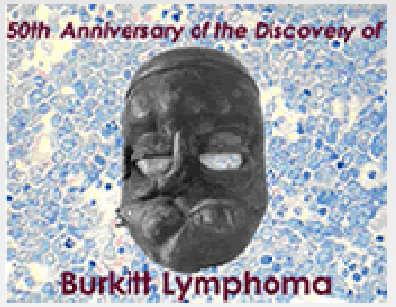
BORDERS BETWEEN DIFFUSE LARGE B-CELL LYMPHOMA AND BURKITT LYMPHOMA

BL

Endemic Burkitt lymphoma
Sporadic Burkitt lymphoma
AIDS related

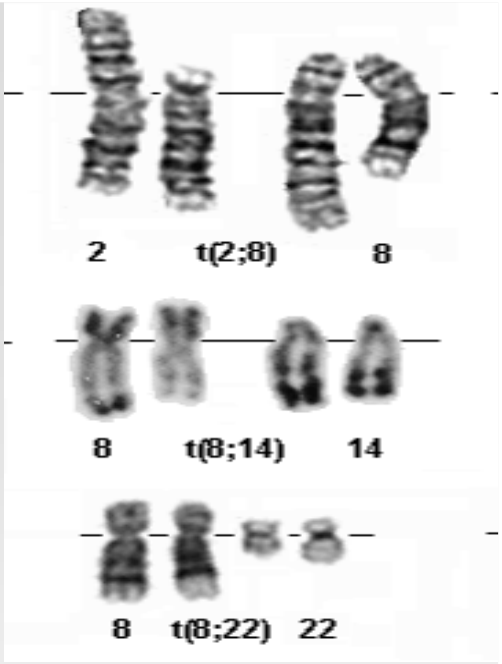


DLBCL

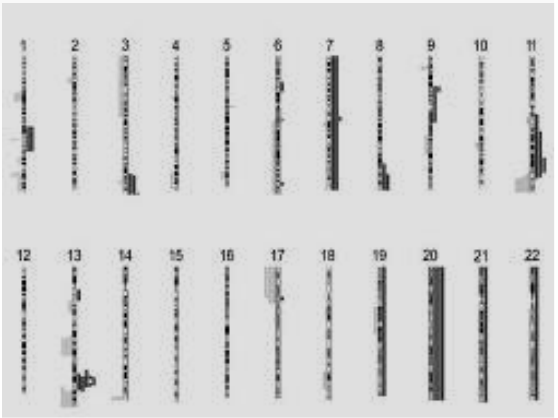
Many subtypes

Philip Kluin

BURKITT LYMPHOMA: PRESENT KNOWLEDGE

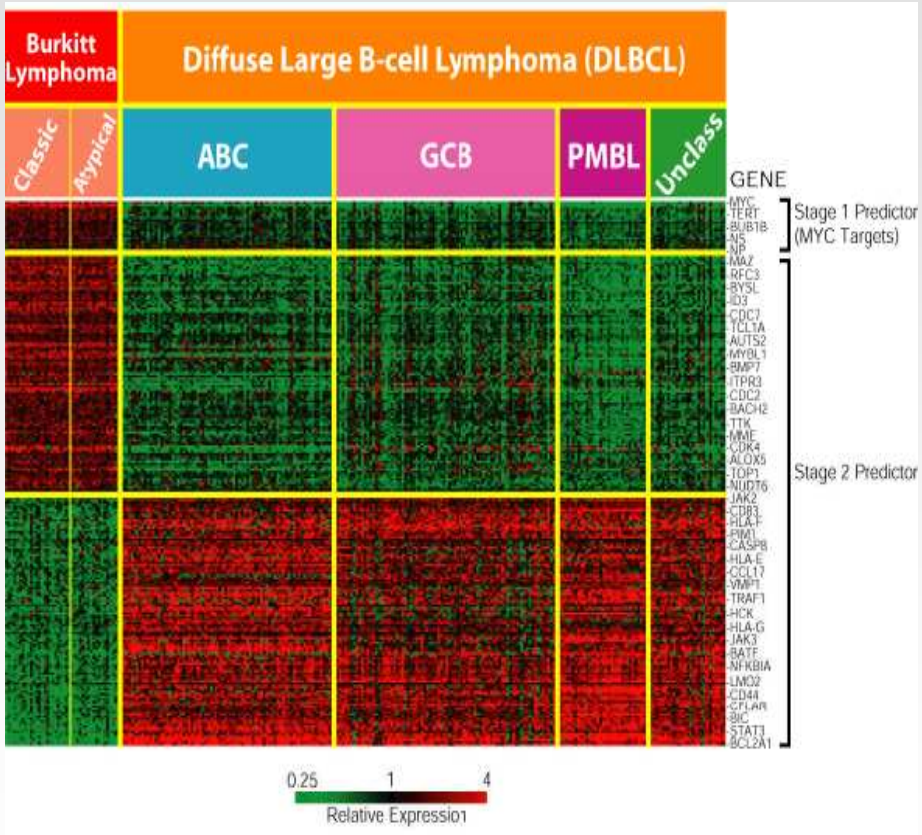


- Mature B cell lymphoma: IgM+, k/l+ and TdT-
- Germinal center cell derived: morphology, CD10+, BCL6+ , CD38+, CD77+(etc)
- Highly proliferative (Ki67/MIB1 almost 100%)
- Ig genes hypermutated but no class switch
- Carries the t(8;14) in 85-90%, and the variant t(2;8) and t(8;22) in 10-15% of the cases
- Genomically simple entity with only few aberrations. Gains: 1q, 7, and 12; losses: 6q, 17p, 13q32-q34
- Highly distinct gene expression pattern



Molecular diagnosis of Burkitt's lymphoma.

S Dave et al, NEJM 2006; 354:2431-2442



Two-sided approach

Step 1: comparison of 21 MYC target genes (MYC transfection in DLBCL cell line)

Step 2: Separate comparisons of reference BL with:

- 78 DLBCL-ABC, 100 top genes
- 82 DLBCL-GCB, idem
- 33 PMBL, idem
- 30 Unclassifiable DLBCL, idem

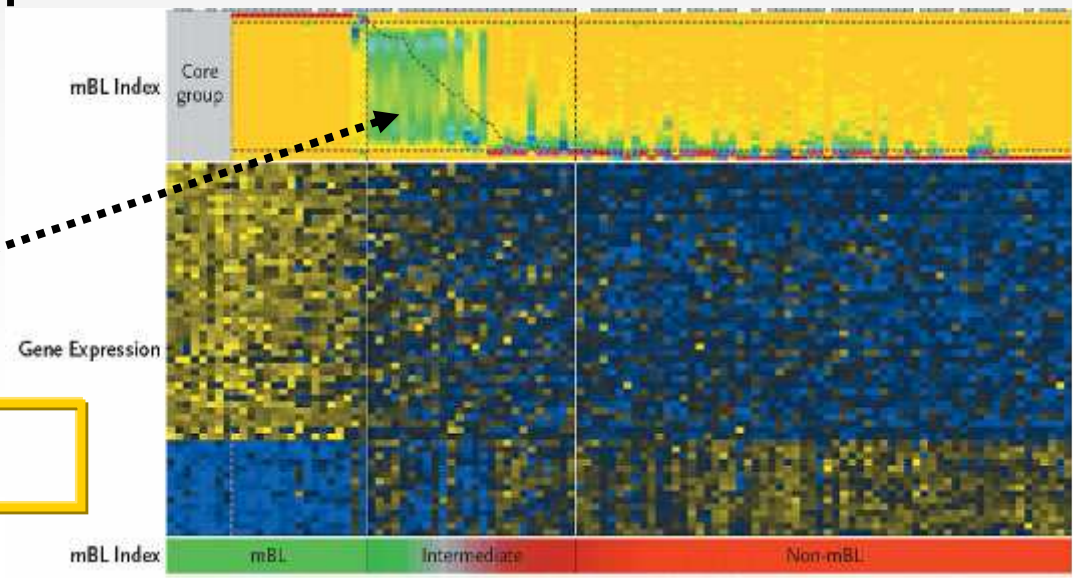
Stap 3: Construction of a Burkitt lymphoma predictor

No independent validation series

A Biologic Definition of Burkitt's Lymphoma from Transcriptional and Genomic Profiling.

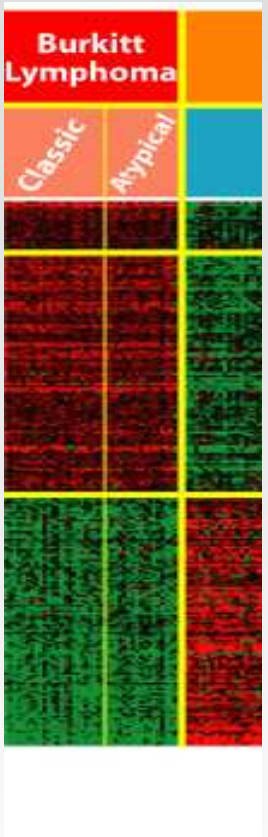
M Hummel et al, NEJM 2006; 354:2419-2430

- Core group BL (N=8)
  - IHC: CD20+, bcl6+, CD10+, bcl2–, CD5–, Ki-67> 95%,
  - FISH IG-myc fusion+
- training set of 105 lymphomas: 58 genes determined molecular BL signature (mBL)
- Validation in 107 lymphomas
- BL predictor
  - <0.05: non-mBL
  - >0.95: mBL
  - rest: intermediate



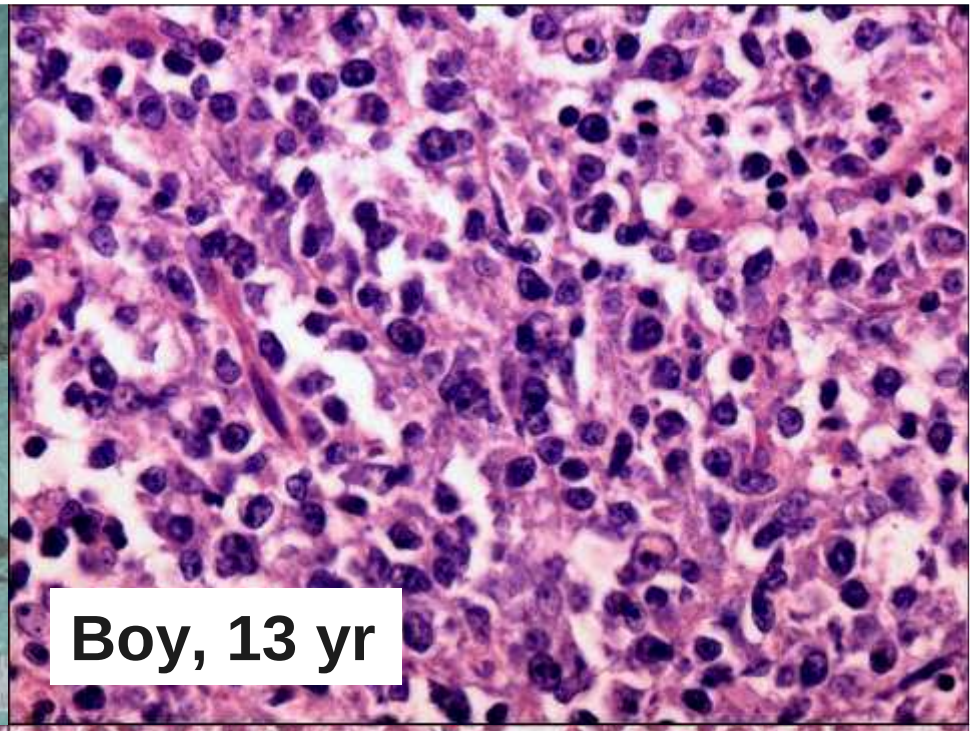
One-sided approach

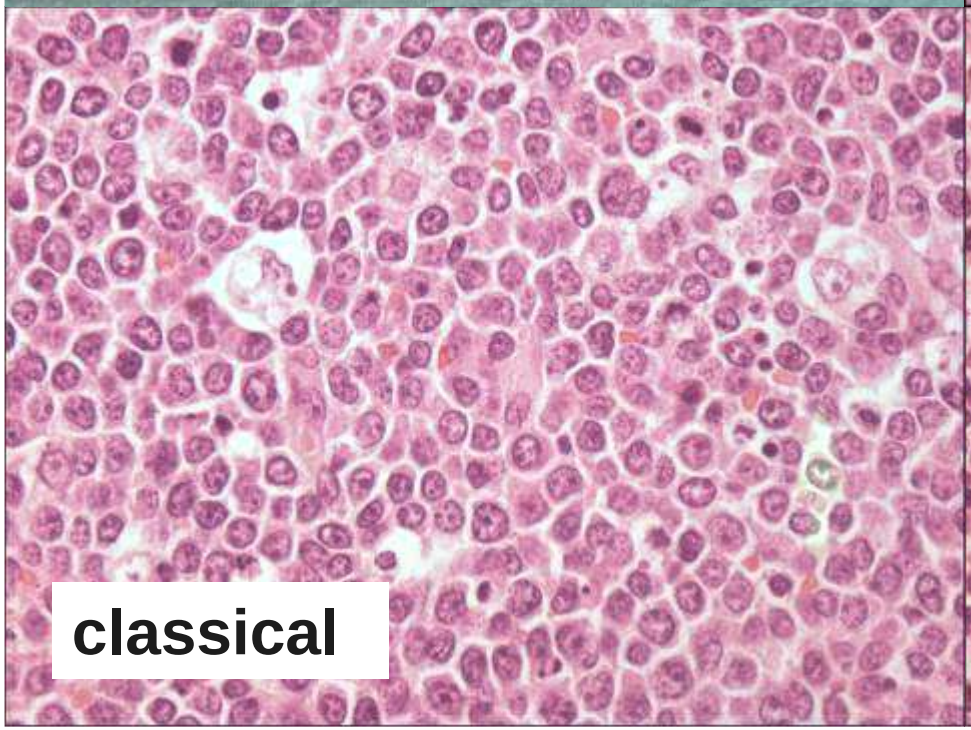
What is atypical Burkitt lymphoma?



- atypical morphology
  - Somewhat more variation in nuclear size and contour
  - Less frequent and bigger nucleoli
  - You need excellent fixation and histotechnology!
- classical phenotype
  - CD10+, bcl6+
  - bcl2-
  - MIB1/Ki67 95-100%
- MYC translocation
- Similar gene expression as typical BL


Boy, 13 yr


Boy, 13 yr


classical


apoptosis : not cohesive

The term “Burkitt-like” is confusing

- REAL classification: morphological variant, but probably more related to DLBCL than BL (based on study of Jaffe group: elderly, poor outcome and more BCL2 than MYC rearrangements)
- Other authors: DLBCL with morphological features of BL
- Other authors: similar to atypical BL

ADULT DIFFUSE LARGE B-CELL LYMPHOMA: PRESENT KNOWLEDGE

- Very heterogeneous disease, = wastebasket
- 45% germinal center, 55% activated B cell (post germinal center?)
- Highly heterogeneous in morphology (from Hodgkin like – Burkitt like)
- Heterogenous for CD10, BCL6, BCL2, MUM1/IRF4 etc
- Majority BCL6 mutations, some activating
- 30-40% BCL6 rearrangement, all activating
- 15-20% BCL2 rearrangements
- 5-10% MYC rearrangement
- Many cases have multiple translocations and complex karyotypes: De novo versus secondary DLBCL

Small minority (2-5%) resembles Burkitt lymphoma

Starting with morphology: 4 major problems

1. 2-5% of DLBCL with multiple features of BL
2. BL morphology with a MYC translocation but an atypical phenotype (mainly bcl2+ protein)
3. BL morphology with typical phenotype but without detectable MYC translocation
4. (Atypical) BL morphology with a double translocation (MYC and BCL2 or BCL6 or CCND1), “double hit cases”

WHO Chapter 62

Why this chapter??

- Meant to keep categories of BL and DLBCL clean
- To prevent that patients who need more intensive therapy do not get just R-CHOP

However, not to be used as a new wastebasket!

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

P.M. Kluin
N.L. Harris
H. Stein
L. Leoncini

M. Raphael
E. Campo
E.S. Jaffe

Definition
B-cell lymphomas with features intermediate between diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL) are aggressive lymphomas that have morphological and genetic features of both DLBCL and BL, but for biological and clinical reasons should not be included in these categories. Some of these cases were previously classified as Burkitt-like lymphoma (BLL).
The majority of the cases in this category have morphological features that are intermediate between DLBCL and BL, with some cells that are smaller than typical DLBCL, resembling BL, and some cells that are larger than typical BL, resembling DLBCL, as well as a high proliferation fraction, starry-sky pattern, and an immunophenotype consistent with BL. Some cases may be morphologically more typical of BL but have an atypical immunophenotype or genetic features that preclude a diagnosis of BL. The diagnosis of this type of unclassifiable B-cell lymphoma category should not be made in cases of morphologically typical DLBCL that have a *MYC* rearrangement, or in otherwise typical BL in which a *MYC* rearrangement cannot be demonstrated. Some transformed follicular lymphomas may fall into this category. This is a heterogeneous category that is not considered a distinct disease entity, but is useful in allowing the classification of cases not meeting criteria for classical BL or DLBCL.

ICD-O code 9680/3

Table 18.18 Morphologic, immunophenotypic, and genetic features that may be useful in distinguishing BL from DLBCL

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
<50% or heterogeneous	No	Sometimes	Common
BCL2 expression			
Negative / weak	Yes	Sometimes	Sometimes
Strong	No	Sometimes	Sometimes
Genetic features			
MYC rearrangement	Yes*	Common	Rare
/*G-MYC***	Yes	Sometimes	Rare
Non /*G-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

* Approximately 5% of otherwise classical BL lack a detectable *MYC* rearrangement [891A, 994].
**/G-MYC: juxtaposition of *MYC* to one of the /G loci: /GH@ at 14q32, /GL@ at 22q11 or /GK@ at 2p12. Non /G-MYC tumours contain a *MYC* rearrangement but no juxtaposition to one of the /G loci.
Double hit lymphomas contain a *MYC*/8q24 breakpoint in combination with a BCL2/18q21 (by far most frequent) and/or BCL6/3q27 breakpoint. The partner of BCL2/18q21 breakpoint mostly is the /GH locus at 14q32. In some cases a t(8;14;18) is present (1320A).
****Simple karyotype: no or only few cytogenetic or (array) CGH abnormalities other than the *MYC* rearrangement. For array CGH a lymphoma with 6 or more abnormalities has been assigned as "*MYC*-complex" [994].

Epidemiology
These lymphomas are relatively infrequent and mainly diagnosed in adults.

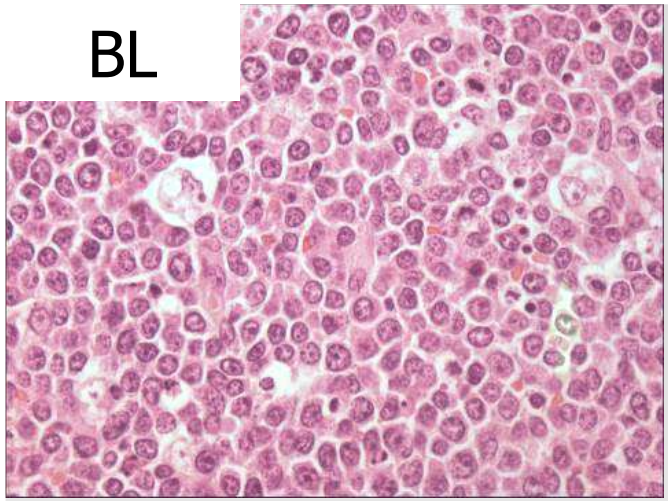
Sites of involvement
More than half of the patients present with widespread, often extranodal disease. Unlike BL, there is no preferential localization in the ileocecal region or jaws. The bone marrow (BM) and peripheral blood (PB) may be involved as well.

Clinical features
Patients present with lymphadenopathy or mass lesions in extranodal sites. Some patients have a leukaemic presentation.

Morphology
These lymphomas are typically composed of a diffuse proliferation of medium- to large-sized transformed cells with few admixed small lymphocytes and no stromal reaction or fibrosis. Starry sky macrophages are typically present, as well as many mitotic figures and prominent apoptosis, causing a resemblance to BL. The cellular morphology is variable. In some cases, the cells resemble those of BL, but with more variation in nuclear size and contour than is considered acceptable for BL; some cases are consistent with BL morphologically but have an atypical immunophenotype and/or genetic features; other cases with an immunophenotype that is consistent with BL have a variable nuclear size that is intermediate between BL and DLBCL, often with either irregular nuclear contours or relatively large nucleoli. In rare cases the nuclei are relatively small and the chromatin is finely granular, resembling lymphoblastic lymphoma. Some of these latter cases have been classified as "blastic" or "blastoid". Immunohistochemistry for TdT is required to exclude lymphoblastic lymphoma.
Cases of morphologically typical DLBCL with a very high proliferation index should not be included in this category [441].

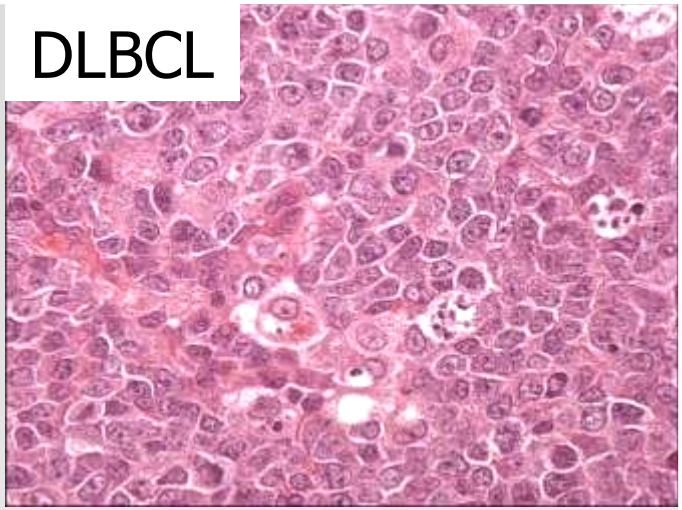
Immunophenotype
These lymphomas express B-cell markers, CD19, CD20, CD22 and CD79a and

BL



1. DLBCL with BL features

DLBCL



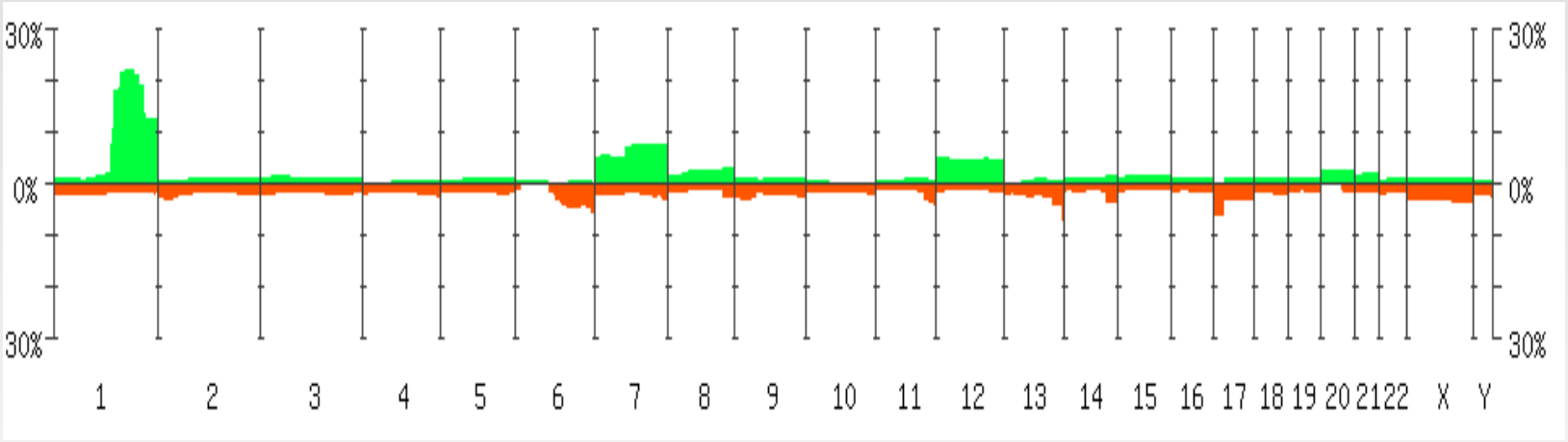
- Shares morphological features with BL
  - mainly monomorphic centroblasts
  - starry sky and many mitotic figures
  - cohesiveness
  - few T cells
- Ki67/MIB1 mostly >80%, sometimes heterogeneous
- Phenotype variable (CD10, bcl6, bcl2, MUM1/IRF4)
- At most 30-40% of these cases MYC rearrangement

- Older patients
- More nodal disease

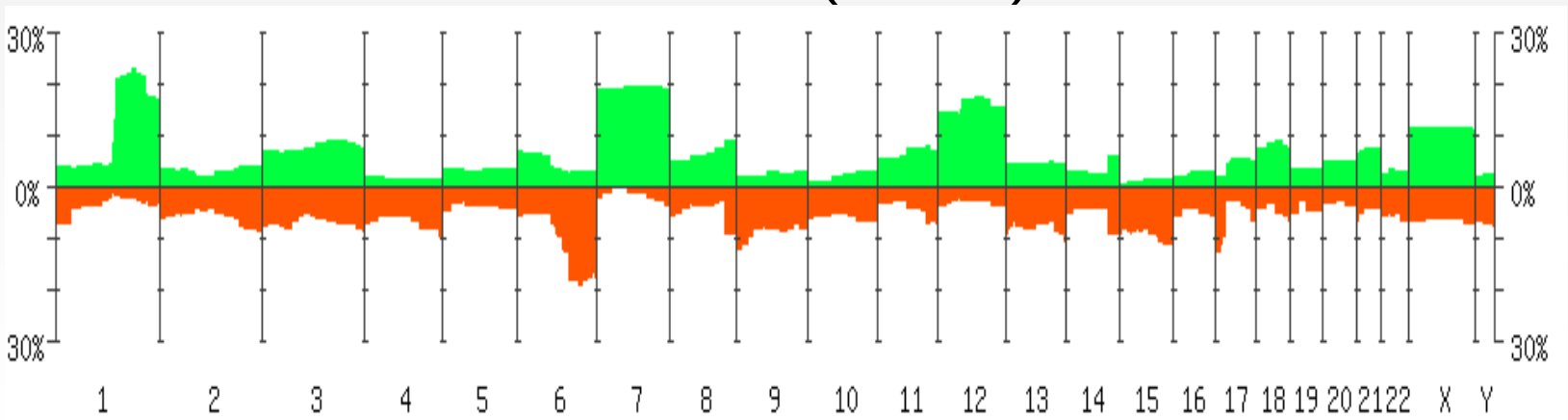
1. DLBCL with BL features

- Genetics
  - DLBCL with MYC translocation have more complex karyotypes than BL (Barth et al J Path 2004;203:940-5; Mitelman database)
- Gene expression
  - 7% of DLBCL in the German MMML study had a molecular expression profile of BL
  - 3% of all DLBCL, but 31% of the really difficult DLBCL in the LLMPP study had a molecular profile of BL
  - 6 unequivocal DLBCL with MYC translocation did not have a mBL profile
  - In children situation is different: 30% of all DLBCL are mBL (W Klapper et al, Blood 2008)
- Very recently published data on treatment outcome in a selected group (Ki67 // 100%), Mead et al. Blood 2008, Sept 15, 112:2245-60

1. DLBCL with BL features: karyotypes (Mitelman database)



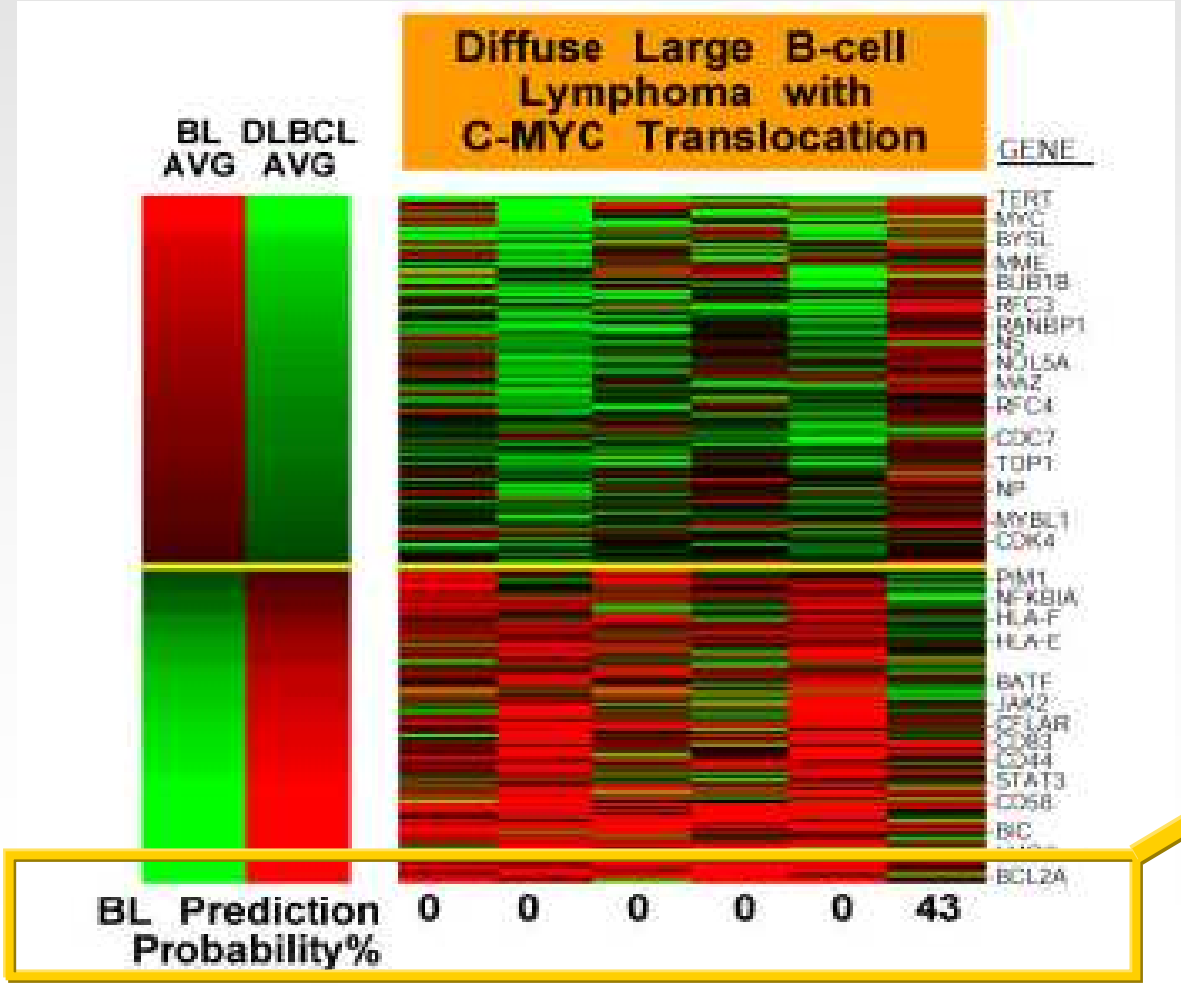
“BL” IG-MYC (n=481)



“Other NHL” with MYC translocation (n=327)

Gene expression in DLBCL with MYC/8q24 breakpoint (N=6)

S Dave et al, NEJM 2006; 354:2431-2442



See also: Nakamura et al, Mod Path 2002;15:771-6

These cases are NOT mis-classified Burkitt lymphomas

1. Conclusions DLBCL with BL features

- Not all DLBCL with high proliferation rate and BL phenotype are misclassified BL
- Similar cases with a MYC translocation should be thoroughly investigated (clinical presentation, morphology, phenotype, karyotype, FISH for mutiple targets), but still are not just BL
- In case of persistent doubt such tumours should be diagnosed separately from DLBCL and BL

WHO 2008

- If true DLBCL morphology: keep them in DLBCL (exception: double hits)

- If they share many features with BL: put them in the novel category:
  B cell lymphoma unclassifiable with features intermediate between DLBCL and BL ("intermediate between DLBCL and BL")

2. BL morphology & MYC translocation but atypical phenotype

- Consensus that virtually all BL are BCL6+, CD10+, sIgM+, k/l+
- 20% of all BL may show some bcl2 expression
  - Due to double hit (see later; then no Dx of BL)
  - Due to other mechanisms that up-regulate bcl2 such as EBV (many EBV+ BL cell lines are bcl2+!)
- Some cases have mBL gene expression profile

2. BL with atypical phenotype

M Hummel et al, NEJM 2006; 354:2419-2430

Characteristic	Lymphoma		
	mBL	Non-mBL	Intermediate
	number (percent)		
Total	44	128	48
Age at diagnosis			
<60 Yr	40 (91)	39 (31)	21 (45)
≥60 Yr	4 (9)	88 (69)	26 (55)
Sex			
Female	13 (30)	56 (45)	22 (47)
Male	30 (70)	68 (55)	25 (53)
Morphologic diagnosis			
Burkitt's lymphoma (core group)	8 (18)	0	0
Atypical Burkitt's lymphoma‡	21 (48)	3 (2)	4 (8)
Diffuse large-B-cell lymphoma	11 (25)	115 (90)	39 (81)
Mature aggressive B-cell non-Hodgkin's lymphoma, unclassifiable	4 (9)	9 (7)	5 (10)
Burkitt's lymphoma–leukemia	0	1 (1)	0
CD10 expression§			
Absence	0	95 (79)	20 (43)
Presence	42 (100)	26 (21)	26 (57)
BCL6 expression§			
Absence	0	26 (23)	7 (15)
Presence	39 (100)	87 (77)	39 (85)
BCL2 expression§			
Absence	33 (79)	20 (16)	8 (17)
Presence	9 (21)	104 (84)	40 (83)
Ki-67 score§			
<95%	15 (34)	107 (88)	40 (85)
≥95%	29 (66)	15 (12)	7 (15)

No problem

The main problem

Technical problem?

2. BL with atypical phenotype: bcl2 and t(14;18)

M Hummel et al, NEJM 2006; 354:2419-2430

S Dave et al, NEJM 2006; 354:2431-42

c-myc FISH	+	+	+	+	+	+	+	+	+
CD10	+	+	+	+	+	–	–	+	+
Ki-67 score (%)	100	90	100	100	90	70	100	60	95
BCL2 mRNA	6.3	5.8	5.8	5.6	6.1	8.2	8.0	7.4	7.5
BCL2 staining	–	–	–	–	+/–	+	+	+	+
BCL2 FISH	NA	NA	–	NA	–	–	+	+	+
Probability of Burkitt's lymphoma (%)	100	100	100	100	100	99	99	99	98

5 / 53 mBL bcl2 protein+: 9%

3 / 5 / 53 mBL t(14;18)+: 6%

NB. 2 / 5 atypical phenotype

Characteristic	mBL
Total	44
ABC or GCB signature¶	
ABC	0
GCB	40 (91)
Unclassified	4 (9)
myc partner‖	
IG-myc	38 (88)
Non–*IG-myc*	1 (2)
myc-negative	4 (9)
***IGH-BCL2* fusion‖**	
Absent	43 (98)
Present	1 (2)
***BCL6* breakpoint‖**	
Absent	43 (100)
Present	0
Chromosomal complexity score	
Low (<6)	31 (79)
High (≥6)	8 (21)

9 / 44 mBL bcl2 protein + : 21%

1 / 9 mBL t(14;18)+ : 2%

2. Conclusions BL with atypical phenotype

- May be mixed bag
  - Real BL
  - Double hit lymphomas
  - Other mechanisms that activate BCL2?
- No data on clinical outcome
- Needs further study

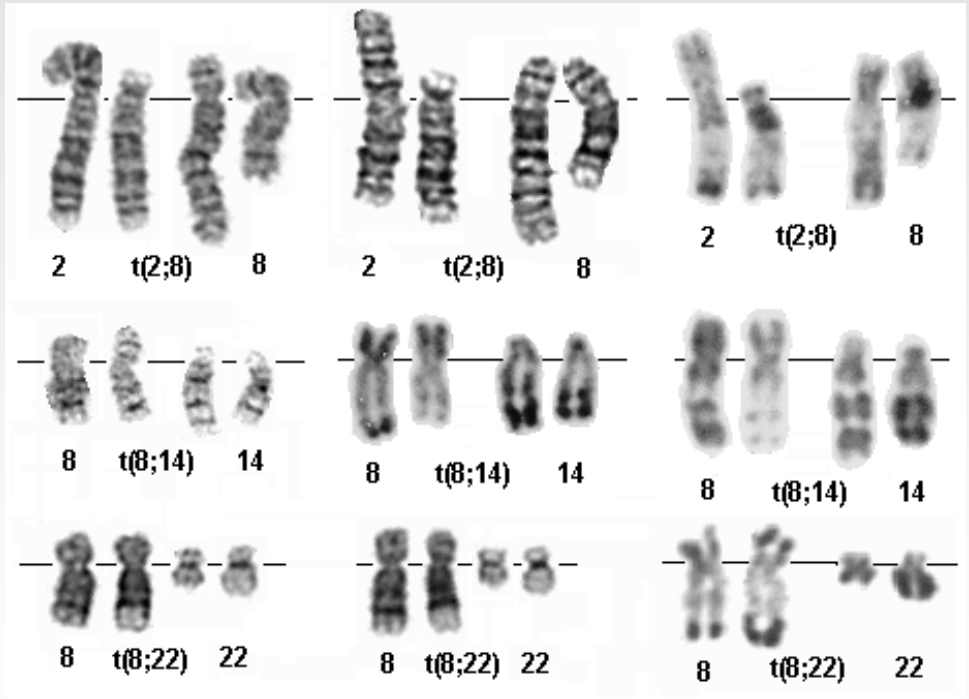
WHO 2008

- Only acceptable as BL if bcl2 expression is NOT due to BCL2 or BCL6 breakpoints and if the case otherwise is a perfect BL

- Other cases go to the novel category ("intermediate between DLBCL and BL")

3. Otherwise typical BL without a detectable MYC translocation

- t(8;22)(q24;q11) in 15%
- t(8;14)(q24;q32) in 80%
- t(2;8)(p11;q24) in 5%

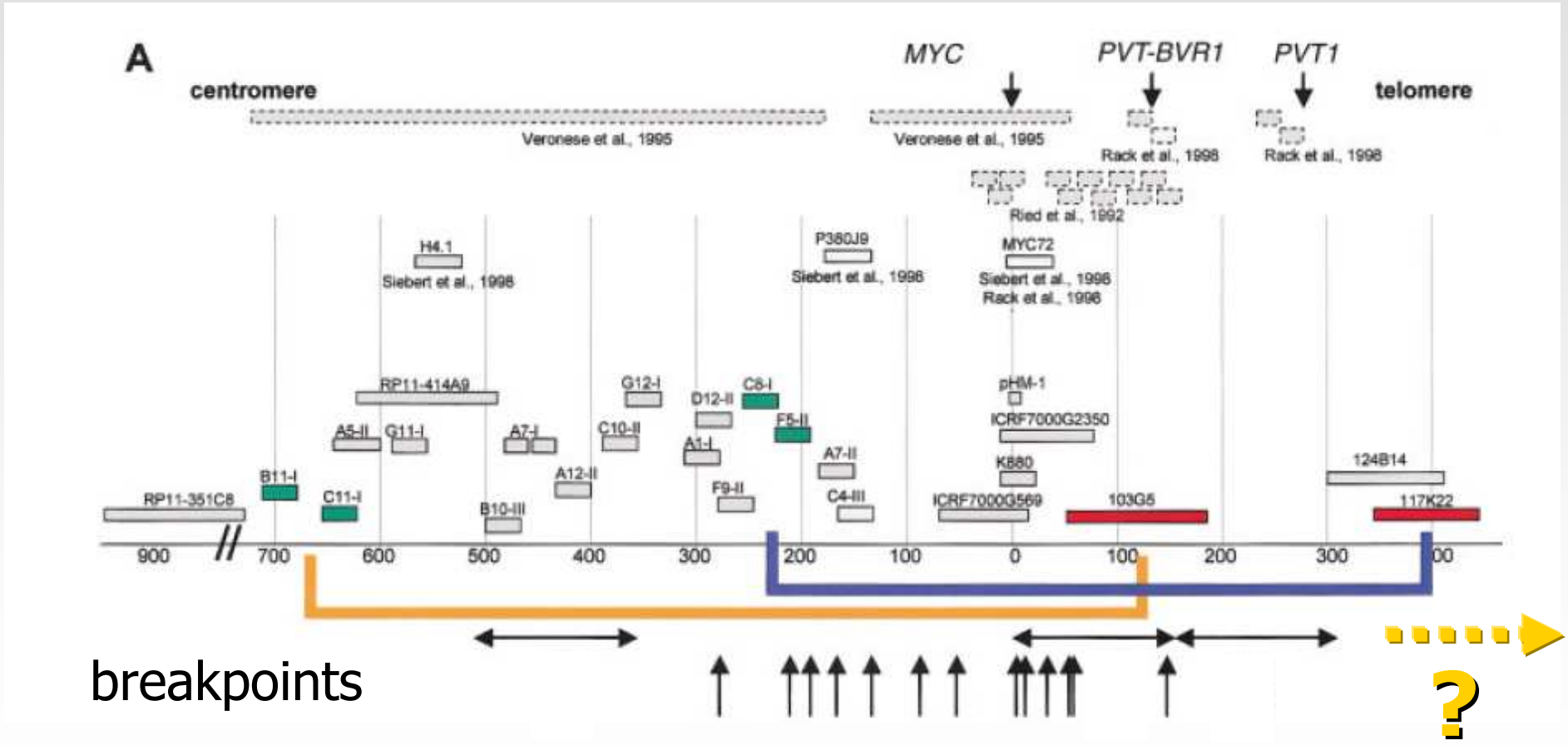


3. BL without detectable MYC translocation

- Karyotype Mitelman's database*: 108/646 (17%)
- FISH study of Haralambieva 5/47 cases (11%) (GCC 2004;40:10-8)
- FISH study of Hummel on molecular BL 4/44 (9%) (NEJM 2006; 354:2419-2430)

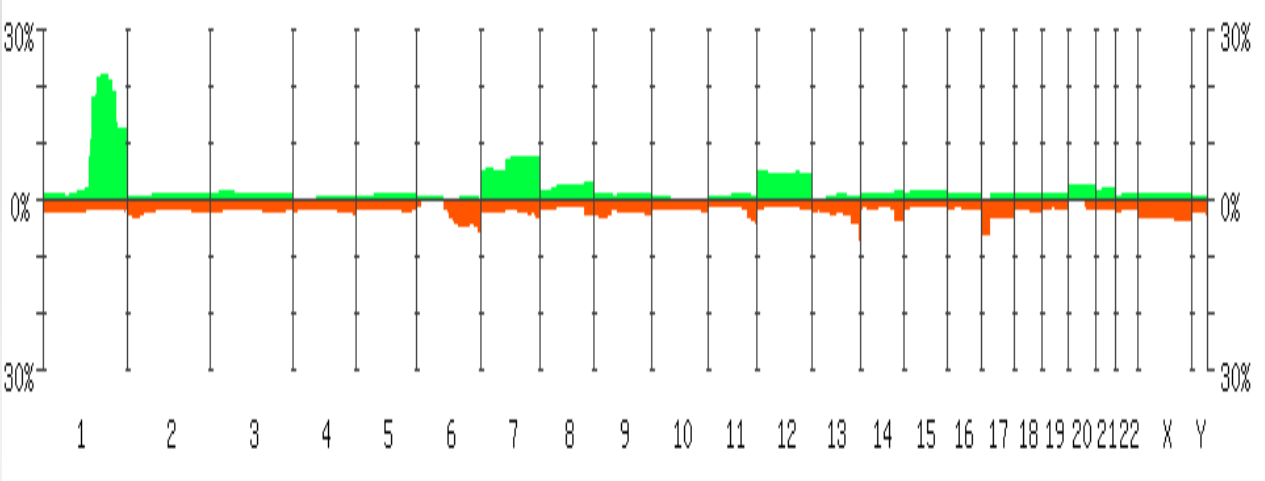
*Diagnosis of many cases without extensive IHC

3. BL without detectable MYC translocation: FISH might not cover all breakpoints

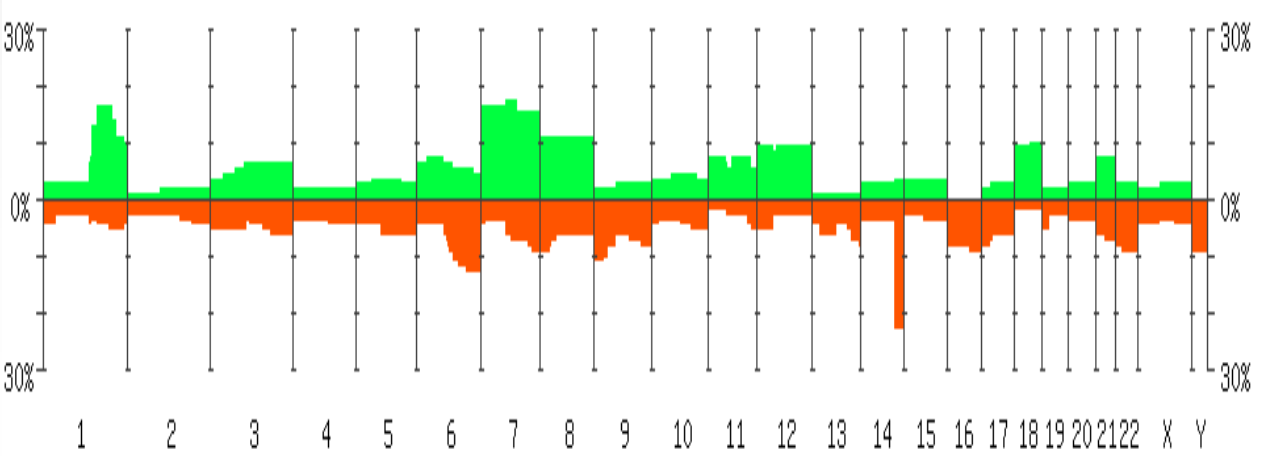


E Haralambieva et al. Genes Chromosomes Cancer. 2004 ;40:10-8
R Einerson et al, Leukemia. 2006 Oct;20:1790-9

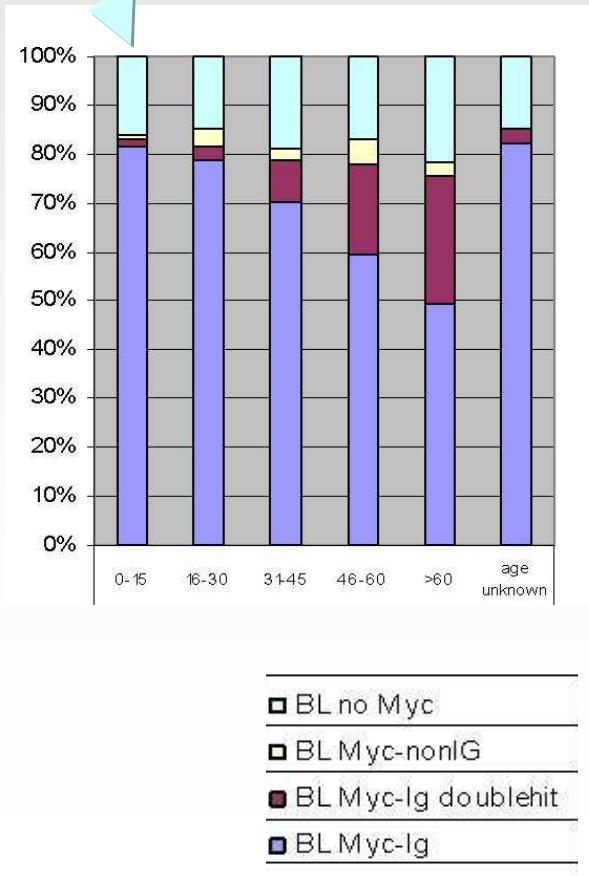
3. “BL” without detectable MYC translocation: in all age groups, but higher complexity than in translocation+ “BL”



“BL” IG-MYC (n=481)



“BL” without MYC (n=108)



3. Conclusions BL without detectable MYC translocation

- Heterogenous
  - Missed (variant) breakpoints that are further downstream of MYC
  - Other mechanisms leading to constitutive MYC activation
  - Incorrect diagnosis

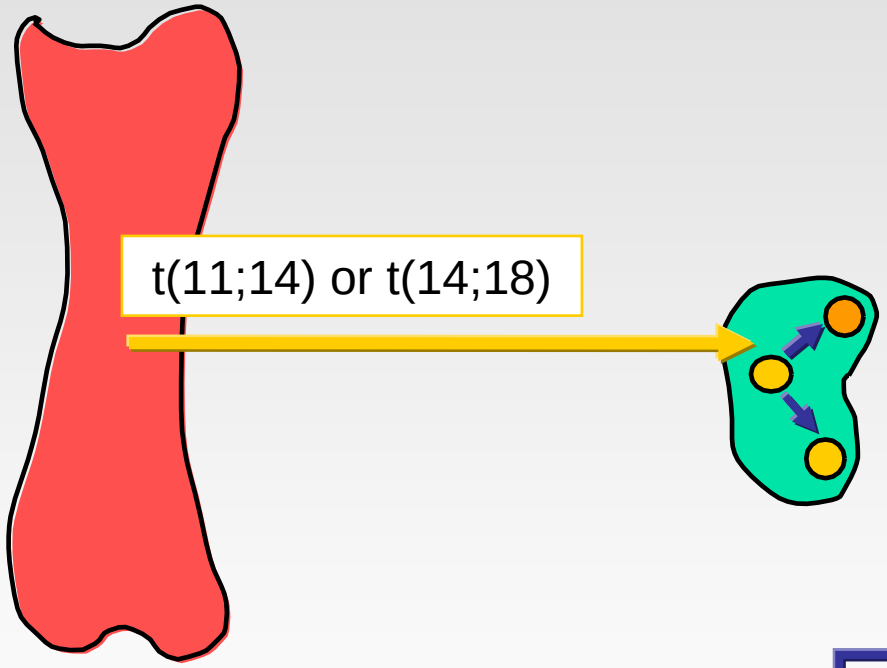
WHO 2008

- Perform multiple FISH tests (not only the IGH-MYC fusion probes!; if possible also cytogenetics)
- Only acceptable as BL if lack of the breakpoint is the only abnormal feature
- Other cases, including cases with MYC amplification, go to novel category ("intermediate between DLBCL and BL")

4. Double hit lymphomas

- Some lymphomas have 2 or 3 recurrent translocations.
- Mitelman data base: 53 / 538 “BL” (10%)
  - Double hit:
    - 31 MYC & BCL2
    - 11 MYC & BCL6
    - 5 MYC & CCND1
  - Triple hit
    - 6 MYC & BCL2 & BCL6

4. Double hit lymphomas: origin



bone marrow :
-VDJ recombination by RAG1/2

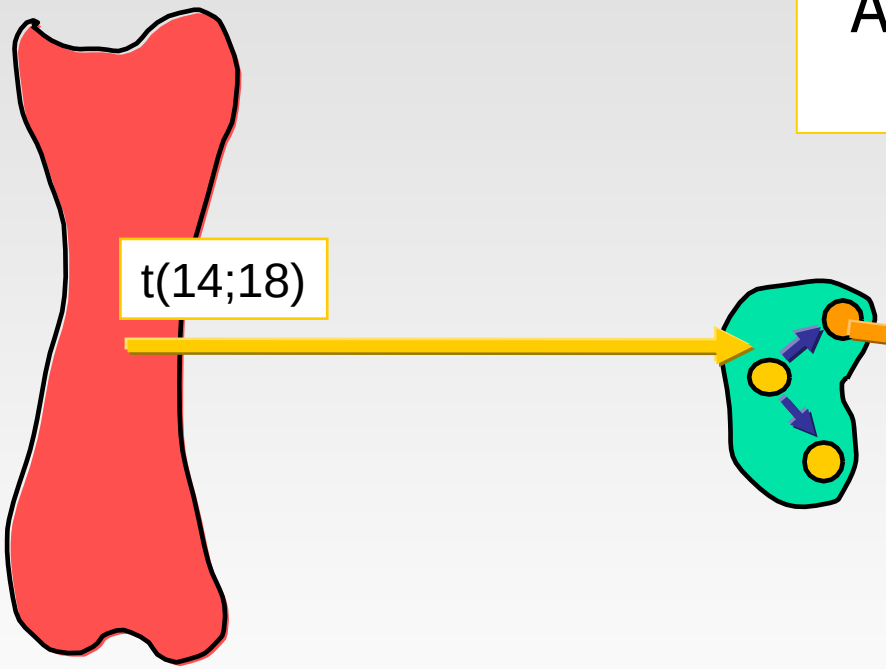
Mantle cell lymphoma

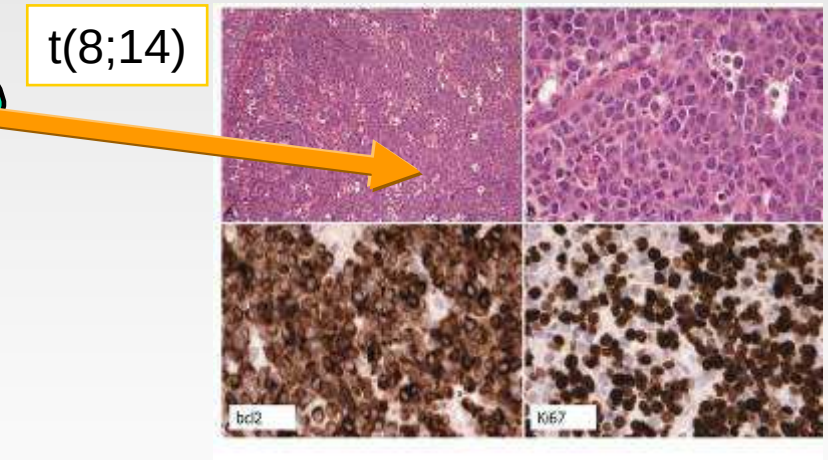
&

Follicular lymphoma

4. Double hit lymphomas: origin

Almost all cases are strongly bcl2 protein positive



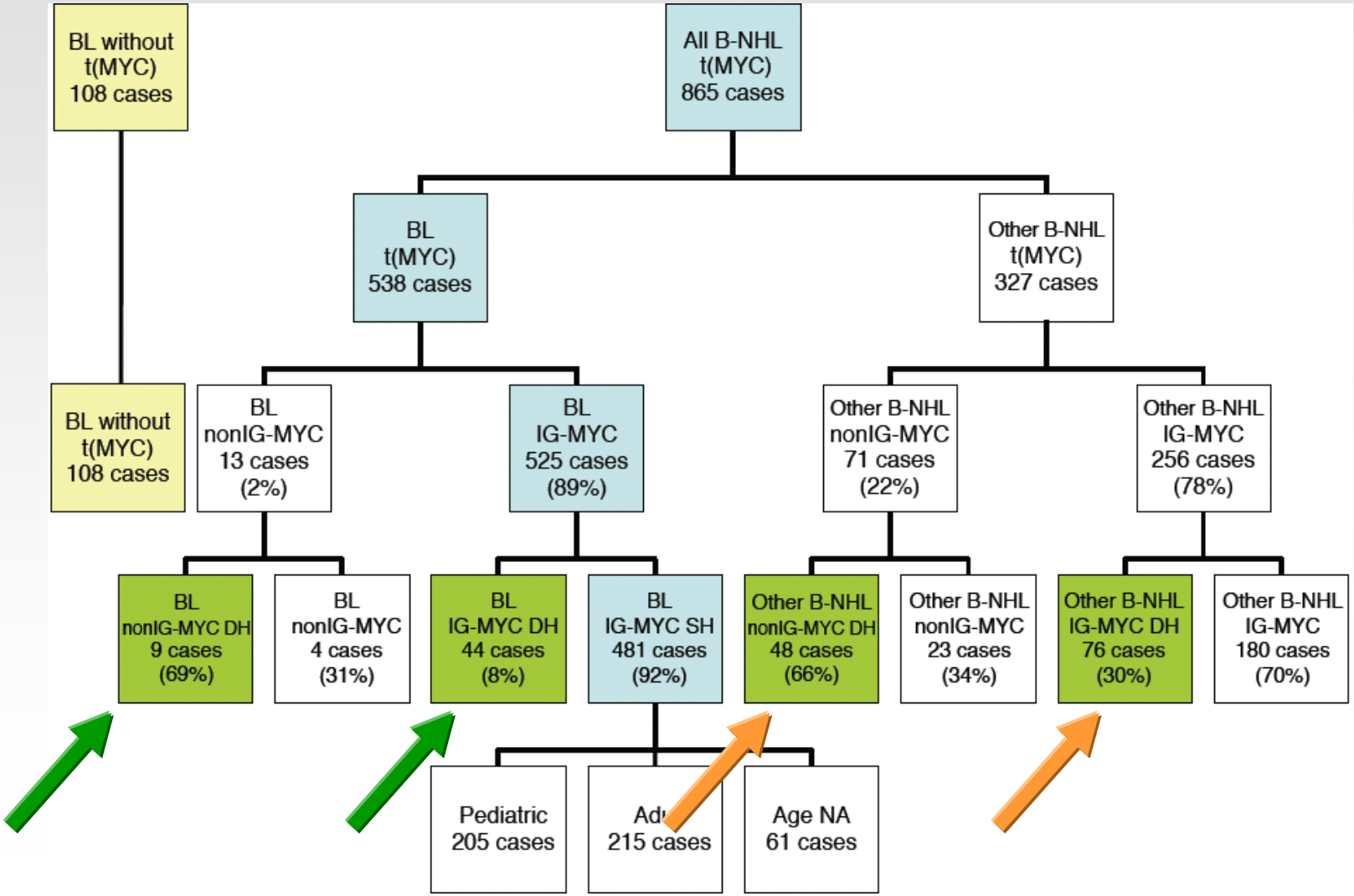


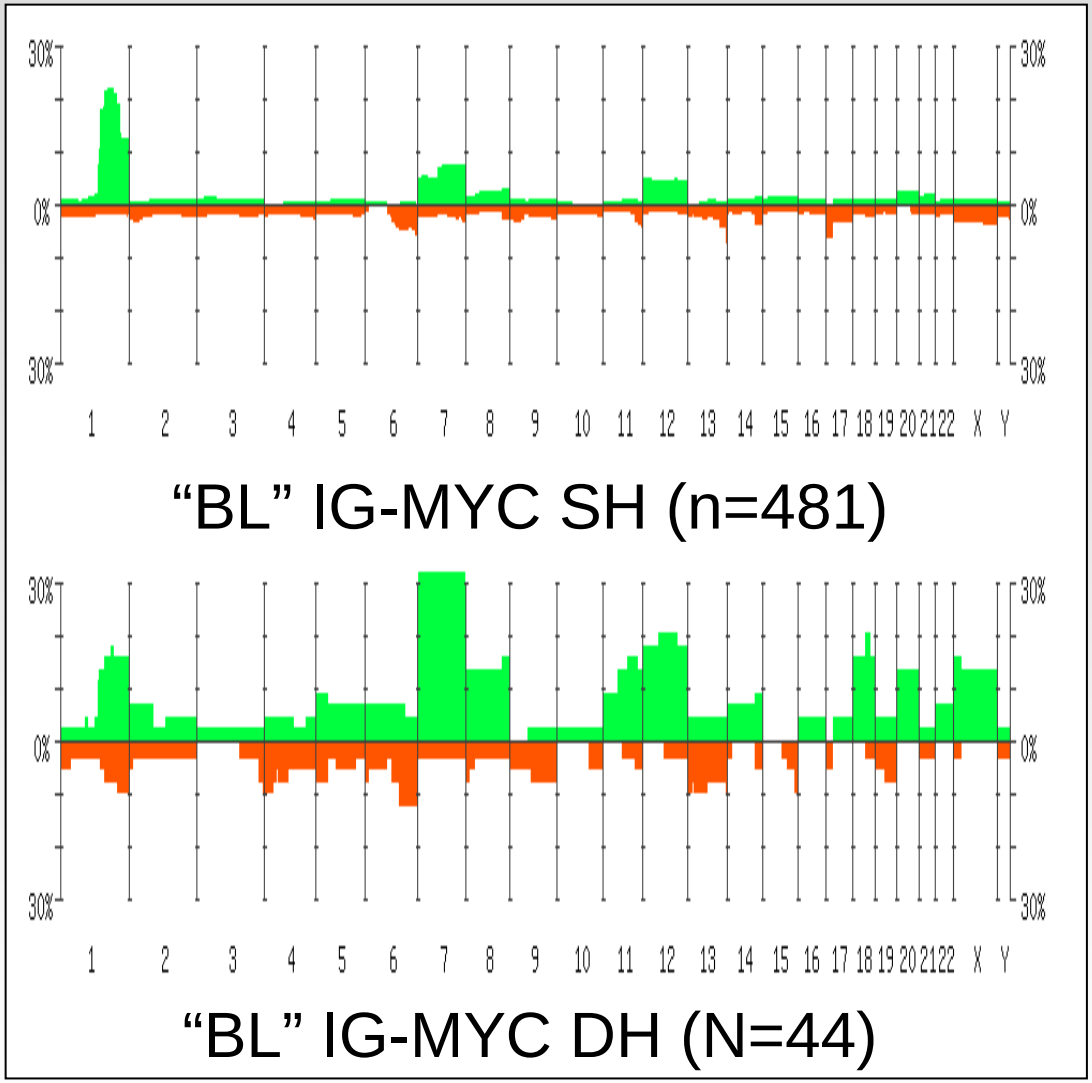
bone marrow :
-VDJ recombination by RAG1/2

germinal center and possibly rare extrafollicular blasts:
-AID mediated SHM and class switching

4. Double hit lymphomas in Mitelman database

- 10% of all cases classified as "BL"
- 38% of "other B-NHL" with MYC translocation!!

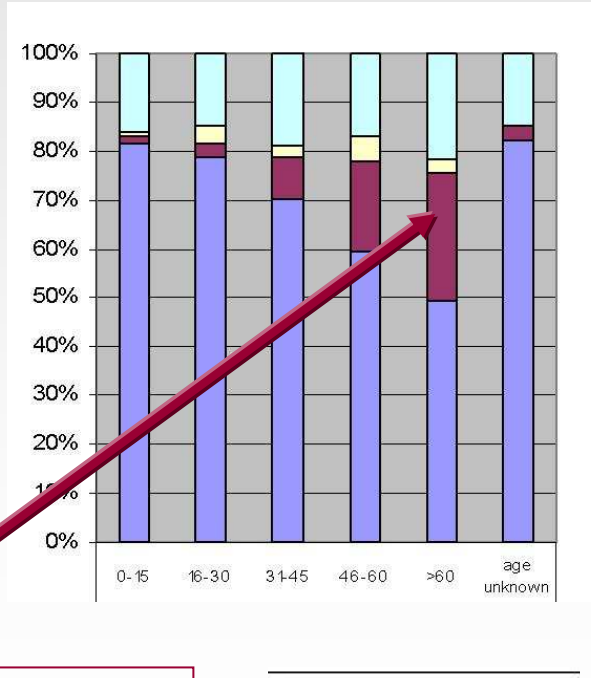




"BL" IG-MYC SH (n=481)

"BL" IG-MYC DH (N=44)

4. Double hit "BL" in Mitelman database: more complex karyotype than "true BL"



Incidence of double hit cases rises in elderly patients up to 30% of all "BL" > 60yrs

4. Double hit lymphomas: clinical significance

P Lin, J Medeiros. Haematologica 2007; 92:1297-1301

Table 1. Summary of previously published series of M B high-grade B-cell lymphoma/leukemia.

Authors	Number of cases	Prior or concurrent FL	Morphology	Survival (months)
Stamatoullas A *et al.*[27]	5	0	5 ALL-L3	<7
Thangavelu M *et al.*[17]	6	2	3ALL-L2, 2 ALL-L 1 DLBCL	5/6 ≤12
D'Achille P *et al.*[37]	7	0	5 ALL-L3, 2 ALL-L2	5/7 ≤6
Cogliatti SB *et al.*[3]	4	Not specified	1 BL, 2 BLL, 1 DLBCL	Not specified
Haralambieva E *et al.*[32]	5	Not specified	1 BLL, 4 DLBCL	Not specified
McClure RF *et al.*[34]	5	Not specified	3 BLL, 2 DLBCL	4/5 <12
Macpherson N *et al.*[26]	13	6	13 BLL	<7
LeGouill S *et al.*[7]	16	4*	16 DLBCL	15/16 ≤10
Kanungo A *et al.*[8†]	23	6	4 BL, 12 BLL, 7 DLBCL	8/10 ≤12

*BL: Burkitt's lymphoma; ALL: acute lymphoblastic leukemia; BLL: Burkitt's like lymphoma; DLBCL: diffuse large B-cell lymphoma; *Two of the 6 patients had a presumptive diagnosis of FL based on bone marrow histology. †Eleven additional cases were identified after the original report of 14 cases, one case of myeloma and one case of low-grade B-cell lymphomas excluded. see Table 2 for details.*

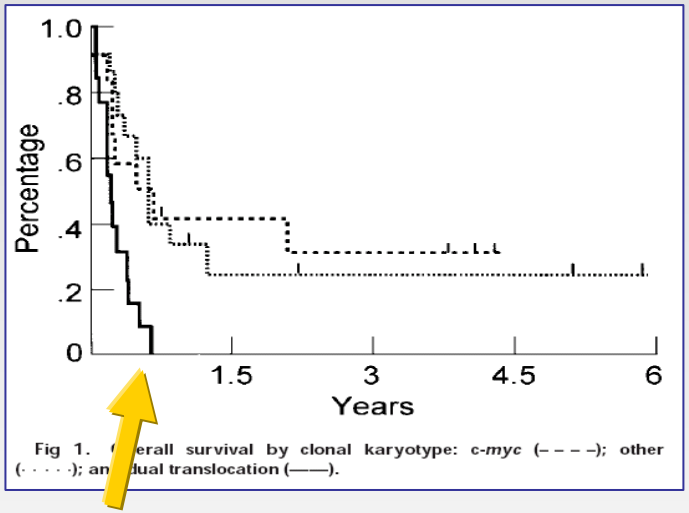
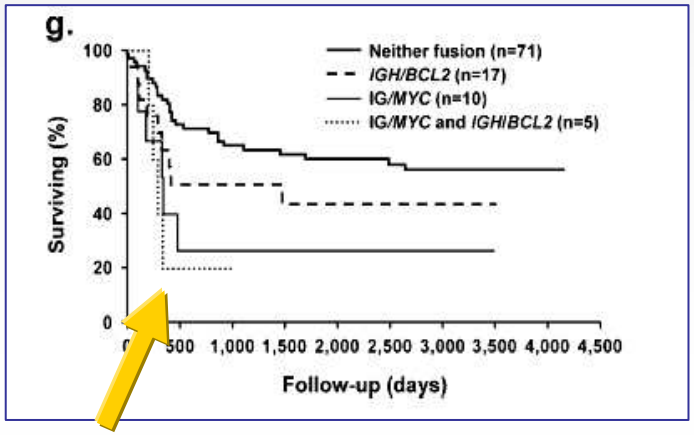


Fig 1. Overall survival by clonal karyotype: c-*myc* (– – –); other (· · · ·); and dual translocation (——).

Macpherson et al JCO 1999;17:1558-67



McClure, AJSP 2005;29:1652-60

Ca	A/G	BM	Extramedullary sites	Therapy	Follow-up (mo.)	Histology	CD10	BCL-2	Ki-67
1	54/F	-	Small intestine	R-CHOP RICE R-HCVAD	A (7)	DLBCL	+	+	95
2	54/M	-	Lung, chest wall, testis	R-CHOP R-ESHAP	D (10)	DLBCL	+	+	95
3	64/M	+	–	HCVAD	D (81)	DLBCL	ND	+	90
4	29/M	+	–	R-CHOP RICE R-HCVAD	D (5)	BL	+	+	99-100
5	72/M	+	–	R-HCVAD	A (11)	BL	+	+	99-100
6	50/F	+	–	R-HCVAD	D (3)	BL	+	+	95
7	32/M	+	Mesenteric LN	HCVAD	D (8)	BL	+	+	95
8	67/M	+	Pelvic LN, small intestine	R-HCVAD Velcade	D (9)	BLL	+	+	70
9	61/M	+	Retroperitoneal LN, colon, prostate	HCVAD MOAP	D (9)	BLL	ND	+	80
10	42/F	+	Small intestine, omentum, breast	ProMACECytaBOM CHOP, ESHAP H-CVAD, BMT, RT	D (12)	BLL	+	+	90
11	63/M	+	Testis, lip	Magrath regimen CHOP, DT-PACE HCVAD	D (18)	BLL	+	+	95
12	55/M		Ileocecal valve	H-CVAD	A (5)	BLL	ND	+	99-100
13	65/M	u	Inguinal and cervical LN	R-CHOP HCVAD + SCT	D (7)	BLL	+	–	100
14	77/M	–	Cervical LN	R-CHOP	Lost	BLL	+	+	100
15	43/M	–	Cervical LN	R-HCVAD	A (6)	BLL	+	–	100
16	42/M	+	–	R-HCVAD	Lost	BLL	+	ND	ND
17	45/M	+	Abdominal LN	R-HCVAD	A (1)	BLL	–	+	100
18	64/M	+	–	R-HCVAD	A (2)	BLL	+	+	90
19	58/M	+	Testicle Kidney, Inguinal LN	R-CODOX-M + IVAC	A (21)	BLL	+	+	99-100
20	58/M	–	Cervical LN	R-CHOP	A (21)	DLBCL + FL	+	ND	ND
21	58/M	u	Abdominal LN	U	Lost	DLBCL + FL	+	+	90
22	53/M	+	Inguinal LN	RFND R-Cytoxan+Paxil	A (2)	DLBCL + FL	+	+	90
23	72/M	u	Abdominal L	U	Lost	DLBCL	+	+	60

Double hit (MYC & BCL2) MD Anderson

- Most CD10+, bcl2+
- Poor outcome, perhaps incidental patients might be rescued (very short follow up)

P Lin, J Medeiros. Haematologica 2007;92:1297-1301

Mead et al, Blood 2008; 112: 2245-60 (CODOX-M/IVAC)

N= 128 B cell lymphomas with // 100% Ki67.

•Subdivided into GC vs non-GC (BCL-6, CD10, and IRF4).
•Bcl2+ and bcl2-
•TP53 status (TP53 and P21)
•FISH for MYC, BCL2 and BCL6

N=58: Ki67100%, CD10+, Bcl6+, Bcl2-, p53+, p21-

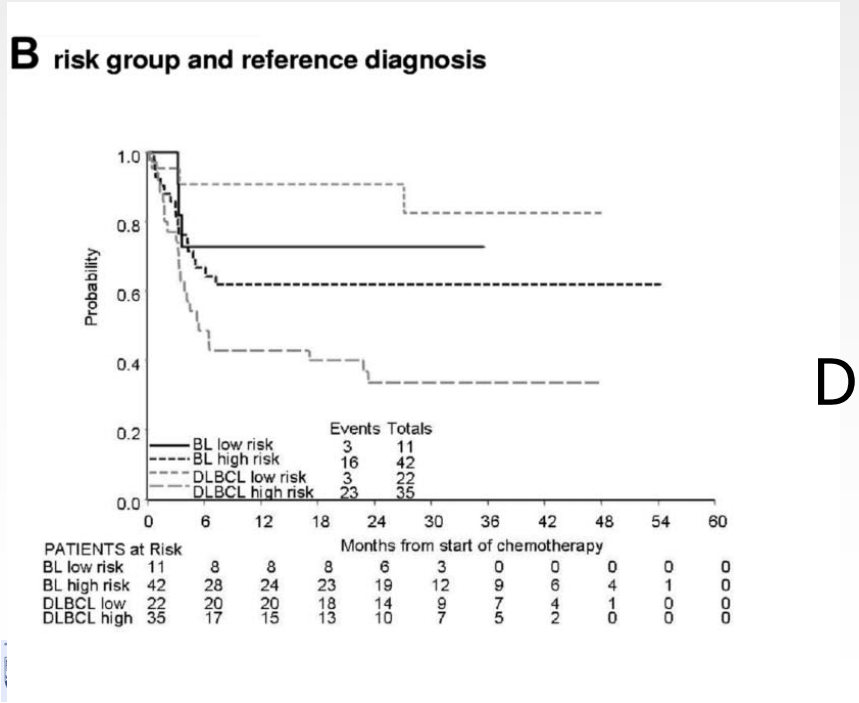
•70% of these cases had a MYC rearrangement (33% of total group)
•*MYC* rearrangement as the sole cytogenetic abnormality only in this subgroup.

Double hit BCL2 & MYC rearrangement only in GC group, all Bcl2 protein+

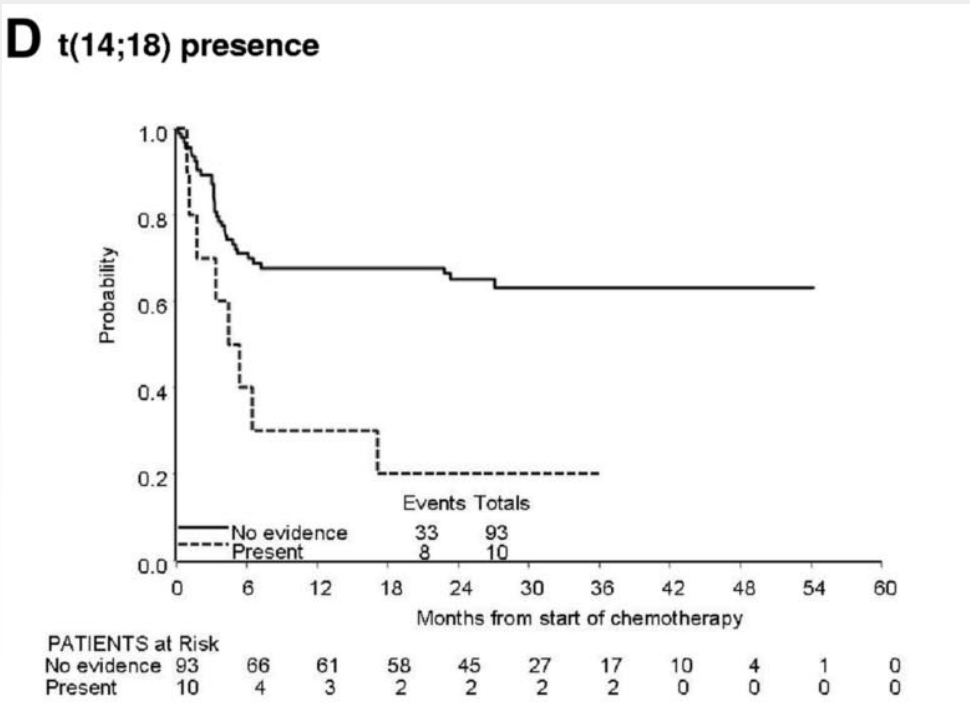
BCL6 rearrangements in GC and non-GC phenotypes.

Mead et al, Blood 2008; 112: 2245-60 (CODOX-M/IVAC)

BL N=58: "GC", absence of bcl2 expression, abnormal TP53 expression, *cMYC* rearrangement, and no t(14;18) or 3q27 rearrangements.



DFS



4. Conclusions double hit lymphomas

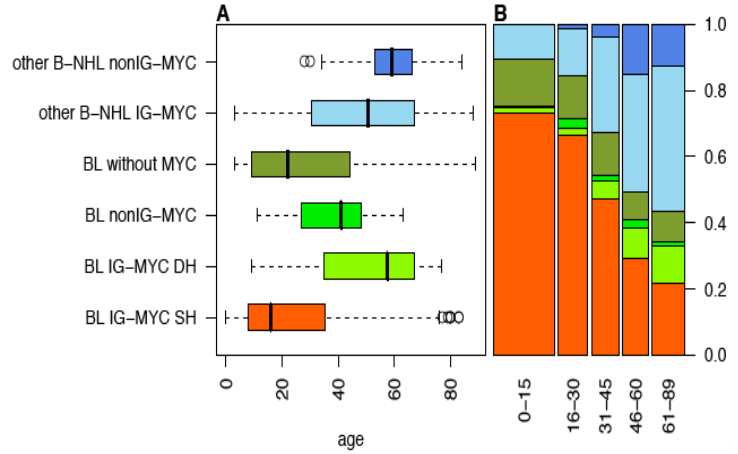
- Mostly BCL2 & MYC translocation
- Increasing confounder at higher age
- Each BL with bcl2 expression should be thoroughly tested by karyotyping & FISH (also for BCL6 breakpoints)
- Only few cases have features of (preexistent) FL
- Very poor outcome in almost all patients
- Should be separated from BL & DLBCL

WHO 2008

- All double hits* go to the novel category
- Even DLBCL DH cases should preferably go to this category ("intermediate between DLBCL and BL")
- Still discussion possible on the best classification of DH MYC & BCL6 cases

*Should have a MYC breakpoint, not a combination of BCL2 and BCL6 breakpoints only

GENERAL CONCLUSIONS.1



- The diagnosis of Burkitt lymphoma can be reliably made with a high specificity when strict criteria are used
- This is possibly at cost of the sensitivity
- "True BL" has a low genetic complexity, also in elderly patients
- Double hit cases should be separated from BL and DLBCL
- Except for possible "true BL" without a detectable MYC translocation, all BL imitators increase with age and have a higher genetic complexity than "true BL".

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