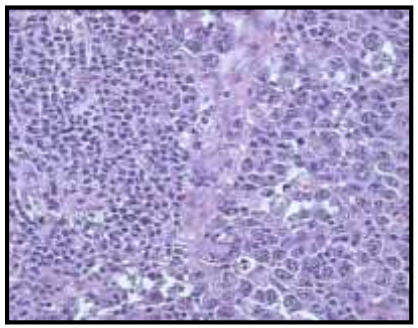
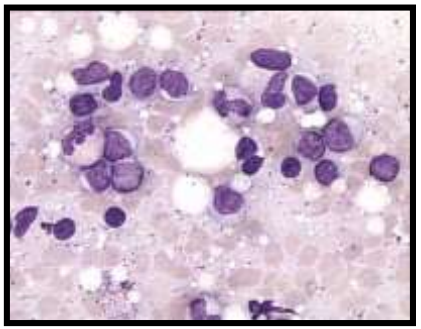
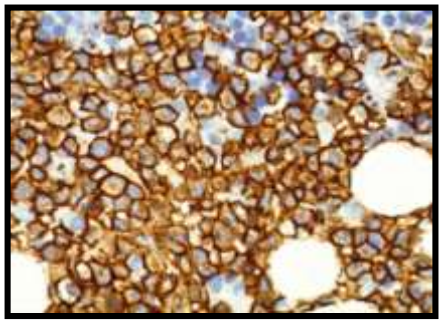
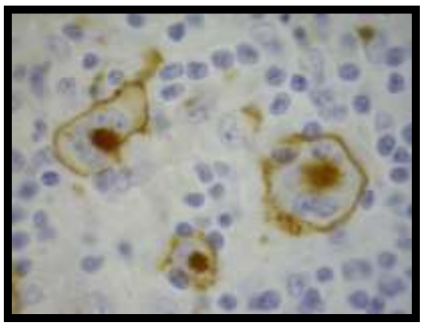
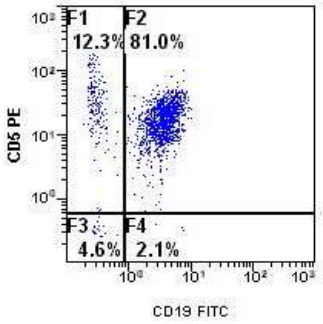
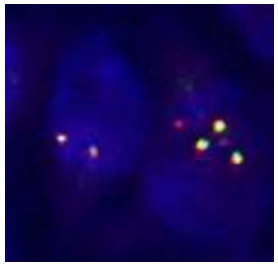
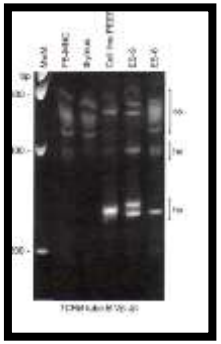
Hodgkin Dışı Lenfoma Sınıflaması

IŞINSU KUZU
Ankara Üniversitesi Tıp Fakültesi
Patoloji Anabilim Dalı

SUNUM AKIŞI

- Sınıflama tarihçesi
- Lenfosit ve Lenfoma gelişimi ilişkisi
- Çocukluk çağında görülen lenfomalar ve karakteristik özellikleri
- Sınıflamadaki son değişiklikler

Lenfoma Sınıflamalarının Tarihi

Gall-Mallory	(1940)
Rappaport	(1960)
B.N.L.I	(1973)
Lukes-Collins	(1974)
Lennert	(1974)
WF	(1980)
REAL	(1994)
WHO	(2001)
WHO	(2008)
WHO	(2017)

Morfoloji

İmmunfenotip

Morfoloji

Klinikopatolojik antite

LENFOMA

The International Lymphoma Study Group

Nancy Harris - Boston
Elaine Jaffe - Bethesda
Harald Stein - Berlin
Peter Banks - San Antonio
John Chan - Hong Kong
Michael Cleary - Stanford
Georges Delsol - Toulouse
Chris De Wolf-Peeters - Leuven
Brunangelo Falini - Perugia
Kevin Gatter - Oxford
Thomas Grogan - Tucson
Peter Isaacson - London
Daniel Knowles - Cornell
David Mason - Oxford
Konrad Müller-Hermelink - Würzburg
Stefano Pileri - Bologna
Miguel Piris - Toledo
Elizabeth Ralfkiaer - Copenhagen
Roger Warnke - Stanford

PERSPECTIVE

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

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

Lenfosit biyolojisi ve lenfomagenez moleküler mekanizmalar ve sonuçları

Lenfoma Sınıflamalarının Tarihi

LENFOMA

Gall-Mallory		(1940)
Rappaport		(1960)
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Lukes-Collins		(1974)
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REAL		(1994)
WHO	LENFOMA & LÖSEMİ	(2001)
WHO		(2008)
WHO		(2017)

Morfoloji

İmmunfenotip

Morfoloji

Klinikopatolojik antite

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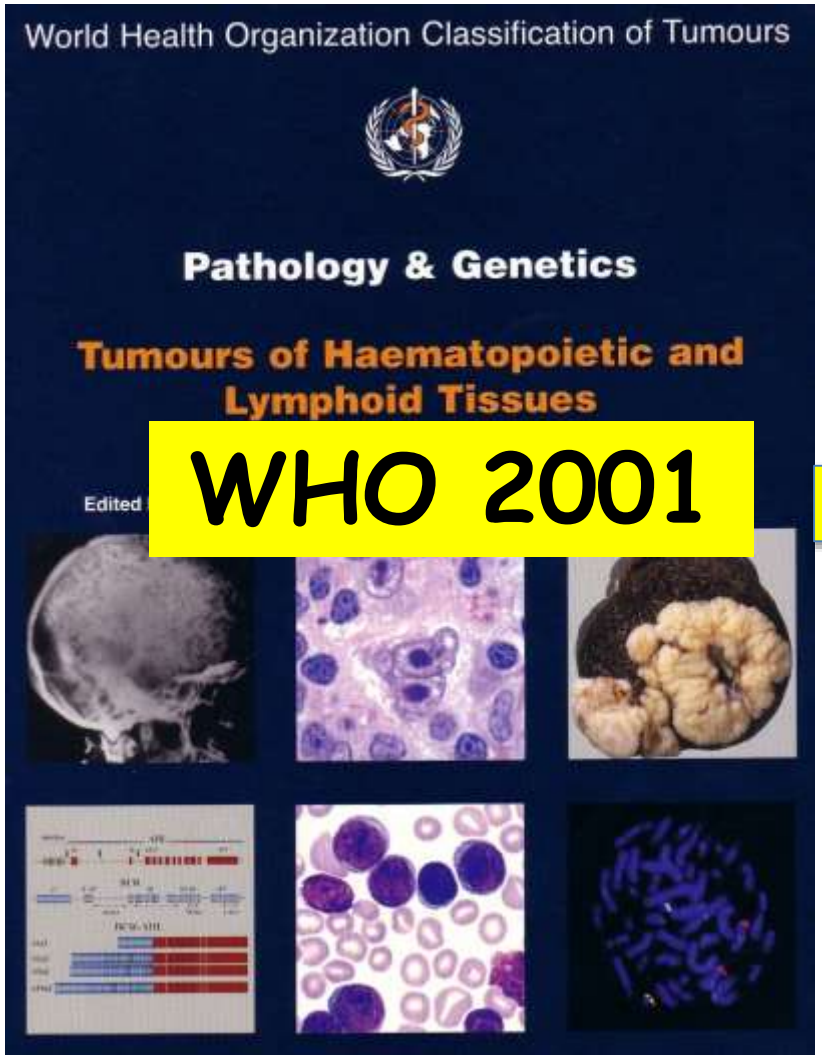
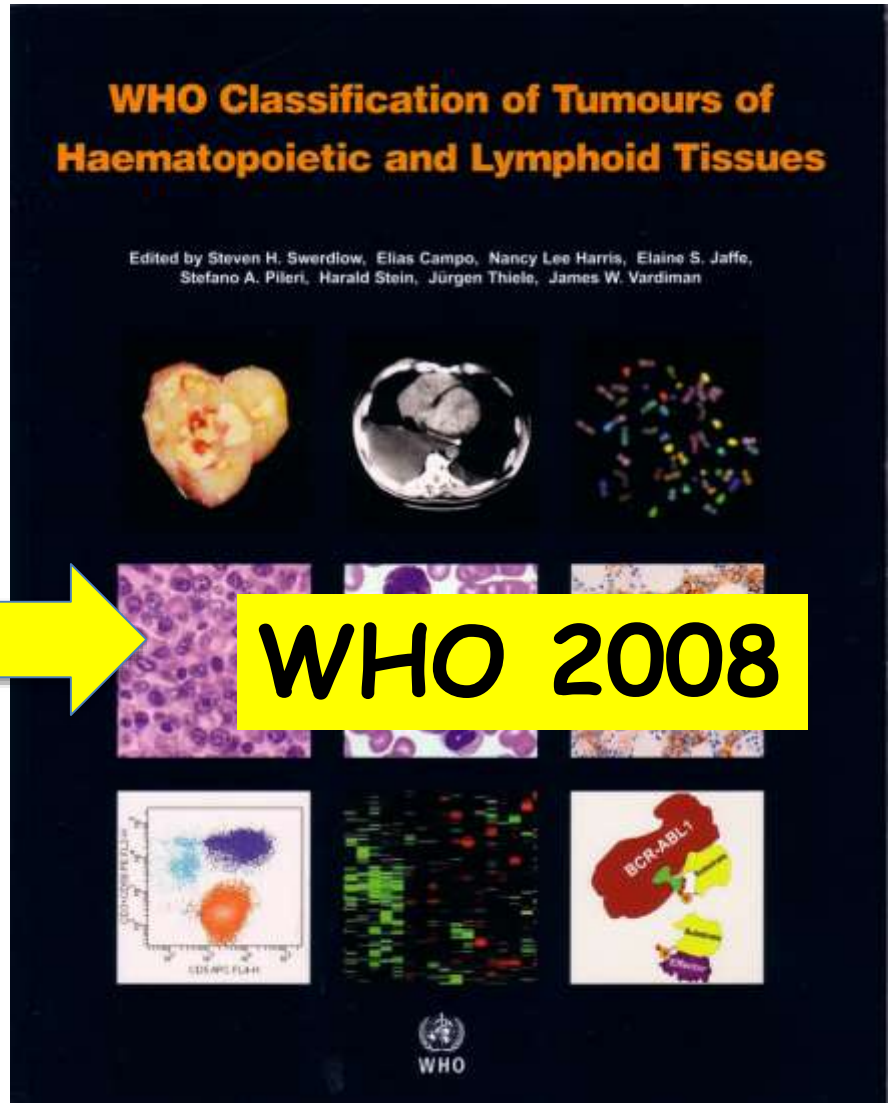
Lenfosit biyolojisi ve lenfomagenez moleküler mekanizmalar ve sonuçları

WHO BLUE BOOK





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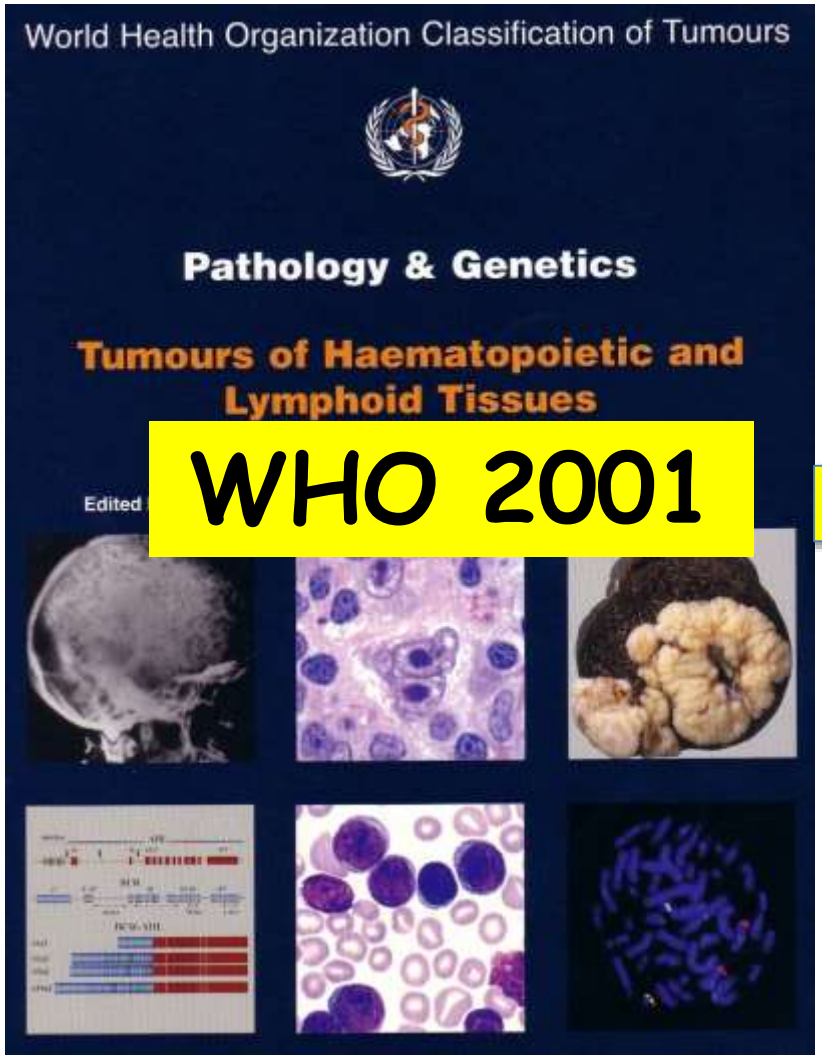
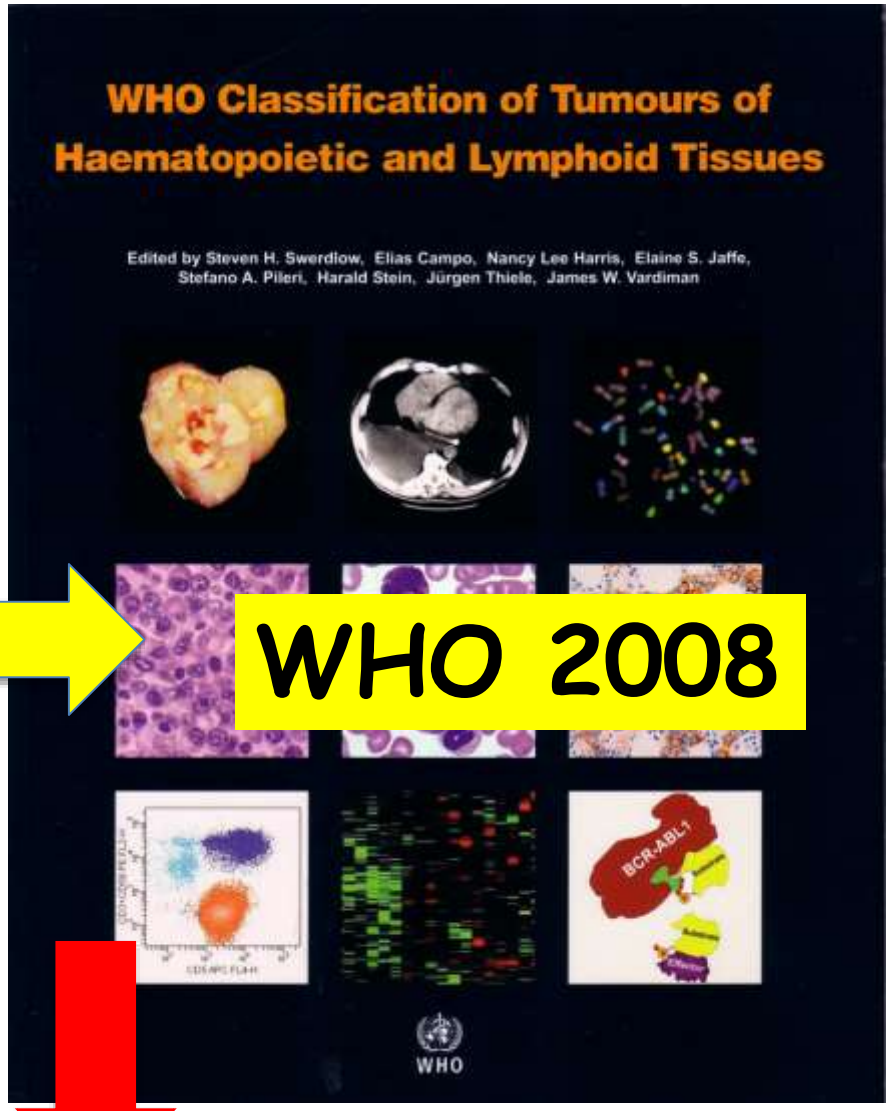
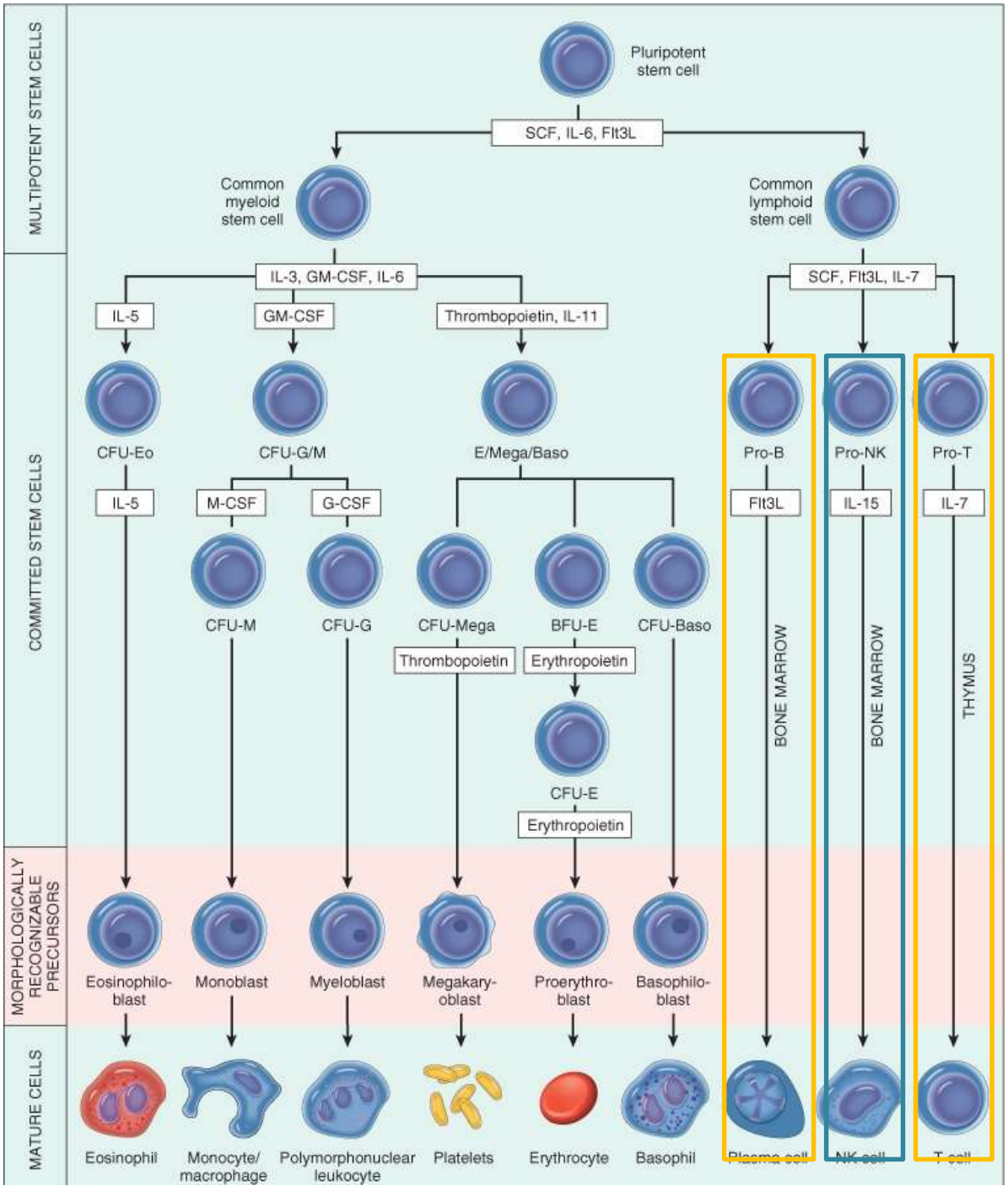
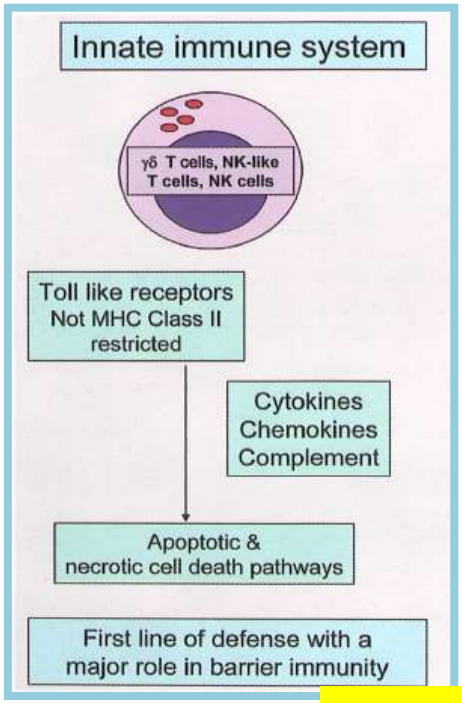




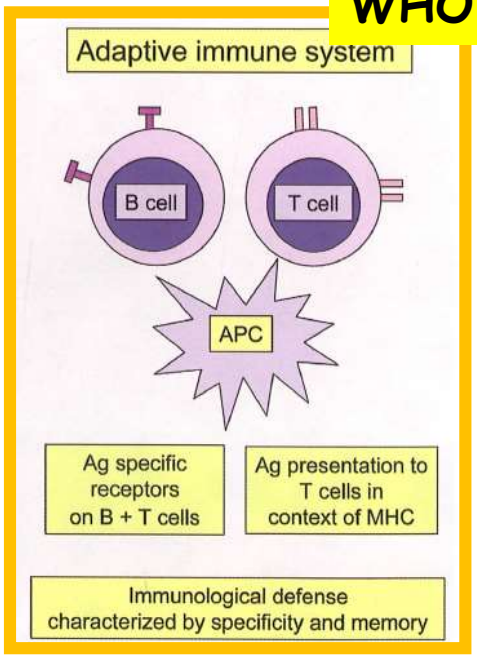
WHO 2017


"UPDATES IN WHO LYMPHOMA CLASSIFICATION: 2008-2016"
PRACTICAL DIAGNOSTIC APPROACH WITH CLINICAL ASPECTS
April 16-17, 2016 WOW Hotels Convention Center
Istanbul - TURKEY
COURSE ORGANIZED BY:
TURKISH DIVISION OF THE INTERNATIONAL ACADEMY OF PATHOLOGY (IAP)
& EUROPEAN ASSOCIATION FOR HAEMATOPATHOLOGY (EAHP)
WHO 2017
HOŞ GELDİNİZ
WELCOME


MULTIPOTENT STEM CELLS
COMMITTED STEM CELLS
MORPHOLOGICALLY RECOGNIZABLE PRECURSORS
MATURE CELLS
Pluripotent stem cell
SCF, IL-6, Flt3L
Common myeloid stem cell
Common lymphoid stem cell
IL-3, GM-CSF, IL-6
SCF, Flt3L, IL-7
IL-5
GM-CSF
Thrombopoietin, IL-11
CFU-Eo
CFU-G/M
E/Mega/Baso
Pro-B
Pro-NK
Pro-T
IL-5
M-CSF
G-CSF
Flt3L
IL-15
IL-7
CFU-M
CFU-G
CFU-Mega
BFU-E
CFU-Baso
BONE MARROW
BONE MARROW
THYMUS
Thrombopoietin
Erythropoietin
CFU-E
Erythropoietin
Eosinophilo-blast
Monoblast
Myeloblast
Megakary-oblast
Proerythro-blast
Basophilo-blast
Eosinophil
Monocyte/ macrophage
Polymorphonuclear leukocyte
Platelets
Erythrocyte
Basophil
Plasma cell
NK cell
T cell


Innate immune system
γδ T cells, NK-like T cells, NK cells
Toll like receptors Not MHC Class II restricted
Cytokines Chemokines Complement
Apoptotic & necrotic cell death pathways
First line of defense with a major role in barrier immunity

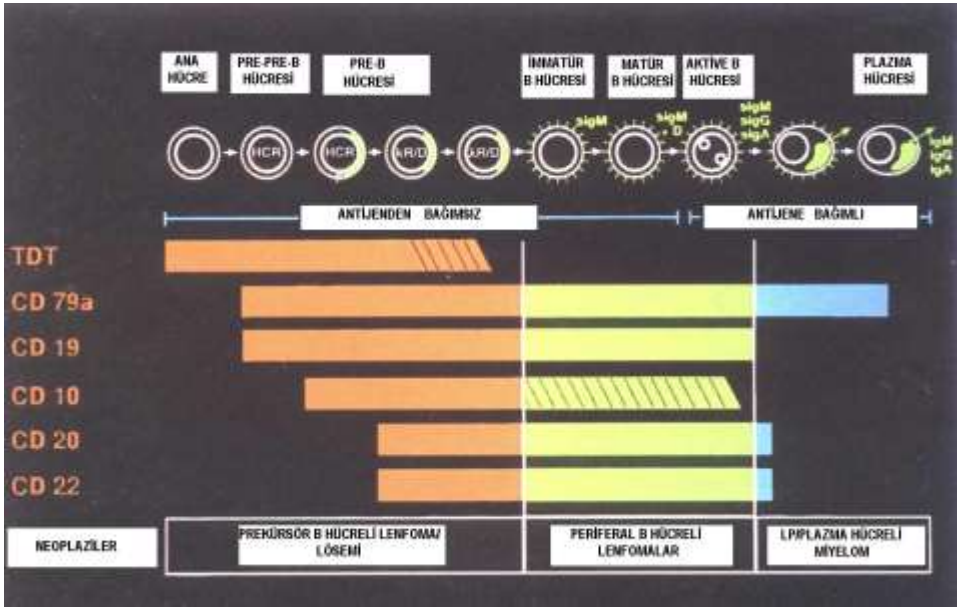
WHO 2008

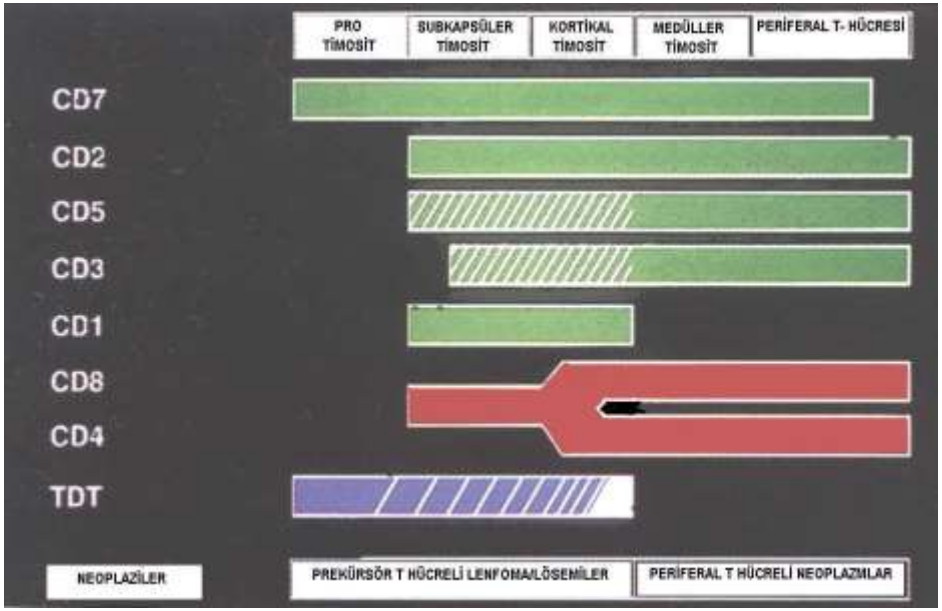

Adaptive immune system
B cell
T cell
APC
Ag specific receptors on B + T cells
Ag presentation to T cells in context of MHC
Immunological defense characterized by specificity and memory

Prekürsor hücreli lenfoma - lösemiler

B HÜCRELİ LENFOBLASTİK

T HÜCRELİ LENFOBLASTİK





WHO 2008

Prekürsor hücreli lenfoma - lösemiler

B HÜCRELİ LENFOBLASTİK

T HÜCRELİ LENFOBLASTİK

Olgun B hücreli lenfomalar

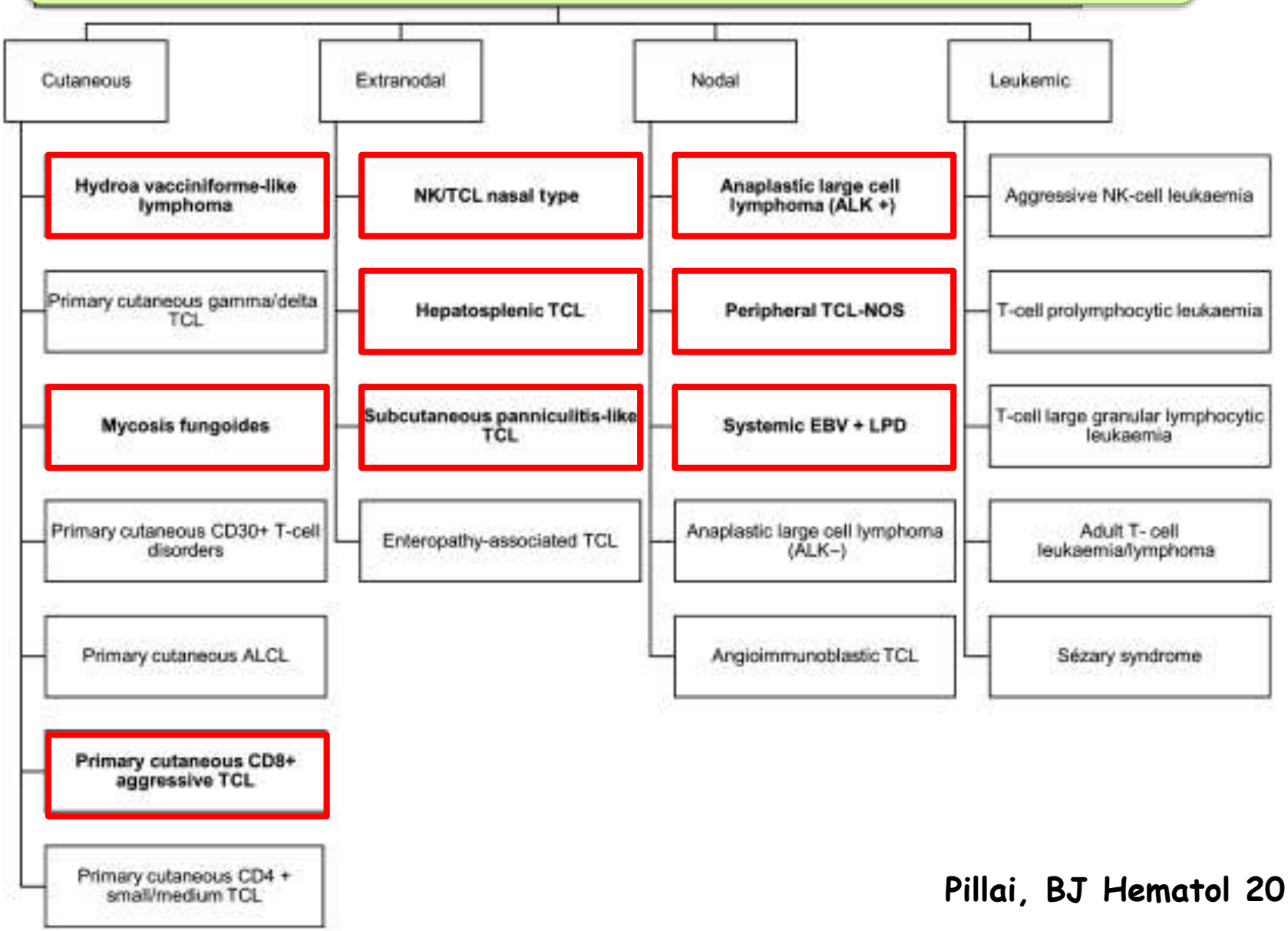
Yavaş Klinik Seyirli

- PEDİATRİK TİP FOLLİKÜLER LENFOMA
- PEDİATRİK MARJİNAL ZON LENFOMA

Agressif Klinik Seyirli

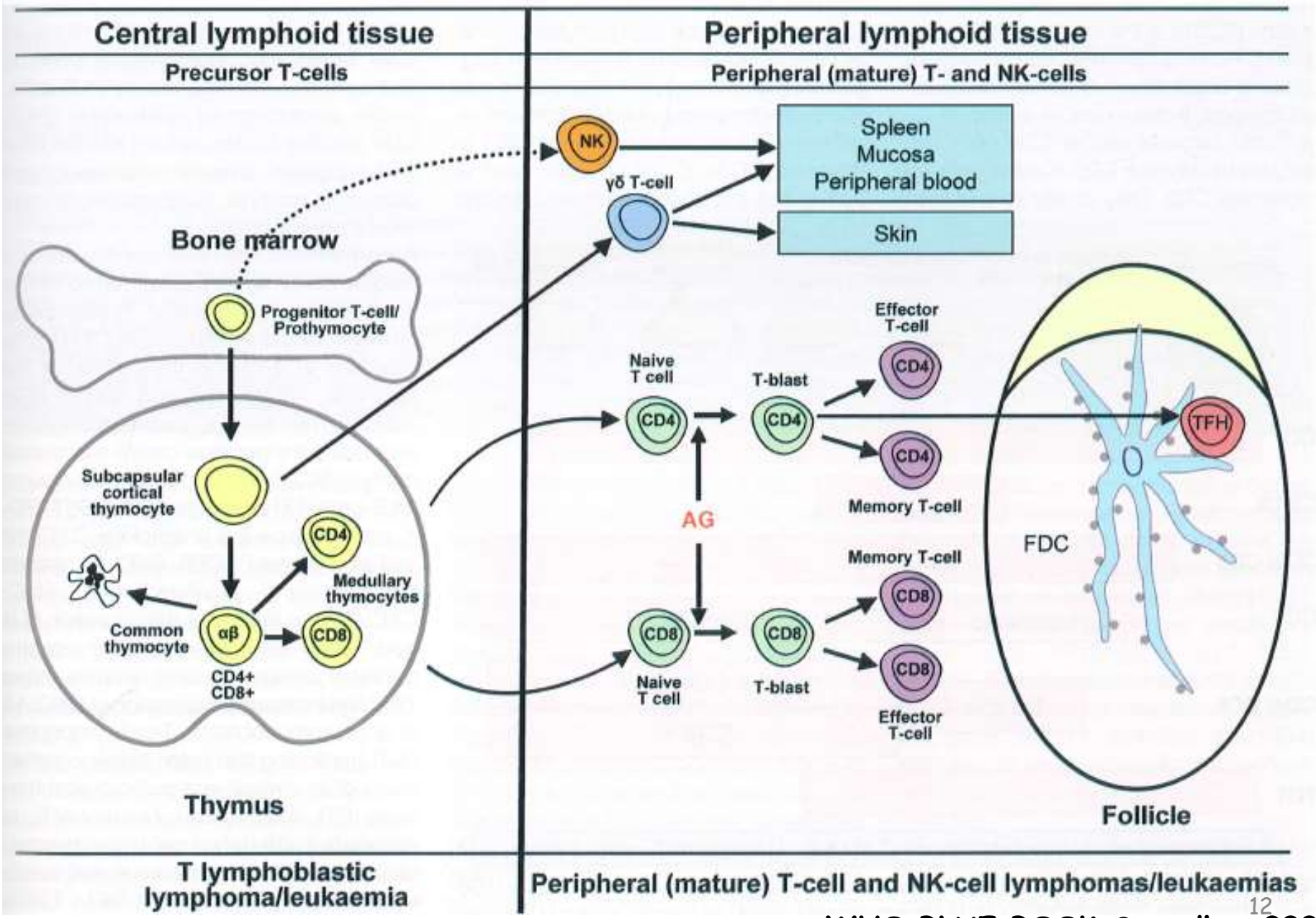
- DİFFÜZ BÜYÜK B HÜCRELİ LENFOMA
- BURKITT LENFOMA
- PRİMER MEDİASTİNAL BÜYÜK B HÜCRELİ LENFOMA

Olgun T hücreli lenfomalar



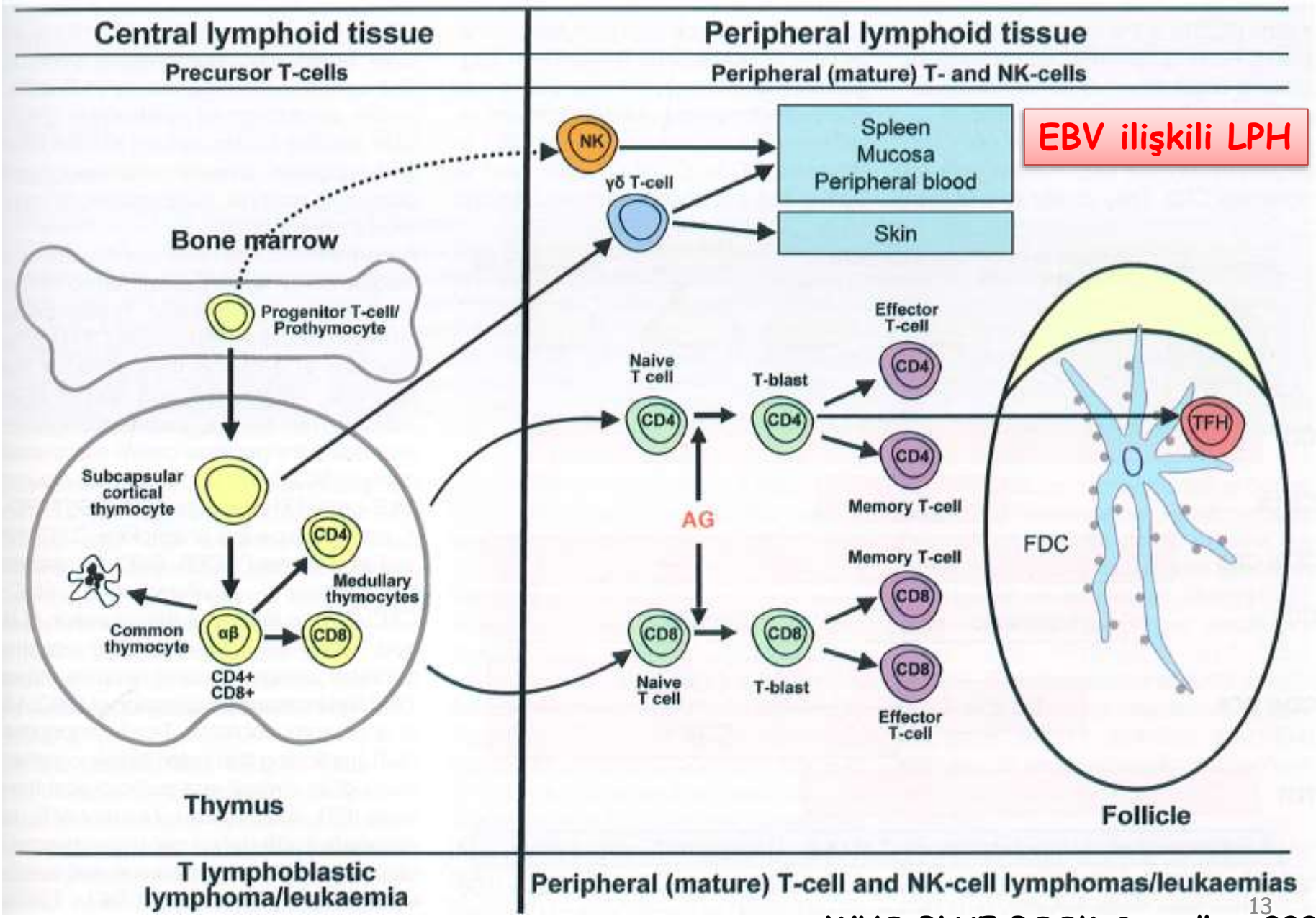
Pillai, BJ Hematol 2016

T lenfositlerin gelişimi



WHO BLUE BOOK Swerdlow 2008

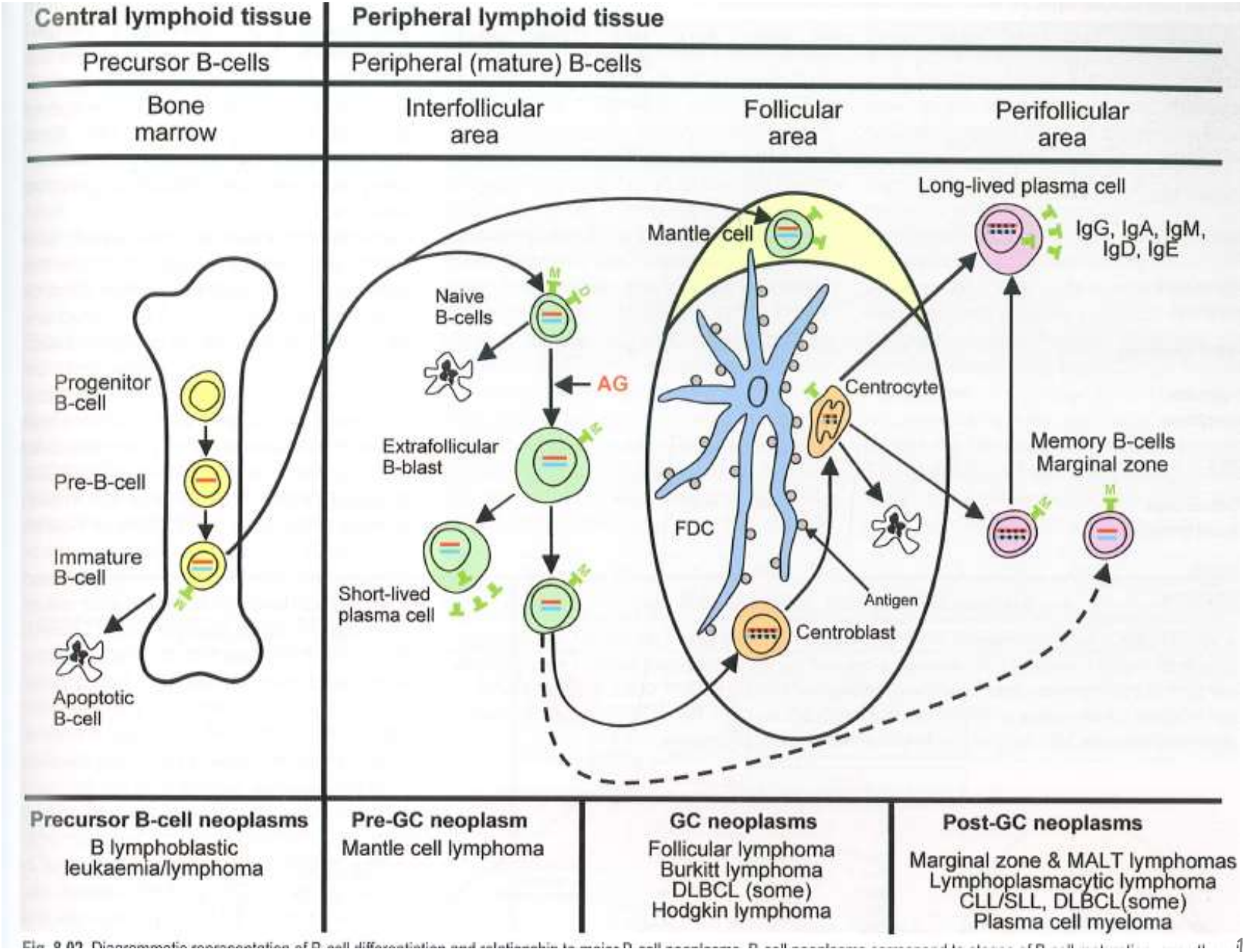
T lenfositlerin gelişimi



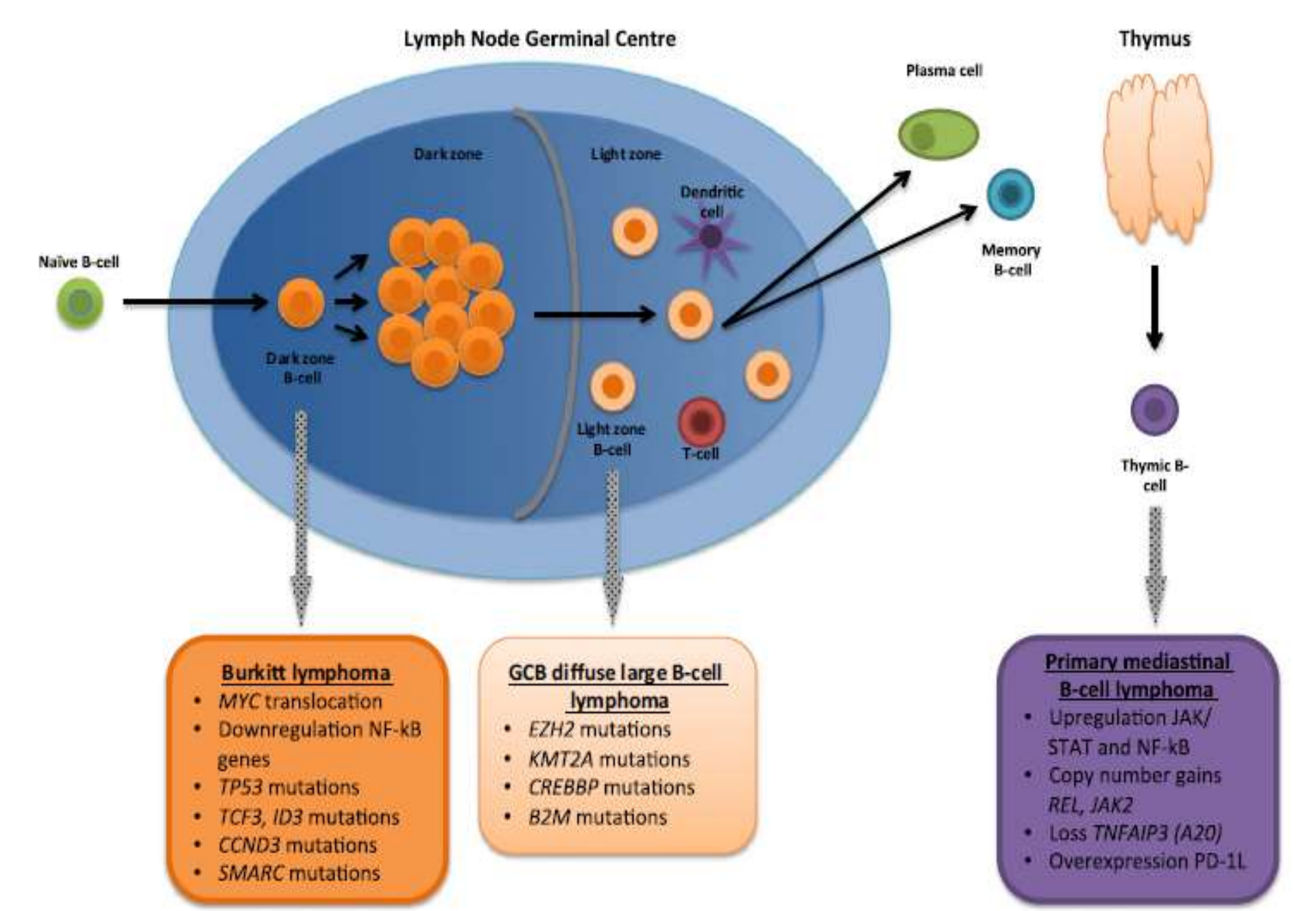
WHO BLUE BOOK Swerdlow 2008

ALCL DIŞI EBV İLİŞKİLİ T HÜCRELİ LENFOMALARIN DAĞILIMI

B lenfositlerin gelişimi

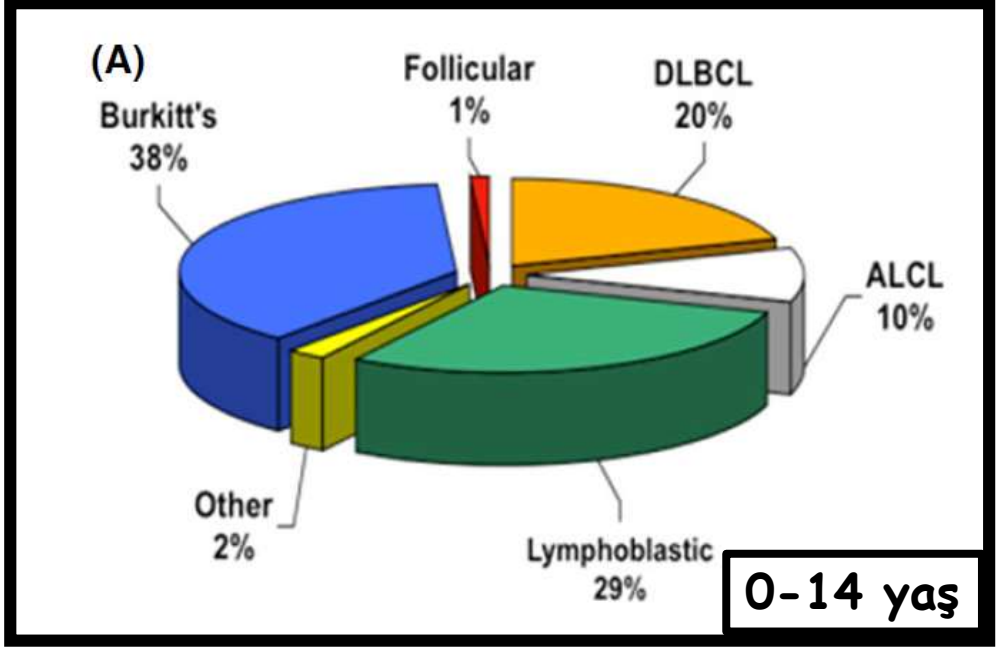


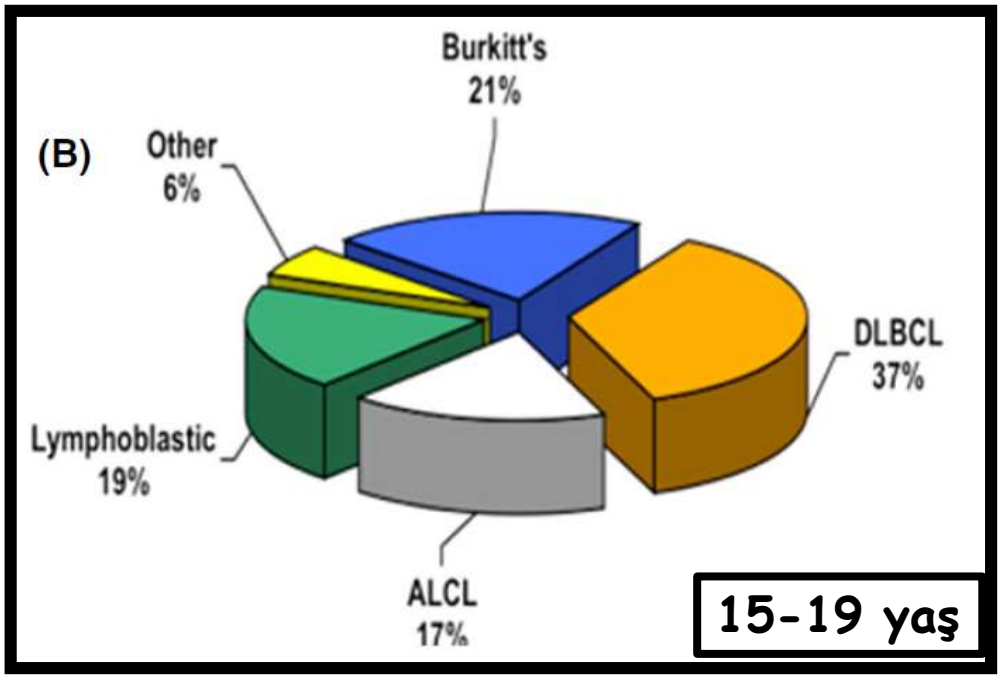
WHO BLUE BOOK Swerdlow 2008

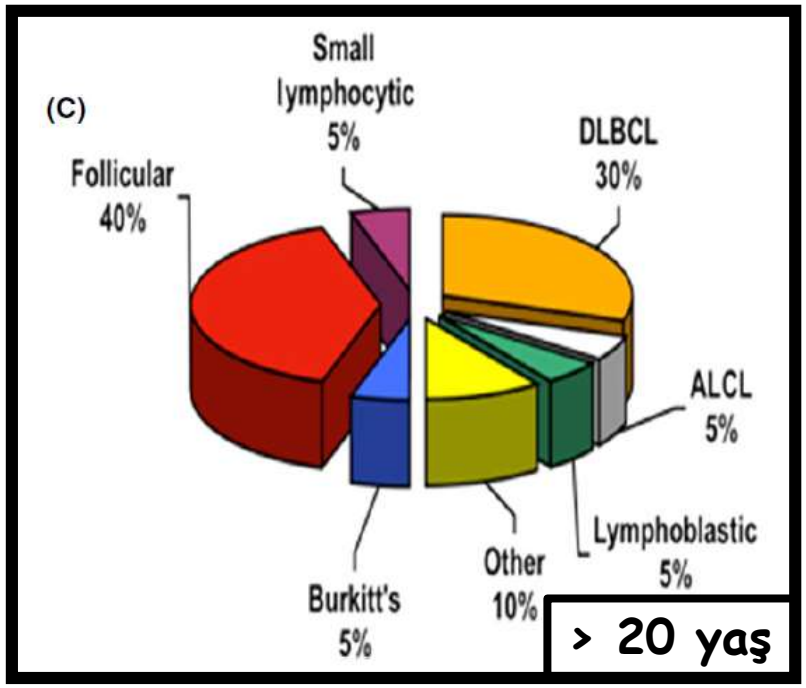


Lisa Giulino-Roth BJH 2016

ÇOCUKLUK VE ADOLESAN ÇAĞIN FARKLI DÖNEMLERİNDE LENFOMA GÖRÜLME ORANLARI





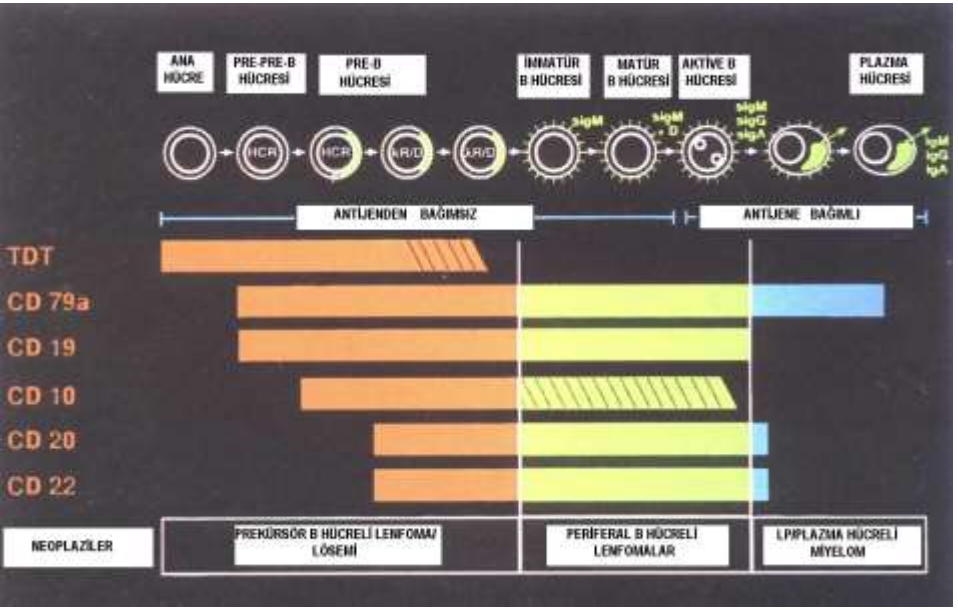


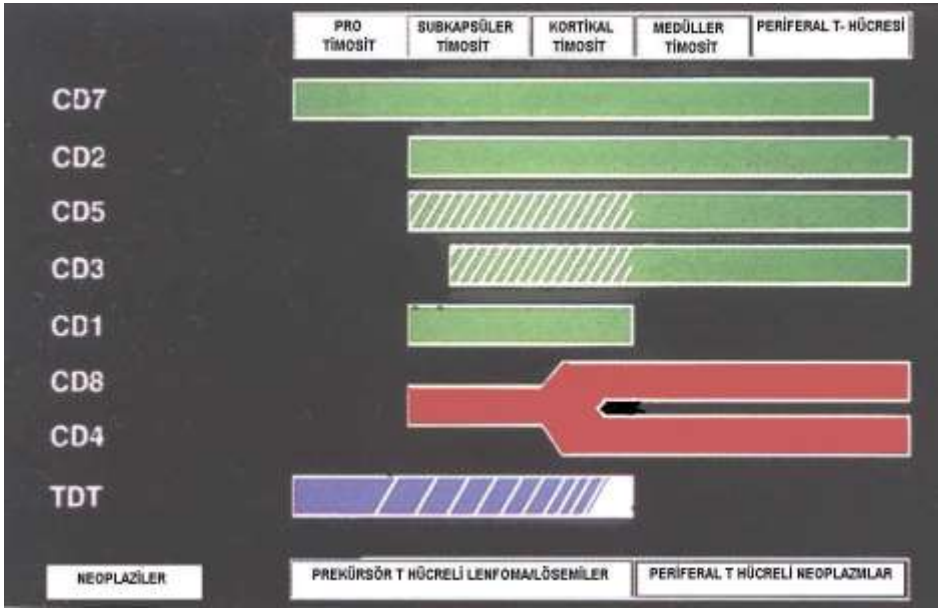
Hochberg J BJ Hematol 2016

Prekürsor hücreli lenfoma - lösemiler

B HÜCRELİ LENFOBLASTİK

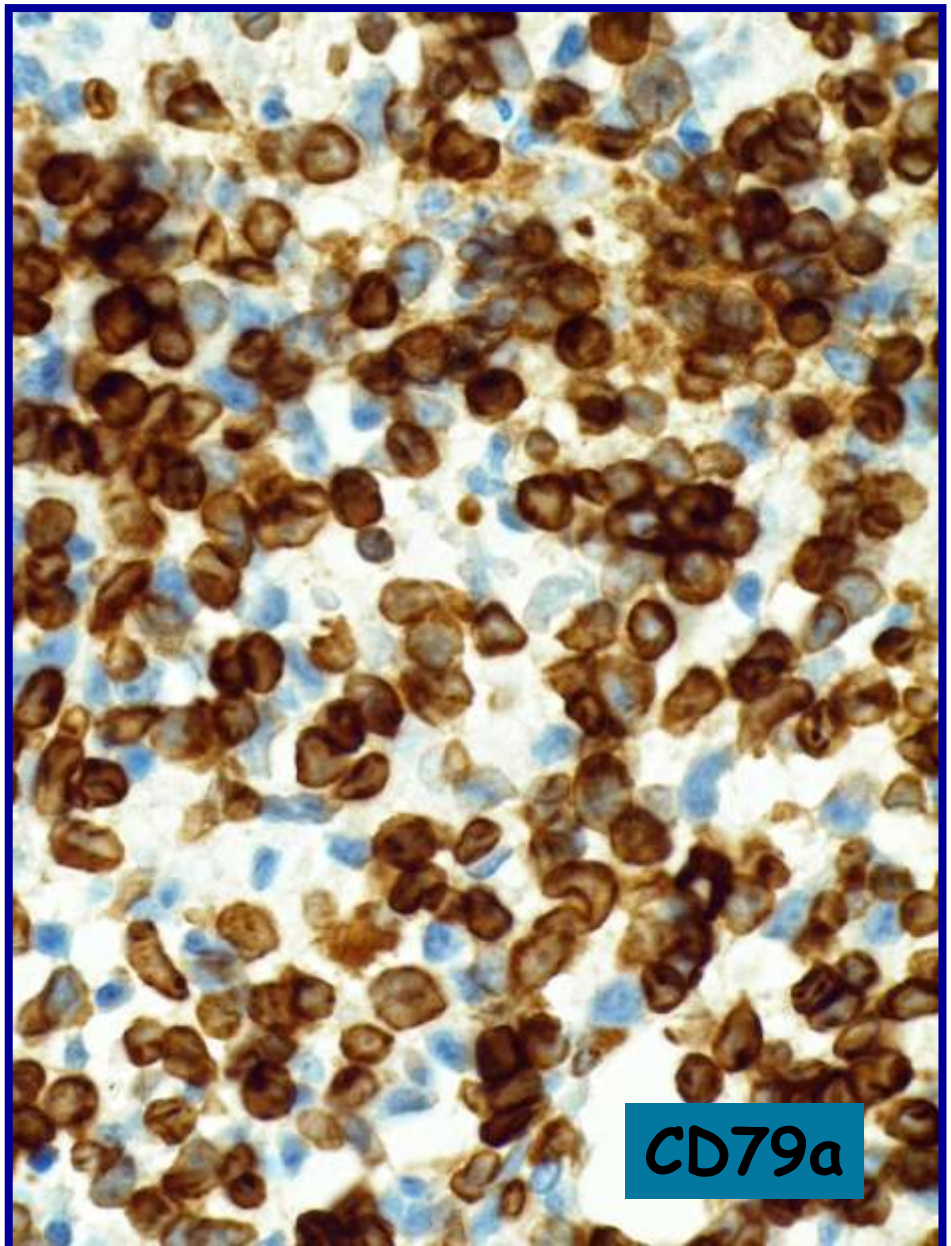
T HÜCRELİ LENFOBLASTİK

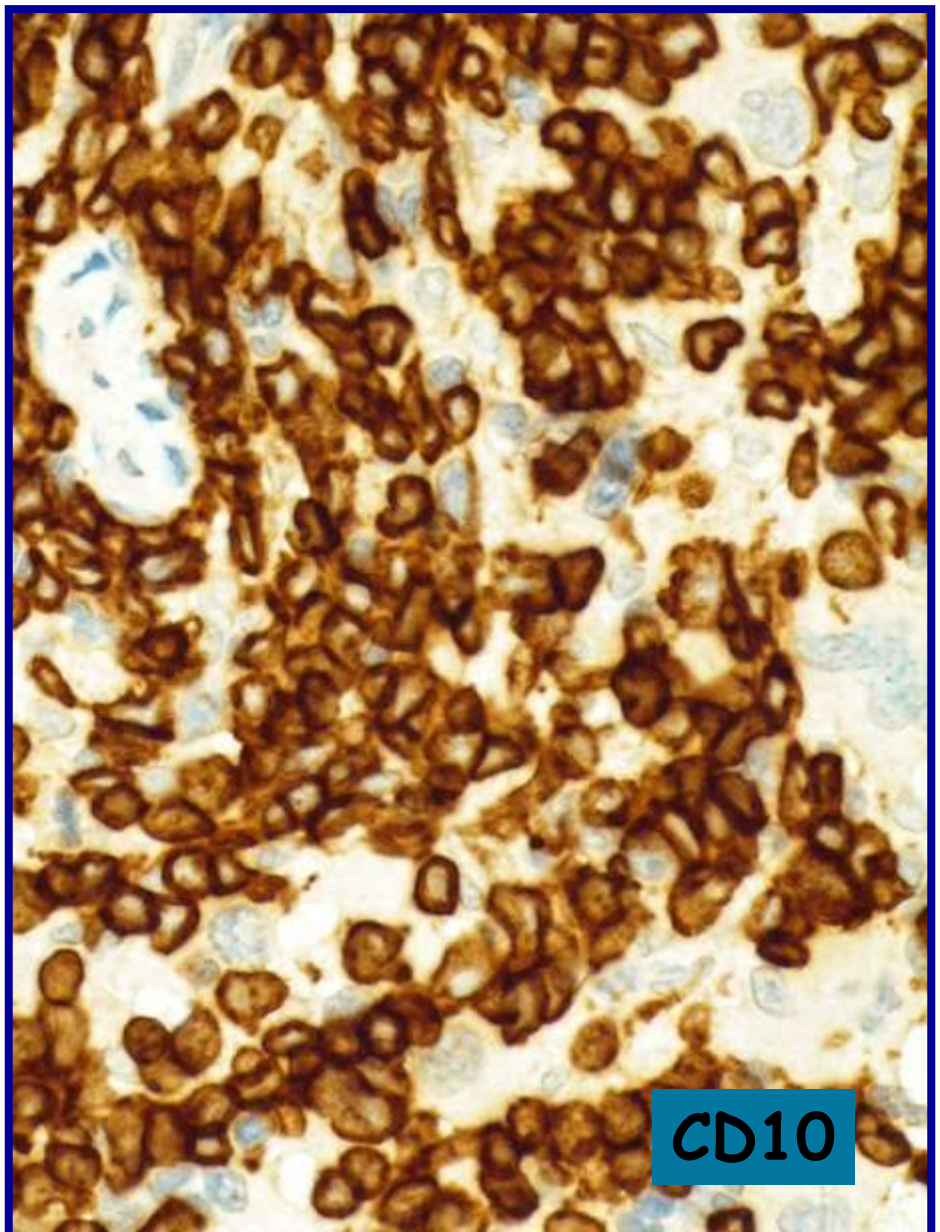




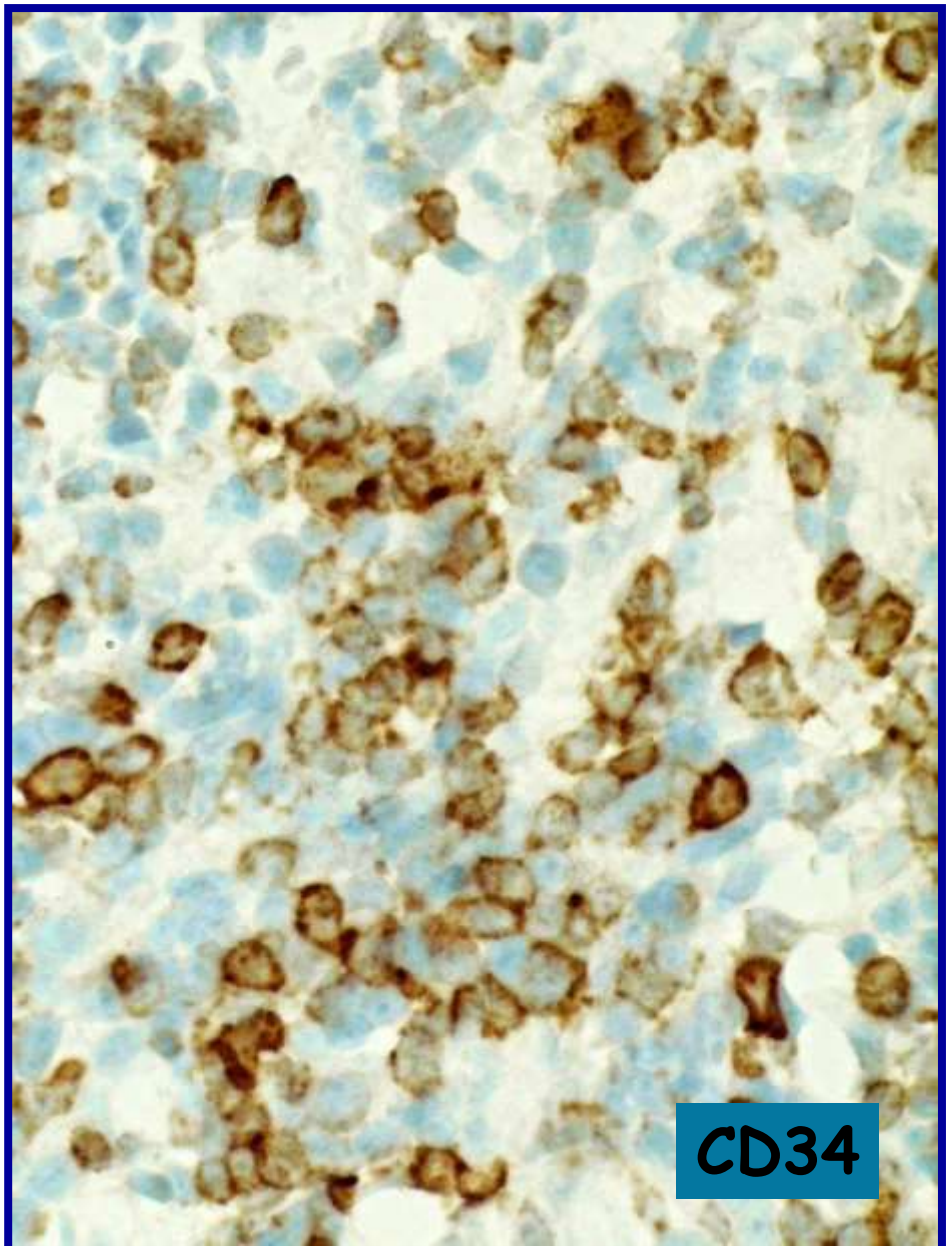
WHO 2008

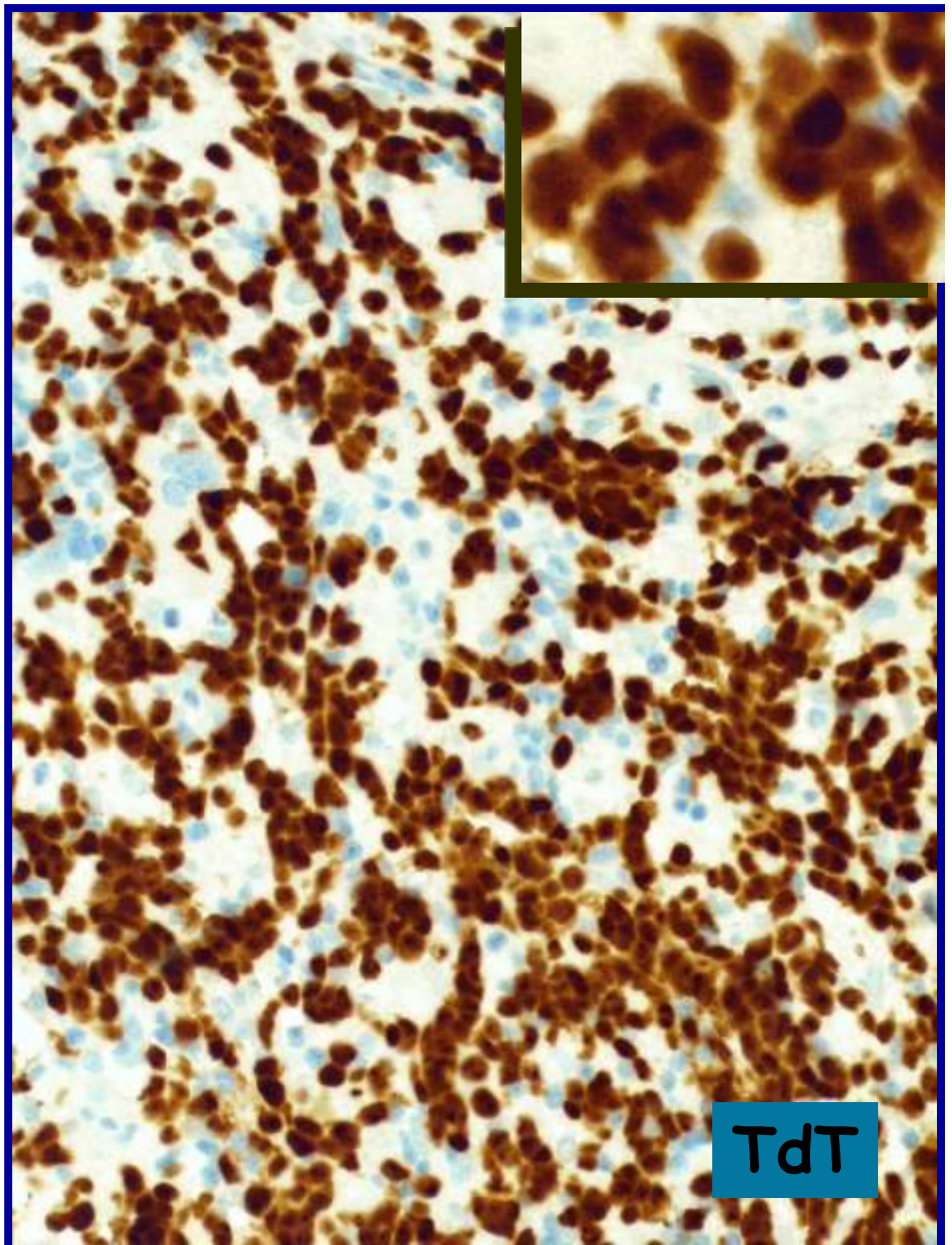
B-ALL/LBL





B-ALL/LBL





PRECURSOR LYMPHOID NEOPLASMS

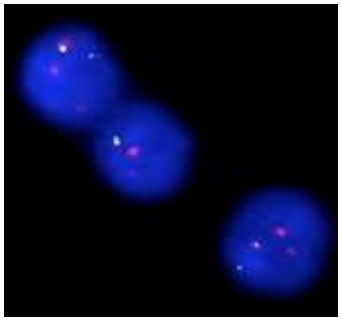
B lymphoblastic leukaemia/lymphoma

B lymphoblastic leukaemia/lymphoma, NOS *9811/3*

B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities

- B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1* *9812/3*
- B lymphoblastic leukaemia/lymphoma with t(v;11q23); *MLL* rearranged *9813/3*
- B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22); *TEL-AML1 (ETV6-RUNX1)* *9814/3*
- B lymphoblastic leukaemia/lymphoma with hyperdiploidy *9815/3*
- B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL) *9816/3*
- B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); *IL3-IGH* *9817/3*
- B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PBX1 (TCF3-PBX1)* *9818/3*

PREKÜRSOR B LEFOBLASTİK LENFOMA



SİTOGENETİK PROGNOSTİK PARAMETRELER

WHO 2008

Table 1. Aneuploidy in BCP-ALL

Cytogenetic subtype	Common gene implicated	Clinical relevance	Cooperating aberrations	Prevalence	Ref.
Hyperdiploidy (>50 chromosomes)		Excellent prognosis, especially in pediatric cases	Mutations in *FLT3*, *NRAS*, *KRAS*, or *PTPN11* Microdeletions of *CDKN2A*, *ETV6*, *IKZF1*, *PAX5*, *RB1*, and *TCF3* Mutation/deletion in *CREBBP* in relapsing cases	25%–30% of pediatric cases and ≤9% of adults	[45,47–50,56–58]
Hypodiploidy (<44 chromosomes)		Progressively poor prognosis with decreasing chromosome number		5%–8%	[59,60]
Near-haploid (24–31 chromosomes)			Activating mutations of tyrosine kinase (RTK)-RAS pathway (*NF1*, *NRAS*, *KRAS*, *MAPK1*, *FLT3*, *PTPN11*) and mutations/deletions in *IKZF3*	0.7%–2.4%	
Low hypodiploidy (32–39 chromosomes)			Mutations in *TP53*, *RB1*, *CDKN2A/2B* and *IKZF2*		
Hypodiploidy (40–43 chromosomes)					
Near-diploid (44–45 chromosomes)					

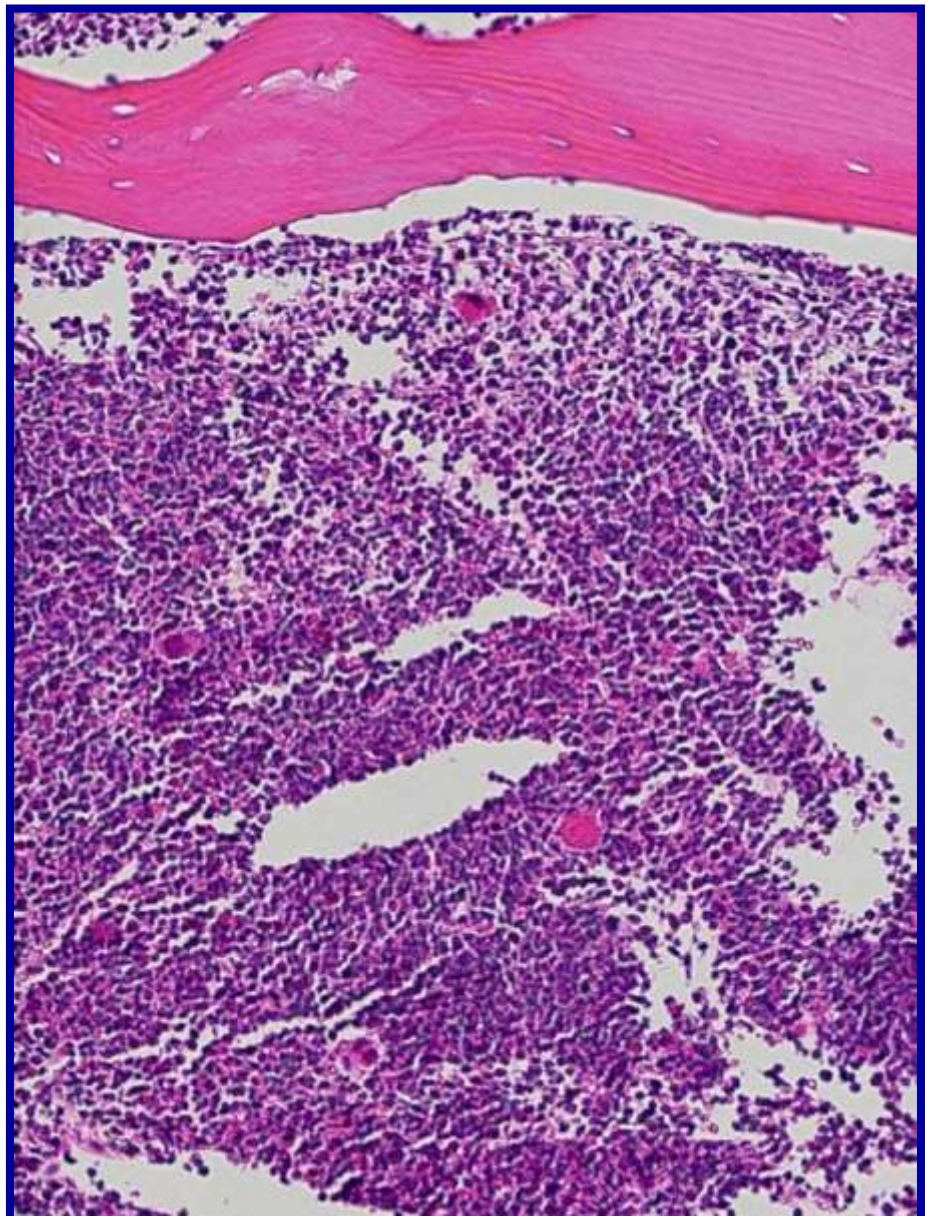
Ghazavi 2015

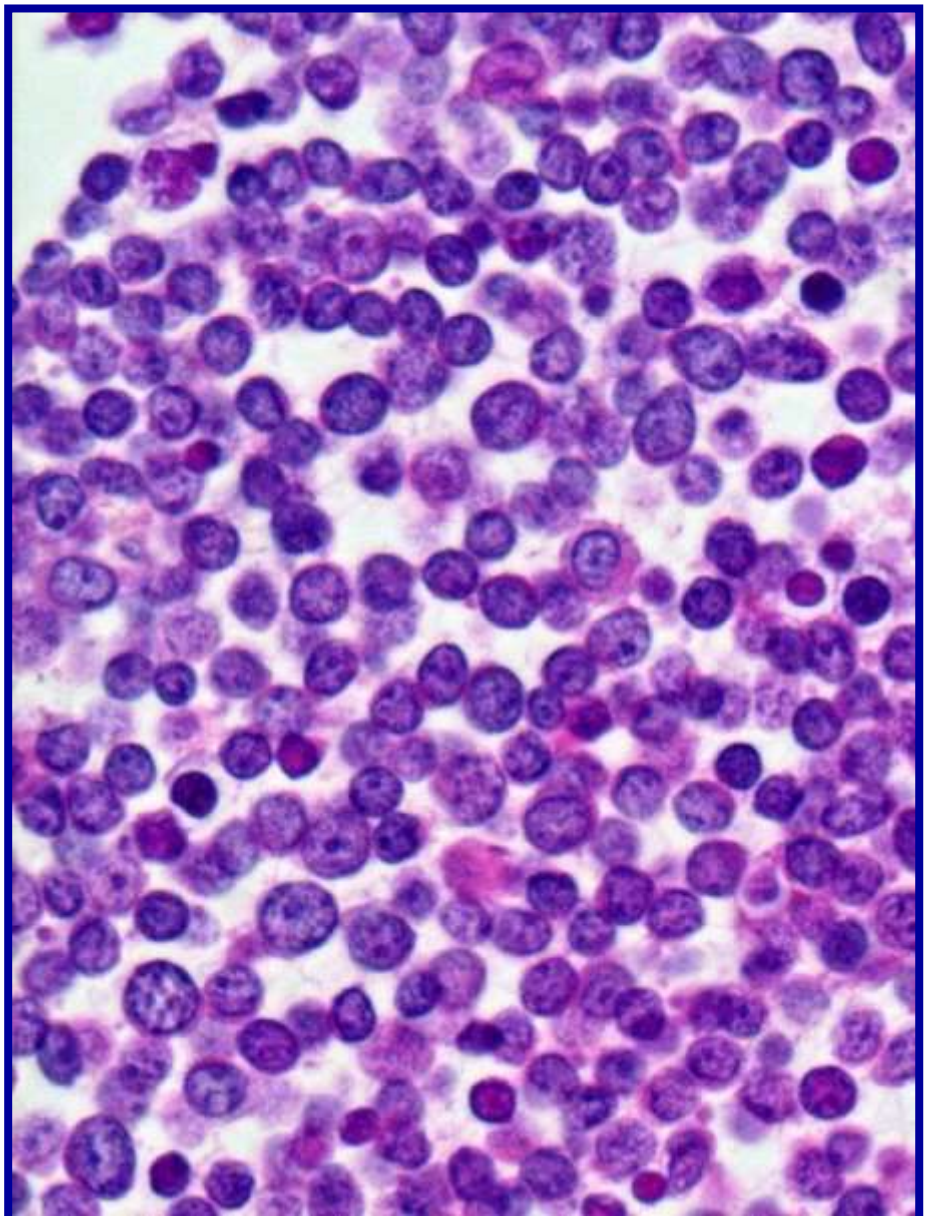
Table 3. Additional genetic alterations in BCP-ALL

Cytogenetic subtype	Common gene implicated	Clinical relevance	Cooperating aberrations	Prevalence	Ref.
BCR-ABL1-like ALL		Poor prognosis	Deletions in *IKZF1*, *TCF3*, *EBF1*, *PAX5*, and *VPREB1* Dic(9;20) and iAMP21 Deletions of *IKZF1*, deregulated *CRLF2* expression with *JAK* family mutation Rearrangements involving *ABL1*, *JAK2*, *CRLF2*, *PDGFRB*, *EBF1*, *EPOR*; activating mutations of *IL7R* and *FLT3*; and deletion of *SH2B3*	10%–15% of pediatric cases and one third of adolescents and young adults	[10,99,121–123,125]
iAMP21		Poor prognosis	Deletion of *IKZF1*, *CDKN2A*, *PAX5*, *ETV6*, and *RB1*; gain of X chromosome; and presence of *P2RY8-CRLF2* translocation	~2%	[125,130–133,135,136
t(v;14q32)	*IGH* with multiple fusion partners such as *CRLF2*, *ID4*, *CEBP*, *BCL2*, *EPOR*, *LHX4*, and *IL-3*	Poor prognosis		<5%, more frequent in adolescents	[99,137–143]
Translocation/ deletion/mutation on Xp22.3/Yp11.3	*CRLF2-IGH*, *P2RY8-CRLF2*	Poor prognosis	Associated with *JAK1/2* mutation in ≤50% of cases; in high-risk BCP-ALL, associated with both *IKZF1* deletion and/or mutation and *JAK1/2* mutation	≤7% of BCP-ALL cases, >50% of Down syndrome-ALL cases, 50% of BCR-ABL1-like ALL cases	[123–125,144,145]
Deletion on 21q22	*ERG*	Favorable prognosis		3% or 7% of pediatric cases	[147,148,150]
Deletion/translocation on 9p13	*PAX5* with multiple partners such as *ETV6*, *ELN*, *POM121*, *PML*, *FOXP1*, *MLLT3*, *JAK2*, *C20orf112*, *AUTS2*, *CHFR*, *SOX5*, and *POM121C*	Important in leukemogenesis, but not associated with adverse outcome		*PAX5* deletions: 30% *PAX5* mutations: 5%–7% *PAX5* rearrangements: 2%–3%	[151–157]
Focal deletions/ mutations on 7p12.2	*IKZF1*	Poor prognosis		15% of pediatric cases	[10,14]
Dic(9;20)		Unfavorable prognosis	*CDKN2A* deletion, iAMP21, chromosome X amplification	2%–3% of pediatric cases and ~0.5% of adults	[152,158]

Ghazavi 2015

T-ALL/LBL





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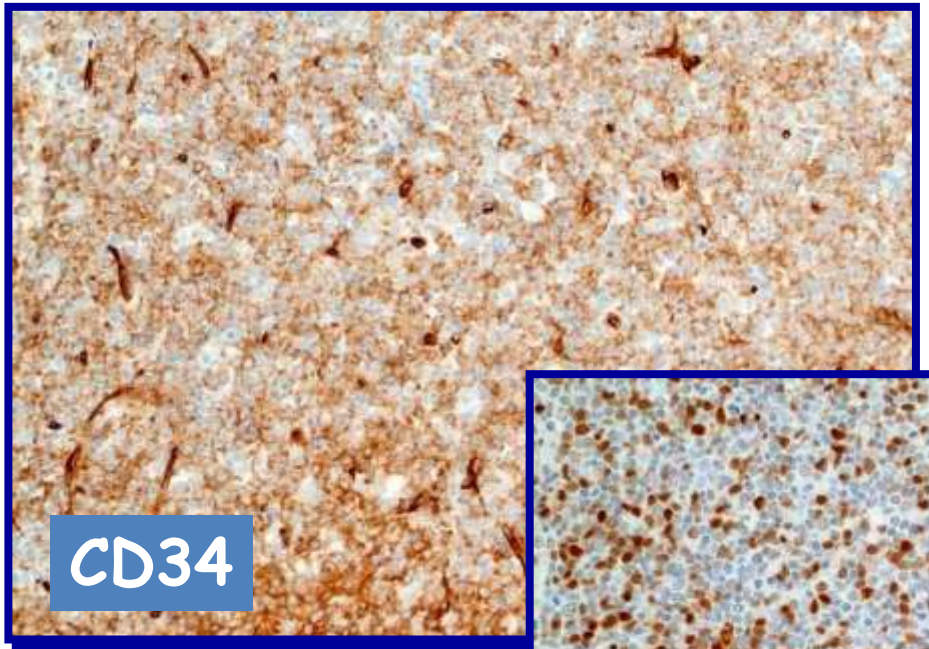
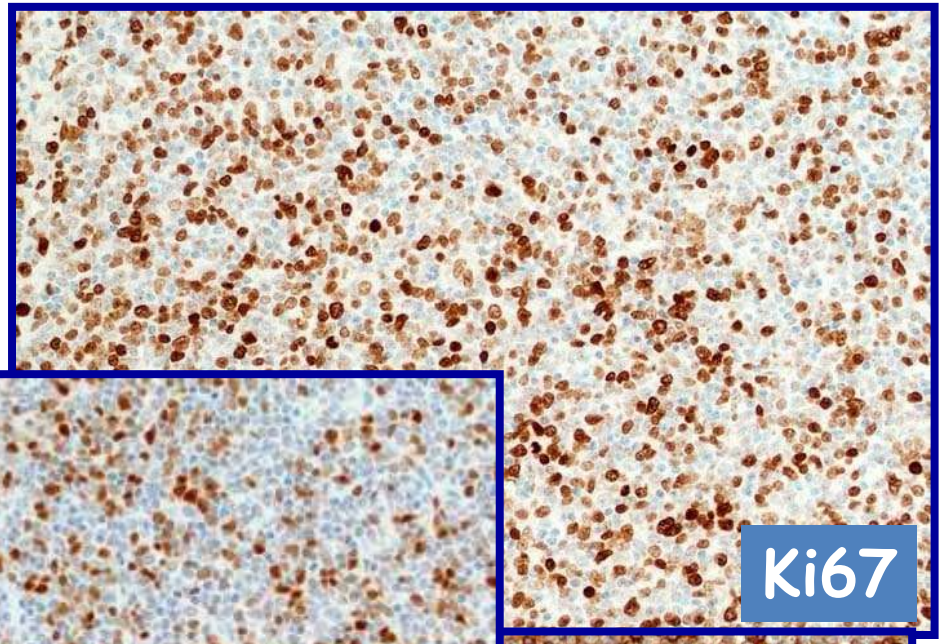
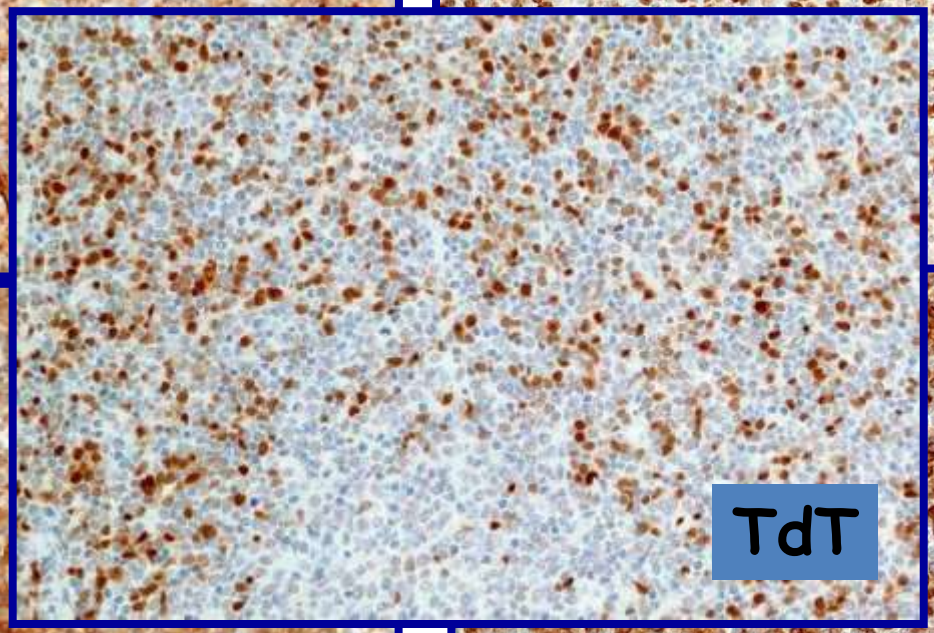
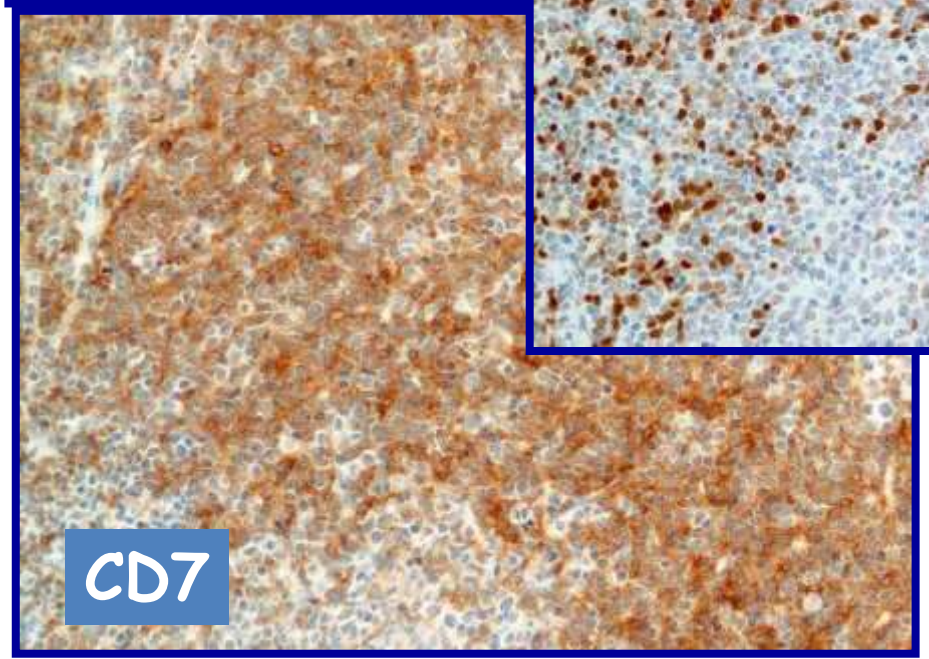
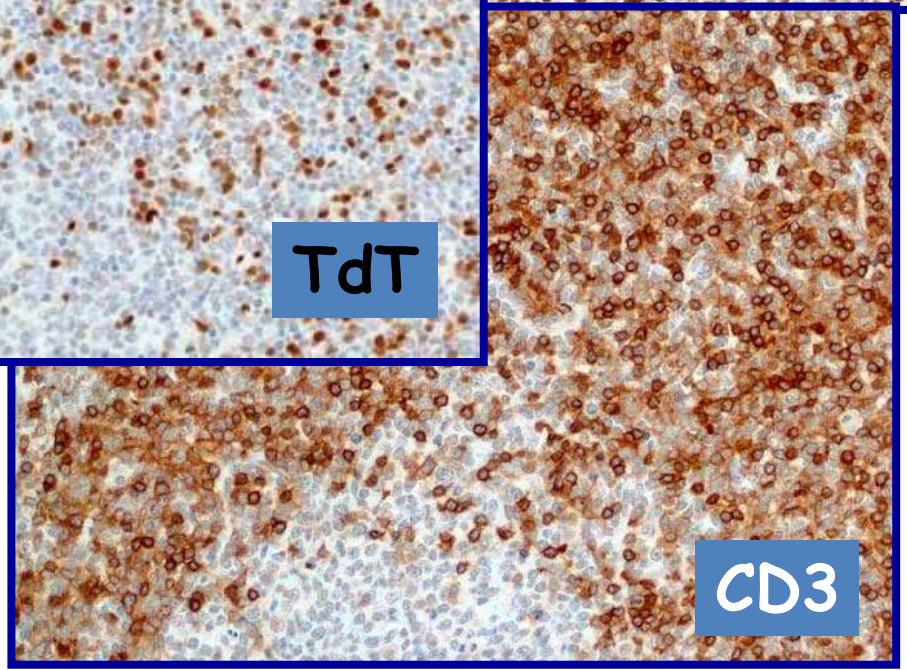










T & B LBL-L

GENETİK ANOMALİLER (TRANSKRİPSİYON FAKTÖRLERİ) ÇOK ÇEŞİTLİ .

TABLE II. Genetic Features of Lymphoblastic Lymphoma [4,129,133]

Phenotype	Genetic alteration	Dysregulated gene
T-cell*	t(1;14)(p32-34;q11)	*TAL1*
	t(1;7)(p32;q35)	*TAL1*
	TAL1 deletion	*TAL1*
	t(7;9)(q34;q32)	*TAL2*
	t(7;19)(q35;p13)	*LYL1*
	t(8;14)(q24;q11)	*MYC*
	t(10;14)(q24;q11)	*HOX11*
	t(7;10)(q34;q24)	*HOX11*
	t(11;14)(p15;q11)	*RHOM1*
	t(11;14)(p13;q11)	*RHOM2*
	t(7;11)(q34;p13)	*RHOM2*
	t(10;11)(p13;q14)	*AF10-CALM*
	t(1;7)(p34;q34)	*LCK*
	t(7;9)(q34;p34)	*TAN1*
	del(9)(p21-22)	*MTS1/MTS2*
B-precursor	t(1;19)(q23;p13)	*PBX1-E2A*
	21q addition	*Unknown*

Cairo, Pediatr Blood Cancer 2005;45:753–769

T & B LBL-L

HASTALIĞIN KLİNİK DAVRANIŞININ YANİ PROGNOZUN BELİRLENMESİNDE

SİTOGENETİK ÖZELLİKLERİN ÖNEMİ BULUNMAKTADIR.

TABLE I. Translocations in Pediatric T-Cell LBL/T-ALL

Chromosome rearrangement	Gene rearrangement	Prognosis[a]	Frequency[a]
t(1;14)(p32;q11.2)[b]	*TAL1(SCL)/TCR*	Not prognostic	3% t(1;14); 15–25% SCL-TAL1 rearrangement
t(5;14)(q35;q32)	*TLX3(HOX11L2)/BCL11B(CTIP2)*	Varies	18%
t(8;14)(q24;q11.2)	*CMYC/IgH*	Intermediate with current treatment regimens	2%
t(10;14)(q24;q11.2)	*HOX11/TCR*	Good	5–10%
t(11;14)(p13;q11.2)	*LMO2/TCR*	Not known	5–10%
t(11;14)(p15;q11.2)	*LMO1/TCR*	Not known	<1%
t(7;19)(q34;p13.2)	*TCR/LYL1*	Unfavorable	<1%
t(11;19)(q23;p13.3)	*MLL/ENL*	Unfavorable	2%
t(7;9)(q34;q34.3)	*TCR/NOTCH1(TAN1)*	Not known	<1%

[a]T-ALL, unknown in T-cell LBL.
[b]Rare variants with 7q34-35 or 7p15 breakpoints occur for translocations with 14q11.2 breakpoints.

Heerema, Pediatr Blood Cancer 2005;45:616-622

Olgun B hücreli lenfomalar

Yavaş Klinik Seyirli

- PEDİATRİK TİP FOLLİKÜLER LENFOMA (FL)
- PEDİATRİK MARJİNAL ZON LENFOMA

Agressif Klinik Seyirli

- DİFFÜZ BÜYÜK B HÜCRELİ LENFOMA
- BURKITT LENFOMA
- PRİMER MEDİASTİNAL BÜYÜK B HÜCRELİ LENFOMA

Pediatrik FL

Lymphoma subtype	Children (<18 years)	Adults (>18 years)
Hodgkin lymphoma	46%	13%
T-lymphoblastic lymphoma	3%	1%
B-lymphoblastic lymphoma	6%	1%
ALK+ ALCL	6%	2%
Burkitt lymphoma	20%	3%
Diffuse large B-cell lymphoma	6%	27%
Follicular lymphoma	<1%	20%
others	6%	35%

Klapper W, Oschlies I. Klin Padiatr 2012; 224: 183–190

Follicular (nodular) lymphoma in childhood: a rare clinical-pathological entity. Report of eight cases from four cancer centers.

Frizzera G, Murphy SB.

Cancer 1979;44:2218

Follicular (nodular) lymphoma during the first two decades of life: a clinicopathologic study of 12 patients.

Winberg CD, Nathwani BN, Bearman RM, Rappaport H.

Cancer 1981; 48:2223

Primary follicular lymphoma of the testis in childhood.

Finn LS, Viswanatha DS, Belasco JB, Snyder H, Huebner D, Sorbara L, Raffeld M, Jaffe ES, Salhany KE.

Cancer 1999; 85:1626

Grade 3 FL MORFOLOJİSİ
BCL-2 İFADESİ YOK
BCL-2 TRANSLOKASYONU YOK
Tonsil lokalizasyonu

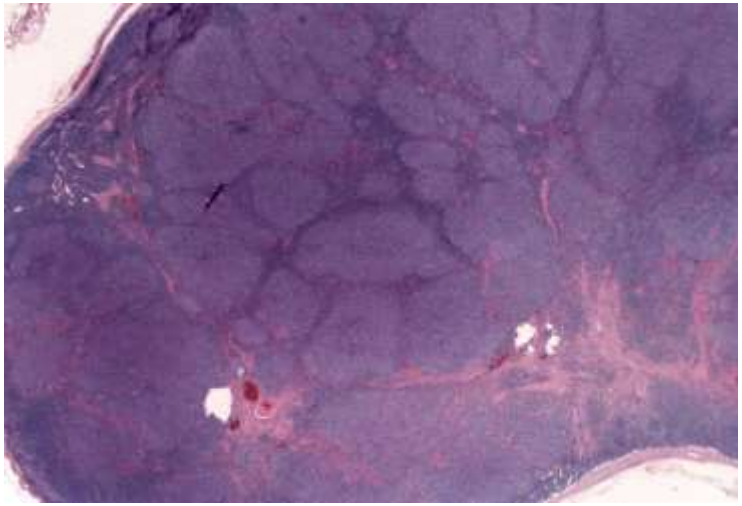
Follicular Lymphomas in Children and Young Adults

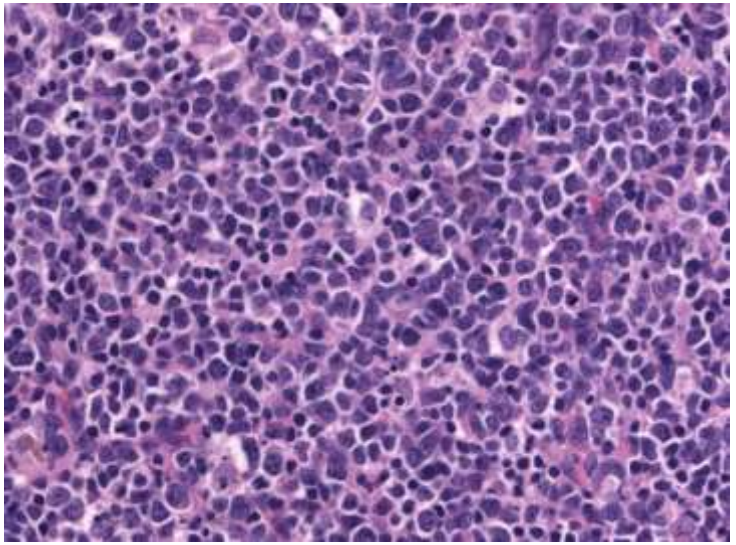
A Comparison of the Pediatric Variant With Usual Follicular Lymphoma

Qingyan Liu, MD, Itziar Salaverria, PhD,† Stefania Pittaluga, MD, PhD,* Armin G. Jegalian, MD, PhD,* Liqiang Xi, MD,* Reiner Siebert, MD,† Mark Raffeld, MD,* Stephen M. Hewitt, MD, PhD,* and Elaine S. Jaffe, MD**

Pediatrik FL

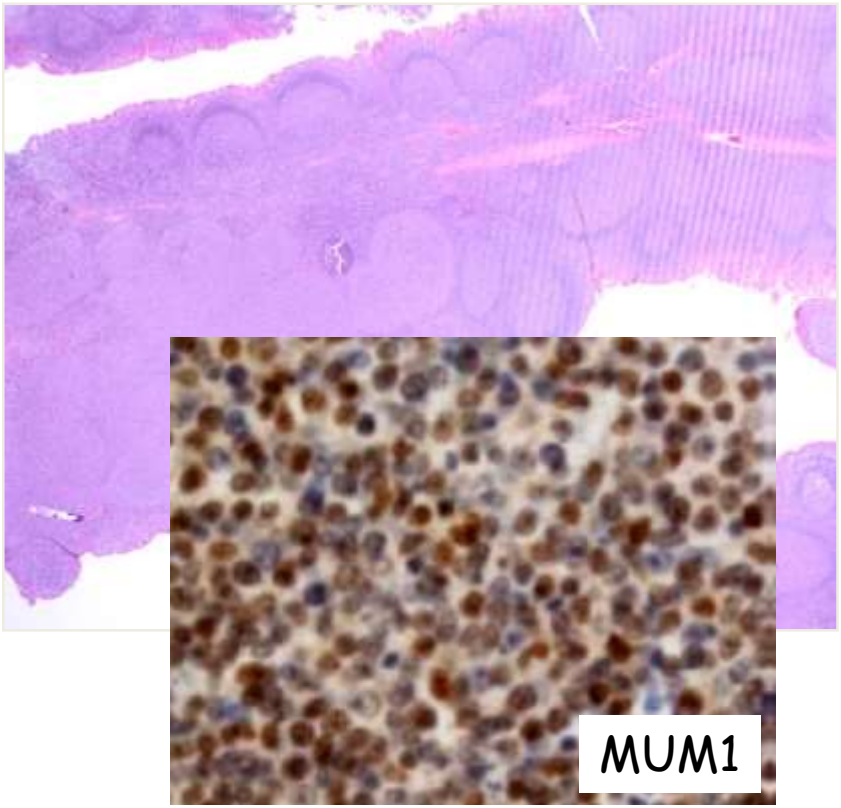
- klinik:
  - Erkeklerde
  - Baş boyun
  - Erken hastalık evresi
  - İyi prognozlu (watch & wait)
- morfoloji:
  - grade 3 büyük folliküller
  - BCL2 ifade kaybı
- Genetik:
  - t(14;18) yoktur
  - Reaktif proliferasyonlardan ayırım : klonalite analizi!
    - *IGH* monoclonal





Pediatrik FL

- MUM1 and BCL6 ifadesi 100%
  - 50% *IRF4* kırıkları
- BCL2 ifadesi 63%
  - t(14;18) yokluğunda
- CD10- 40%
- K:E; 1:1
- Ort yaş 9 (3-18)
- Sıklıkla diffüz alanlar +
- Agressif olma potansiyeli var
- CD10- (40%), BCL6+, MUM1+
- %80 Baş Boyun bölgesi

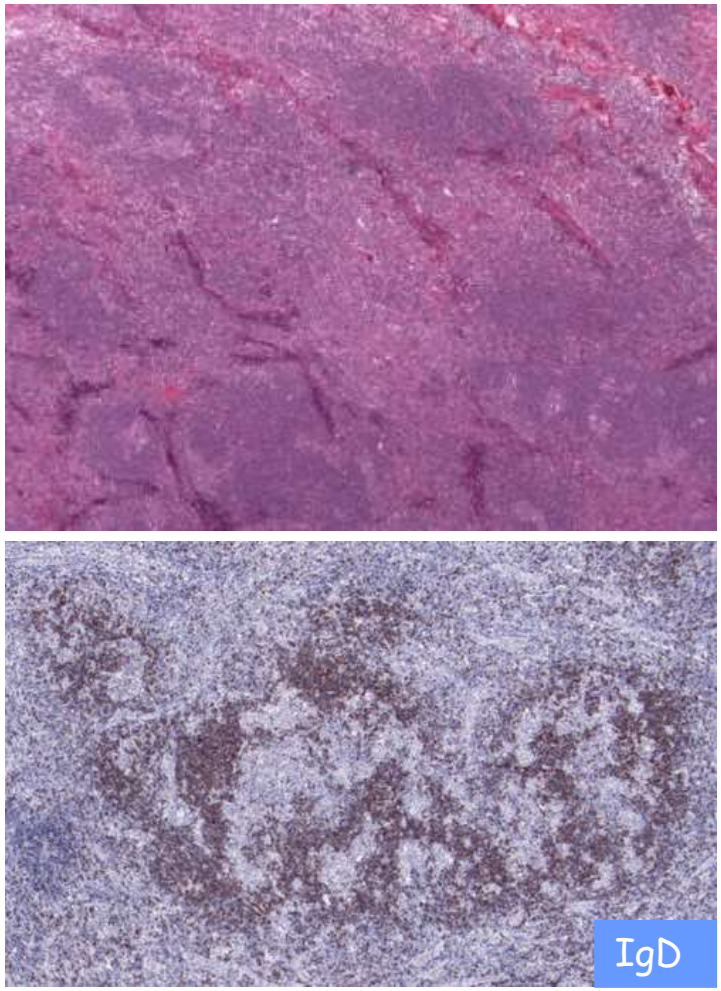


Liu Q et al, Am J Surg Pathol 2013; 37:333

Salaverria I et al, Blood 2011;118:139

Pediatrik Nodal Marginal zon lenfoma

- Klinik
  - Genç erkek
  - Baş boyun bölgesi
  - Ort yaş 16 (2-27)
  - E:K 20:1 (<18 yaş)
  - E:K 5.4:1(19-27 yaş)
  - 90% evre I
  - Rekürrens oranı çok düşük lokal eksizyon
- Morfoloji
  - Germinal merkezlerin progressif transformasyonu benzeri görünüm
  - Folliküller arası dağılım
- Genetik
  - IgH klonalitesi +



Taddesse-Heath et al, Am J Surg Pathol 2003;27:522

Ayırıcı tanı

	Follicular lymphoma, pediatric-type	Nodal marginal zone lymphoma, pediatric
Gender	Predominates in males	Predominates in males
Localization	Head and neck LN	Head and neck LN
Stage	Usually stage I	Usually stage I
Morphology	Marginal zone differentiation may simulate NMZL	Follicular colononization and nodular growth, aberrant expression of CD10 may simulate FL
Genetic	Monoclonal *IGH* *IRF4, TNFRSF14, EZH2* alterations	*Monoclonal IGH* Trisomy 18, trisomy 13

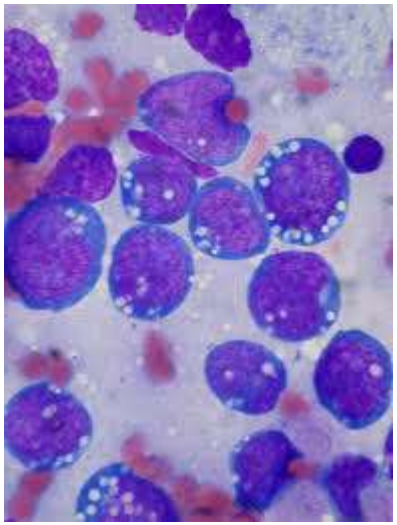
Quintanilla Martinez 2016

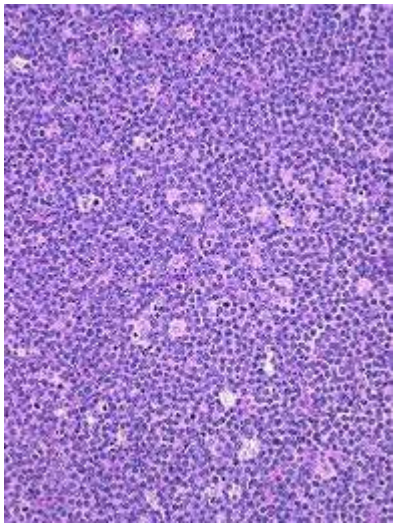
Olgun B hücreli lenfomalar

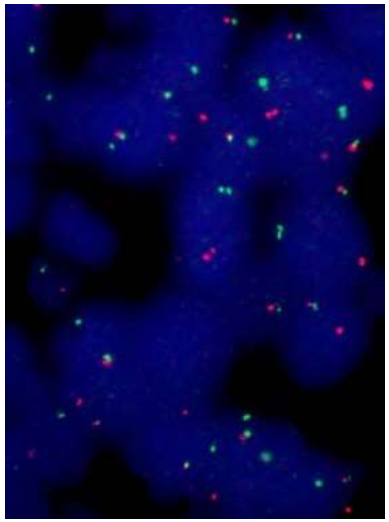
Agressif Klinik Seyirli

- BURKITT LENFOMA
- DİFFÜZ BÜYÜK B HÜCRELİ LENFOMA
- PRİMER MEDİASTİNAL BÜYÜK B HÜCRELİ LENFOMA

BURKİTT LENFOMA (BL)

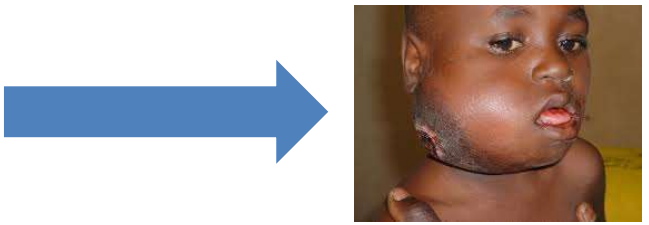






BURKİTT LENFOMA

Epidemiyoloji



ENDEMİK: 4-10 yaş Afrika,
EBV (>%90)+

SPORADİK: Pediatrik , Erişkin ort 30 yaş
Avrupa, Kuzey Amerika
EBV (<%30) +

İMMUNYETMEZLİK İLİŞKİLİ :
HIV + hastalarda %30-40
EBV (%30-40) +

Etiyoloji -Patogenez

Kronik Antijenik uyarı

Afrika kalıcı malarya enfeksiyonu , HIV ilişkili immun yetmezlik zemini

Myc translokasyonu :

Proliferasyon artışı,

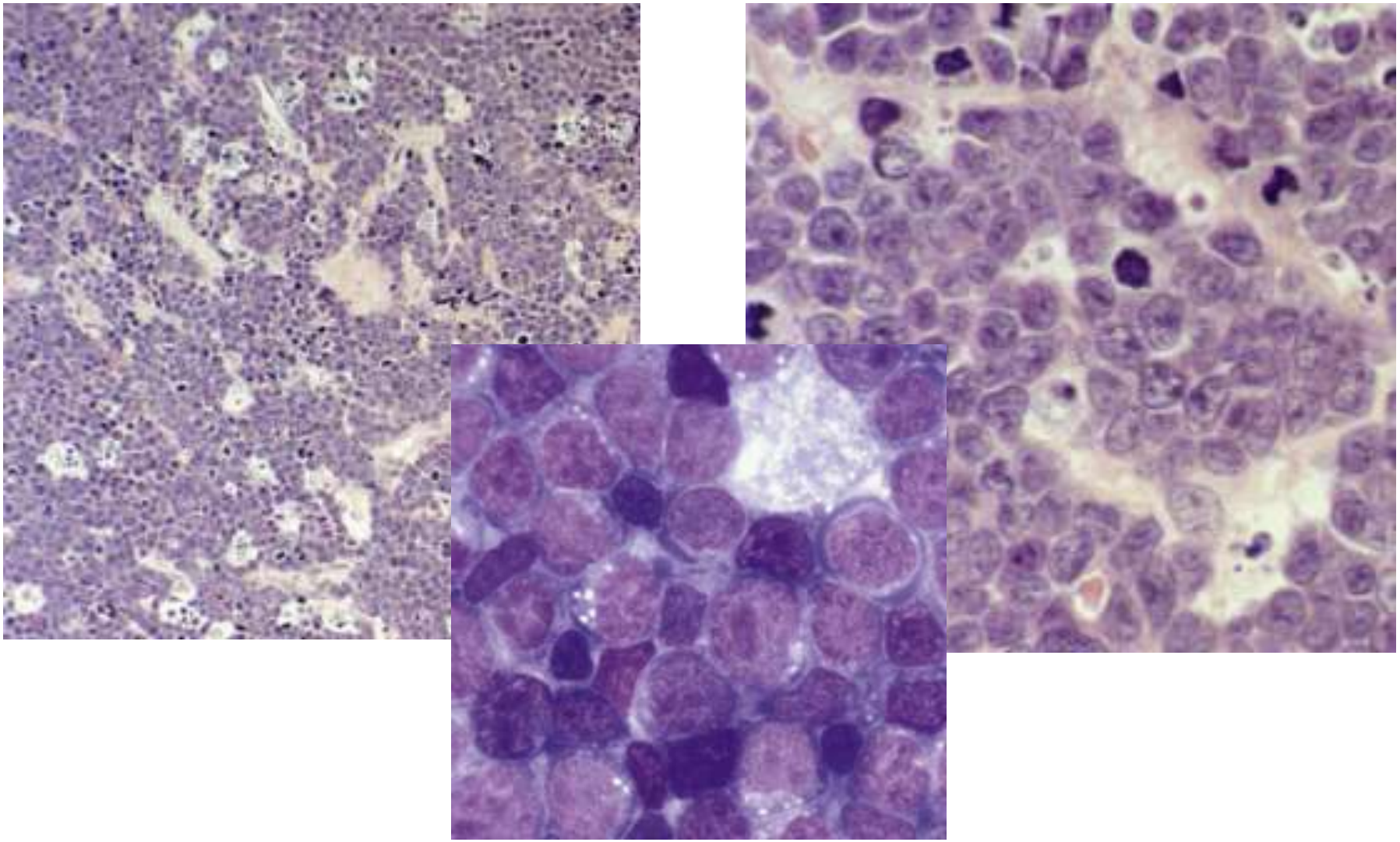
Apopitozun uyarılması ,

HLA Sınıf I molekül ifadesi düşüşü

İmmun sistem kontrolünden kaçış

EBV enfeksiyonu

Karakteristik morfoloji



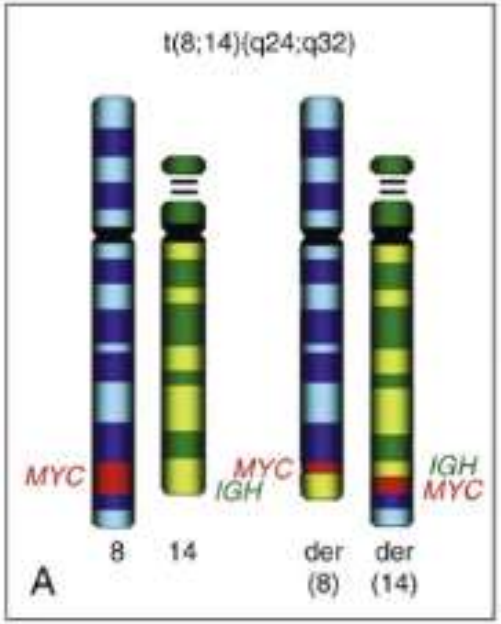
İmmunfenotip

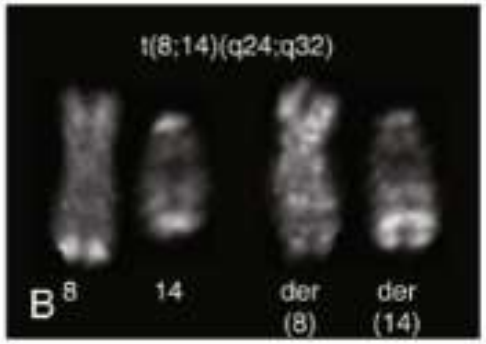
Endemik BL = CD21 +, TdT -, MUM1-
Sporadik BL = CD21-, TdT -, MUM1-

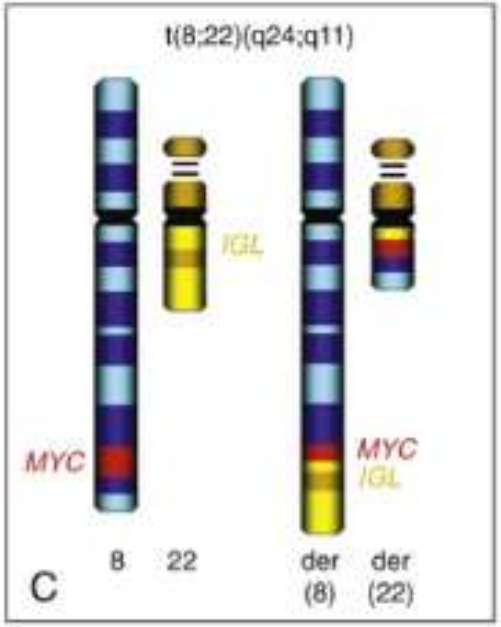
TABLE 24-2 Immunophenotypic and Molecular Features of AIDS-Related Lymphomas

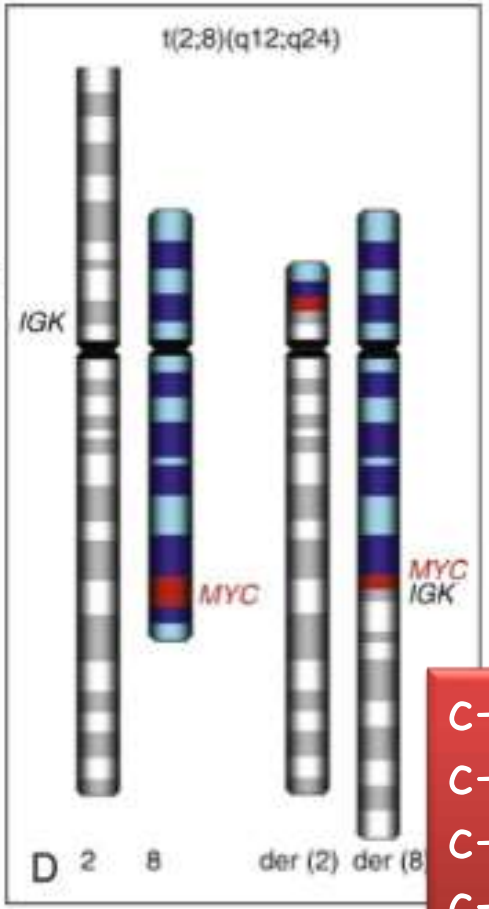
Feature	AIDS BL	AIDS DLBCL	AIDS IBL
EBV infection (EBER positive)	30%	40%	90%
LMP-1 status	–	–	+
BCL6 expression	+	+	–
MUM-1/IRF4	–	–	+
CD138	–	–	+
MYC rearrangement	100%	Some	Some
BCL6 rearrangement	–	20%	–
p53 mutations	60%	Rare	Rare

Myc gen düzenlenmesi

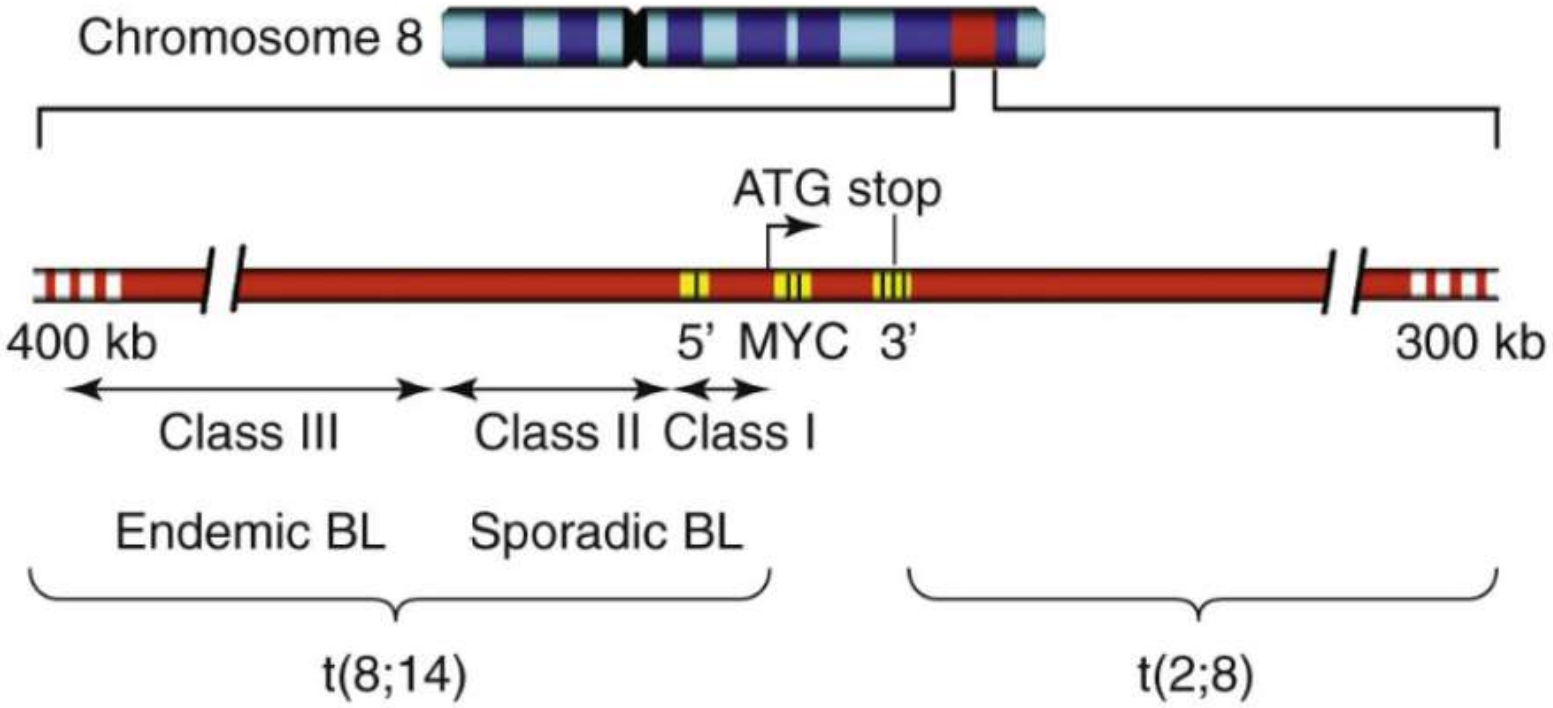








c-myc; IgH	t(8;14)(q24;q32)
c-myc: Igk	t(2;8)(p12;q24)
c-myc: Igl	t(8;22)(q24;q11)
c-myc: TCR-a	t(8;14)(q24;q11)



Feature	Endemic BL	Sporadic BL	AIDS-Associated BL
Predominant *MYC* breakpoint in t(8;14) (q24;q32)	Far 5′ (centromeric) of *MYC* (class III)	Exon and intron 1 (class I) and 5′ (centromeric) of *MYC* (class II)	Exon and intron 1 (class I)
Predominant *IGH@* breakpoint in t(8;14) (q24;q32)	VDJ region	Switch region	Switch region
Somatic *IGH@* mutations	Yes	Yes	Yes
EBV positivity	>90%	5%-30%	25%-40%

R Gascoyne, R Siebert, J Conors, 2011

Borderline cases

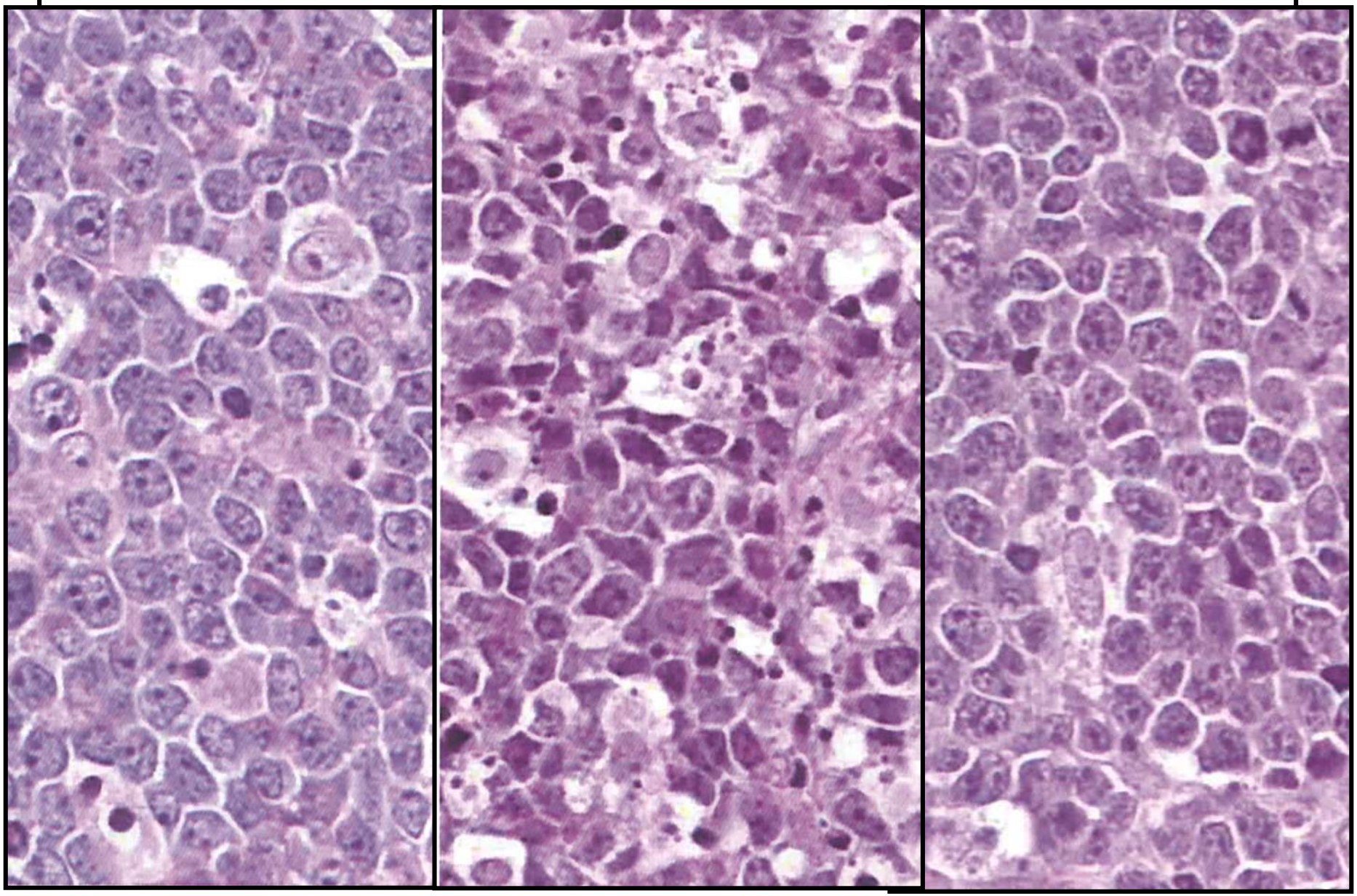
WHO 2008

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma

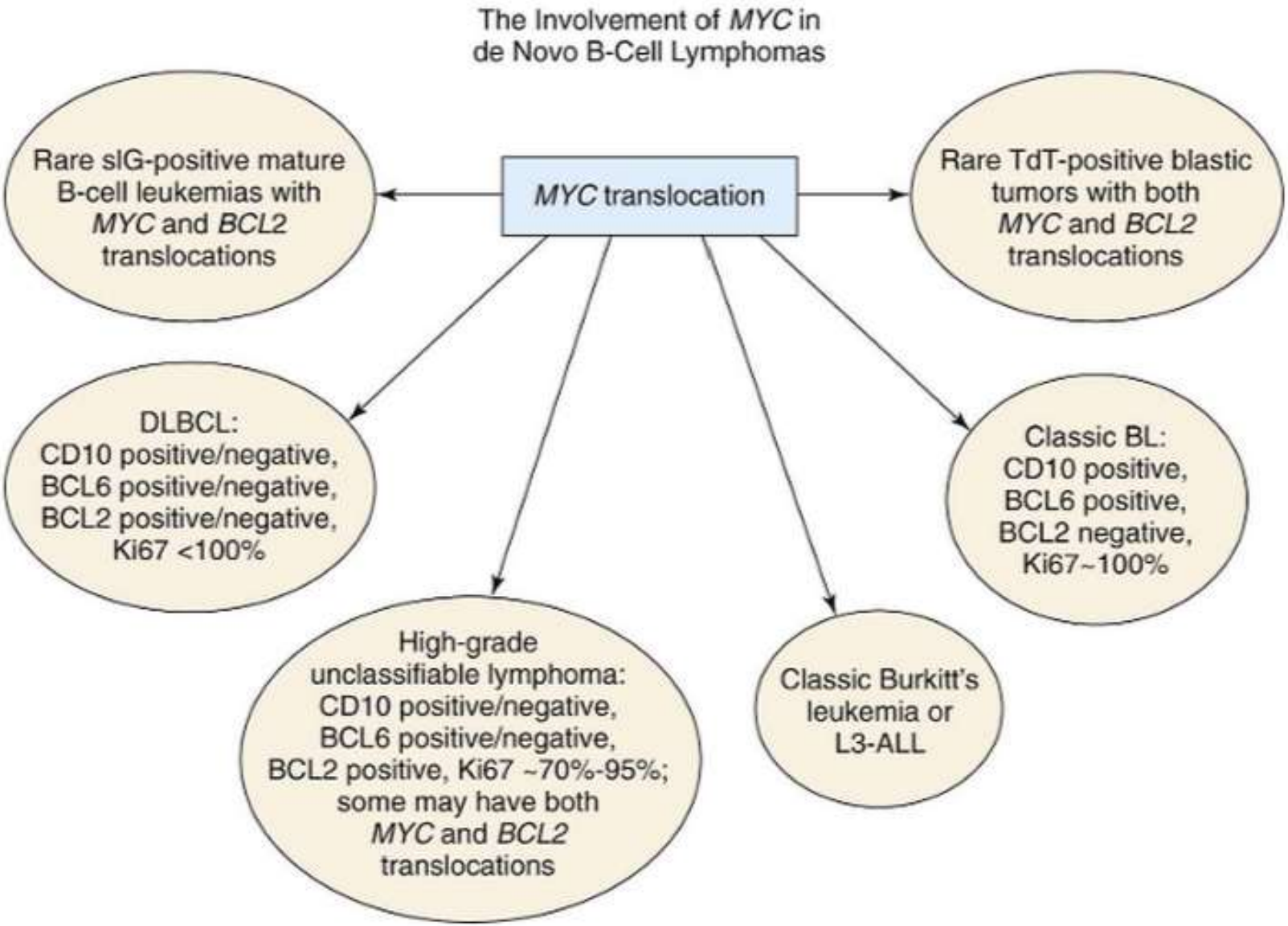
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Characteristic	BL	Intermediate BL/DLBCL	DLBCL
Morphology			
Only small/medium-size cells	Yes	Common	No
Only large cells	No	No	Common
Mixture	No	Sometimes	Rare
Proliferation (Ki67/MIB1)			
>90% and homogeneous	Yes	Common	Rare
<90% or heterogeneous	No	Sometimes	Common
BCL2 expression			
Negative / weak	Yes	Sometimes	Sometimes
Strong	No	Sometimes	Sometimes
Genetic features			
MYC rearrangement	Yes*	Common	Rare
*IG-MYC***	Yes	Sometimes	Rare
Non *IG-MYC***	No	Sometimes	Rare
BCL2 but no *MYC* rearrangement	No	Rare	Sometimes
BCL6 but no *MYC* rearrangement	No	Rare	Sometimes
Double hit#	No	Sometimes	Rare
MYC-Simple karyotype***	Yes	Rare	Rare
MYC-Complex karyotype***	Rare	Common	Rare

WHO 2008



Myc translokasyonu Burkitt lenfomaya özgü müdür?



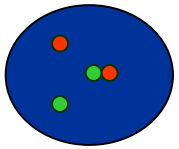
R Gascoyne, R Siebert, J Conors, 2011

Klasik morfoloji Pediatrik Hasta
CD20+, CD10+, Bcl-6+, Ki67(>%95), Bcl2-

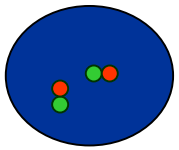
→ BL

Atipik morfoloji /immunfenotip Pediatrik Hasta
Erişkin morfoloji /immunfenotip BL benzer
CD20 +, CD10+, Bcl6+

Myc ayrılma probe FISH



→ Pediatrik vakalar = BL



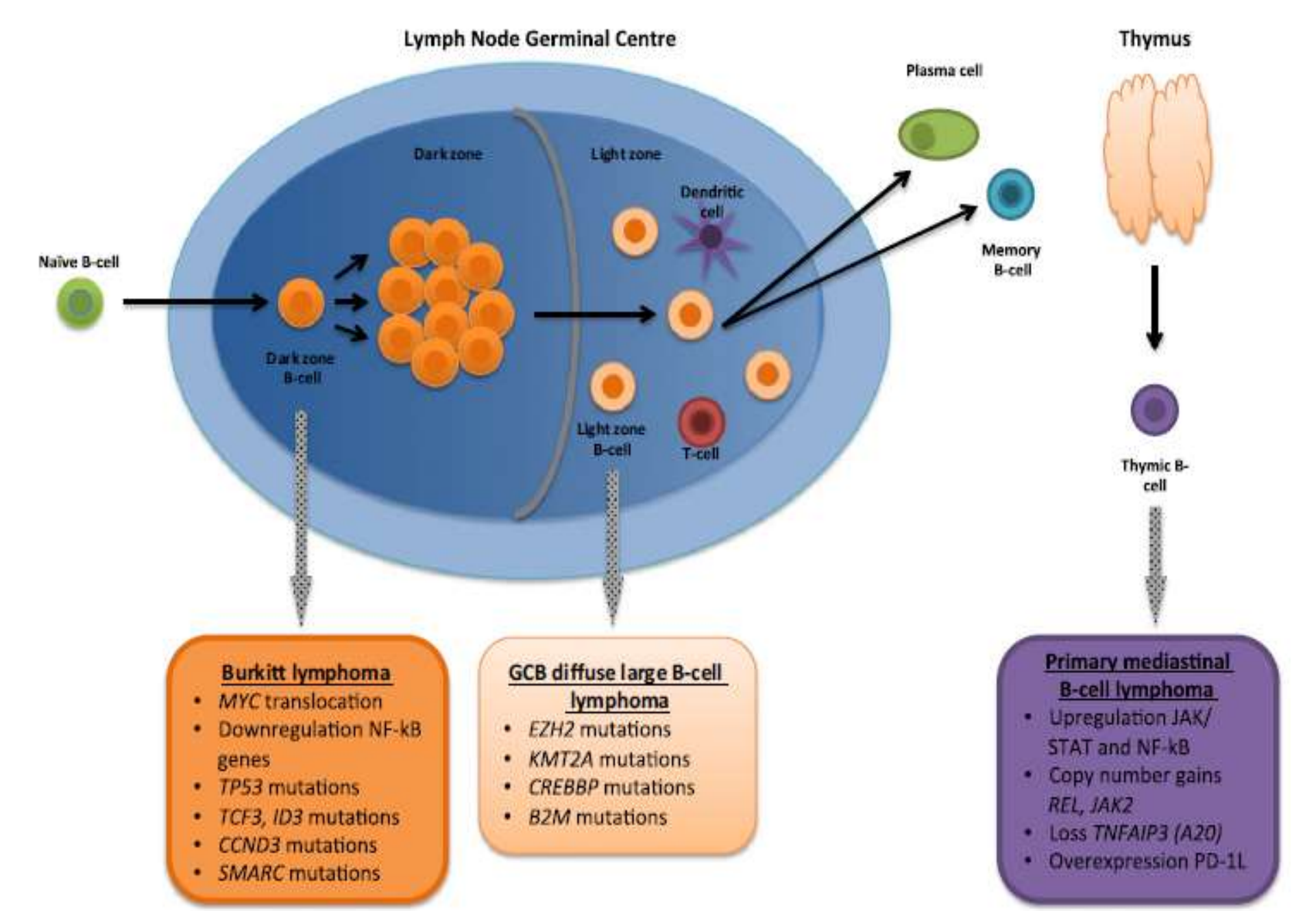
Erişkin
İmmunfenotip
Bcl2, Ki67 >%95
Moleküler :FISH
Bcl2, Bcl6

IHK:Bcl2 ++, Ki67 <%95,
FISH: Bcl2 ve/veya Bcl6+

→ Morfolojiye dayalı olarak BL DBBHL arasında sınıflandırılamayan BHL

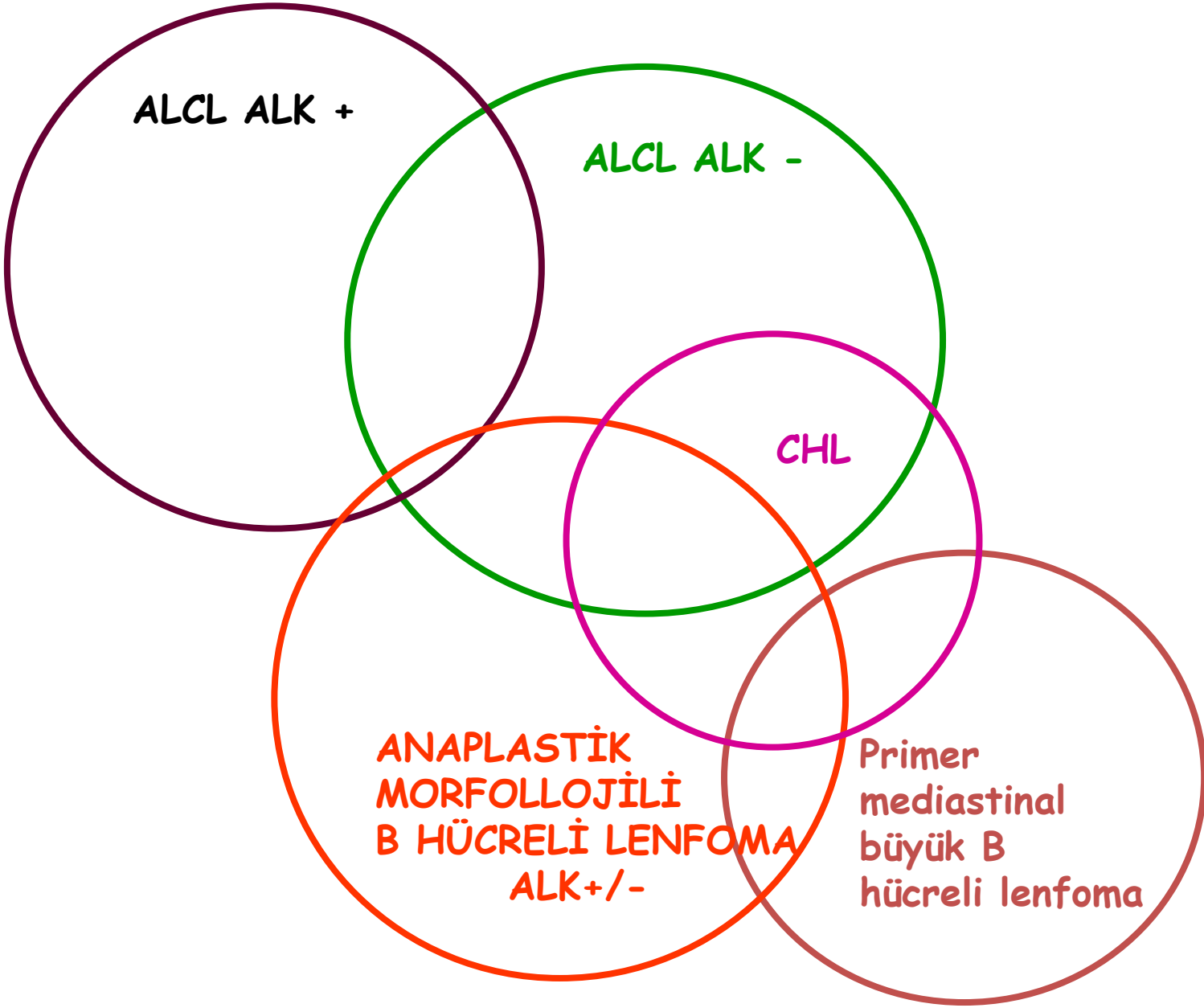
IHK: Bcl2-/+, Ki67 >%95,
FISH: Bcl2 ve Bcl6 -

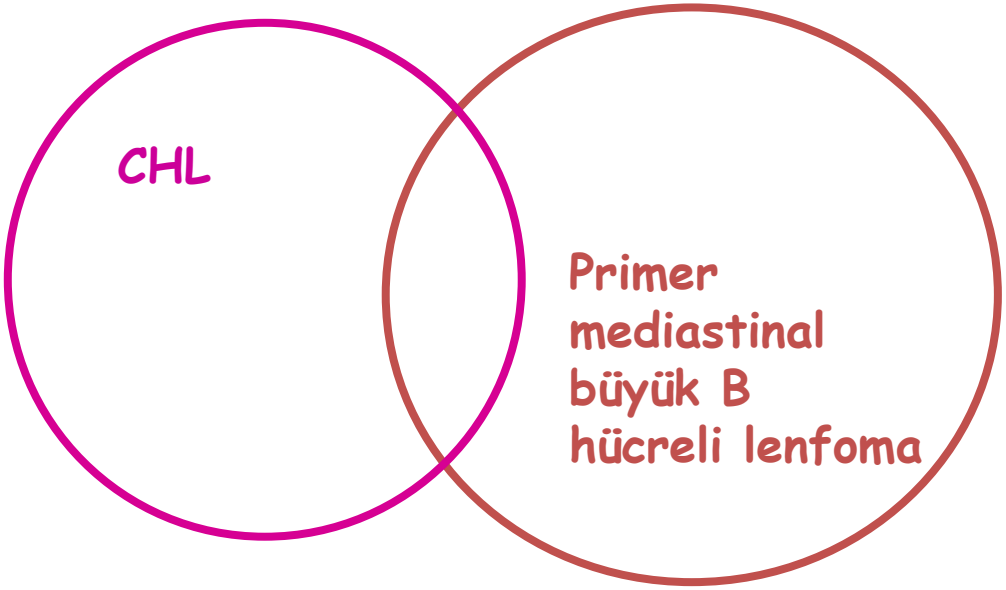
→ BL kabul et



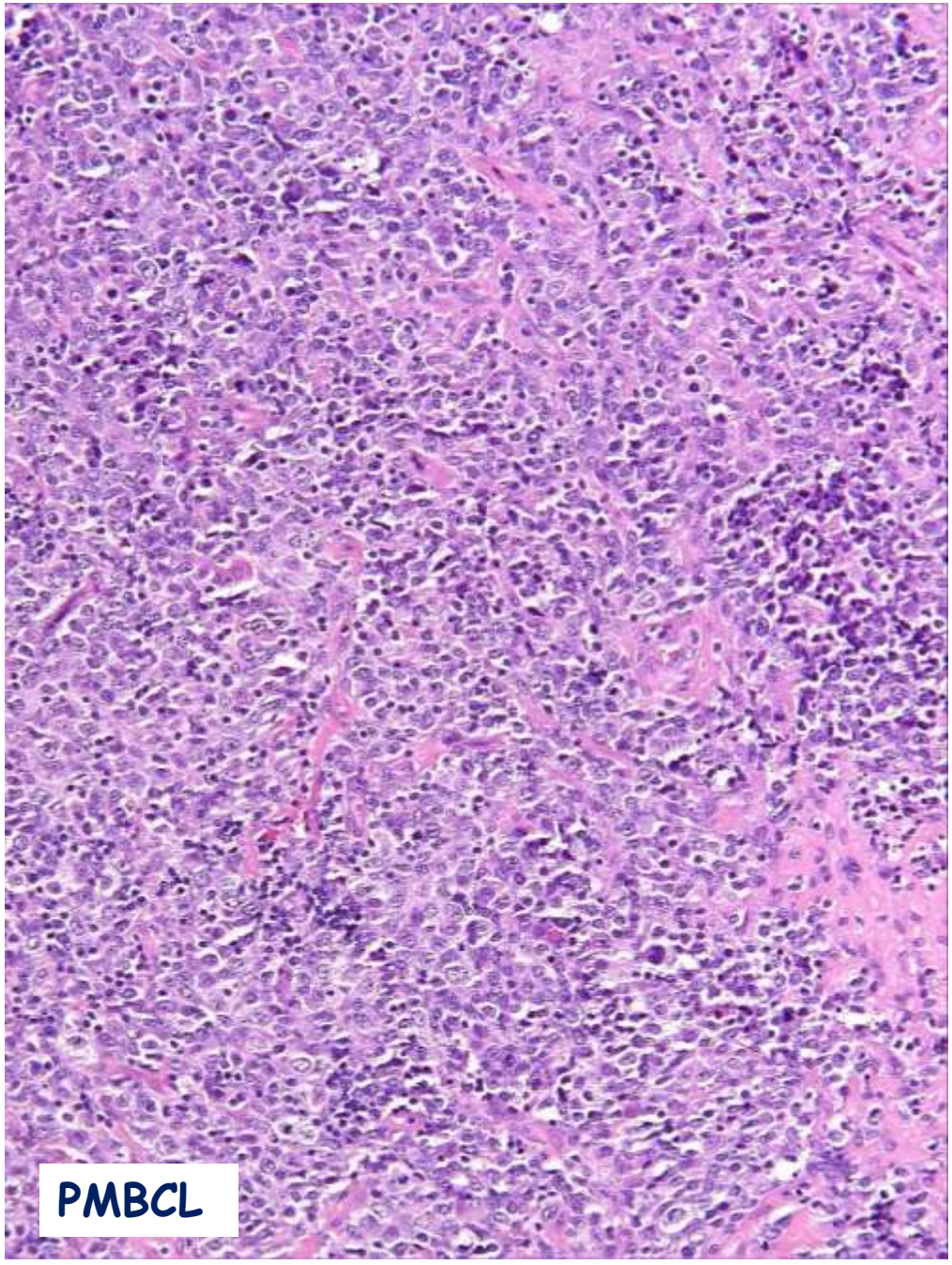
Lisa Giulino-Roth BJH 2016

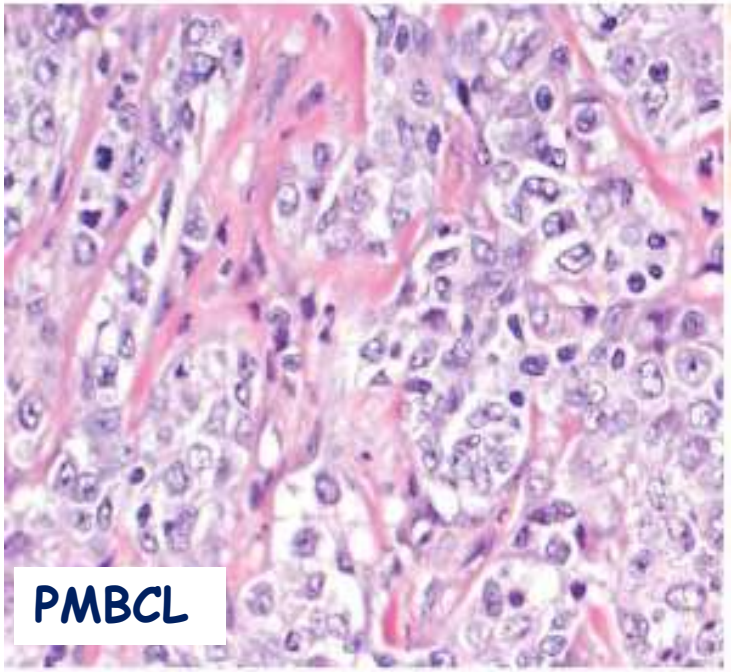
ANAPLASTİK MORFOLOJİLİ LENFOMALARDA AYIRICI TANI

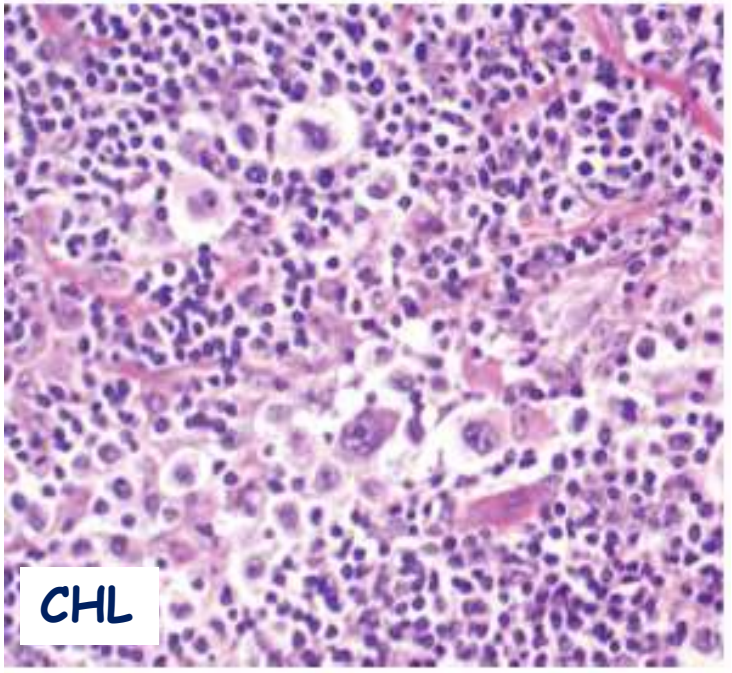




	PMLBCL	NSHL
Clinical presentation	Common to both: • Young adults, female predominance • Mediastinal mass with involvement of thymus and supraclavicular nodes • Often localized disease (stages I-II)	
	Involvement of other distant extranodal sites at presentation or upon recurrence	Usually no Involvement of other extranodal sites
Morphology	Fine compartimentalizing sclerosis, diffuse pattern	Broad bands of collagen fibrosis, nodular pattern
	Medium to large clear cells, Reed-Sternberg-like cells can be present	Reed-Sternberg cells, lacunar cells
	Sheets of tumor cells, little or no inflammatory background	Scattered neoplastic cells in an inflammatory background

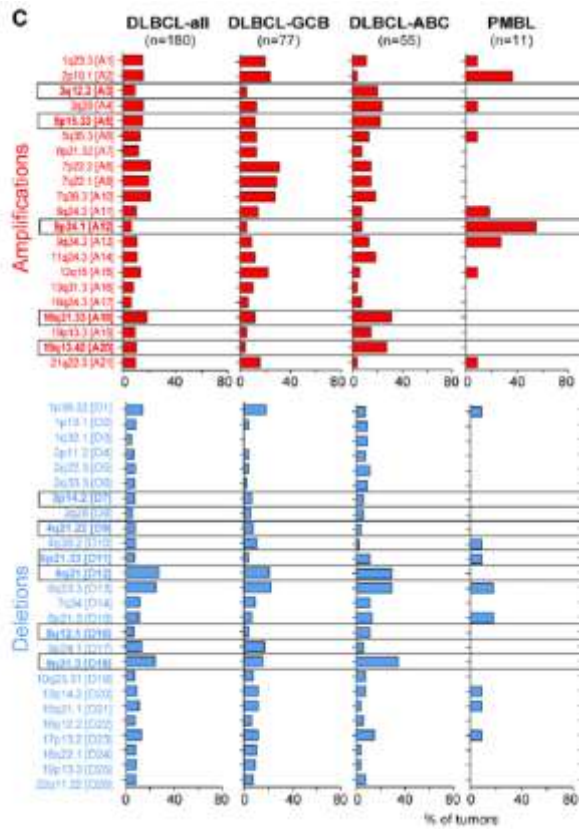

PMBCL


PMBCL


CHL

Klasik Hodgkin lenfoma –Diffüz Büyük B Hücreli lenfoma

- "grey zone" Diffüz büyük B hücreli lenfomadan farklı
- CD15+ LBCL hepsi "grey zone" değil
- CD20+ CHL hepsi "grey zone" değil

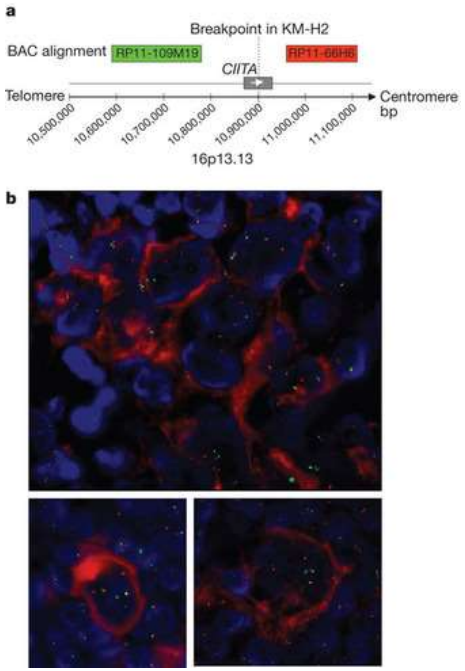


Morfolojik ayırıcı tanı
İle başlangıç

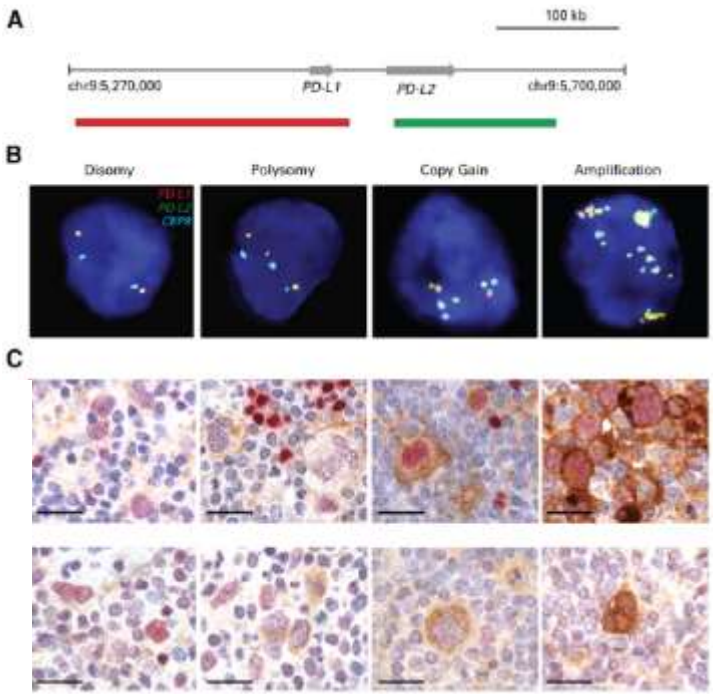
Chapuy Blood 2016;127:869

Klasik Hodgkin lenfoma –Diffüz Büyük B Hücreli lenfoma

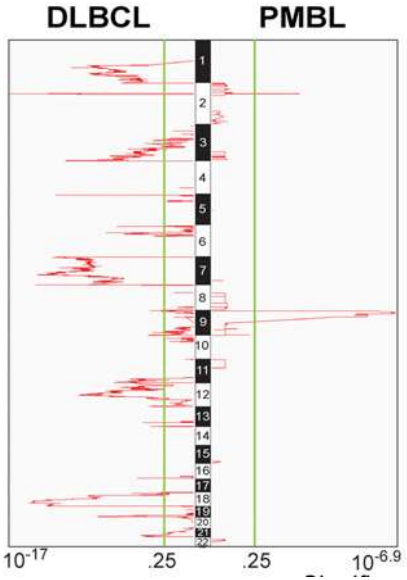
- Genomik değişiklikler ve mutasyon profili PMBCL and CHL lenfomalarda birbirine benzer.
- Fenotipik özellikler benzer



CIITA translocation



9p24 amplification/translocation, REL amplification



Steidl Nature.2010;;471:377Roemer JCO2016;34 on line,Green Blood 2010;116:326, Chapuy Blood 2016;127:869

Savage Blood 2003;102;3871, Rosenwald JExMed 2003;198;851, Green Blood 2010;116:3268, Steidl et al. Nature 2010;471:381, Roemer JCO 2016;34;online

Gri zon lenfoma

Features that favor PMBL

Absence of nodularity, no eosinophils

CD45 + CD20 + CD79a + Bcl6 + CD19 + CD30 weak CD15 –

Features that favor CHL

Prominent nodularity, sclerotic bands, eosinophils

CD45 – CD20 –/+ Pax5 weak Bcl6 – CD30 + + CD15 + Oct2/Bob1 –

Features that favor 'grey-zone lymphoma' intermediate PMBL/CHL

Areas with, lacunar cells, eosinophils, sheets of tumor cells resembling PMBL

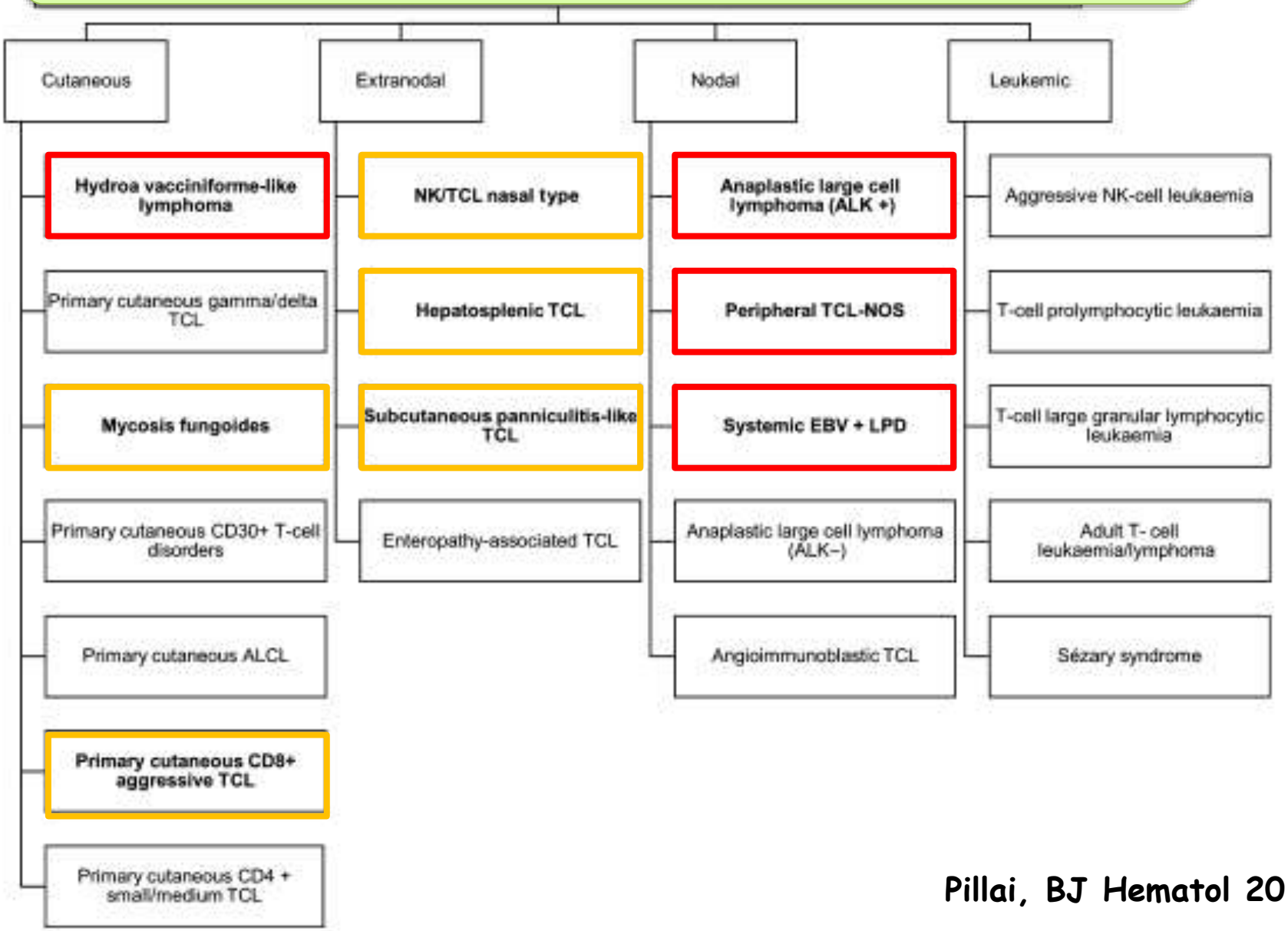
CD45 + CD20 + CD79a + CD30 + + CD15 +

Not all cases of CD20 + CHL belong in this category

The more B-cell antigens expressed in a tumor resembling CHL, the more likely it is to be grey-zone

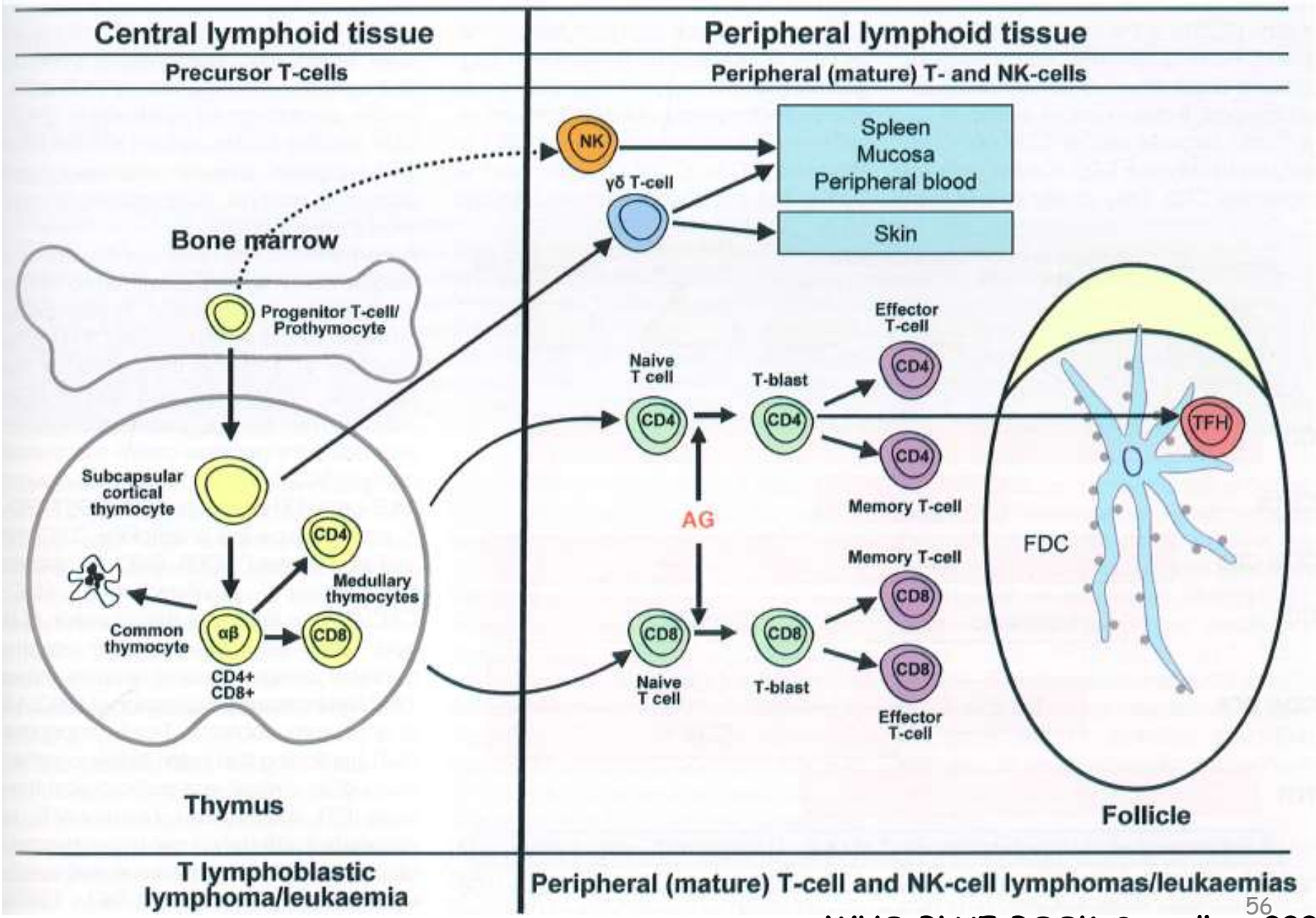
Savage Blood 2003;102;3871, Rosenwald JExMed 2003;198;851, Green Blood 2010;116:3268, Steidl et al. Nature 2010;471:381, Roemer JCO 2016;34;online

Olgun T hücreli lenfomalar



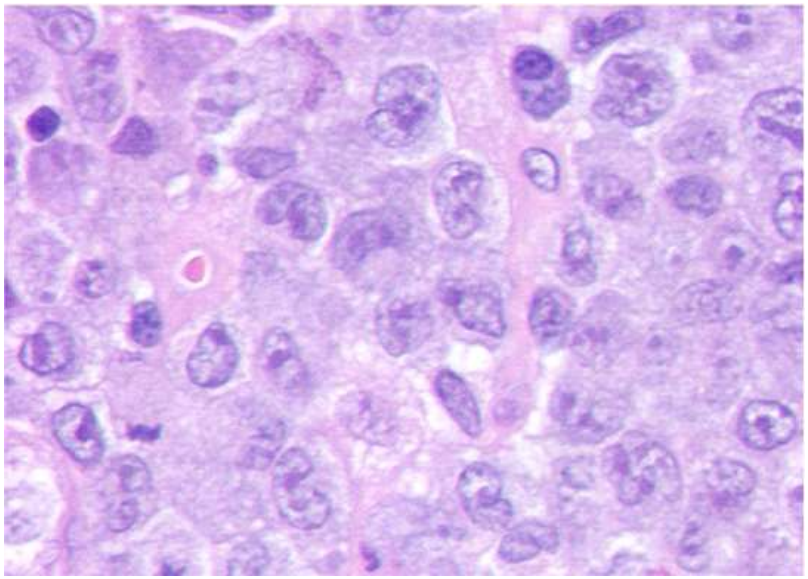
Pillai, BJ Hematol 2016

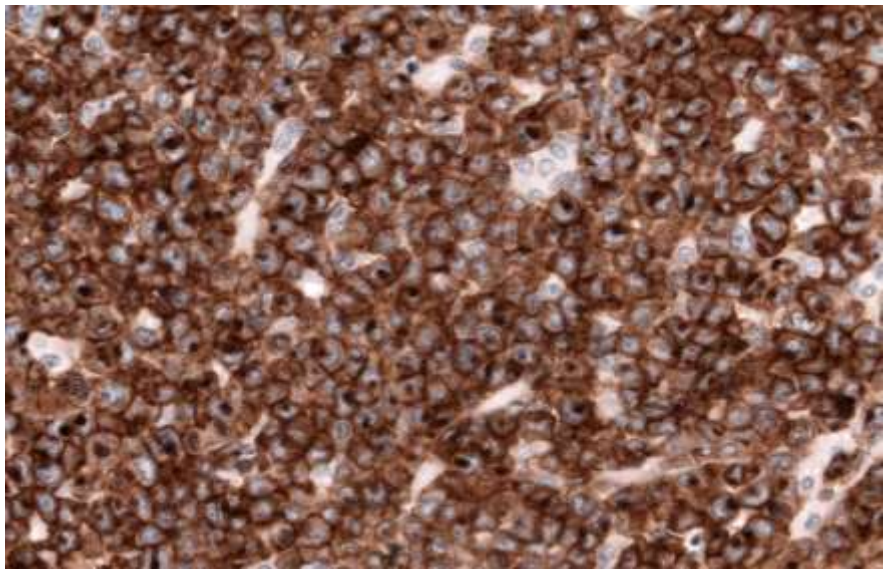
T lenfositlerin gelişimi

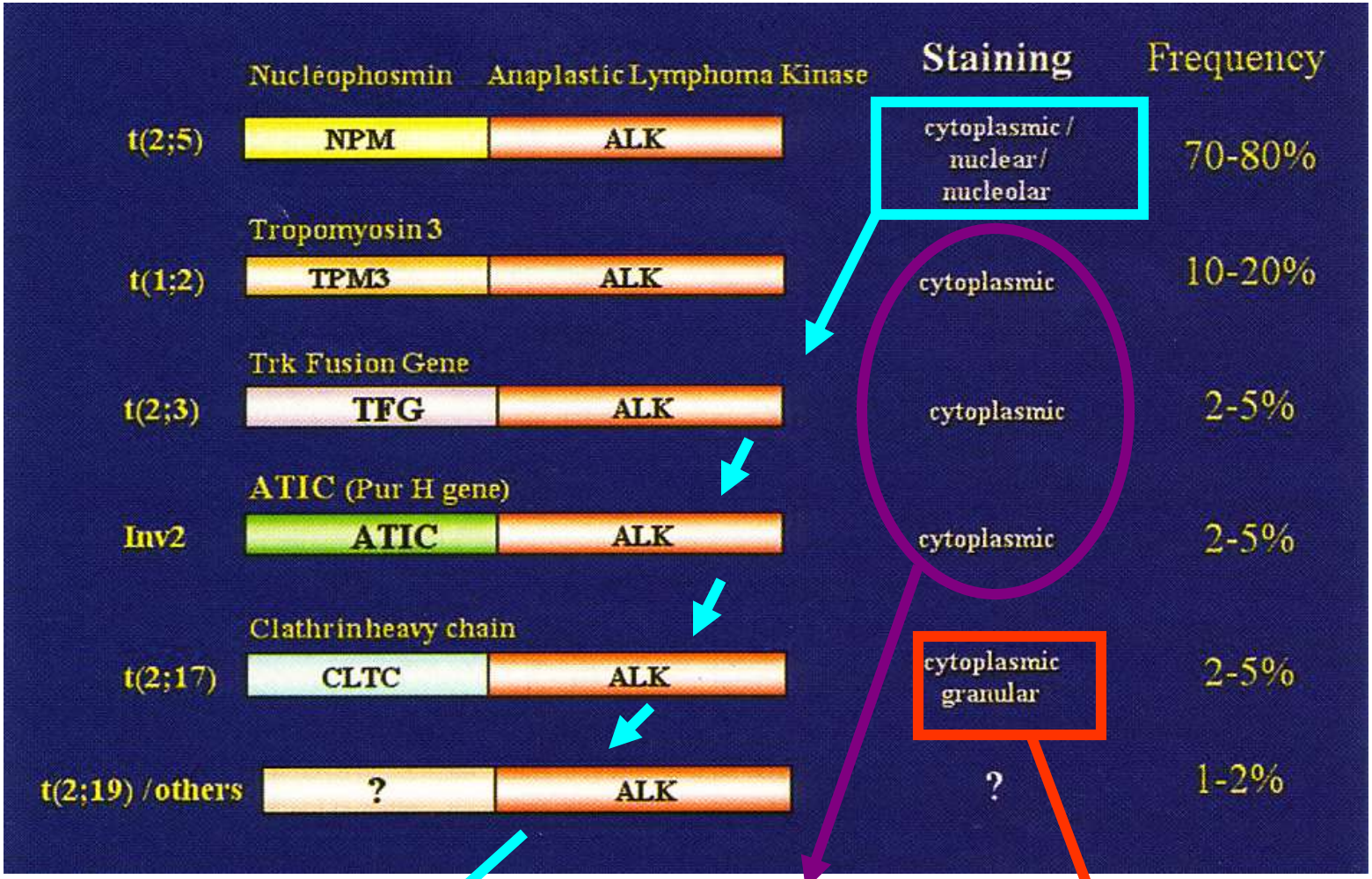


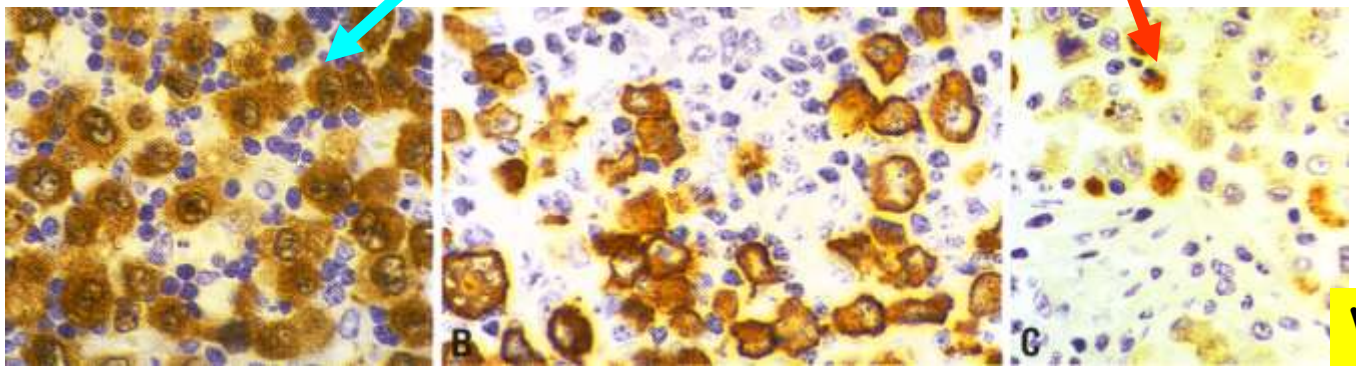
WHO BLUE BOOK Swerdlow 2008

- ALK-positif anaplastic large cell lymphoma (ALCL)
- ALK-negatif anaplastic large cell lymphoma



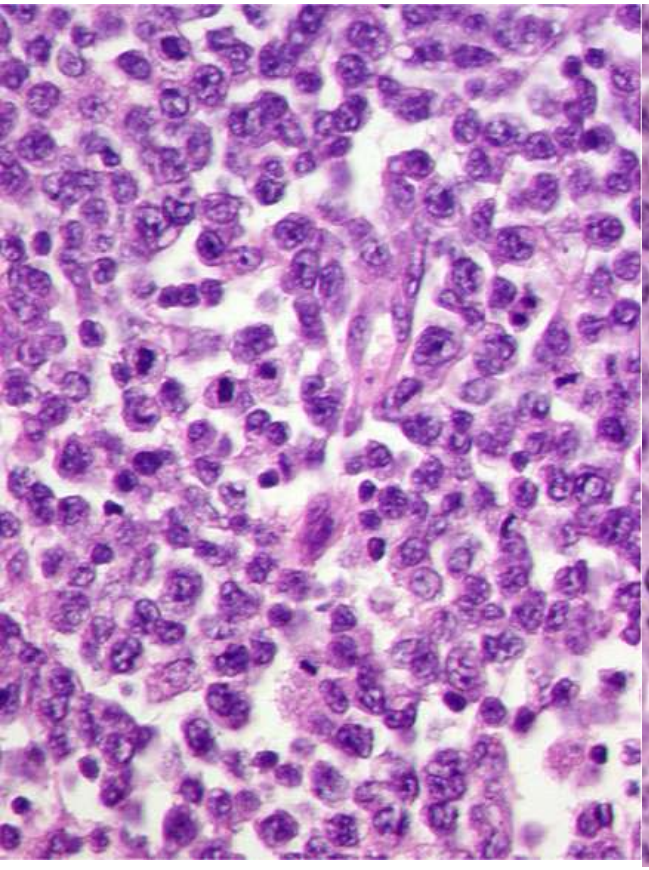



Nucléophosmin
Anaplastic Lymphoma Kinase
Staining
Frequency
t(2;5)
NPM
ALK
cytoplasmic / nuclear / nucleolar
70-80%
Tropomyosin 3
t(1;2)
TPM3
ALK
cytoplasmic
10-20%
Trk Fusion Gene
t(2;3)
TFG
ALK
cytoplasmic
2-5%
ATIC (Pur H gene)
Inv2
ATIC
ALK
cytoplasmic
2-5%
Clathrin heavy chain
t(2;17)
CLTC
ALK
cytoplasmic granular
2-5%
t(2;19) / others
?
ALK
?
1-2%

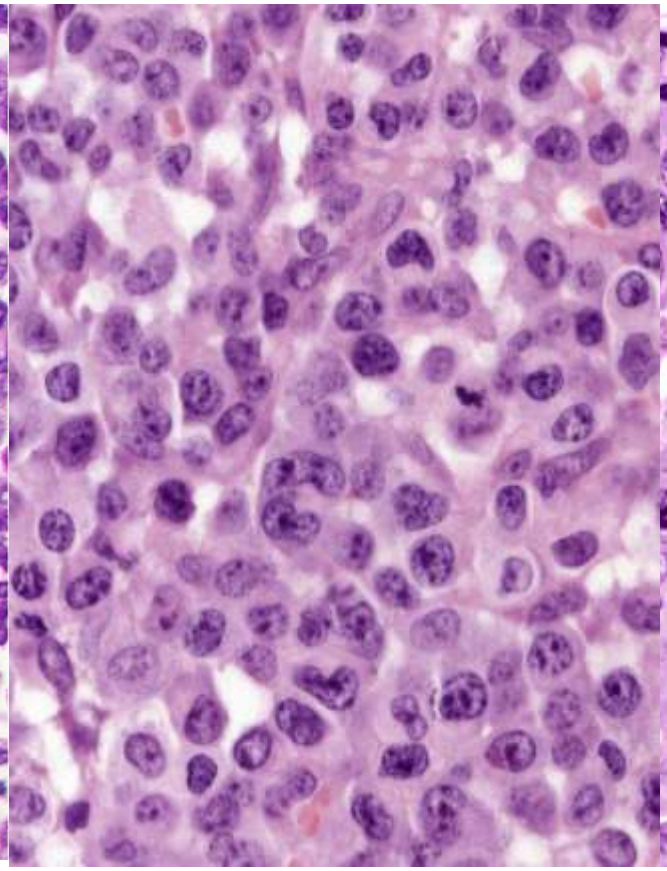

B
C

WHO 2001

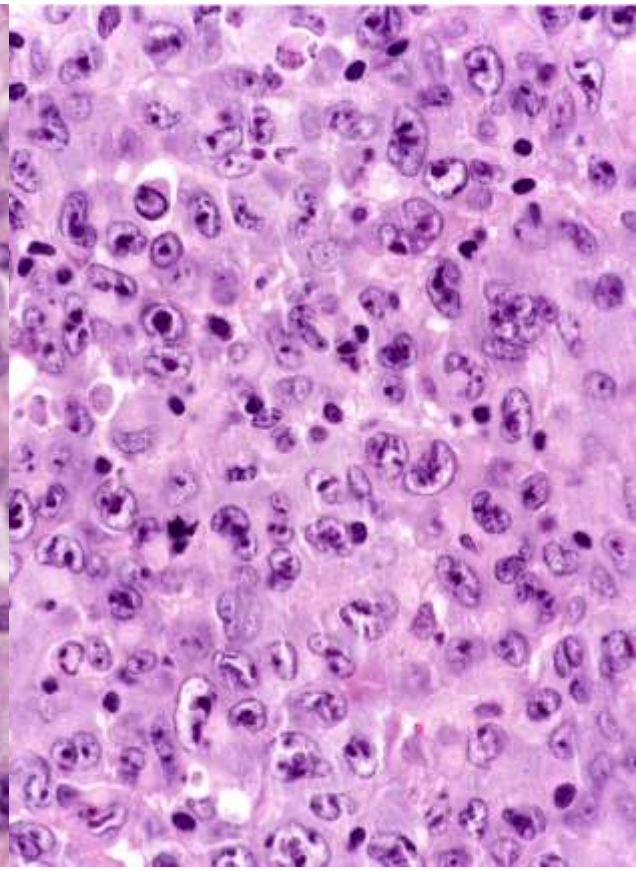
CD30+ T-hücreli lenfomalar



PTCL-nos



ALCL, ALK+

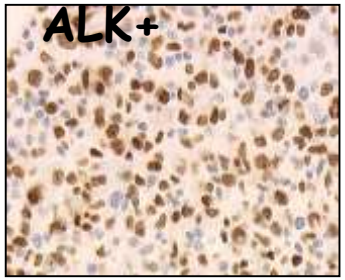


ALCL, ALK-

Quintanilla Martinez 2016

CD30+ T-hücreli lenfomalar

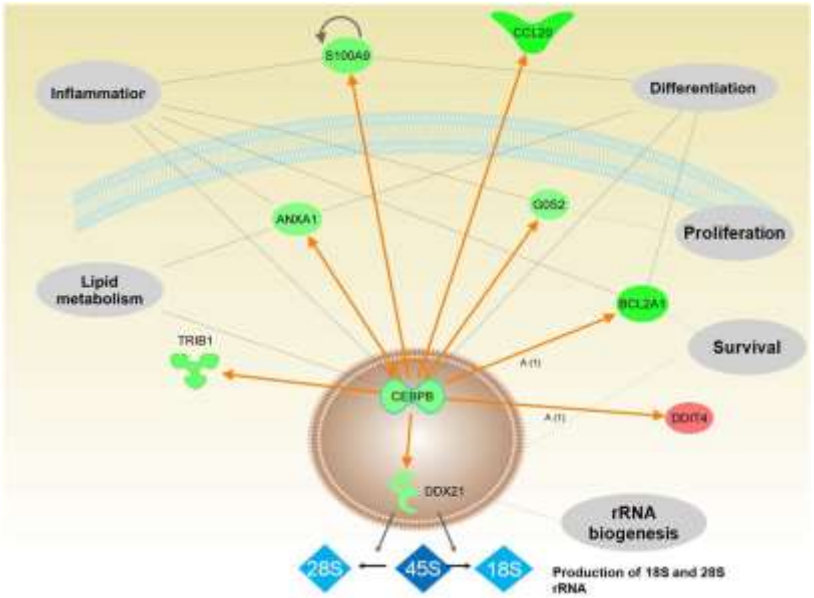
C/EBPβ in ALK+

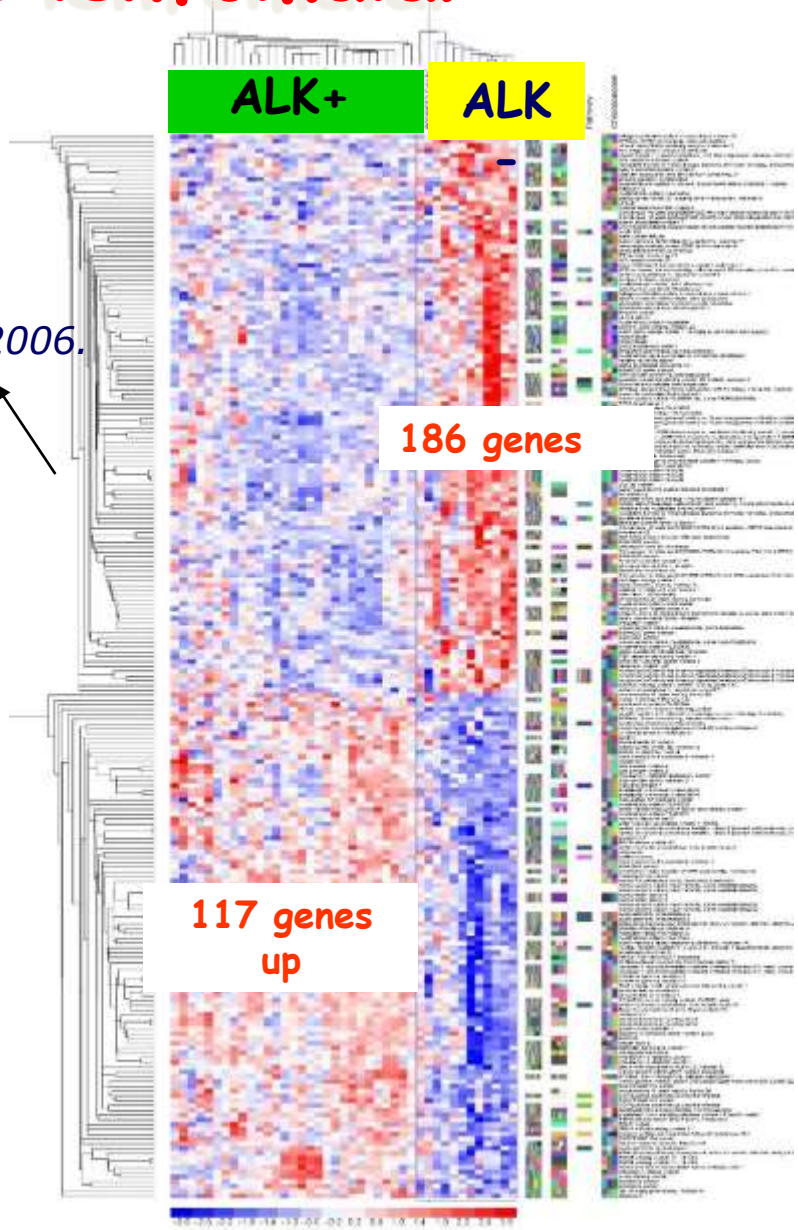


Quintanilla-Martinez L et al. Blood. 2006.

BCL2A1
PTPNP12
SERPINA1
C/EBPβ

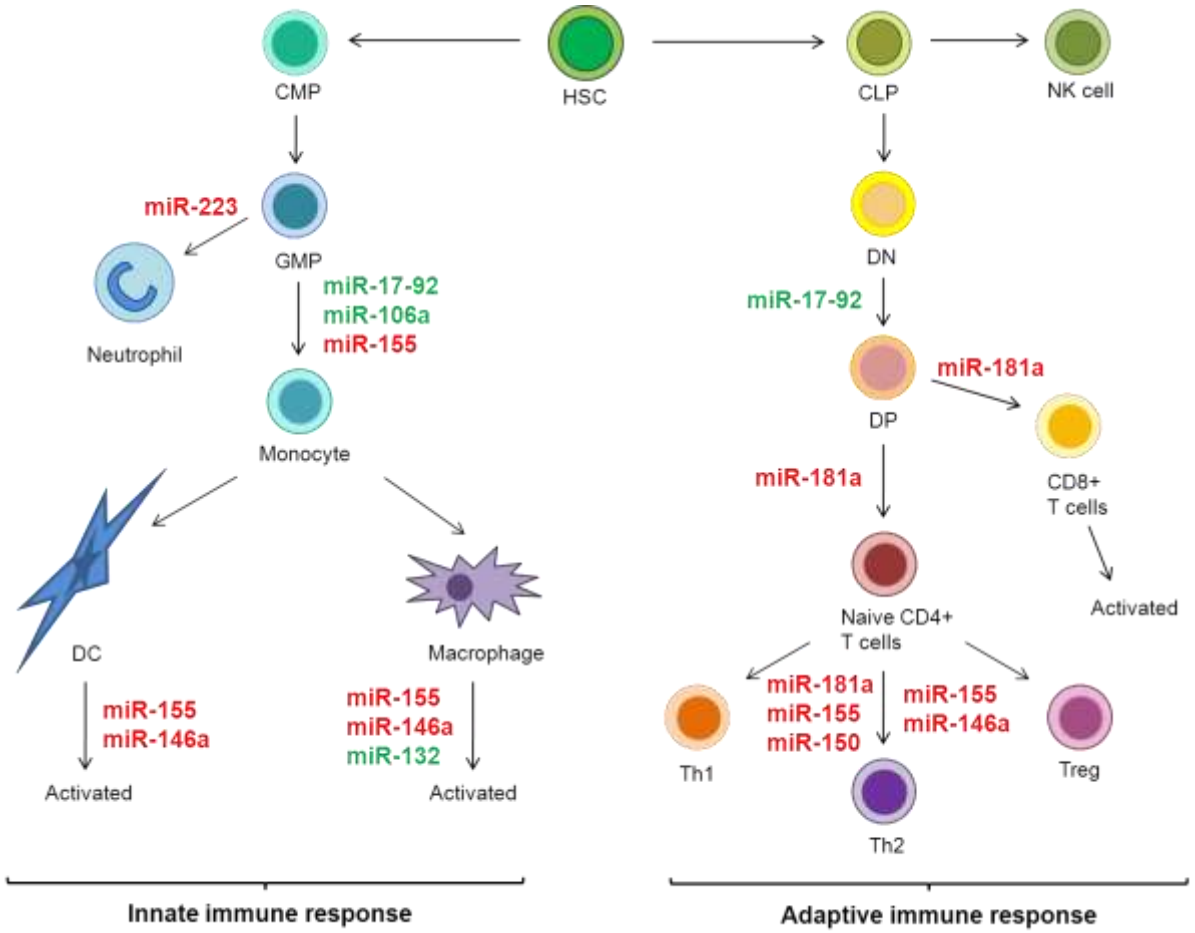
Piva R et al. J Clin Invest. 2006.
Lamant L et al . Blood, 2007





Bonzheim et al, PLOS ONE May 2013 | Volume 8 | Issue 5 | e64544

miRNAs değişiklikleri ve ALCL



PLOS ONE | DOI:10.1371/journal.pone.0117780 February 17, 2015

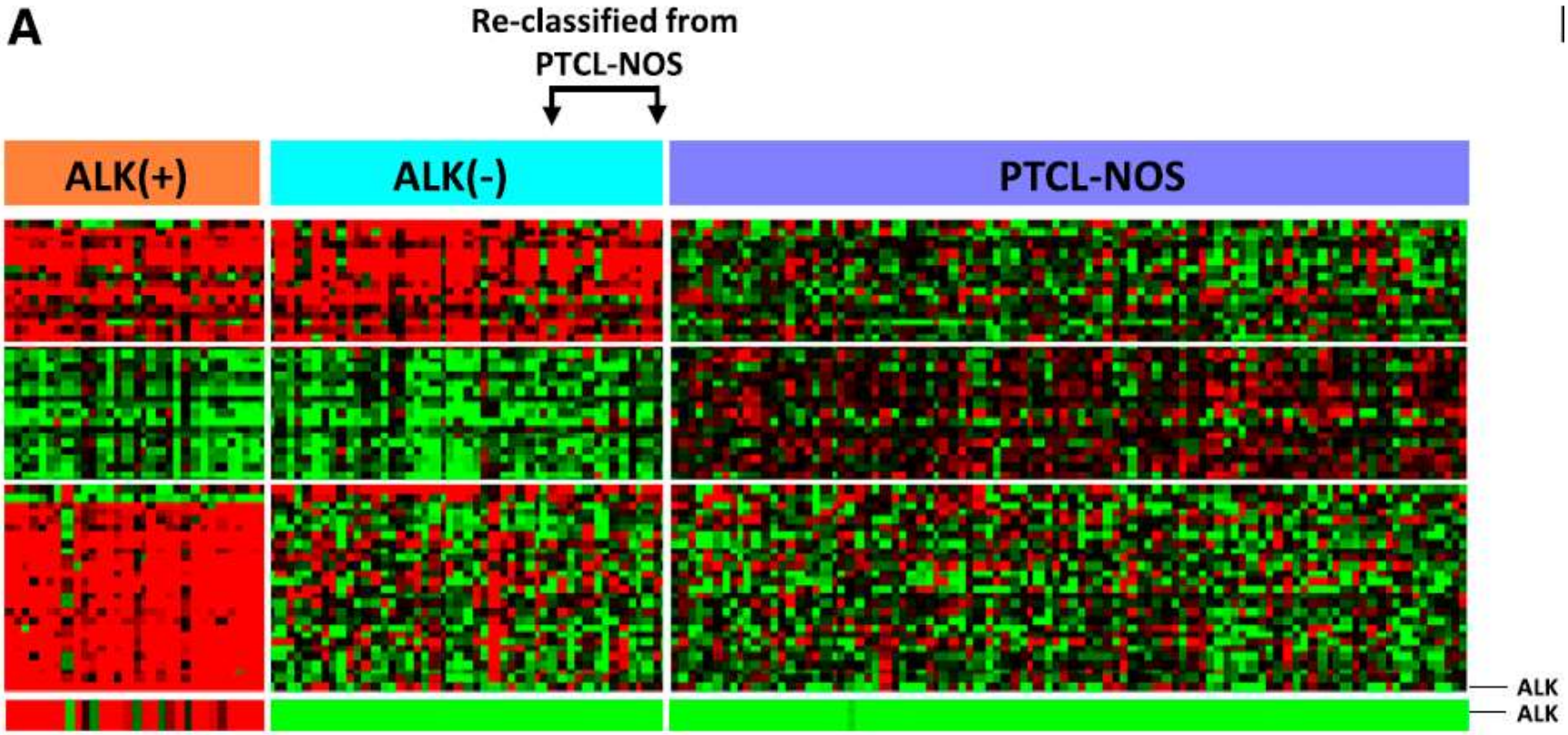
miRNA	ALK+ ALCL baseMean	ALK- ALCL baseMean	T Cells baseMean
hsa-miR-17	2745	2391	615
hsa-miR-18a	487	355	46
hsa-miR-19a	725	598	594
hsa-miR-20a	4616	3631	1638
hsa-miR-19b	2503	1915	3971
hsa-miR-92a	158709	87049	176754
hsa-miR-181a	23243	60934	119105
hsa-miR-150	34	41	365711
hsa-miR-155	1205	44475	3622
hsa-miR-106a	668	101	31
hsa-miR-223	7	0	523
hsa-miR-132	144	54	101

Downregulated in ALK+ ALCL

Upregulated in ALK+ ALCL

Merkel et al PNAS 2010;107:16228
Liu et al Blood 2012;122:2083

ALCL
Gen ekspresyon profili



BLOOD, 8 MAY 2014 • VOLUME 123, NUMBER 19

ALCL ALK- vs. CD30+PTCL-nos

International Peripheral T-Cell lymphoma Proje raporu

	ALK -	PTCL
TIA1, granzyme B & perforin	66%	32%
CD2+	59%	86%
CD3+	45%	93%
EMA	43%	3%
CD43	50%	90%

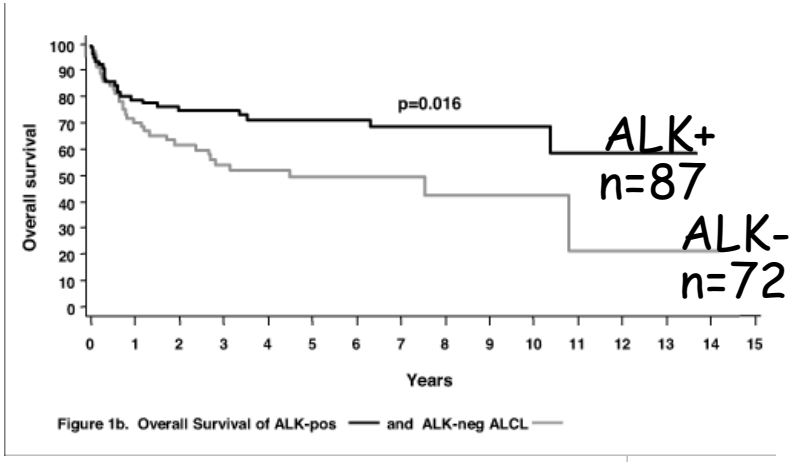


Figure 1b. Overall Survival of ALK-pos and ALK-neg ALCL

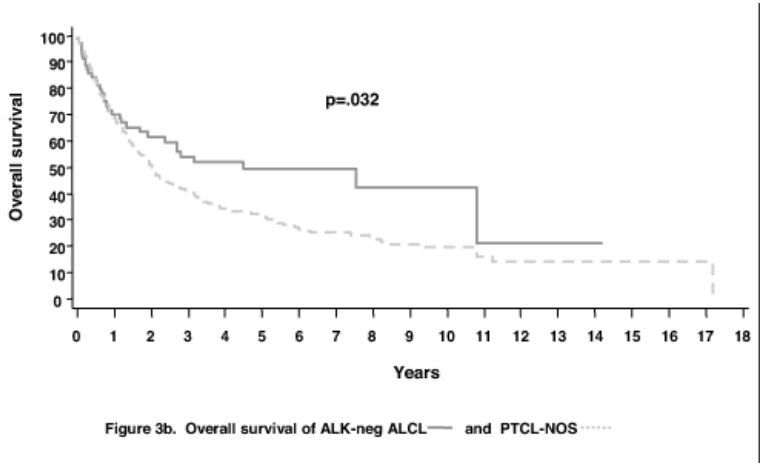


Figure 3b. Overall survival of ALK-neg ALCL and PTCL-NOS

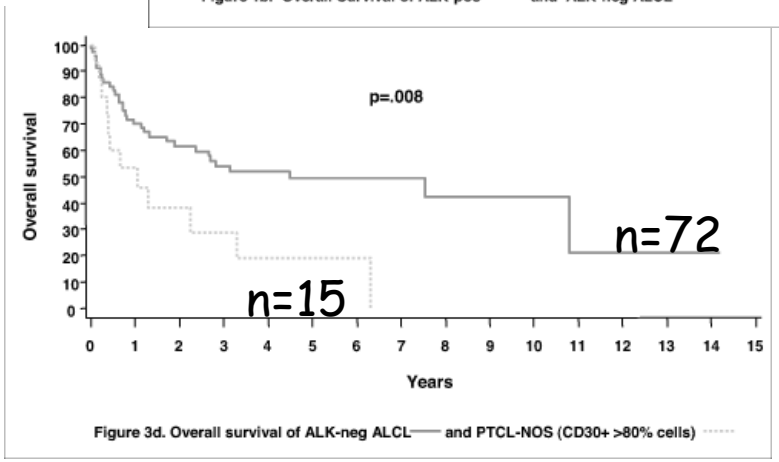


Figure 3d. Overall survival of ALK-neg ALCL and PTCL-NOS (CD30+ >80% cells)

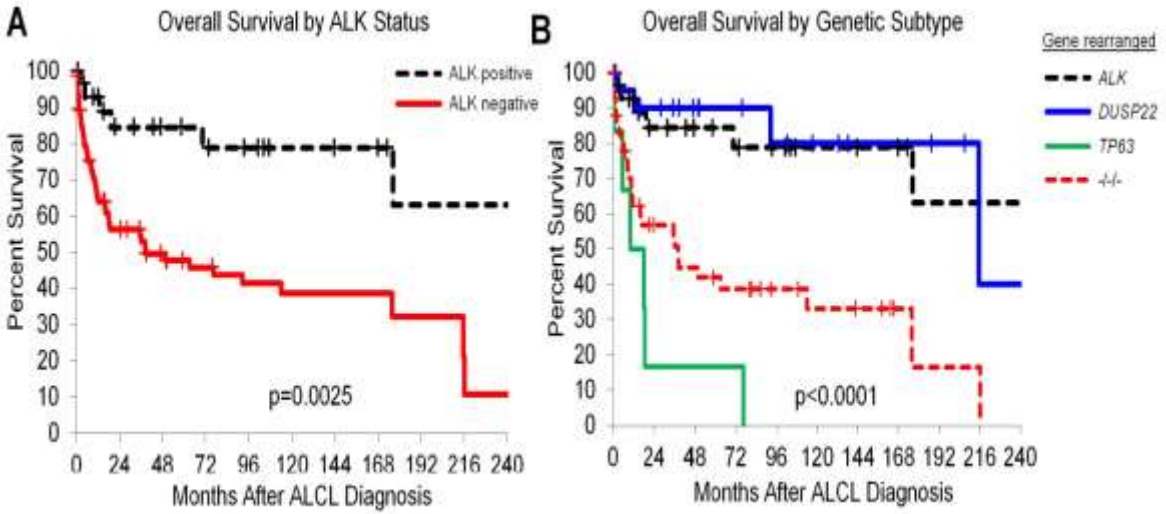
Savage KJ, Blood, April 2, 2008

ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes

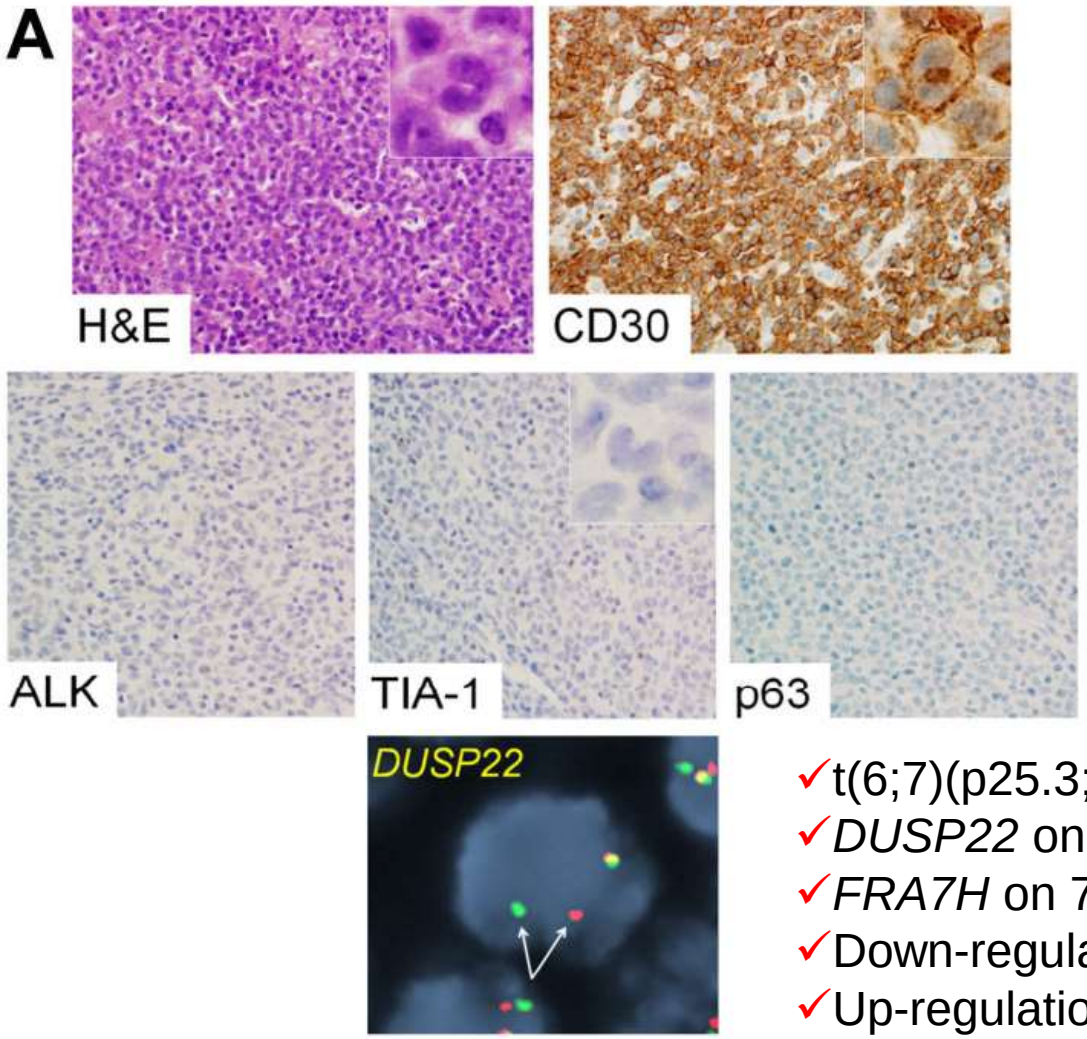
Edgardo R. Parrilla Castellar,[1] Elaine S. Jaffe,[2] Jonathan W. Said,[3] Steven H. Swerdlow,[4] Rhett P. Ketterling,[1] Ryan A. Knudson,[1] Jagmohan S. Sidhu,[5] Eric D. Hsi,[6] Shridevi Karikehalli,[7] Liuyan Jiang,[8] George Vasmatzis,[9] Sarah E. Gibson,[4] Sarah Ondrejka,[6] Alina Nicolae,[2] Karen L. Grogg,[1] Cristine Allmer,[10] Kay M. Ristow,[11] Wyndham H. Wilson,[12] William R. Macon,[1] Mark E. Law,[1] James R. Cerhan,[10] Thomas M. Habermann,[11] Stephen M. Ansell,[11] Ahmet Dogan,[1] Matthew J. Maurer,[10] and Andrew L. Feldman[1]

Key Points

- ALK-negative ALCLs have chromosomal rearrangements of *DUSP22* or *TP63* in 30% and 8% of cases, respectively.
- *DUSP22*-rearranged cases have favorable outcomes similar to ALK-positive ALCLs, whereas other genetic subtypes have inferior outcomes.



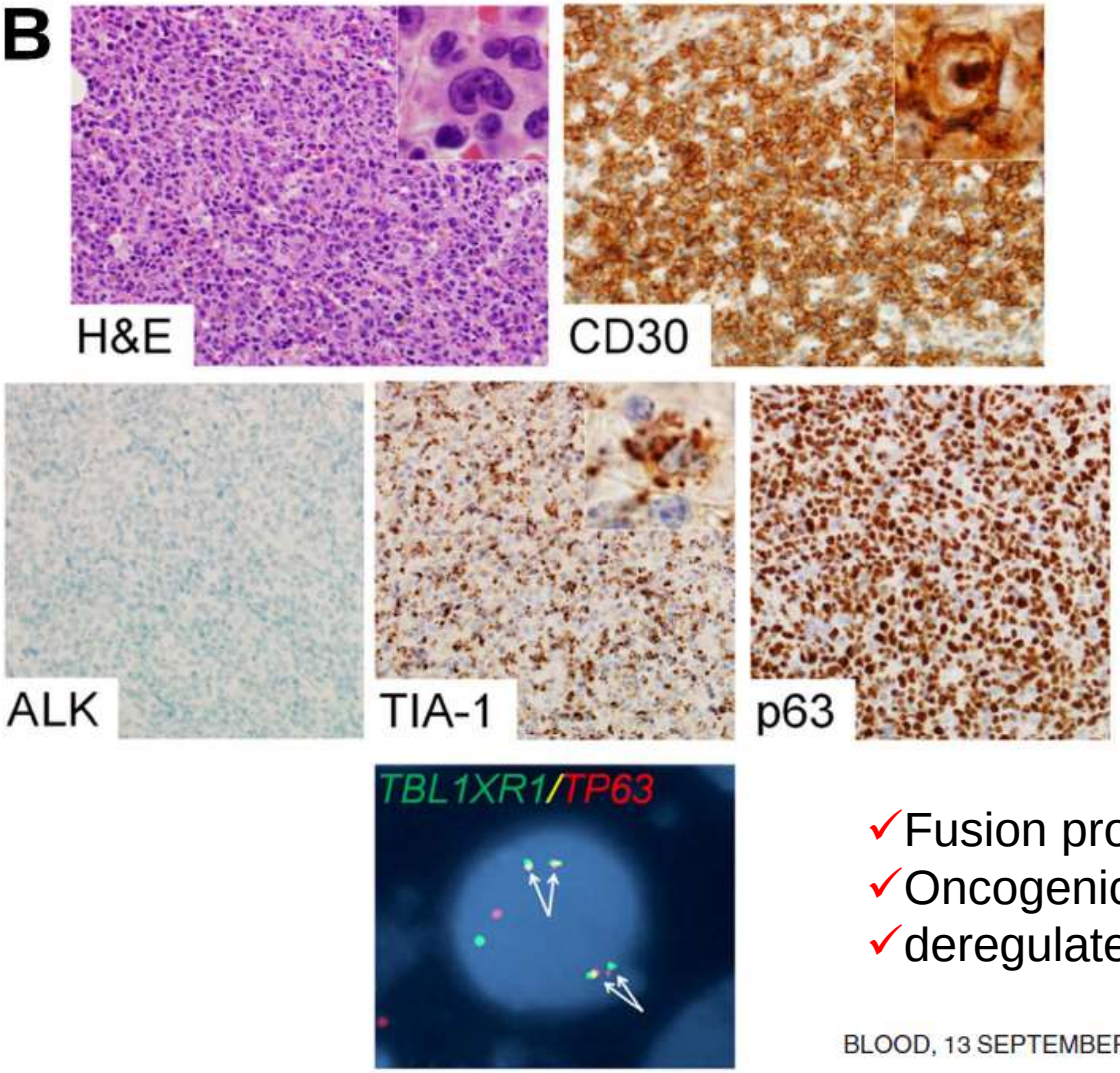
ALK-ALCL with DUSP22 translocation



- ✓t(6;7)(p25.3;q32.3)
- ✓*DUSP22* on 6p25.3
- ✓*FRA7H* on 7q32.3
- ✓Down-regulation of *DUSP22*
- ✓Up-regulation of *MIR29*

Quintanilla Martinez 2016

ALK-ALCL TP63 translocation



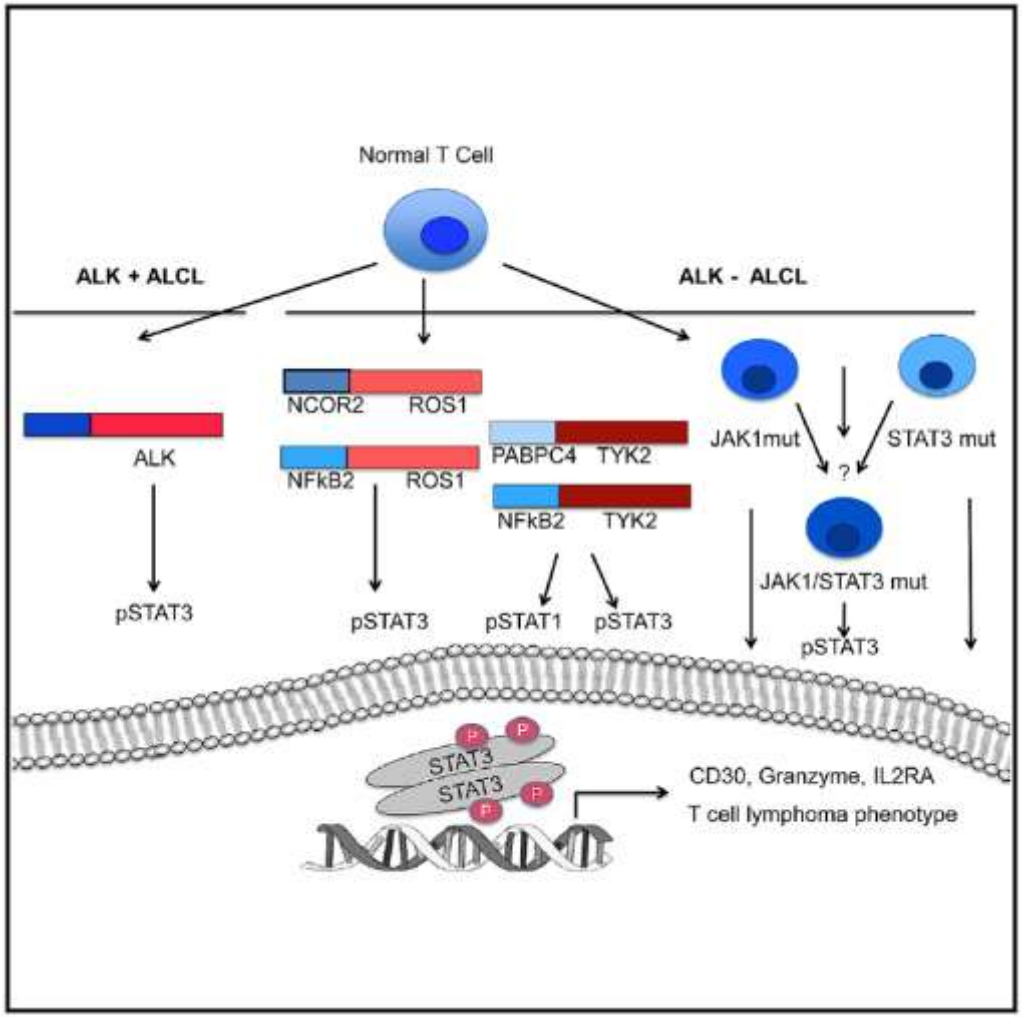
- ✓Fusion protein ΔNp63
- ✓Oncogenic functions
- ✓deregulates the p53 pathway

BLOOD, 13 SEPTEMBER 2012 • VOLUME 120, NUMBER 11

Cancer Cell

Convergent Mutations and Kinase Fusions Lead to Oncogenic STAT3 Activation in Anaplastic Large Cell Lymphoma

Crescenzo et al., 2015, Cancer Cell 27, 516–532



20% ALK-ALCL

EBV associated lymphoproliferations
Chronic active EBV infection*
Systemic form
Cutaneous form
Hydroa vacciniforme LPD*
Severe mosquito bite allergy*
Systemic EBV+T-cell lymphoma of childhood*
Aggressive NK cell leukemia
Extranodal NK/T-cell lymphoma, nasal type
Nodal EBV+ PTCL*

Quintanilla-Martinez et al, Revised 2016 WHO classification

ALCL DIŞI EBV İLİŞKİLİ T HÜCRELİ LENFOMALARIN DAĞILIMI

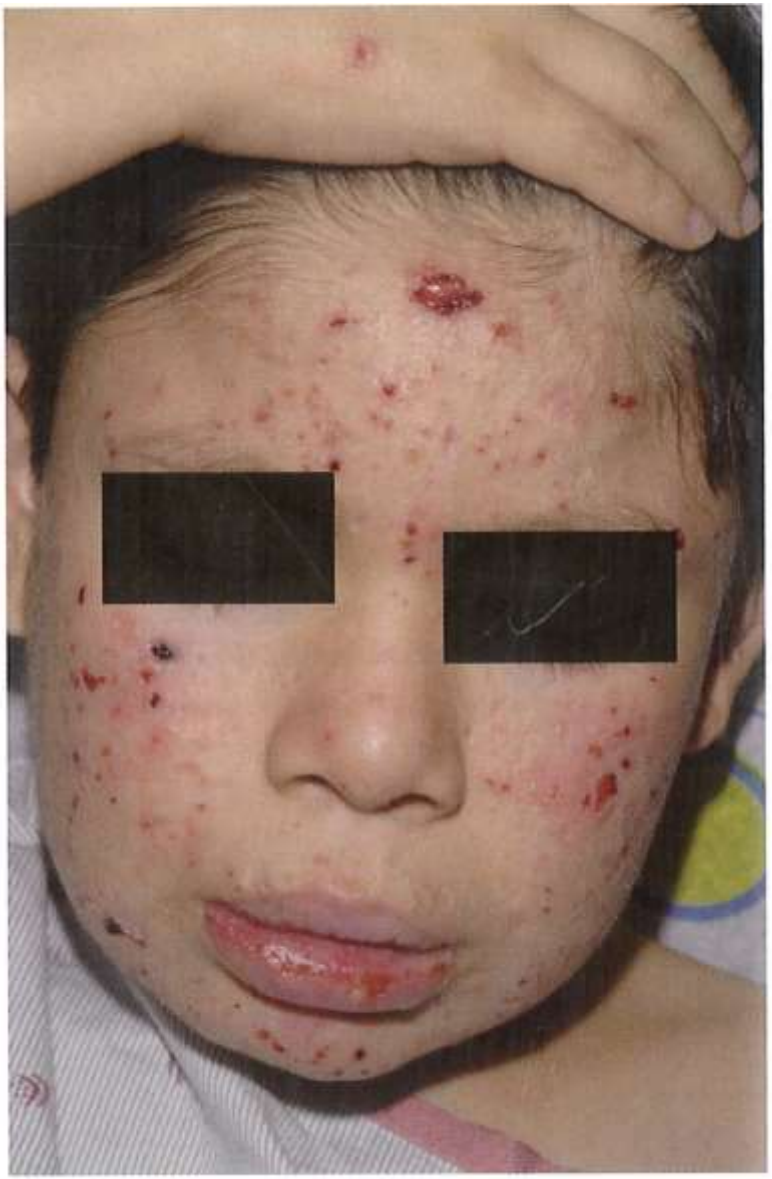
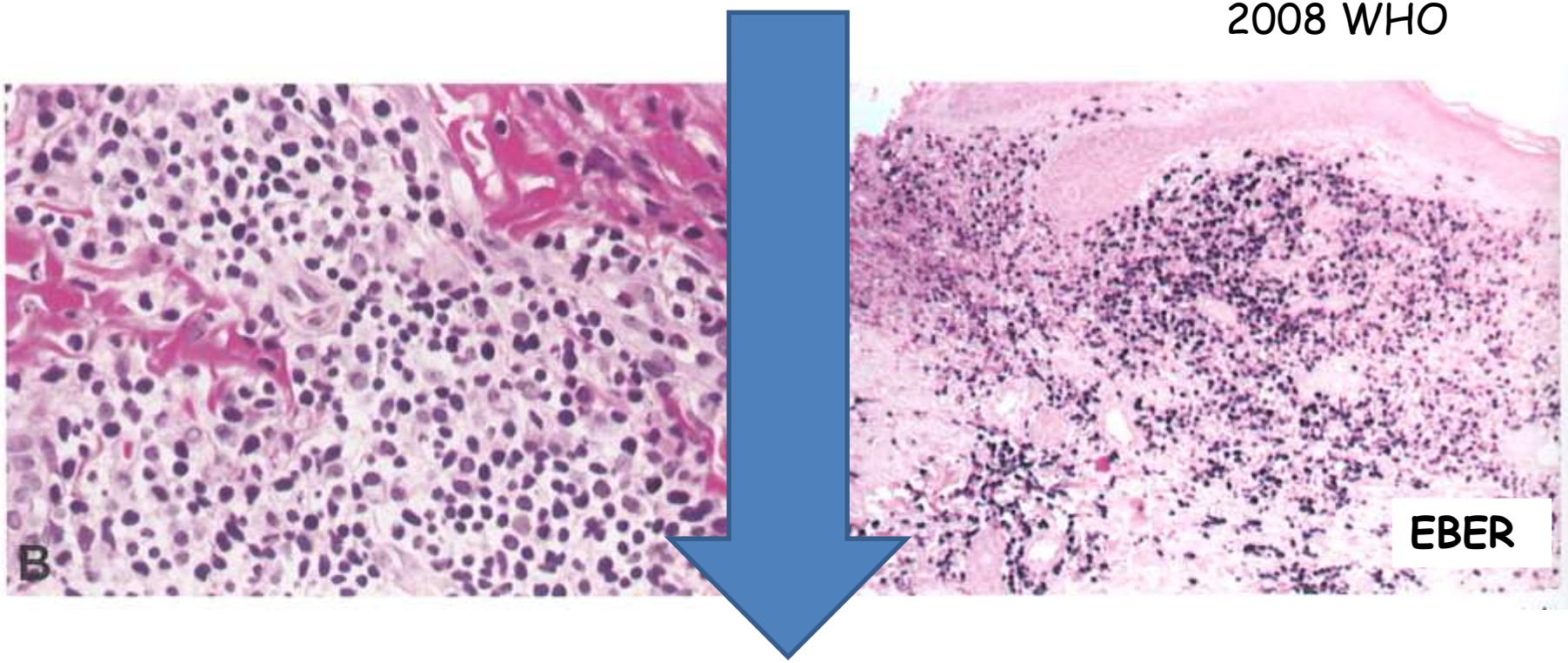


Fig. 11.15 Hydroa vacciniforme-like lymphoma. Sun-

WHO 2008

Hydroa vacciniforme like lenfoprolifertif hastalık

2008 WHO



Hydroa vacciniforme like lenfoma

2017 WHO

WHO 2016 Update

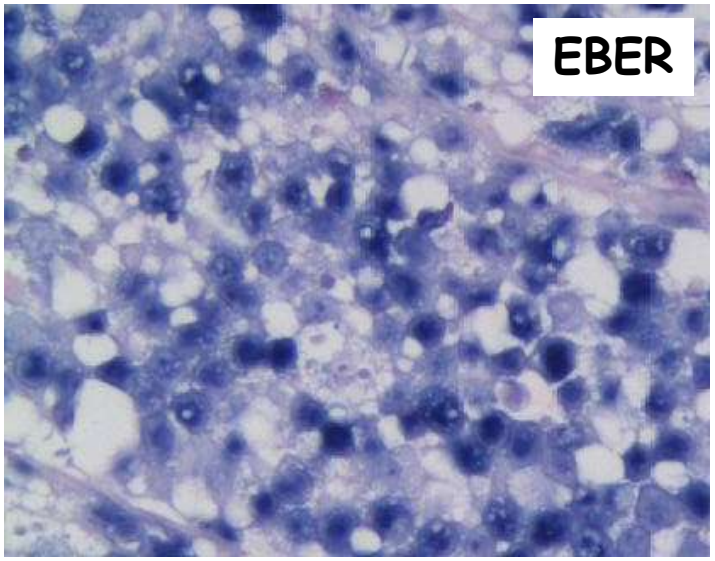
Entity	Notes and updates
Chronic active EBV-infection (CAEBV), and Systemic EBV-positive T-cell lymphoma of childhood	EBV-associated T- and NK-cell lymphoproliferative disorders in the pediatric age group. Both occur with increased frequency in hepato-splenomegaly and lymphadenopathy with or without cutaneous manifestations.
Systemic EBV-positive T-cell lymphoma of childhood	No longer referred to as a lympho-proliferative disorder -- has a fulminant clinical course usually associated with a hemophagocytic syndrome.

Blood. 2016 Mar 15. pii: blood-2016-01-643569. [Epub ahead of print]

The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms.

Swerdlow SH[1], Campo E[2], Pileri SA[3], Harris NL[4], Stein H[5], Siebert R[6], Advani R[7], Ghielmini M[8], Salles GA[9], Zelenetz AD[10], Jaffe ES[11].

EBV VARLIĞININ DEĞERLENDİRİLMESİ



Gizli (Latent) EBV

Tip I → **BL**
EBER-1, EBER-2, EBNA-1

Tip II → HL, PTCL,, PEL
EBER-1, EBER-2, EBNA-1, LMP-1, LMP2A, LMP2B

Tip III → PTLD, BLASTOID
EBER-1, EBER-2, EBNA-1, 2, 3A, 3B, and *3C,* and *LMP-1, 2A,* and *2B.*

EBER ISH

BAŞARILI BİR KONGRE DİLERİM