like
10 patients, 6 deaths
P=0.05
Probability
1.0
0.5
0.0
0 2 4 6 8 10 12
Overall survival (years)



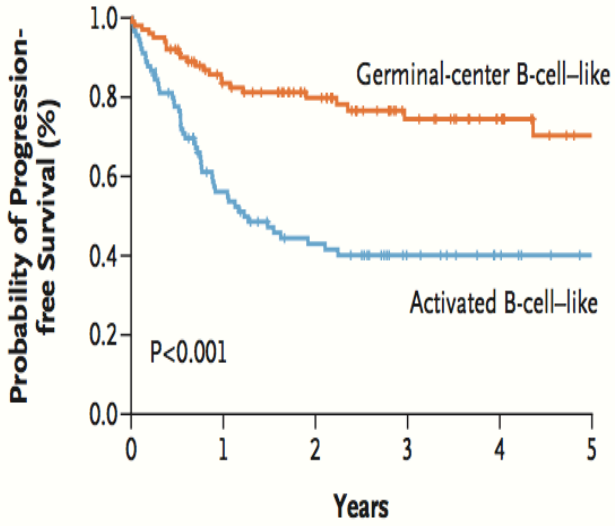


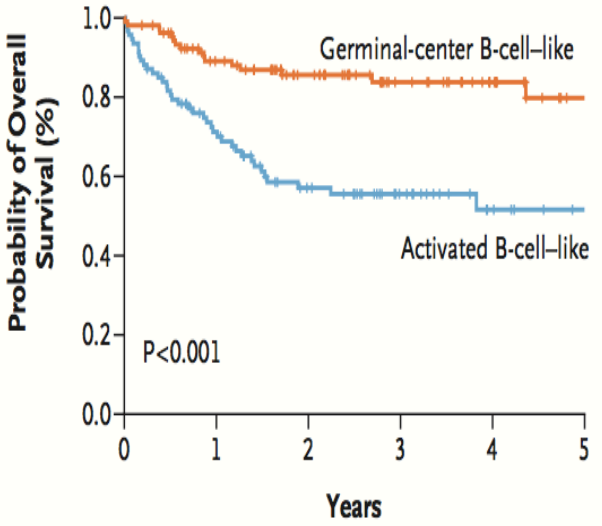


Rosenwald A et.al, The Journal of Experimental Medicine, Volume 198, Number 6, September 15, 2003 851–862



A





No. at Risk

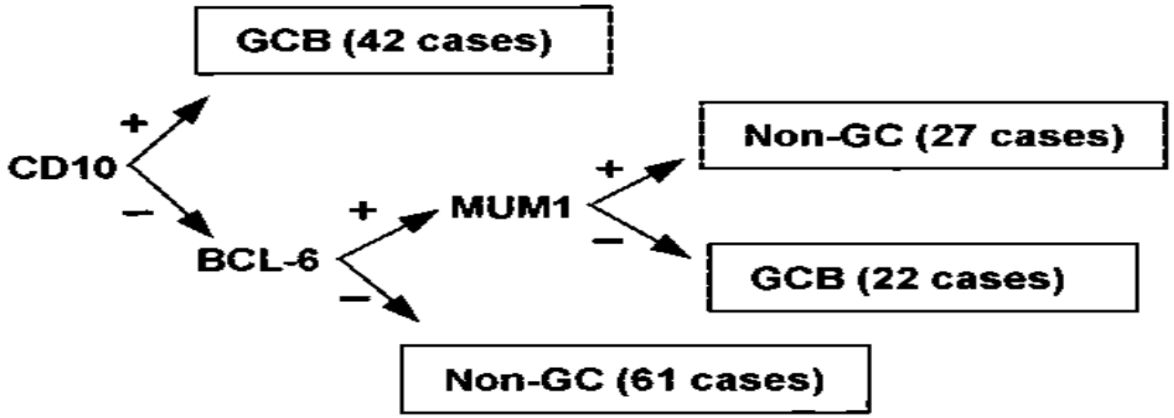
Germinal-center B-cell–like	107	82	61	39	27	15	101	74	56	35	24	14
Activated B-cell–like	93	60	38	23	11	6	90	45	30	17	10	5

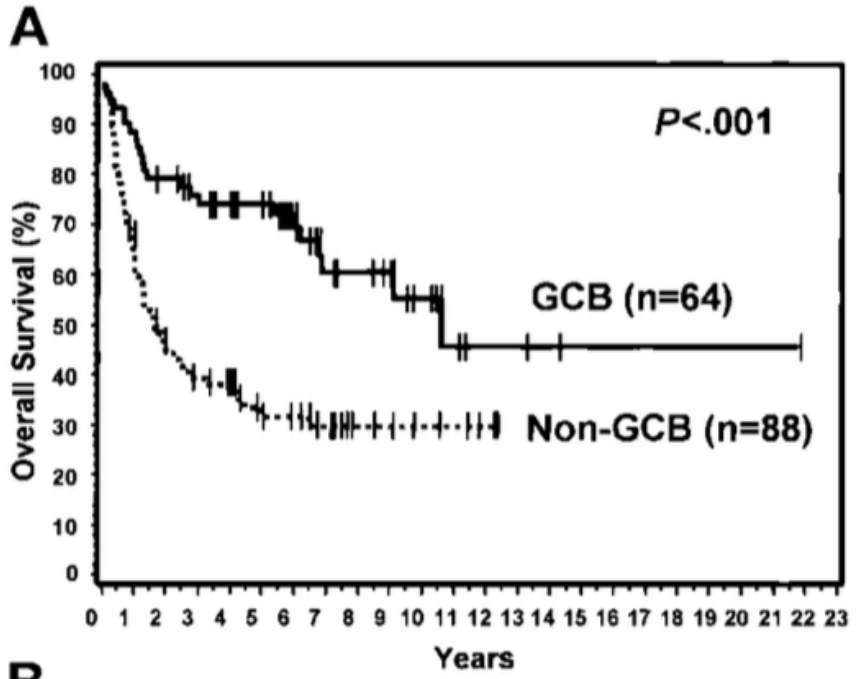
IPI'den bağımsız

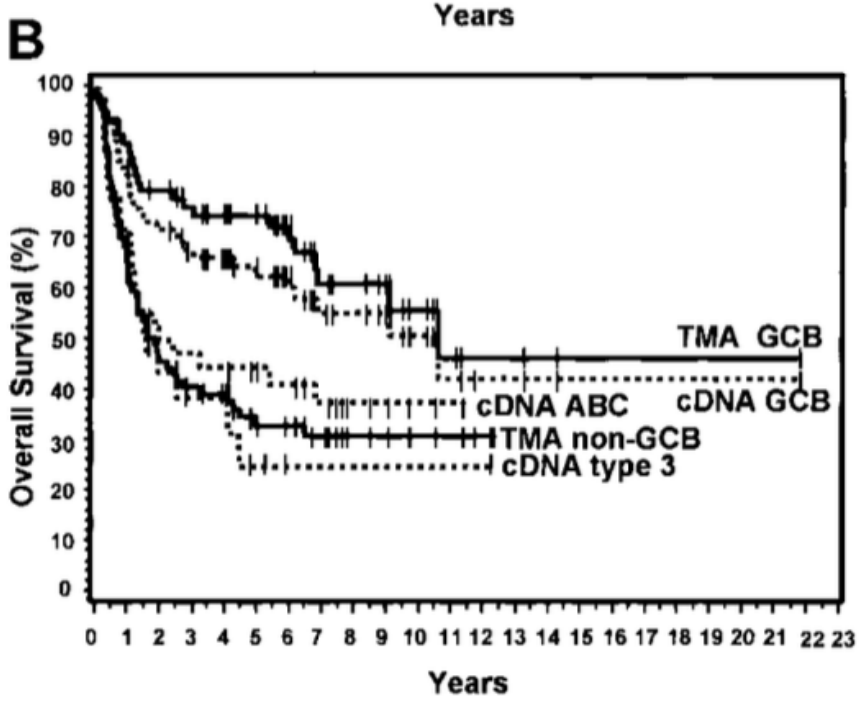
Lenz G, Wright G, Dave SS, et al., N Engl J Med. 2008;359(22):2313-2323.

	No. (%)	5-y OS, % (95% CI)	P*	5-y EFS, % (95% CI)	P*
CD10					
Negative	110 (72)	44 (34-53)	.019	47 (37-57)	.89
Positive	42 (28)	74 (60-87)		51 (35-68)	
Bcl-6					
Negative	67 (44)	30 (18-42)	< .001	35 (22-49)	.013
Positive	85 (56)	69 (59-79)		57 (46-68)	
MUM1					
Negative	80 (53)	66 (55-76)	.009	62 (51-74)	.003
Positive	71 (47)	36 (24-48)		31 (19-43)	
Cyclin D2					
Negative	133 (87)	58 (45-71)	< .001	54 (44-63)	< .001
Positive	19 (13)	11 (0-26)		7 (0-20)	
Bcl-2					
Negative	76 (50)	55 (43-66)	.17	54 (42-67)	.17
Positive	76 (50)	50 (38-61)		42 (30-55)	
FOXP1					
Negative	57 (39)	58 (45-71)	.29	52 (38-66)	.25
Positive	90 (61)	50 (39-61)		48 (36-59)	
TMA					
GCB	64 (42)	76 (66-87)	< .001	63 (50-76)	.007
Non-GCB	88 (58)	34 (24-45)		36 (25-47)	
IPI score					
0-2	84 (66)	68 (58-78)	< .001	65 (54-76)	< .001
3-5	44 (34)	31 (17-45)		23 (9-37)	

*P values were determined by comparing survival distributions using the log-rank test.







Hans, CP. Blood. 2004;103(1):275-282.

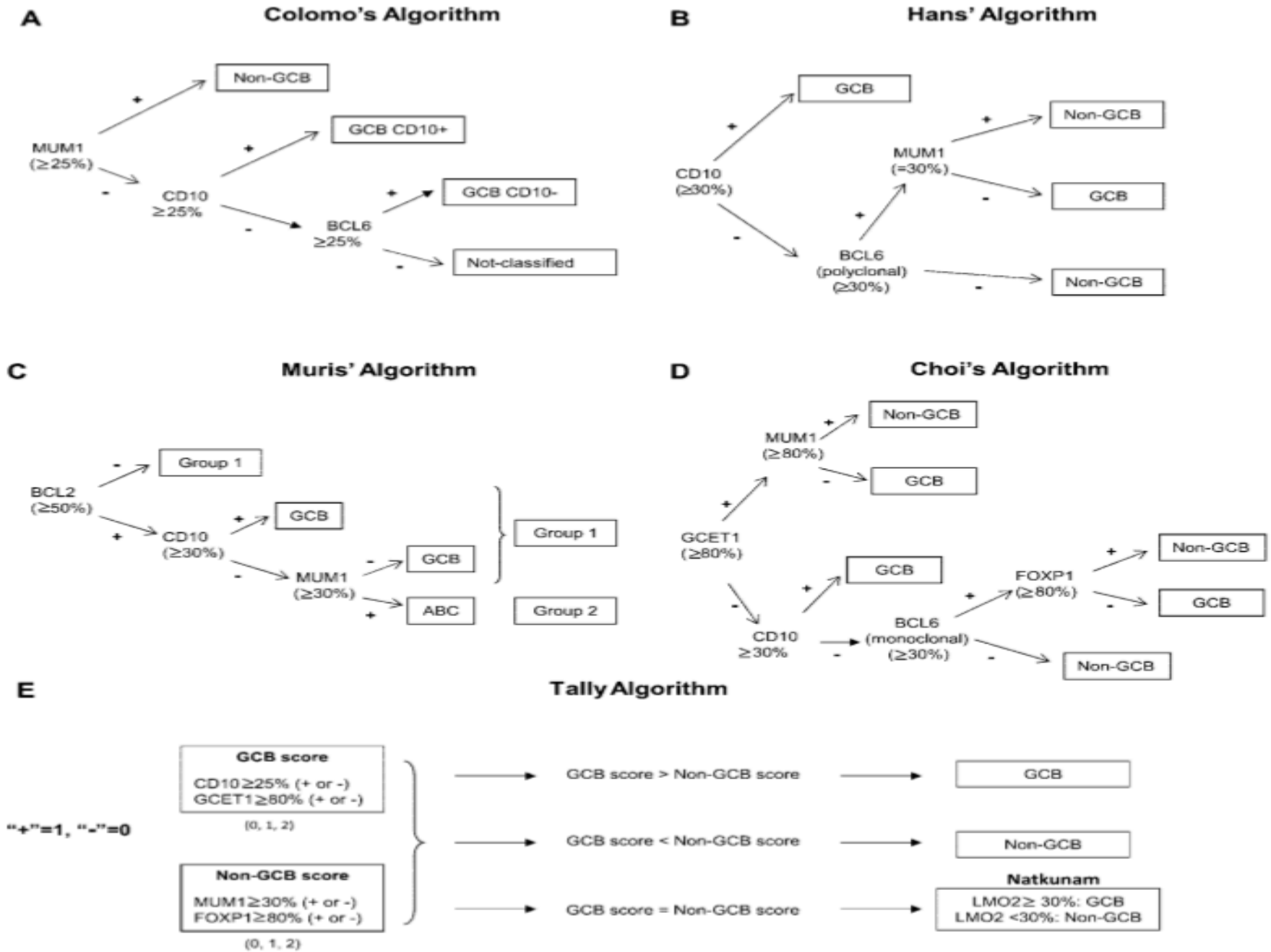


Figure 2. Five immunostaining algorithms used to assess differentiation profile (GCB vs non-GCB) in patients with DLBCL.

Study	Algorithm	N	N (GEP)	Concordance for GC type	GC Sens	GC Spec	GC PPV	GC NPV
Hans	Hans	152	142	NA	71%	NA	87	NA
Choi (training)	Choi	84	84	93	96	89	92	94
	Hans	84	84	86	81	92	93	79
Choi (validation)	Choi	63	63	93	100	85	88	100
Meyer	Choi	169	169	87	95	89	89	85
	Choi*	169	169	87	85	89	89	85
	Hans	169	169	86	82	90	90	82
	Hans*	171	171	87	90	83	85	88
	Tally	170	170	93	86	99	99	87
Visco	Hans	431	431	87.2	NA	NA	NA	NA
	Choi	431	431	90	NA	NA	NA	NA
	Visco-3	431	431	92.6	NA	NA	NA	NA
	Visco-4	431	431	92.8	NA	NA	NA	NA
Collie	Visco Young	63	63	93.6	84.6	100	100	90.2
	Hans	63	63	92.1	88.5	94.6	92	92.1
	Choi	63	63	96.8	96.2	97.3	96.2	97.3
	Tally	63	63	95.2	92.3	97.3	96	94.7

Hans et al *Blood* 2004, Choi et al *Clin Cancer Res* 2009, Meyer et al *J Clin Oncol* 2011, Visco et al *Leukemia* 2011, Collie et al. *Br J Haematol* 2014

Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy

*Gonzalo Gutiérrez-García,[1] *Teresa Cardesa-Salzmann,[1] Fina Climent,[2] Eva González-Barca,[2] Santiago Mercadal,[2] José L. Mate,[3] Juan M. Sancho,[3] Leonor Arenillas,[4] Sergi Serrano,[4] Lourdes Escoda,[5] Salomé Martínez,[5] Alexandra Valera,[1] Antonio Martínez,[1] Pedro Jares,[1] Magdalena Pinyol,[1] Adriana García-Herrera,[1] Alejandra Martínez-Trillos,[1] Eva Giné,[1] Neus Villamor,[1] Elías Campo,[1] Luis Colomo,[1] and Armando López-Guillermo,[1] for the Grup per l'Estudi dels Limfomes de Catalunya I Balears (GELCAB)

[1]Departments of Hematology and Pathology, Hospital Clínic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [2]Hospital Duran i Reynals, Hospitalet de Llobregat, Spain; [3]Hospital Germans Trias I Pujol, Badalona, Spain; [4]Hospital del Mar, Barcelona, Spain; and [5]Hospital Joan XXIII, Tarragona, Spain

Diffuse large B-cell lymphomas (DLBCLs) can be divided into germinal-center B cell–like (GCB) and activated-B cell–like (ABC) subtypes by gene-expression profiling (GEP), with the latter showing a poorer outcome. Although this classification can be mimicked by different immunostaining algorithms, their reliability is the object of controversy. We constructed tissue microarrays with samples of 157 DLBCL patients homogeneously treated with immunochemotherapy to apply the following algorithms: Colomo (MUM1/IRF4, CD10, and BCL6 antigens), Hans (CD10, BCL6, and MUM1/IRF4), Muris (CD10 and MUM1/IRF4 plus BCL2), Choi (GCET1, MUM1/IRF4, CD10, FOXP1, and BCL6), and Tally (CD10, GCET1, MUM1/IRF4, FOXP1, and LMO2). GEP information was available in 62 cases. The proportion of misclassified cases by immunohistochemistry compared with GEP was higher when defining the GCB subset: 41%, 48%, 30%, 60%, and 40% for Colomo, Hans, Muris, Choi, and Tally, respectively. Whereas the GEP groups showed significantly different 5-year progression-free survival (76% vs 31% for GCB and activated DLBCL) and overall survival (80% vs 45%), none of the immunostaining algorithms was able to retain the prognostic impact of the groups (GCB vs non-GCB). In conclusion, stratification based on immunostaining algorithms should be used with caution in guiding therapy, even in clinical trials. (*Blood*. 2011;117(18):4836-4843)

BLOOD RESEARCH
VOLUME 48 · NUMBER 4
December 2013
ORIGINAL ARTICLE

Prognostic value of immunohistochemical algorithms in gastrointestinal diffuse large B-cell lymphoma

Hee Sang Hwang[1], Dok Hyun Yoon[2], Cheolwon Suh[2], Chan-Sik Park[1], Jooryung Huh[1]

Departments of [1]Pathology, [2]Oncology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Background

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous clinicopathological entity, and its molecular classification into germinal center B cell-like (GCB) and activated B cell-like (ABC) subtypes using gene expression profile analysis has been shown to have prognostic significance. Recent attempts have been made to find an association between immunohistochemical findings and molecular subgroup, although the clinical utility of immunohistochemical classification remains uncertain.

Methods

The clinicopathological features and follow-up data of 68 cases of surgically resected gastrointestinal DLBCL were analyzed. Using the immunohistochemical findings on tissue microarray, the cases were categorized into GCB and non-GCB subtypes according to the algorithms proposed by Hans, Muris, Choi, and Tally.

Results

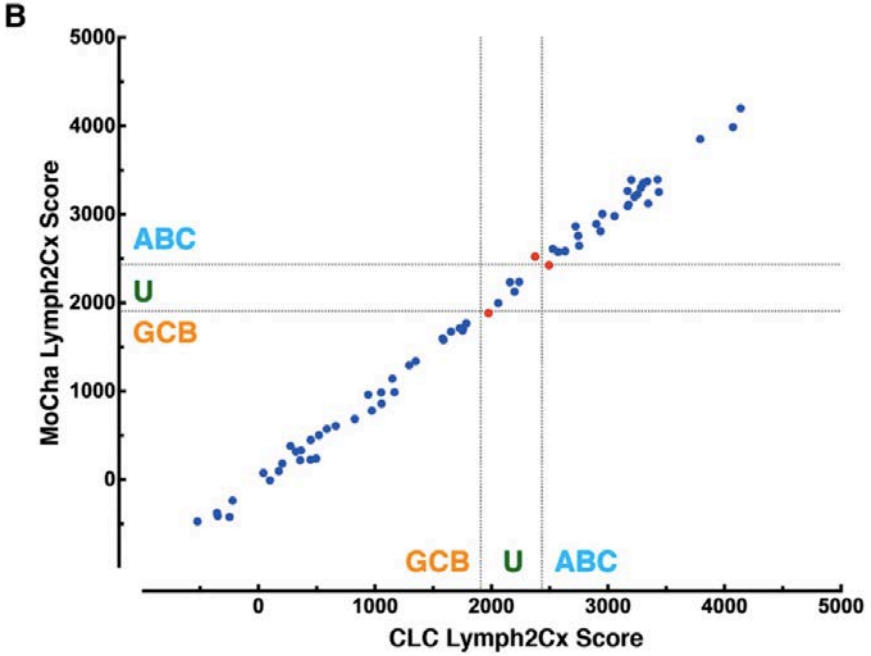
The median patient age was 56 years (range, 26–77 years). Of the 68 cases included, 39.7% (27/68) involved the stomach, and 60.3% (41/68) involved the intestines. The GCB and non-GCB groups sorted according to Hans, Choi, and Tally algorithms, but not the Muris algorithm, were closely concordant (Hans vs. Choi, $\kappa=0.775$, $P<0.001$; Hans vs. Tally, $\kappa=0.724$, $P<0.001$; Choi vs. Tally, $\kappa=0.528$, $P<0.001$). However, there was no prognostic difference between the GCB and non-GCB subtypes, regardless of the algorithm used. On univariate survival analyses, international prognostic index risk group and depth of tumor invasion both had prognostic significance.

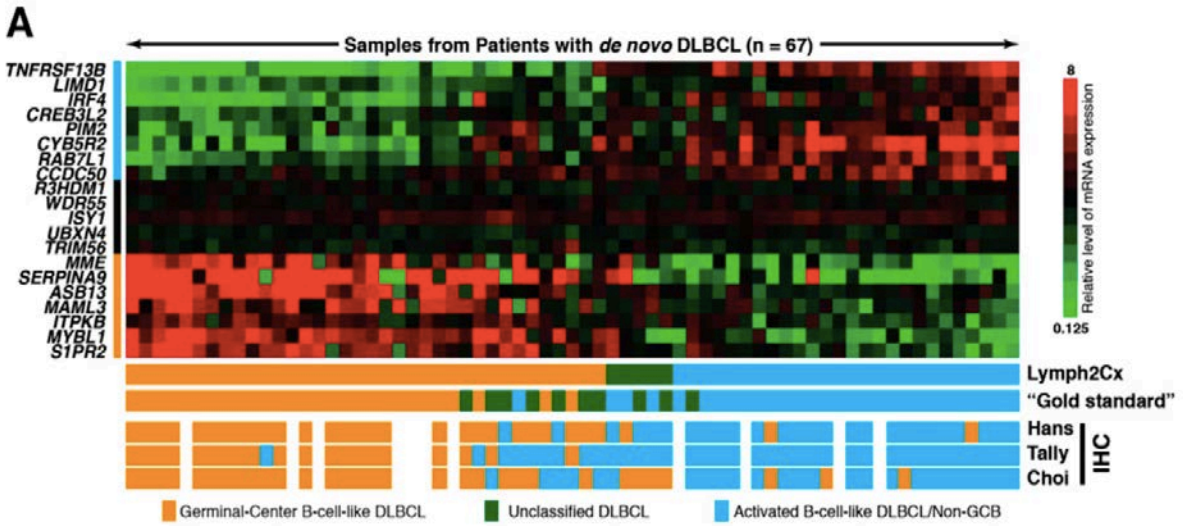
Conclusion

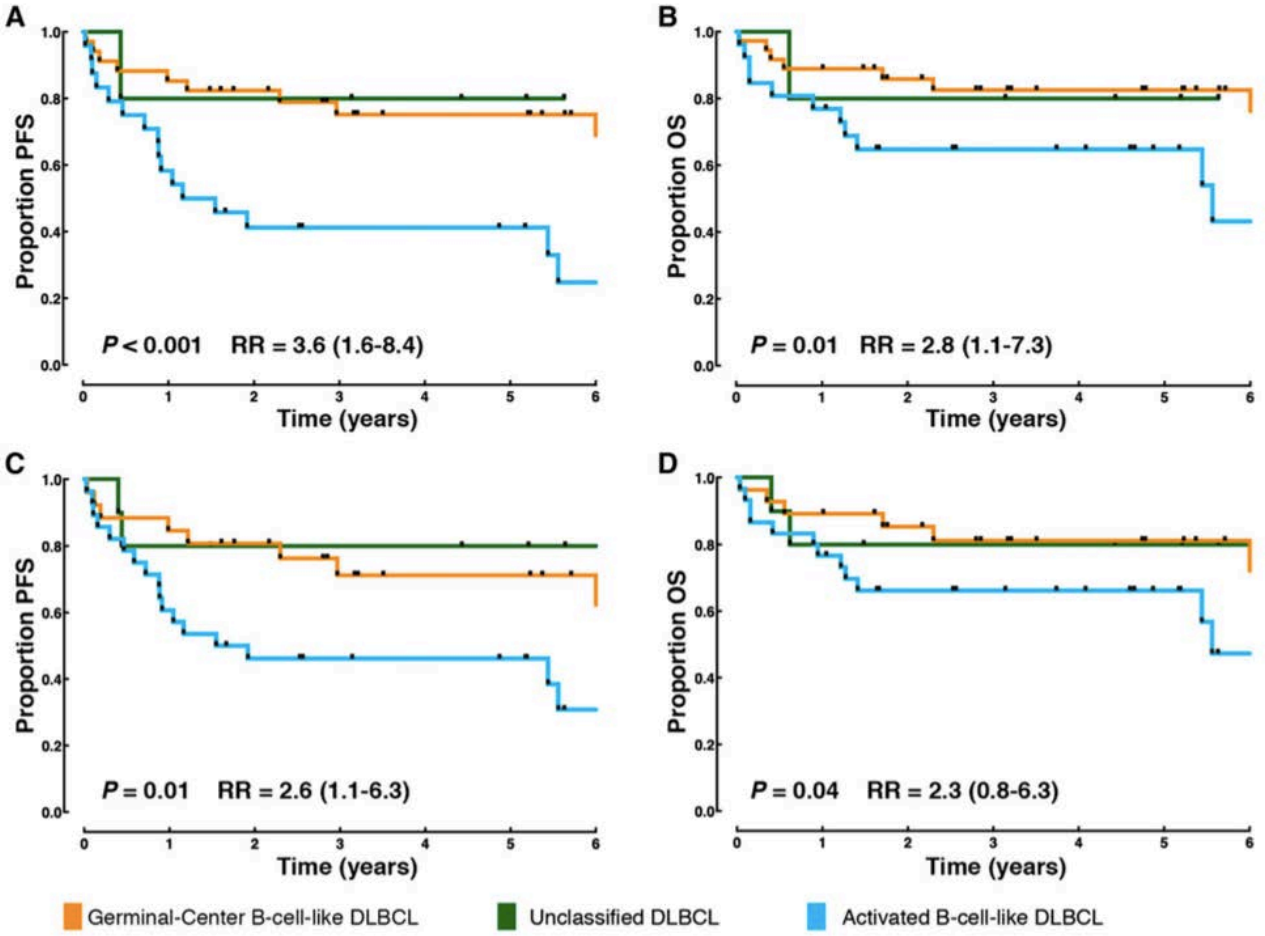
The Hans, Choi, and Tally algorithms might represent identical DLBCL subgroups, but this grouping did not correlate with prognosis. Further studies may delineate the association between immunohistochemical subgroups and prognosis.

İmmünohistokimyasal Algoritmalar

- 3 veya 5 boyalı algoritmalar kullanılabiliyor.
- GEP ile korelasyonu çoğu çalışmada iyi.
- Avantaj: Rutin kullanımda kolayca uygulanabiliyor.
- Dezavantaj: Standardizasyonun olmaması, subjektif değerlendirme.

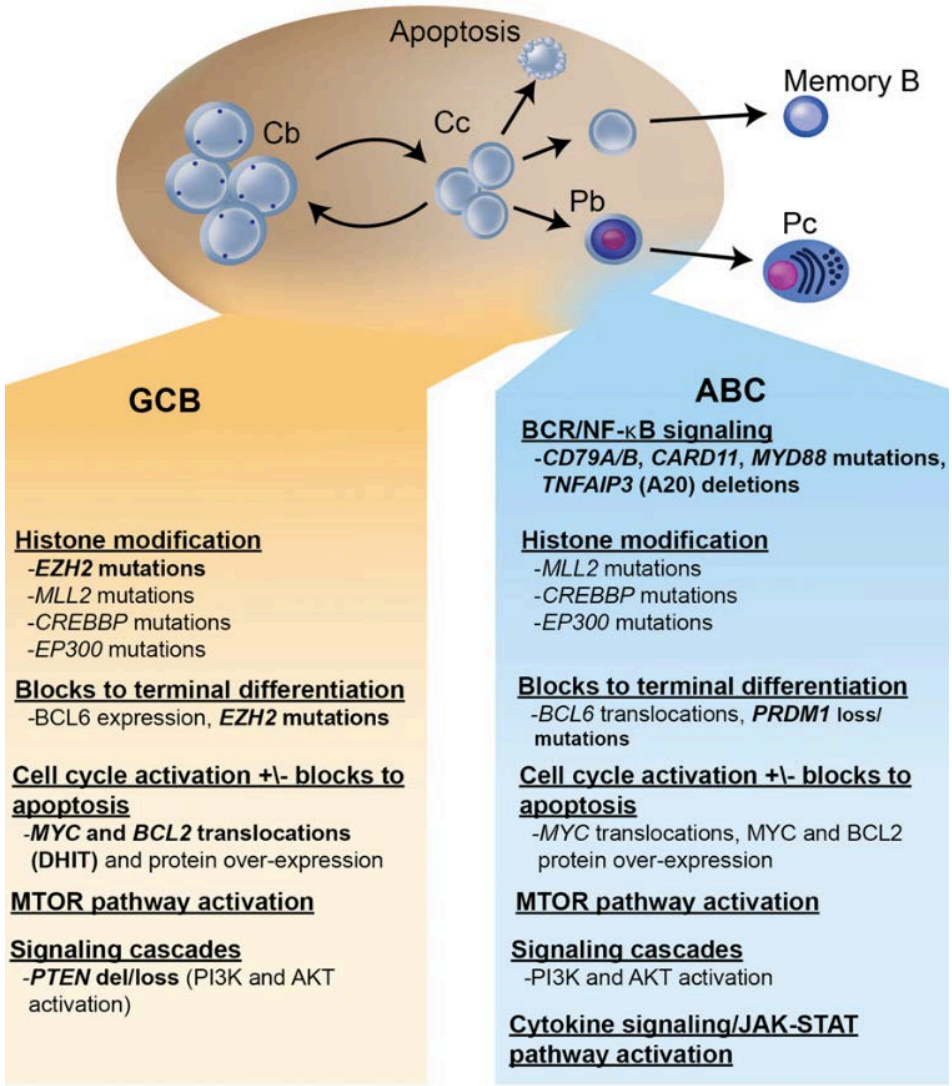






(Nanostring) Lymph2Cx 20 gen, kontrol laboratuarları ile yüksek uyum, hızlı sonuç, parafin blok

Scott DW et.al, Blood. 2014;123(8):1214-1217

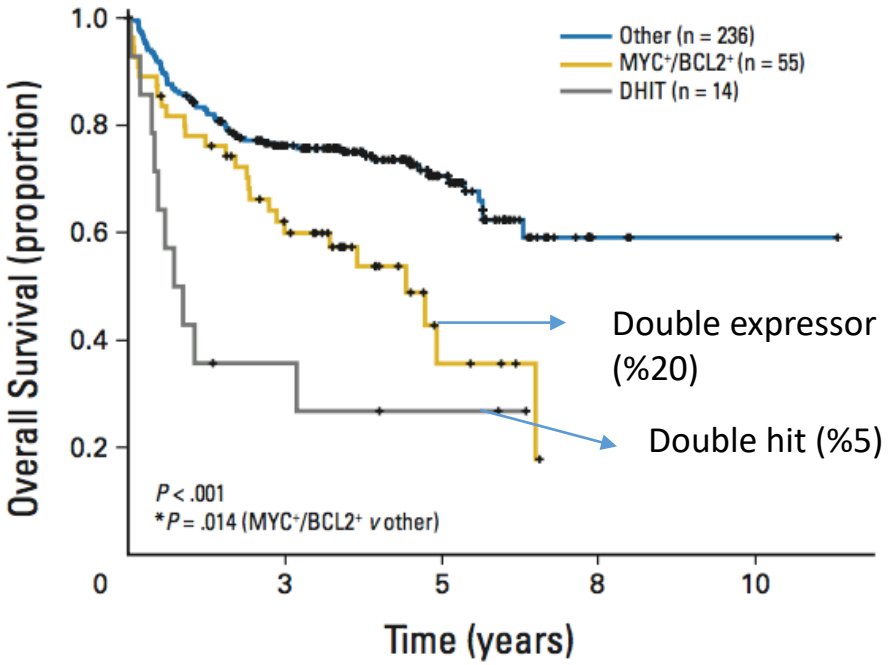


Camicia et al. Molecular Cancer (2015) 14:207, Sandoval et.al, Current Cancer Drug Targets, 2016, 16, 305-322, Sehn, LH et.al, Blood. 2015 Jan 1;125(1):22-32

Molecular subtype	Immuno phenotype	Presume d cell of origin	Diagnostic molecular features	Etiology	Frequency[a]	Clinical features
GCB-DLBCL	CD20, CD10, CD22, (CD30), (BCL2), (MYC), BCL6, GCET, HGAL, LMO2, PTEN$^{+/-}$, IRF4^{-}, FOX $^{-}$,	Germinal center B-cell	Gene expression profiling	Unknown	~17 %	Median age 61 Gender dominance: male ≥ female Nodal and extranodal Bone marrow involvement: ~ 15 % Survival ~ 60 % at 5 years Curable ~ 50 %
ABC-DLBCL	CD20, CD22, (CD30), (CD79A/B), IRF4, FOXP1, (BCL2), (MYC), BCL6$^{+/-}$, GCET^{-}, LMO2^{-},	Post-germinal center B- cell	Gene expression profiling	Unknown	~15 %	Median age: 66 Gender dominance: male ≥ female Nodal and extranodal Bone marrow involvement: ~ 15 % Survival ~ 40 % at 5 years Curable ~30 %

DLBCL Subtype	Cellular Origin (GEP)	Oncogenic Mutations/Pathways	IHC	3 Year-PFS	3 Year-OS
GCB	Germinal center-B cell	EZH2 mutations BCL-2 translocation PI3K/Atk/mTOR activation PTEN deletion Loss of PTEN expression BCL-6 mutations c-rel amplification	GCET (-) CD10 (+) GCET (+) MUM1 (-) GCET (-) CD10 (-) BCL6 (+) FOXP1 (-)	67%-74%*#§	80-85%*#§
ABC	Post-germinal B cell	BCR/NF-kB activation CD79B mutations CARD11 mutations MYD88 mutations TNFAIP3 mutations	GCET (+) MUM1 (+) GCET (-) CD10 (-) BCL6 (-) GCET (-) CD10 (-) BCL6 (+) FOXP1 (+)	40%-52%*#§	45%-69%*#§
PMBL	Thymic B cell	9p24 amplification JAK-STAT activation CIITA translocations REL amplification PDL-1/PDL-2 overexpression	CD20 (+) CD79a (+) PAX5 (+) OCT2 (+) BOB1 (+) CD30 (+ dim) sIg (-),CD15 (-)	86% (with RT)* 93%¶δ	97%¶δ

*R-CHOP like regimens. #Lentz *et al.* 2008. § Fu *et al.* 2008. ¶ At 5 years with DA EPOCH-R regimen. δ Dunleavy *et al.* 2013. Abbreviations: DLBCL, diffuse large B-cell lymphoma; GEP, gene expression profile; IHC, immunohistochemistry; PFS, progression-free survival; OS, overall survival; GCB, germinal center B-cell, ABC, activated B-cell, PMBL, primary mediastinal B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab.



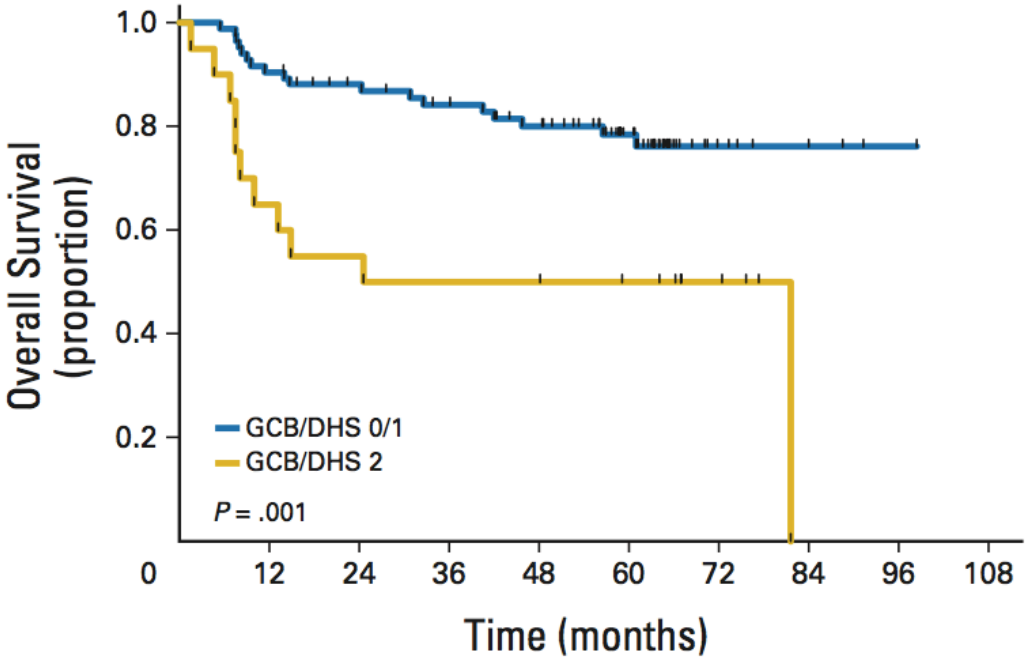
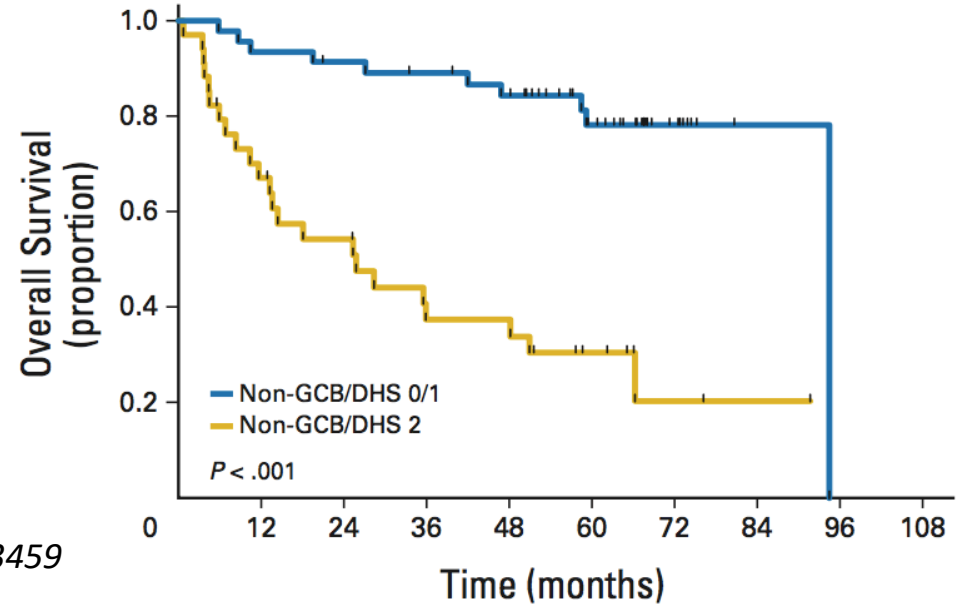


Table 2. Multivariate Analysis of DHS, IPI, and COO Subtype With Progression-Free Survival and Overall Survival in Patients With DLBCL Treated With R-CHOP

	Overall Survival			Progression-Free Survival		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
DHS 2	4.06	2.44 to 6.76	< .001	2.79	1.78 to 4.37	< .001
IPI score of 3-5	2.75	1.64 to 4.60	< .001	2.72	1.72 to 4.29	< .001
Non-GCB	1.08	0.64 to 1.82	.783	1.04	0.65 to 1.67	.876

Abbreviations: COO, cell-of-origin subtype; DHS, double-hit score; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; IPI, International Prognostic Index; non-GCB, non–germinal center B-cell–like; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone.

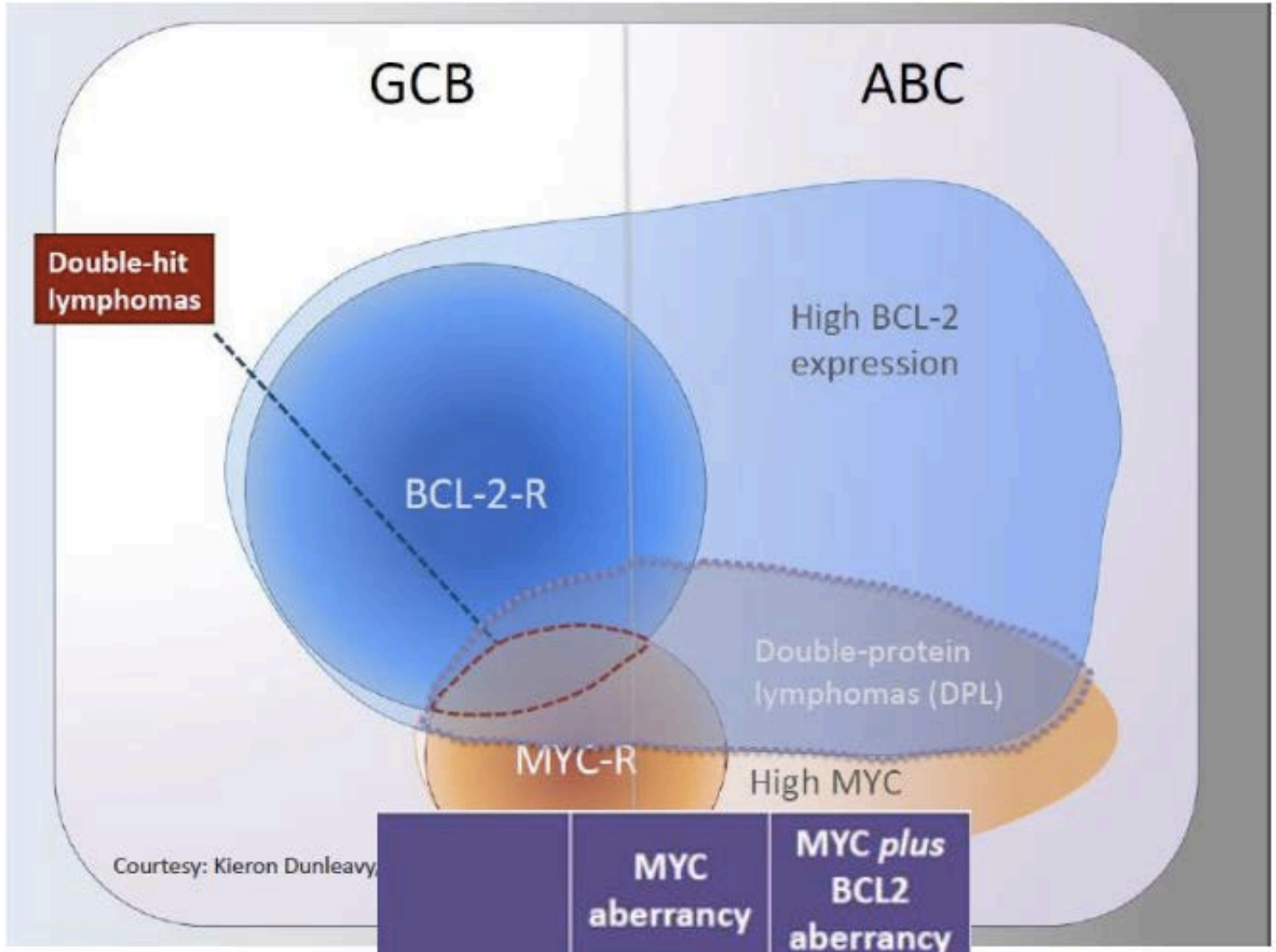


Green et.al, *J Clin Oncol 30:3460-3467, Johnson et.al,J Clin Oncol 30:3452-3459*

Reference*	Frequency (type of lymphomas studied)†	% GC based on GEP or phenotype	Therapy‡	Significant impact on overall survival‡	Mitigating factors	Impact of MYC expression alone on survival
Johnson et al, 2012[18]	19% (DLBCL)	24%	R-CHOP	Adverse	None reported	None
Green et al, 2012[19]	29% (DLBCL)	37%	R-CHOP	Adverse	None reported	None
Hu et al, 2013[17]	34% (DLBCL)	34%	R-CHOP	Adverse	None reported	None
Dunleavy et al, 2013[56]	20%§ (DLBCL, includes 33% HIV+)	42%	DA-EPOCH-R or short course EPOCH-RR	None	None reported	None
Perry et al, 2014[47]	27% (DLBCL)	64%	R-CHOP or CHOP-like	Adverse	No effect in non-GC group	"Intermediate" overall survival
Friedberg et al, 2014[55]	20% (advanced stage DLBCL)	N/A	R-CHOP + iodine-131 tositumomab	None	None reported	N/A

Study	N	BCL2 cutoff	MYC cutoff	% DE	%DE that are GCB	%DE that are ABC/nonGC	% DH that are GCB	% DH that are ABC
Green *J Clin Oncol* 2012*	193	70%	40%	29%	37%	67%	91%	9%
Johnson *J Clin Oncol* 2012*	291	50%	40%	19%	24%	76%	64%	36%
Hu *Blood* 2013*	466	70%	40%	34%	34%	66%	NA	NA
Perry *Br J Haematol* 2014*	106	30%	50%	44%	64%	36%	NA	NA
Scott *J Clin Oncol* 2015†	339	50%	40%	31%	39%	61%	100%	0%

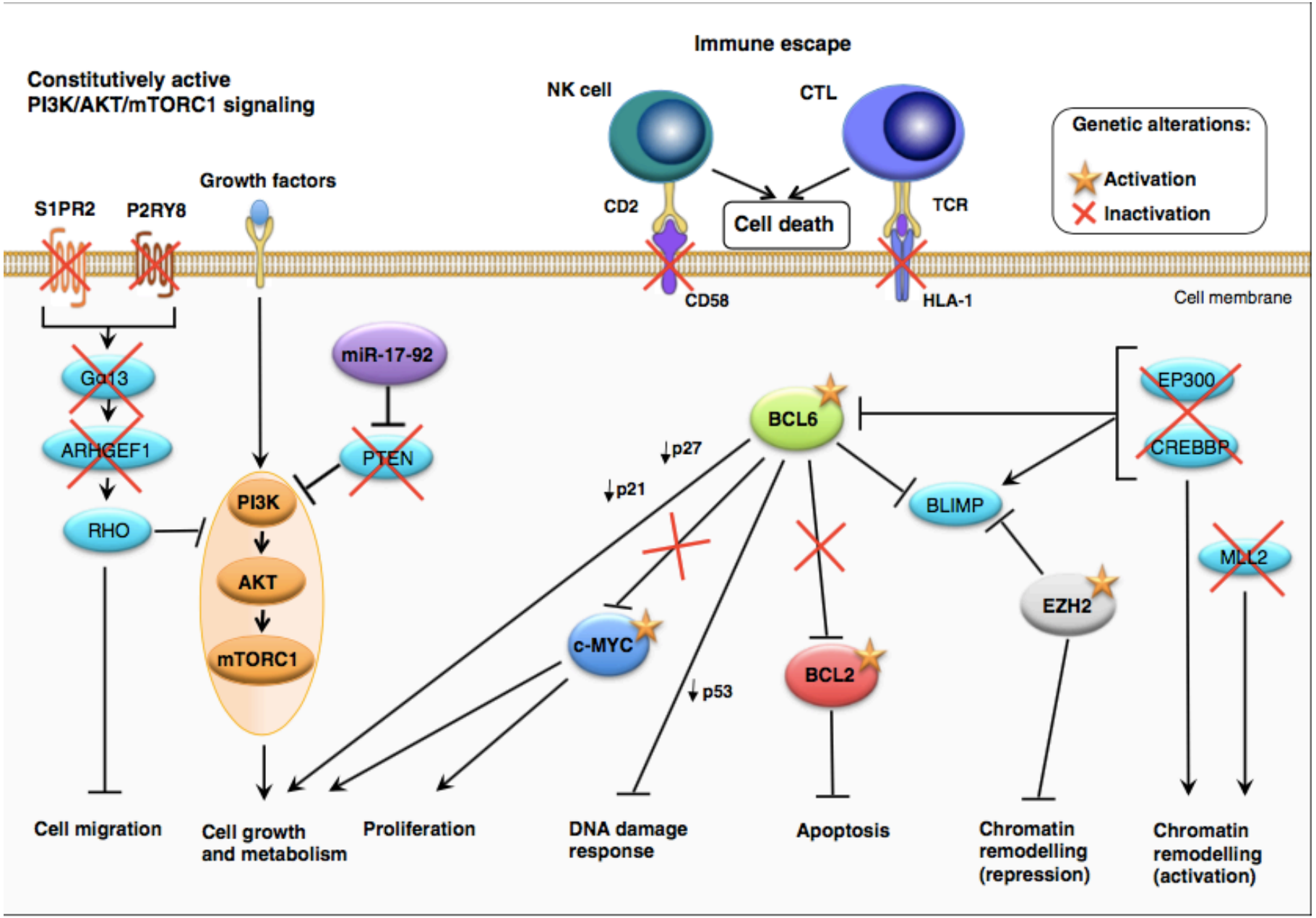
DLBHL'lerin yaklaşık %20-30'u double ekspressör. Double ekspressörlerin çoğu non-GCB, double hitlerin çoğu GCB



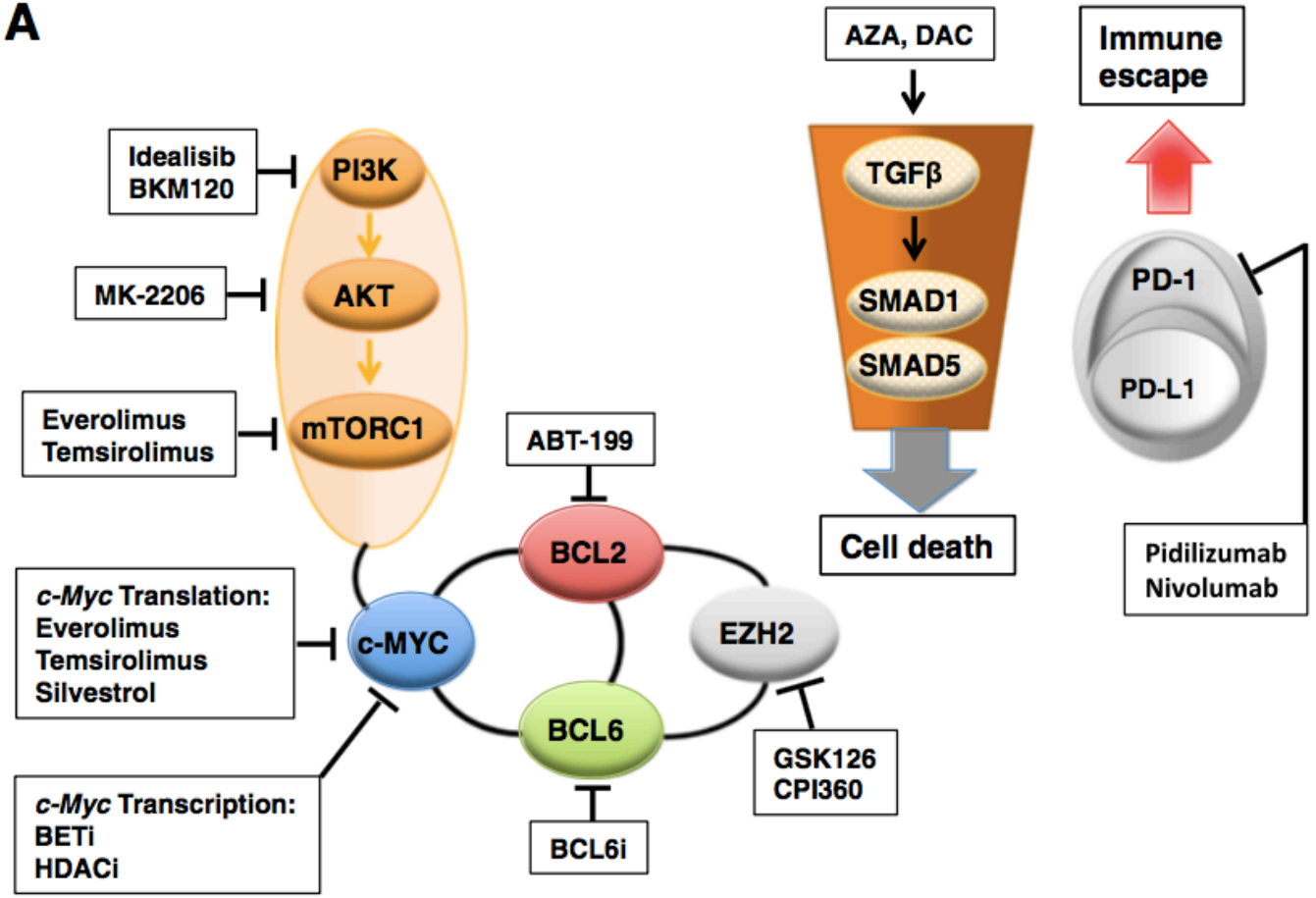
	MYC aberrancy	MYC *plus* BCL2 aberrancy
IHC	37%	26%
FISH	12%	8%

% of DLBCL cases

Germinal Merkez DBBHL'da hedeflenebilecek patogenetik mekanizmalar



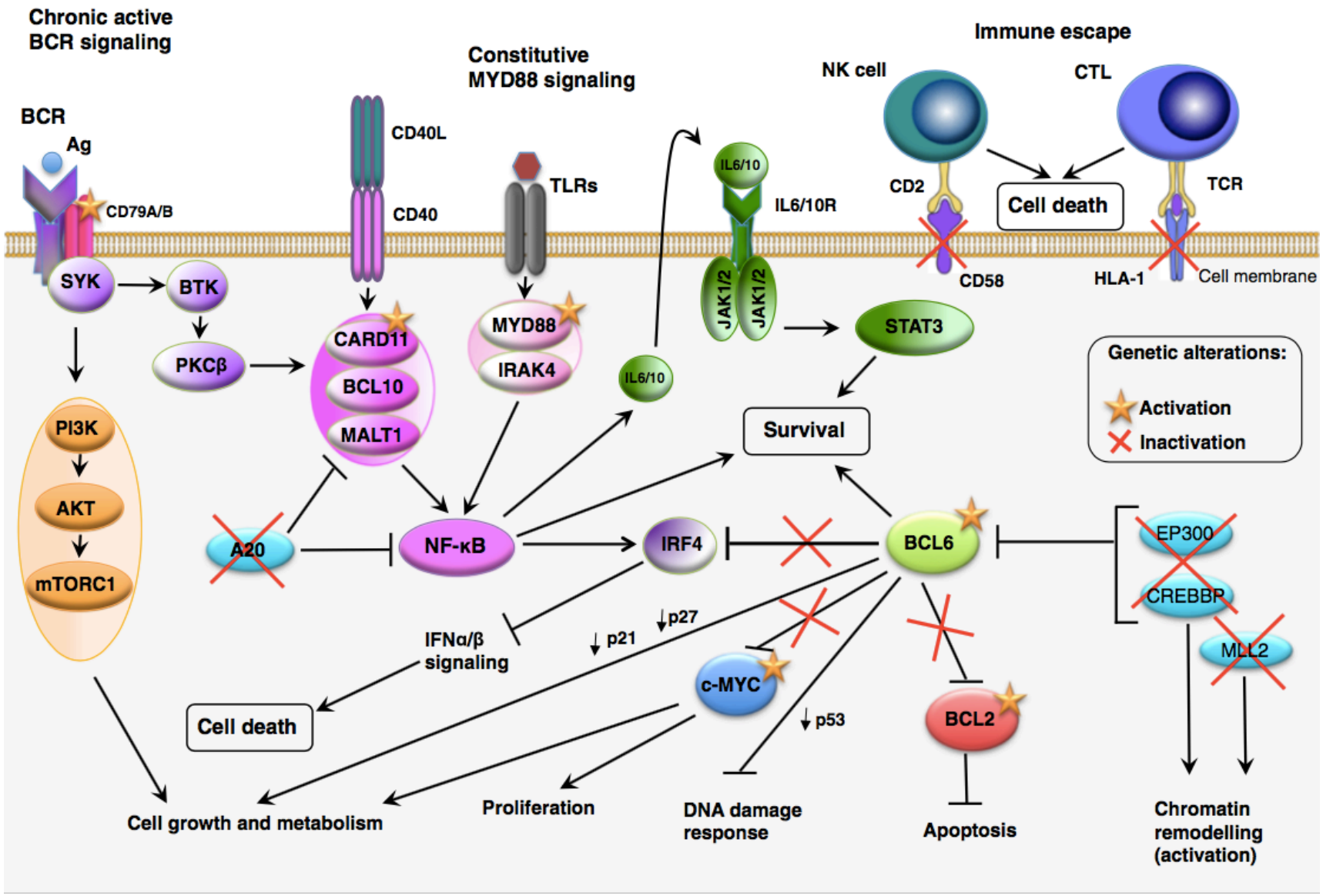
A

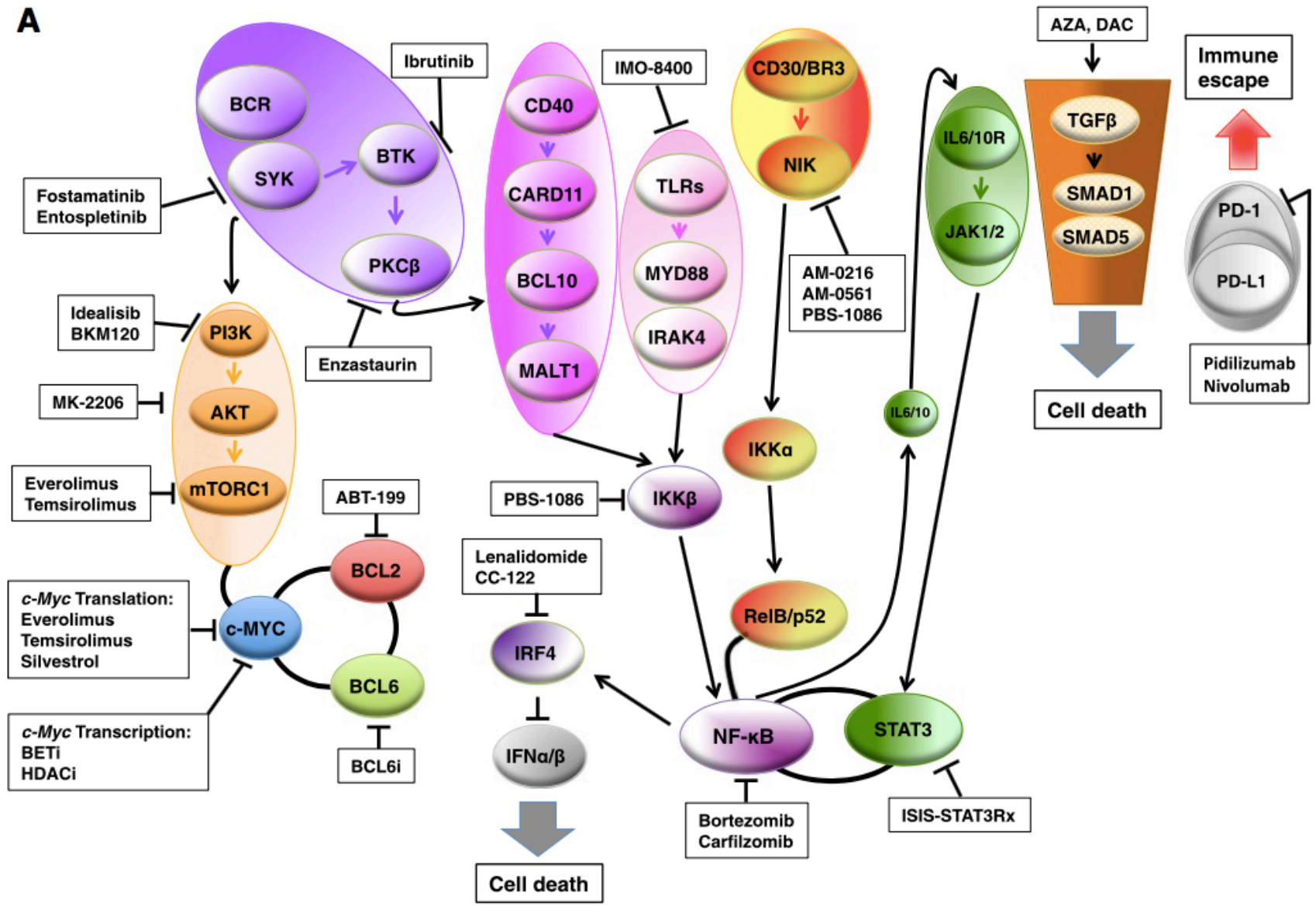


B

Pathways in GCB-DLBCL targeted by rational drug combinations:
c-MYC + BCL2
c-MYC + PI3K/AKT/mTORC1
c-MYC + EZH2
c-MYC + TGFβR/SMAD
BCL2 + PI3K/AKT/mTORC1
BCL2 + EZH2
BCL2 + TGFβR/SMAD
EZH2 + PI3K/AKT/mTORC1
EZH2 + TGFβR/SMAD
PI3K/AKT/mTORC1 + TGFβR/SMAD
PD-1/PD-L1 + C-MYC
PD-1/PD-L1 + BCL2
PD-1/PD-L1 + PI3K/AKT/mTORC1
PD-1/PD-L1 + TGFβR/SMAD
PD-1/PD-L1 + EZH2

Germinal Merkez Dışı DBBHL'da hedeflenebilecek patogenetik mekanizmalar




A
BCR
SYK
BTK
PKCβ
Ibrutinib
Fostamatinib
Entospletinib
Enzastaurin
CD40
CARD11
BCL10
MALT1
IMO-8400
TLRs
MYD88
IRAK4
CD30/BR3
NIK
AM-0216
AM-0561
PBS-1086
IL6/10R
JAK1/2
AZA, DAC
TGFβ
SMAD1
SMAD5
Cell death
Immune escape
PD-1
PD-L1
Pidilizumab
Nivolumab
Idealisib
BKM120
PI3K
AKT
MK-2206
Everolimus
Temsirolimus
mTORC1
IL6/10
IKKα
PBS-1086
IKKβ
ABT-199
BCL2
Lenalidomide
CC-122
RelB/p52
c-Myc Translation:
Everolimus
Temsirolimus
Silvestrol
c-MYC
IRF4
BCL6
c-Myc Transcription:
BETi
HDACi
BCL6i
NF-κB
STAT3
IFNα/β
Bortezomib
Carfilzomib
ISIS-STAT3Rx
Cell death

ABC-DLBCL-specific pathways targeted by rational drug combinations

With inhibitors inhibiting a single molecular target		With dual inhibitors (simultaneously inhibiting two molecular targets i.e. with dual IKK/NIK kinase inhibitors)
BCR + NF-κB (i.e. in mutCARD11/mutMyD88 DLBCL)	NIK + BCL6	BCR + NF-κB + NIK (i.e. in mutCARD11/mutMyD88 DLBCL)
BCR + BCL2	NIK + BCR	NF-κB + NIK + BCL2
BCR + c-MYC	NIK + IRF4	NF-κB + NIK + c-MYC
BCR + PI3K/AKT/mTORC1 (i.e. in PTEN-/- DLBCL)	IRF4 + BCL2	NF-κB + NIK + IRF4
BCR + IRF4	IRF4 + c-MYC	NF-κB + NIK + PI3K/AKT/mTORC1
BCR + STAT3	IRF4 + STAT3	NF-κB + NIK + STAT3
BCR + TGFβR/SMAD	IRF4 + TGFβR/SMAD	NF-κB + NIK + TGFβR/SMAD
BCR + TLRs (i.e. in mutMyD88 DLBCL)	IRF4 + TLRs (i.e. in mutMyD88 DLBCL)	NF-κB + NIK + PD-1/PD-L1 (i.e. in HR-DLBCL)
BCR + PD-1/PD-L1 (i.e. in HR-DLBCL)	IRF4 + PD-1/PD-1L (i.e. in HR-DLBCL)	NF-κB + NIK + BCL6
NF-κB + BCL2	STAT3 + c-MYC	
NF-κB + c-MYC	STAT3 + BCL2	
NF-κB + PI3K/AKT/mTORC1	STAT3 + PI3K/AKT/mTORC1	
NF-κB + STAT3	STAT3 + c-MYC	
NF-κB + TGFβR/SMAD	STAT3 + BCL2	
NF-κB + NIK	STAT3 + TGFβR/SMAD	
NF-κB + PD-1/PD-L1 (i.e. in HR-DLBCL)	STAT3 + PD-1/PD-L1 (i.e. in HR-DLBCL)	

Germinal Merkez ve Germinal Merkez Dışı Lenfoma'da Faz 1-1b ve 2 Çalışmaları Yapılmış Ajanlar

DLBCL Molecular Subtype	Molecular Target	Targeted Therapy	No. of Patients	ORR (%)	PFS (Months)
GCB	BCL-2	ABT-199	9	33%	N/A
		ABT-199 + Rituximab	8	37.50%	N/A
	PI3K/Akt/mTOR	Idelalisib	9	0%	N/A
		Everolimus	47	30%	5.7
		Everolimus + Rituximab	24	38%	8.1
		Temserolimus	32	28%	2.4
ABC	NF-kB	Bortezomib + DA-EPOCH-R	12	83%	N/A
		Bortezomib + R-CHOP	40	88%	N/A
	BTK (BCR pathway)	Ibrutinib	7	29%	N/A
		Ibrutinib	25	40%	2.5
		Ibrutinib + R-CHOP	23	95%	N/A
	Syk (BCR pathway)	Fostamatinib	23	22%	N/A
	PKC-β (BCR pathway)	Enzastaurin	55	22%	N/A
	Immunomodulation	Lenalidomide	108	28%	2.7
		Lenalidomide	11	45%	20.5
		Lenalidomide+ Rituximab	32	28%	2.8
		Lenalidomide + R-CHOP	60	98%	NR

Germinal Merkez ve Germinal Merkez Dışı Lenfomalar'da Özellikler Patogenetik Mekanizmaları Hedef Alan Ajanlar'n Süregiden Faz 1-2 çalışmaları

Oncogenic Mutation/Pathway	DLBCL Molecular Subtype	Therapeutic Agents	Clinical Trials
EZH2	GCB	EZH2 inhibitors (*i.e.* E7438)	Ongoing phase I[91, 92]
BCL-6	GCB	BCL6 inhibitors	Preclinical trials[95]
BCL-2	GCB/ABC	BH-3 mimetics (*i.e.* ABT-199)	Phase I[104-107]
PI3K/AKT/mTOR	GCB	PI3K inhibitors (*i.e.* idelalisib, copanlisib, IPI145) mTOR inhibitors (*i.e.* everolimus, temsirolimus) AKT inhibitors (*i.e.* nelfinavir, MK-2206)	Phase I[114] Phase I/II[116,117] Phase I/II[118,119]
NF-kB pathway	ABC	Proteasome inhibitors (*i.e.* bortezomib, carfilzomib) Lenalidomide	Phase I/II and ongoing phase III[124-126,128,131] Phase I/II and ongoing phase III[159-161,165-167]
BCR pathway-BTK	ABC	BTK inhibitors (*i.e.* ibrutinib)	Phase I/II and ongoing phase III[136-139]
BCR pathway-Syk	ABC	Syk inhibitors (*i.e.* fostamatinib)	Phase I/II[144]
BCR pathway-PKC-β	ABC	PKC inhibitors (*i.e.* enzastaurin sotrastaurin)	Phase II/III[149,150]
JAK/STAT pathway	ABC	JAK2 inhibitors (*i.e.* ruxolitinib and pacritinib)	Phase I and ongoing phase II[156,157]

VOLUME 33 · NUMBER 3 · JANUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Lenalidomide Combined With R-CHOP Overcomes Negative Prognostic Impact of Non–Germinal Center B-Cell Phenotype in Newly Diagnosed Diffuse Large B-Cell Lymphoma: A Phase II Study

Grzegorz S. Nowakowski, Betsy LaPlant, William R. Macon, Craig B. Reeder, James M. Foran, Garth D. Nelson, Carrie A. Thompson, Candido E. Rivera, David J. Inwards, Ivana N. Micallef, Patrick B. Johnston, Luis F. Porrata, Stephen M. Ansell, Randy D. Gascoyne, Thomas M. Habermann, and Thomas E. Witzig

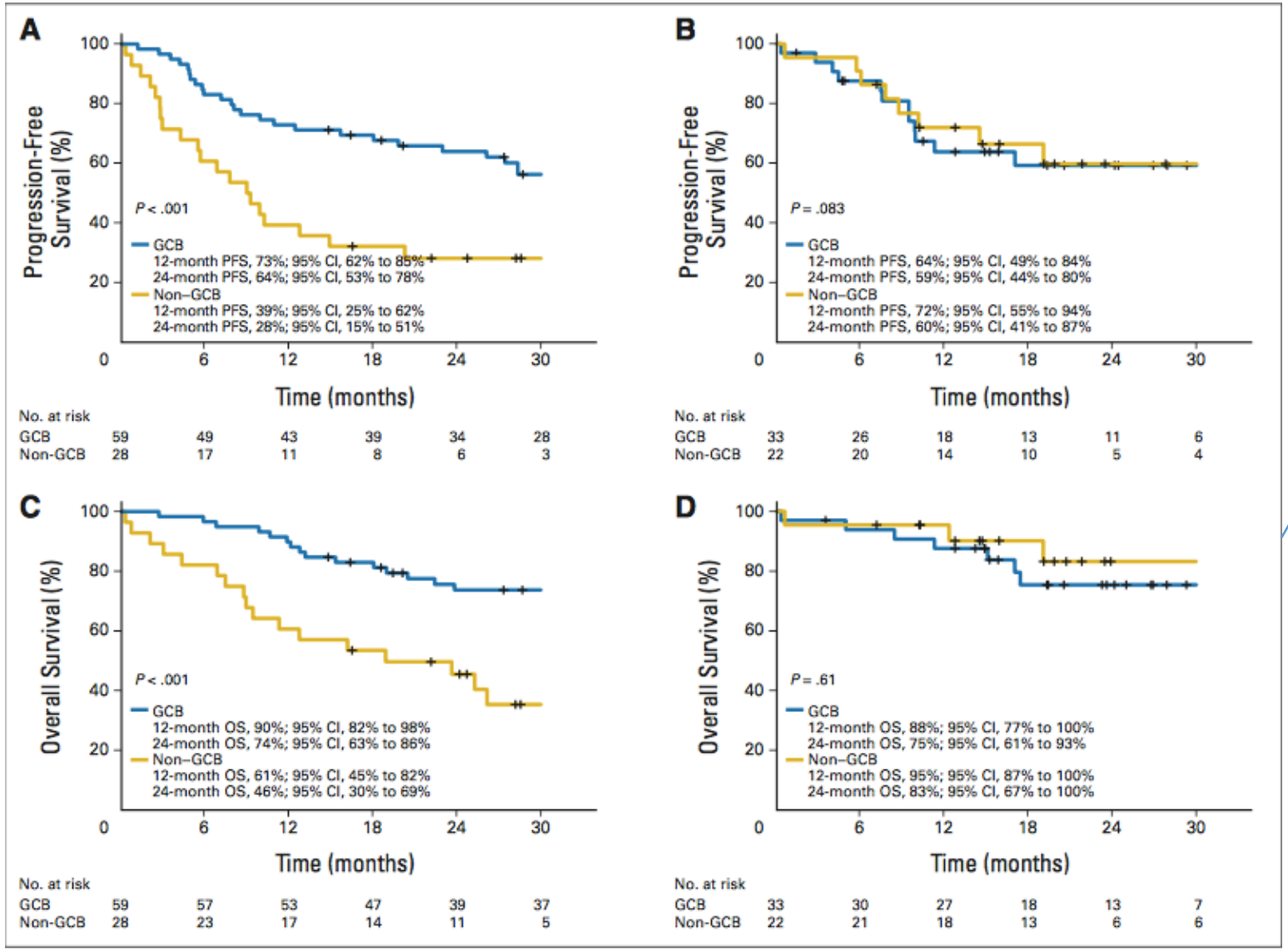


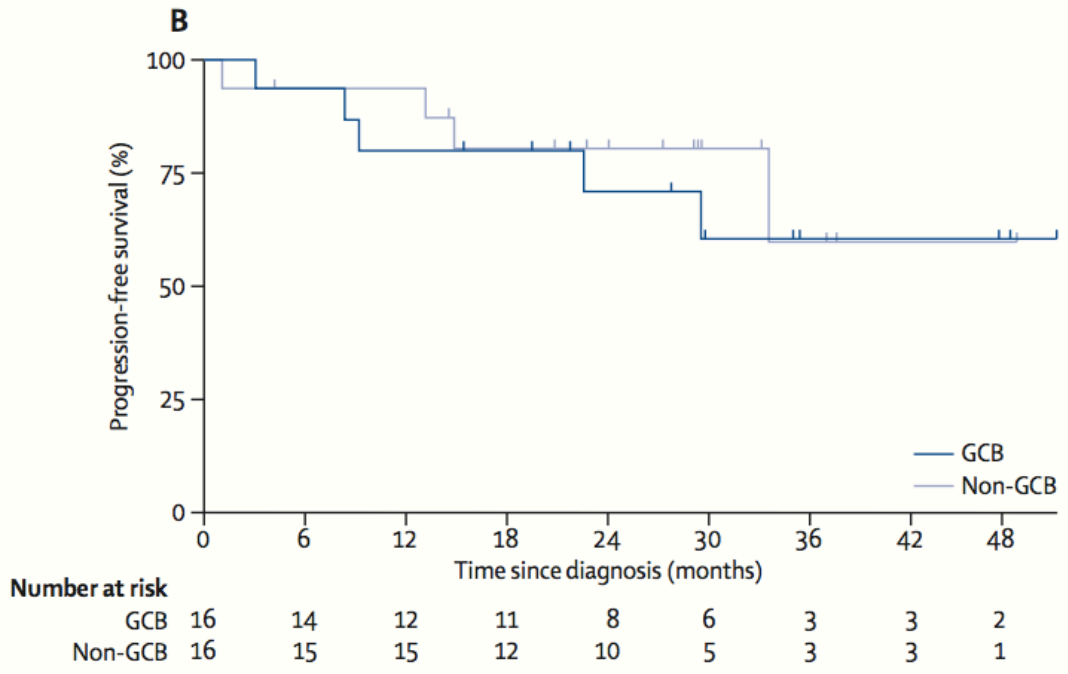
Fig 2. Outcomes of historical control patients treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) and study patients treated with R2CHOP (lenalidomide added to R-CHOP) based on germinal center B-cell (GCB) versus non-GCB diffuse large B-cell lymphoma (DLBCL) subtype. (A) Progression-free survival in patients treated with R-CHOP in non-GCB versus GCB DLBCL. (B) Progression-free survival in patients treated with R2CHOP in non-GCB versus GCB DLBCL. (C) Overall survival in patients treated with R-CHOP in GCB versus non-GCB DLBCL. (D) Overall survival of patients treated with R2CHOP in non-GCB versus GCB DLBCL.

18 yaş üzeri Evre 2-4 65 DBBHL hastası, Hans Algoritması, Lenalidomide 25 mg 1-10.gün + R-CHOP 21

Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial

Umberto Vitolo, Annalisa Chiappella, Silvia Franceschetti, Angelo Michele Carella, Ileana Baldi, Giorgio Inghirami, Michele Spina, Vincenzo Pavone, Marco Ladetto, Anna Marina Liberati, Anna Lia Molinari, Pierluigi Zinzani, Flavia Salvi, Pier Paolo Fattori, Alfonso Zaccaria, Martin Dreyling, Barbara Botto, Alessia Castellino, Angela Congiu, Marcello Gaudiano, Manuela Zanni, Giovannino Ciccone, Gianluca Gaidano, Giuseppe Rossi, on behalf of the Fondazione Italiana Linfomi

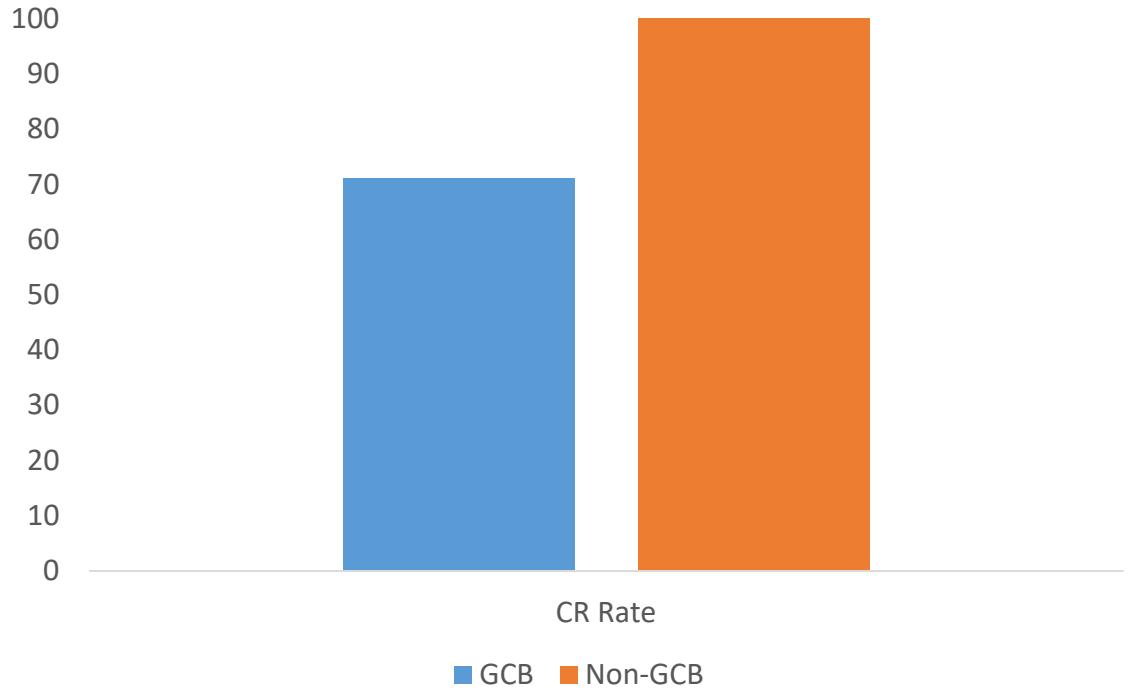
İtalya ve Almanya'dan 13 merkez, 60-80 yaş hastaların dahil edildiği Faz 1 ve 2 uzatma çalışması. Toplam 49 hasta Faz 2 koluna dahil edilmiş. Lenalidomide 15 mg 1-14.günler + R-CHOP 21
32 hastada hücre kökeni verisi mevcut, 16'sı GCB 16'sı Non-GCB GCB hastalarında %81 tam yanıt Non-GCB hastalarda %88 tam yanıt.



Lancet Oncology Volume 15, No.7, p730-737,June 2014

Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naive patients with CD20-positive B-cell non-Hodgkin lymphoma: a non-randomised, phase 1b study

Anas Younes, Catherine Thieblemont, Franck Morschhauser, Ian Flinn, Jonathan W Friedberg, Sandy Amorim, Benedicte Hivert, Jason Westin, Jessica Vermeulen, Nibedita Bandyopadhyay, Ronald de Vries, Sriram Balasubramanian, Peter Hellemans, Johan W Smit, Nele Fourneau, Yasuhiro Oki

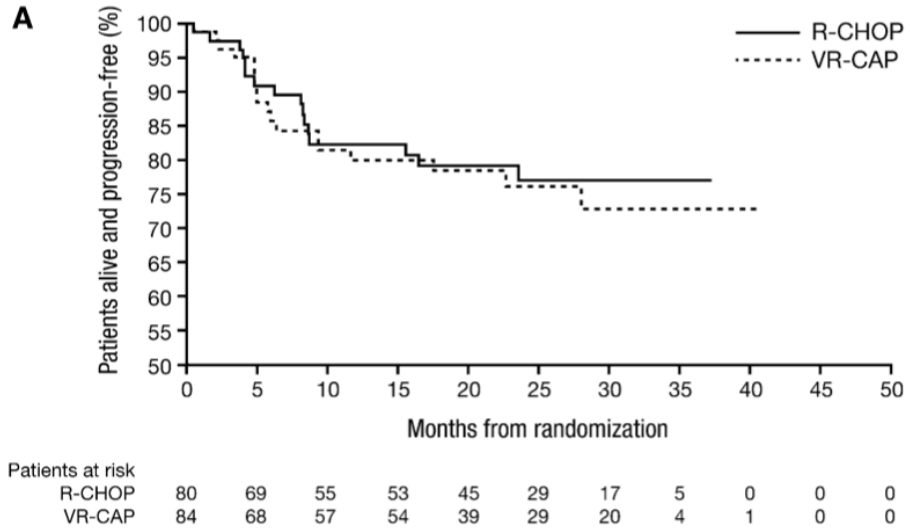


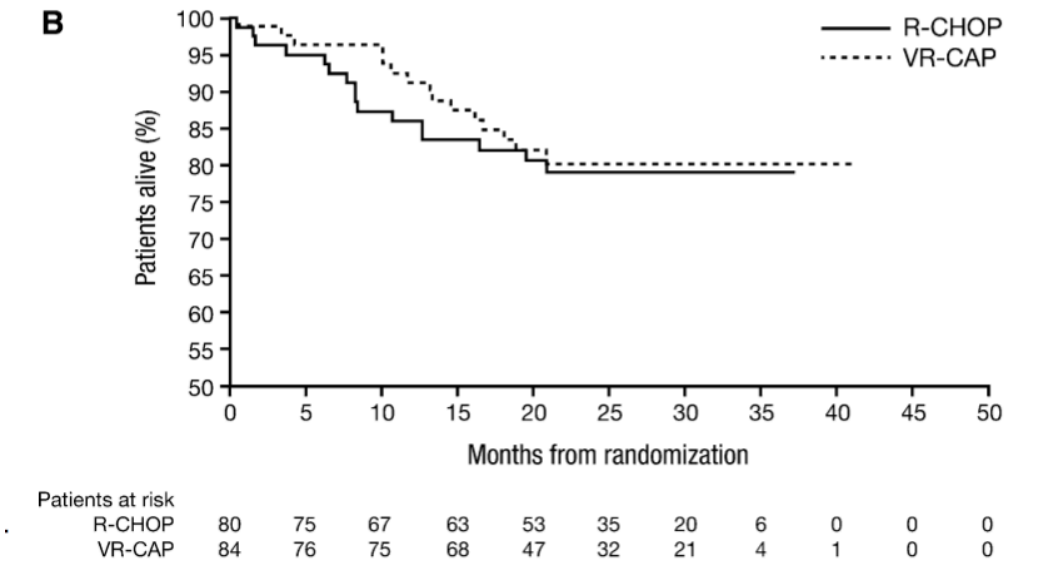
www.thelancet.com/oncology Vol 15 August 2014

Frontline rituximab, cyclophosphamide, doxorubicin, and prednisone with bortezomib (VR-CAP) or vincristine (R-CHOP) for non-GCB DLBCL

Fritz Offner,[1] Olga Samoilova,[2] Evgenii Osmanov,[3] Hyeon-Seok Eom,[4] Max S. Topp,[5] João Raposo,[6] Viacheslav Pavlov,[7] Deborah Ricci,[8] Shalini Chaturvedi,[9] Eugene Zhu,[8] Helgi van de Velde,[10] Christopher Enny,[8] Aleksandra Rizo,[8] and Burhan Ferhanoglu[11]

164 evre 2-4 non gcb dbbhl hastası, Hans algoritması, randomize-kontrollü, VR-CAP (Bortezomib, Rituksimab, Siklofosfamid, Doksorubisin, Prednizolon) – R-CHOP





Blood. 2015 Oct 15; 126(16): 1893–1901

Randomized Phase 2 Open-Label Study of R-CHOP ± Bortezomib in Patients (Pts) with Untreated Non-Germinal Center B-Cell-like (Non-GCB) Subtype Diffuse Large Cell Lymphoma (DLBCL): Results from the Pyramid Trial (NCT00931918)

John P. Leonard, Kathryn Kolibaba, James A. Reeves, Anil Tulpule, Ian W. Flinn, Tatjana Kolevska, Robert Robles, Christopher Flowers, Robert Collins, Nicholas J. DiBella, Steven W. Papish, Parameswaran Venugopal, Andrew Horodner, Amir Tabatabai, Julio Hajdenberg, George Mulligan, Rachel Neuwirth, Kaveri Suryanarayan, Dixie-Lee Esseltine, Sven de Vos

Blood 2015 126:811;

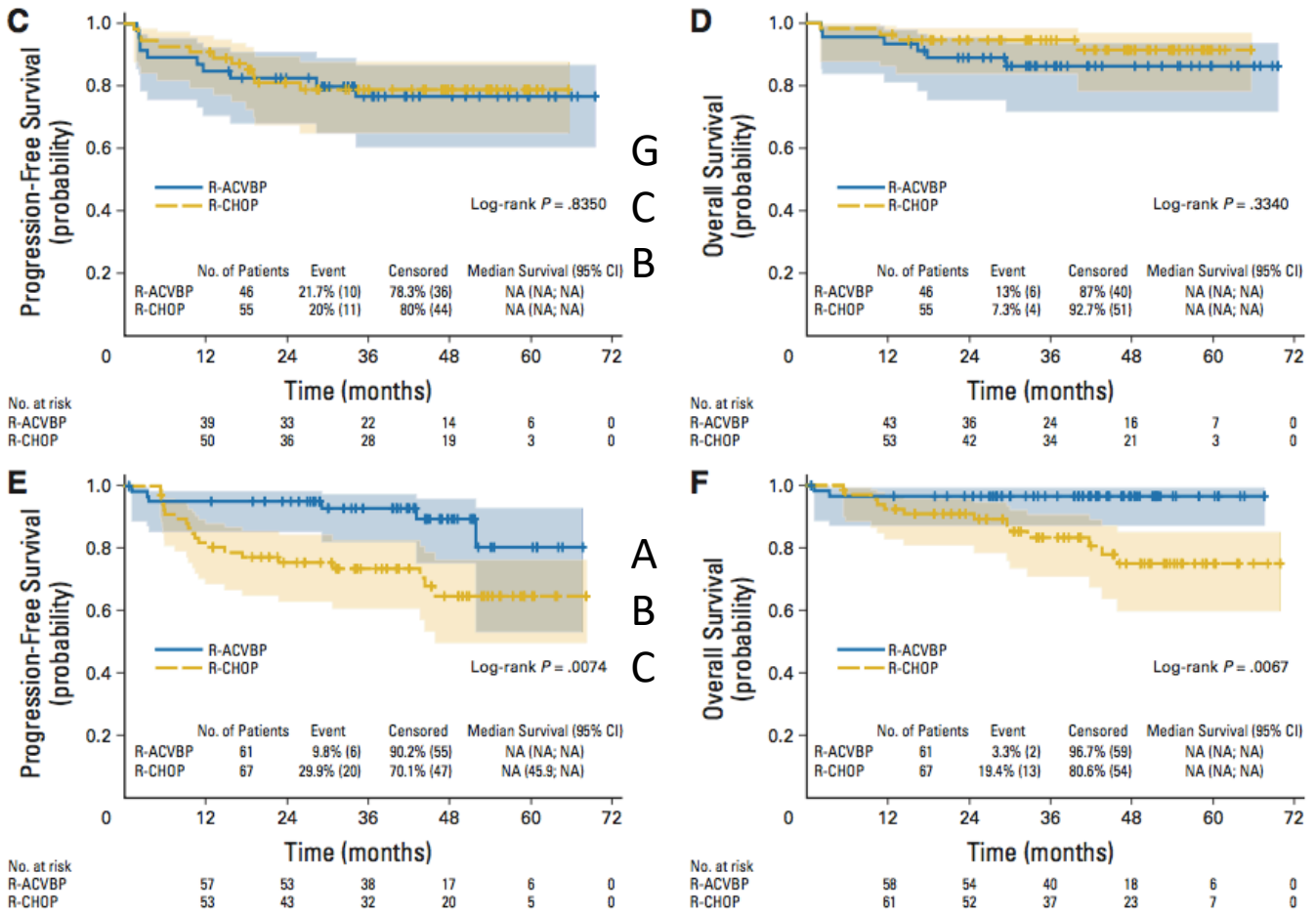
11% vs 14%; IPI low/low-int/high-int/high 24/25/38/12% vs 26/28/33/13%. After a median follow-up of 31.5 mos, 2-yr PFS was 77% vs 82% (HR 0.77; 90% CI: 0.45, 1.30; p=0.70). In pts with high-int/high IPI, 2 yr PFS was 64% vs 72% (HR 0.66; 90%

Progresyonsuz sağkalım farkı yok, GEP yerine Hans algoritmasının kullanılması, R-CHOP kolunda dahi beklenenden yüksek PFS

Young Patients With Non–Germinal Center B-Cell–Like Diffuse Large B-Cell Lymphoma Benefit From Intensified Chemotherapy With ACVBP Plus Rituximab Compared With CHOP Plus Rituximab: Analysis of Data From the Groupe d'Etudes des Lymphomes de l'Adulte/Lymphoma Study Association Phase III Trial LNH 03-2B

Thierry Jo Molina, Danielle Canioni, Christiane Copie-Bergman, Christian Recher, Josette Brière, Corinne Haioun, Françoise Berger, Christophe Fermé, Marie-Christine Copin, Olivier Casasnovas, Catherine Thieblemont, Tony Petrella, Karen Leroy, Gilles Salles, Bettina Fabiani, Franck Morschauser, Nicolas Mounier, Bertrand Coiffier, Fabrice Jardin, Philippe Gaulard, Jean-Philippe Jais, and Hervé Tilly

379 hasta, hans algoritması R-ACVBP (R-doxorubicin, siklofosfamid, vindesin, bleomisin, prednisolone – R-CHOP), 18-59 yaş



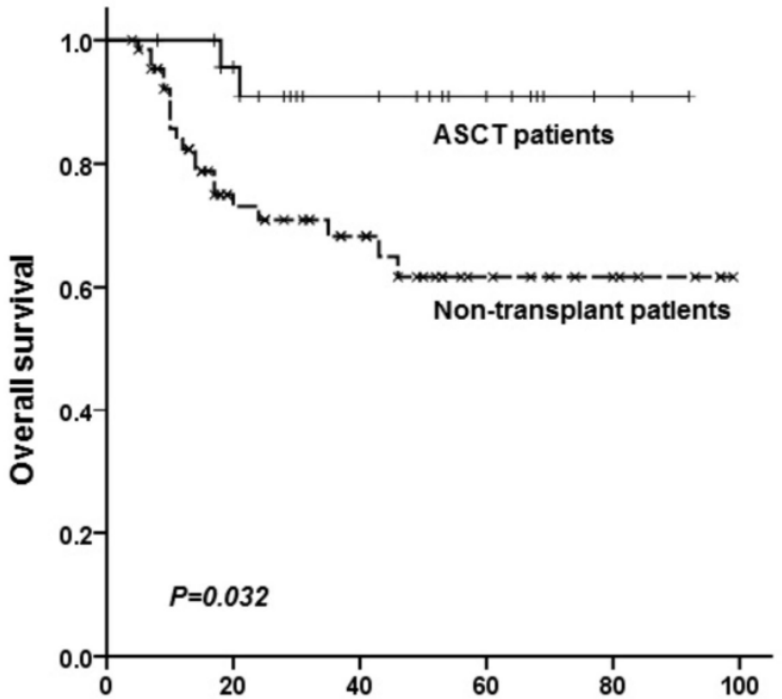
Jo Molina et.al, *J Clin Oncol 32:3996-4003*

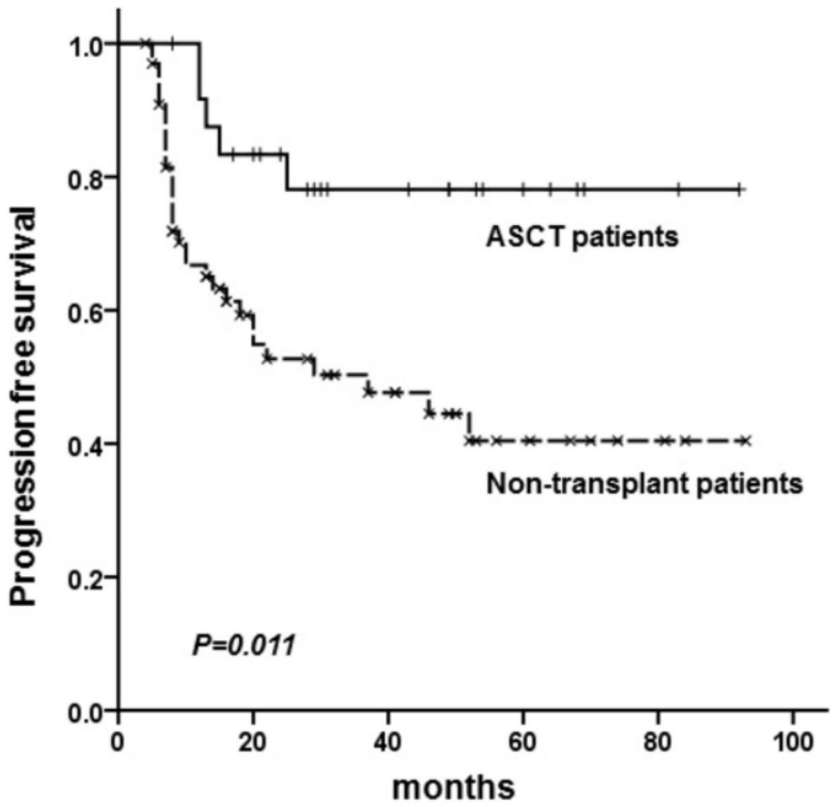
Upfront Autologous Stem Cell Transplantation Overcome the poor Prognosis of Non-Germinal Center Subtype of diffuse Large B-Cell Lymphoma in Patients with Advanced Stage and Elevated Serum Lactate Dehydrogenase

Yu Ri Kim, Soo-Jeong Kim, June-Won Cheong, Yundeok Kim, Ji Eun Jang, Jung Yeon Lee, Deok-Hwan Yang, Hyewon Lee, Hyeon-Seok Eom, Yoo Hong Min, Jin Seok Kim

Blood 2014 124:3998;

195 ileri evre ve yüksek ldh'lı Non GCB hastası, Hans algoritması, konvansiyonel R-CHOP tamamlandıktan sonra en az PR ise Otolog KHN





Overall survival and progression free survival according to autologous hematopoietic stem cell transplantation in non-GCB type DLBCL.

The different roles of molecular classification according to upfront autologous stem cell transplantation in advanced-stage diffuse large B cell lymphoma patients with elevated serum lactate dehydrogenase

Yu Ri Kim[1] · Soo-Jeong Kim[1] · June-Won Cheong[1] · Deok-Hwan Yang[2] · Hyewon Lee[3] · Hyeon-Seok Eom[3] · Yong Oh Sung[4] · Hyo Jung Kim[5] · Hye Jin Kang[6] · Won-Sik Lee[7] · Yong Park[8] · Woo-Ick Yang[9] · Yoo Hong Min[1] · Jin Seok Kim[1]

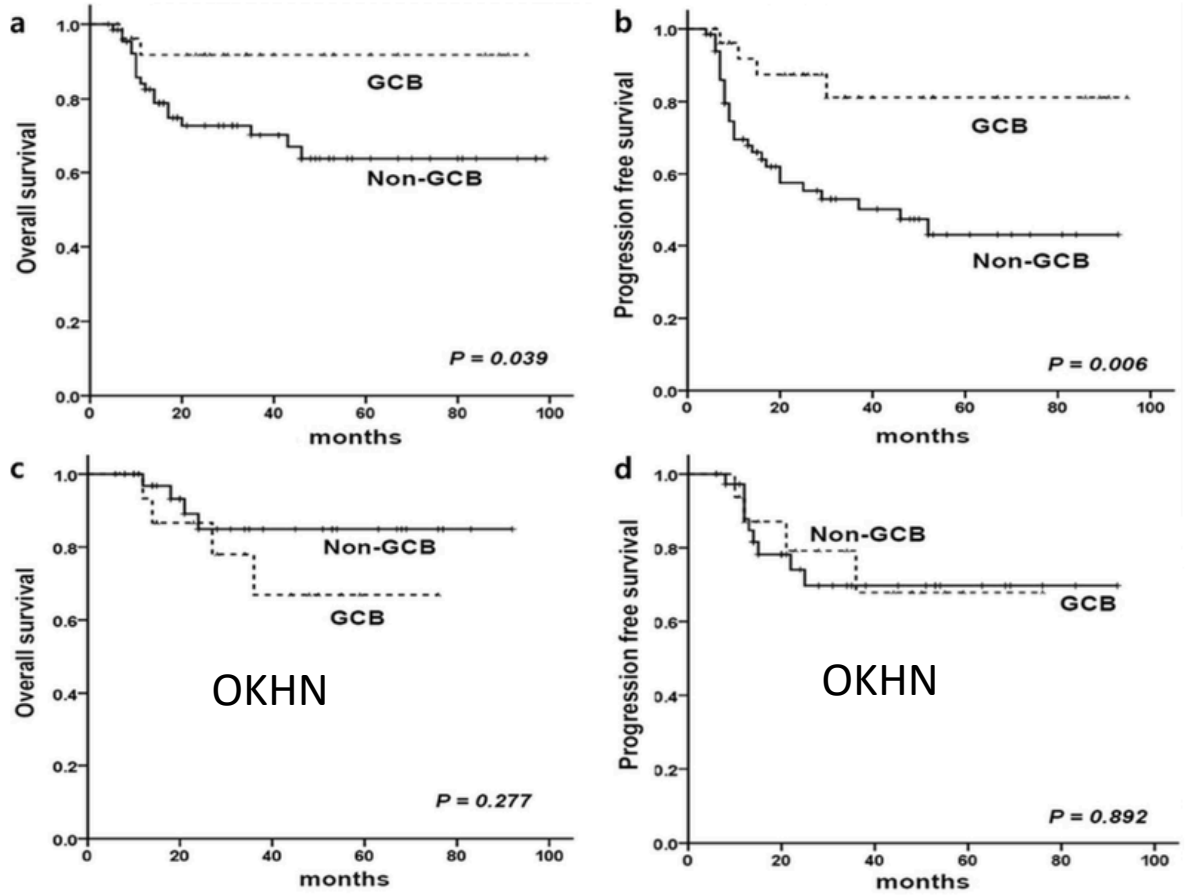


Fig. 2 Kaplan-Meier analysis according to the germinal center B cell (GCB) subtype and non-GCB subtype between the ASCT and non-ASCT groups. **a** Shows overall survival (OS) and **b** shows progression-free survival (PFS) according to molecular classification in the non-ASCT group. OS and PFS according to molecular classification in the ASCT group are shown in **c**, **d**, respectively

219 evre 3-4 DBBHL hastası, 4-8 kür RCHOP sonrası OKHN veya izlem

Ann Hematol, epub

Germinal Merkez Dışı Lenfomalı Hastaları İçeren ve Sonuçları Beklenen Faz 2-3 Çalışmalar

Study	Eligibility	Arms	Study agent
REMoDLB	Newly diagnosed patients with DLBCL. Stage I bulky and stages II–IV. All receive 1 cycle of R-CHOP. Then, ABC patients are randomized.	R-CHOP vs. R-CHOP-B	Bortezomib
PYRAMID	Newly diagnosed non-GCB patients, all stages.	R-CHOP vs. Vc-R-CHOP	Bortezomib
LYM2034	Newly diagnosed non-GCB patients, stages II–IV.	R-CHOP vs. Vc-R-CAP	Bortezomib
PHOENIX	Newly diagnosed non-GCB patients, stages II–IV.	R-CHOP vs. I-R-CHOP	Ibrutinib
ECOG1412	Newly diagnosed DLBCL, stage II bulky disease and stages III–IV.	R-CHOP vs. R2-CHOP	Lenalidomide

Everolimus combined with R-CHOP-21 for new, untreated, diffuse large B-cell lymphoma (NCCTG 1085 [Alliance]): safety and efficacy results of a phase 1 and feasibility trial

Patrick B Johnston, Betsy LaPlant, Ellen McPhail, Thomas M Habermann, David J Inwards, Ivana N Micallef, Joseph P Colgan, Grzegorz S Nowakowski, Stephen M Ansell, Thomas E Witzig

26 DBBHL hastası, Lymph2Cx algoritması ile %46 GCB %54 Non-GCB, Everolimus 10 mg 1-14.günler+R-CHOP 21, %100 Tam metabolik yanıt, 12. Ayda %100 Olaysız Sağkalım, Hastaların 9'u 12.ayı geçmiş ve halen olaysız takip ediliyor.

Lancet Haematol 2016 , June 2016, epub

Double HIT Lenfomalar'da RCHOP ile Kıyaslamalı Birinci Sıra Tedavi Çalışmaları

Reference	No. of Patients	Treatment	Outcome (Median)	Comments
Petrich et al[50]	311	R-CHOP (32%)	PFS: 10.9; OS: 21.9 mo	Median follow-up: 23 mo
		R-Hyper CVAD/MA (21%)	PFS (R-CHOP): 7.8 mo versus 26.6 mo (for any "intensive" regimen; p = 0.001)	No difference between intensive regimens
		R-EPOCH (21%)		Consolidative SCT: no improvement in OS in CR patients (p = 0.14)
		R-CoDox-M/IVAC (14%)		
Oki et al[60]	129 (93 with both MYC and BCL2 translocation)	R-CHOP	2-yr EFS	Increased OS with R-EPOCH c/w R-CHOP (p = 0.057)*
		R-Hyper CVAD/MA	Overall: 33% (overall)	
		R-EPOCH	R-CHOP: 25%	
			R-Hyper CVAD/MA: 32%	CNS involvement: 13% at 3 yrs
			R-EPOCH: 67%	
			CR	
			R-CHOP: 20%	
			R-EPOCH: 68%	
			R-Hyper CVAD/MA: 70%	
Johnson et al[61]	54	CHOP-like (43%)	OS	BCL2 protein-negative cases (more favorable)
	BCL-U (36 patients)	R-CHOP (20%)	R-CHOP: 1.4 yr	
	DLBCL (17 patients)	HDT (11%)	CHOP: 5 mo	
		Palliative (26%)		
Li et al[62]	BCL-U (33 patients)	R-CHOP (39%)	OS: 18.6 mo	Median age: 55
	DLBCL (23 patients)	R-Hyper CVAD/MA (57%)		Aggressive chemotherapy nor SCT associated with increased PFS/OS

Abbrevations: BCL-U, B-cell lymphoma, unclassifiable with features intermediate between DLBCL and BL; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; Hyper CVAD/MA, hyper-fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone/methotrexate, cytarabine; EPOCH, etoposide, prednisone, doxorubicin, cyclophosphamide, doxorubicin; CoDox-M/IVAC, cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine; PFS, progression-free survival; OS, overall survival; SCT, stem cell transplant.
*Consolidative SCT in 50% R-EPOCH versus 4% R-CHOP group.

R-CHOP bütün çalışmalarda yetersiz kalıyor. En ideal yanıtlar DA-EPOCH-R, R-Hyper-CVAD/MA, R-CODOX-M/IVAC ile elde edilebiliyor.

ÖZET

- Double HIT lenfomalar ayıklanınca Germinal Merkez Lenfoma hastalarının RCHOP ile yanıtları yeterli düzeyde görülmektedir. Bu nedenle DHL patoloji raporlarında yer almalı.

- Double Ekspressör hastaların prognozu hücre kökeninden bağımsız olarak daha kötü, bu nedenle daha efektif tedaviler almaları gerekmekte, double ekspressörlük durumu mutlaka patoloji raporunda yer almalı.

- Double HIT ve Double Ekspressör hastalar ayıklandıktan sonra Germinal Merkez Dışı Lenfomaların prognozu Germinal Merkez Lenfomalara göre izole R-CHOP ile belirgin kötü, bu nedenle hücre kökeni hakkında bilgi mutlaka bulunmalıdır.

- Germinal Merkez Lenfomalar için R-CHOP iyi bir seçenek olarak görülse de hedefe dönük toksisitesi düşük tedaviler ile yanıt oranları daha da iyileştirilebilir. Bu nedenle eğer mümkünse bu hasta grubu da klinik çalışmalara dahil edilebilir.

ÖZET

- Double HIT Lenfomalar için herhangi bir standart indüksiyon rejimi henüz kanıt düzeyi yüksek bir şekilde önerilememektedir. Mümkünse bu hastalar klinik çalışmalara dahil edilmeli, eğer mümkün değil ise daha etkin (DA-R-EPOCH, R-HyperCVAD gibi) indüksiyon rejimleri ile tedavi edilmeliler. Mevcut indüksiyon tedavisi sonrası veya konvansiyonel R-CHOP sonrası ilk sıra otolog kök hücre nakline yönlendirilebilirler.

- Germinal Merkez Dışı Lenfomaların prognozu Germinal Merkez Lenfomalara göre daha kötü olduğundan mümkünse bu hastalar klinik çalışmalara yönlendirilmeli eğer mümkün değil ise patogenetik mekanizmaları hedef alacak ek tedaviler (İbrutinib, Lenalidomid, Everolimus gibi) konvansiyonel R-CHOP tedavisine eklenmelidir.

- Yine bu hastalarda ilk sıra otolog kök hücre nakli mevcut kötü prognostik etkiyi elimine edebileceğinden bir tedavi seçeneği olarak özellikle kemosensitif hastalarda düşünülebilir.

- Double Ekspressör lenfomalar ile ilgili ciddi bir literatür eksikliği mevcut. Double HIT'ler bu gruptan ayrıştırılmalı. Kalan hastaların büyük çoğunluğunun Germinal Merkez Dışı Lenfomalar olacağını bilmek Germinal Merkez Dışı Lenfomalar için gündeme gelecek her yaklaşımın bu gruba da yansıtılabileceğini düşündürmekte.