

The young side of
LYMPHOMA

gli under 40 a confronto

Pescara, Auditorium Petruzzi
11-12 ottobre 2024

DLBCL vs HGBL

Ruolo del patologo

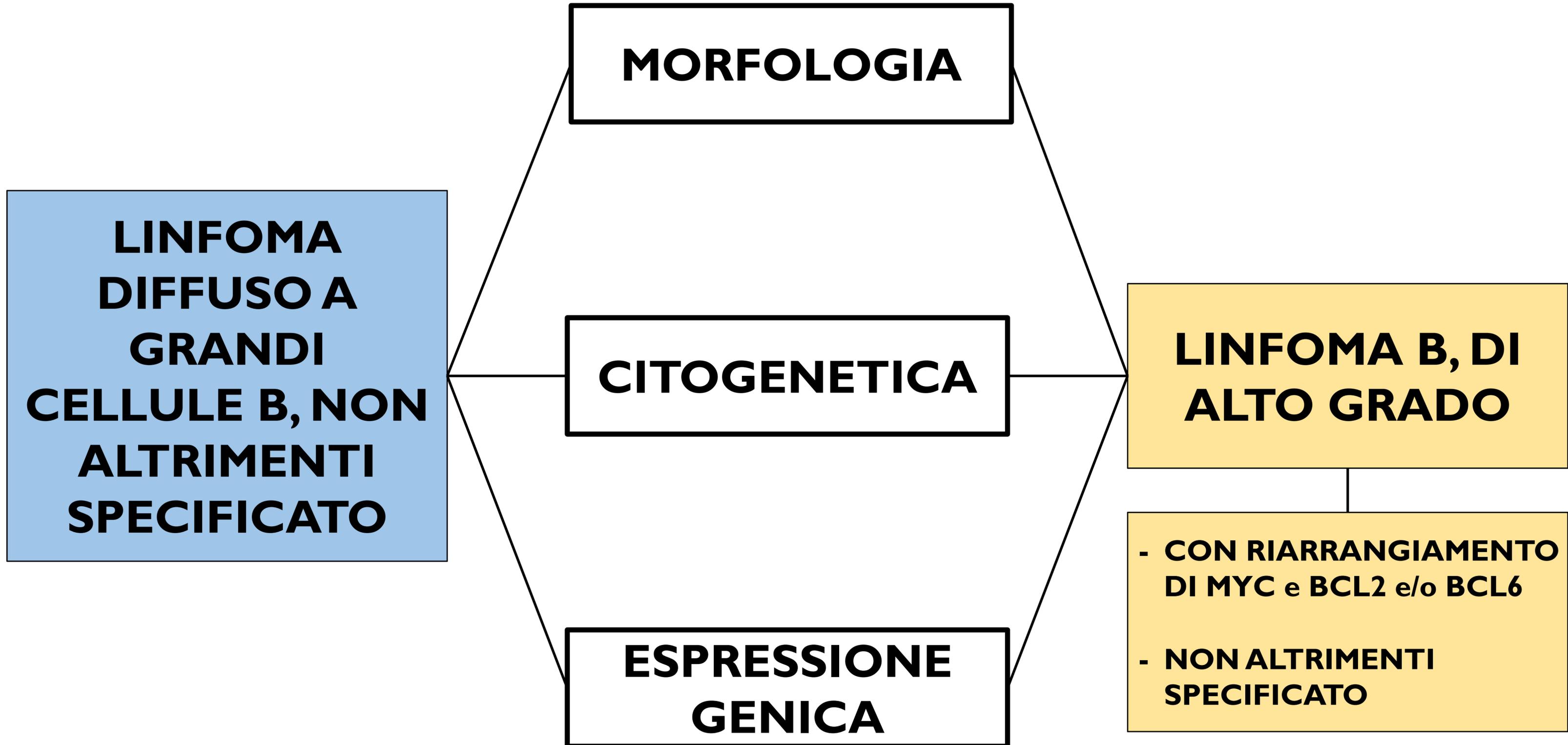
Mattia Facchetti

ASST Spedali Civili di Brescia



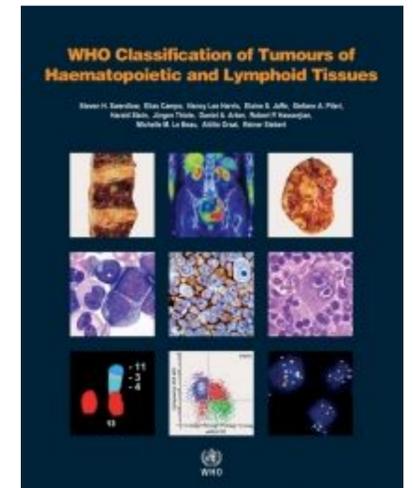
No disclosures.

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other



LINFOMA DIFFUSO A GRANDI CELLULE B, NAS

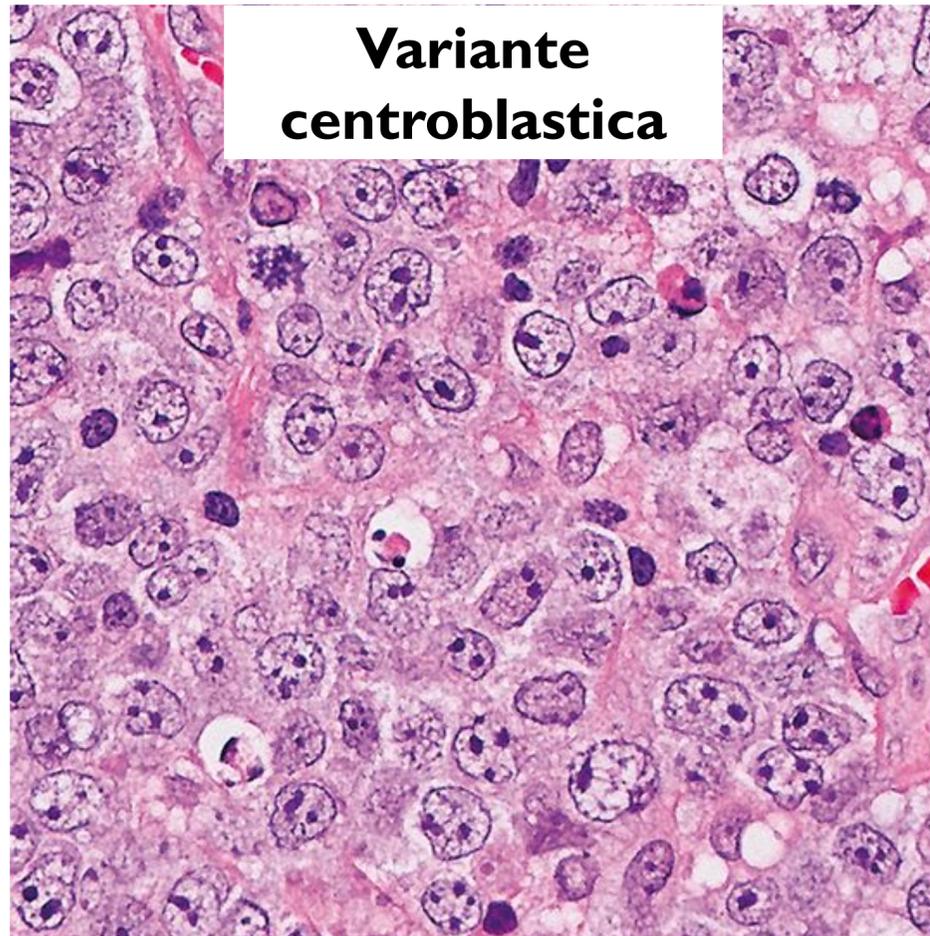
WHO 2017



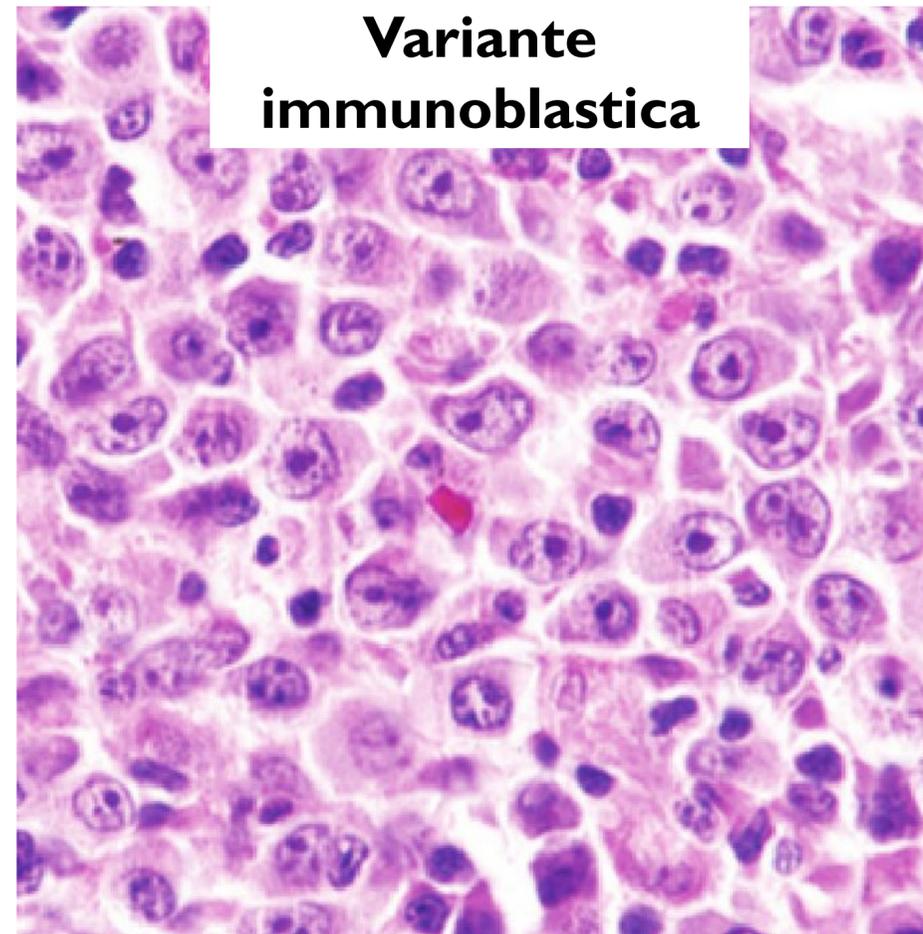
Cellule di media-grande taglia a crescita diffusa.

Entità eterogenea dal punto di vista morfo-fenotipico e molecolare.

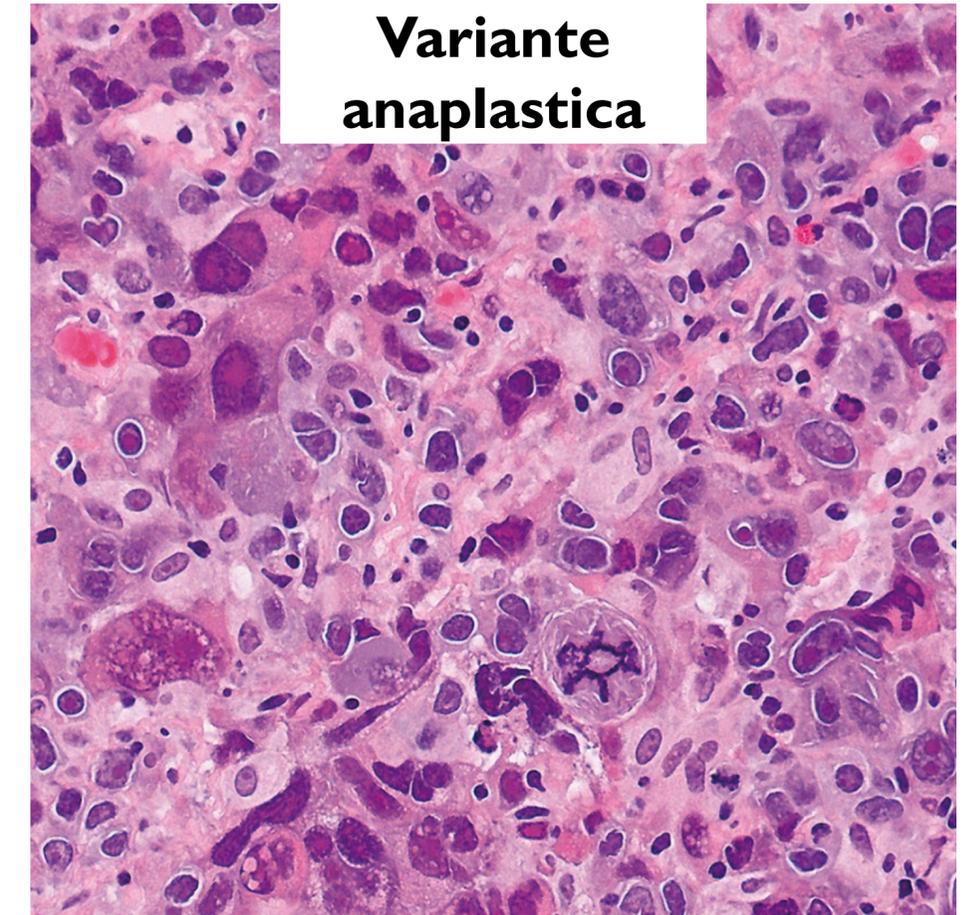
Non soddisfa i criteri diagnostici per uno specifico linfoma a grandi cellule B.



**Variante
centroblastica**



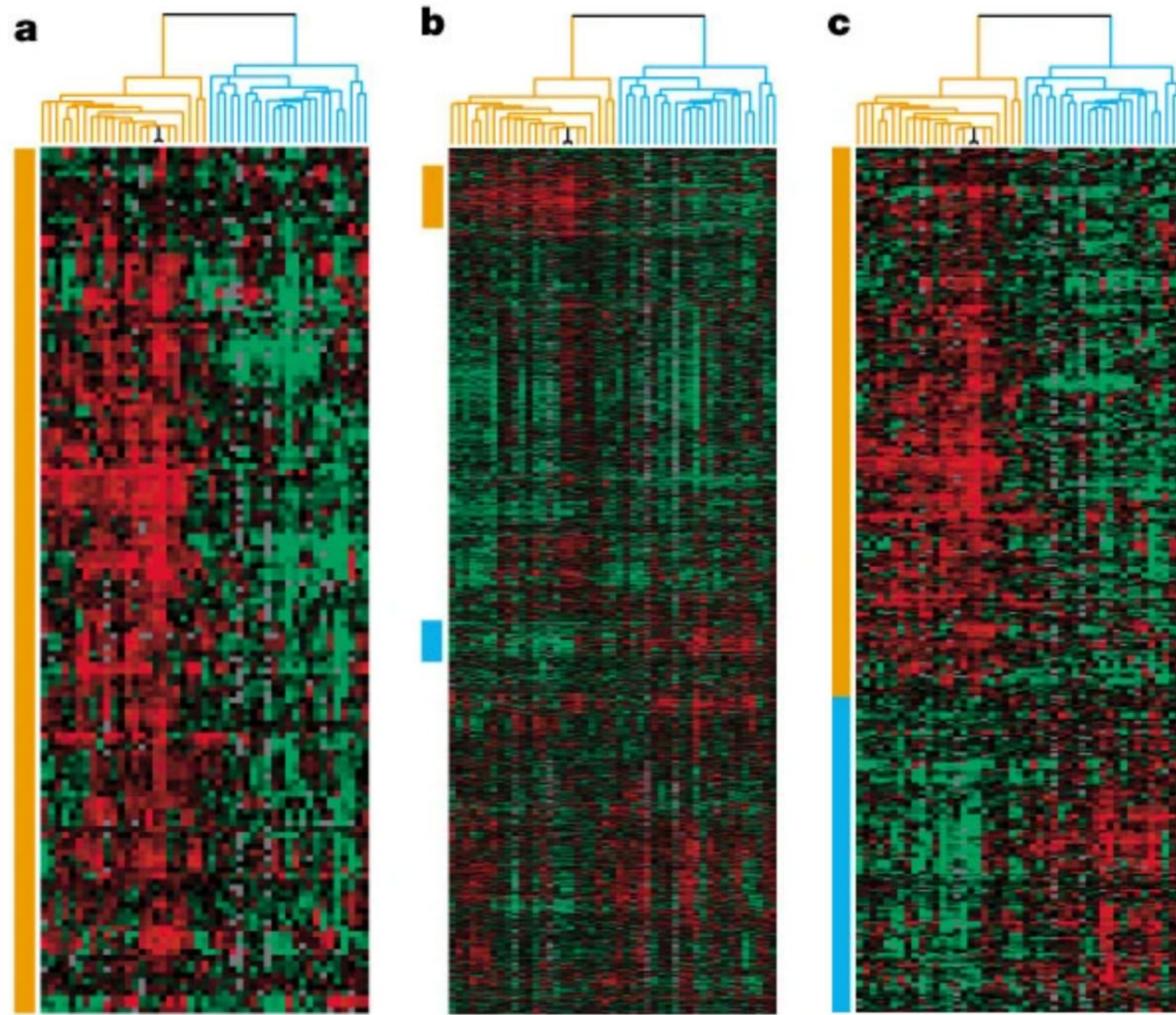
**Variante
immunoblastica**



**Variante
anaplastica**

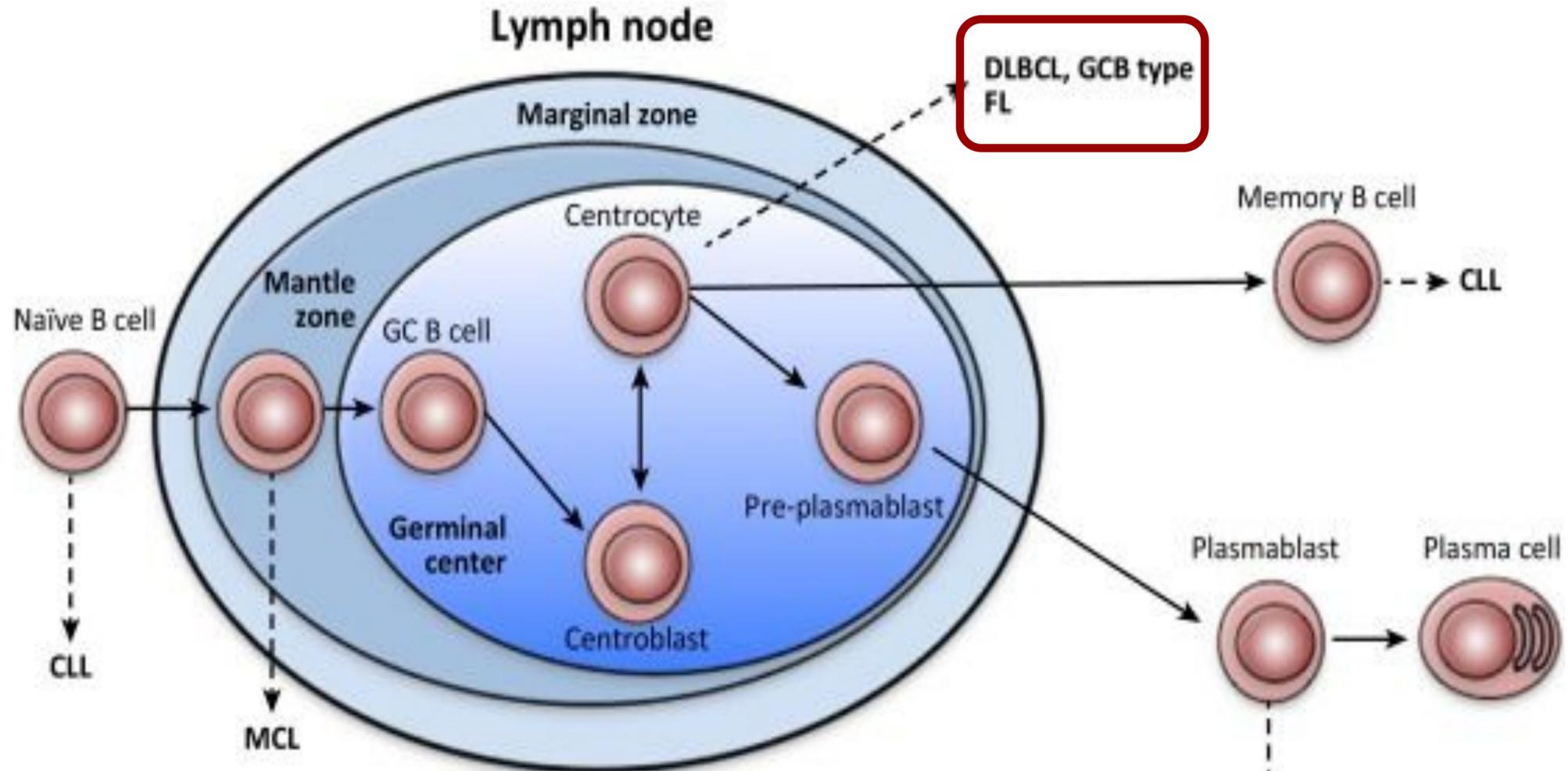
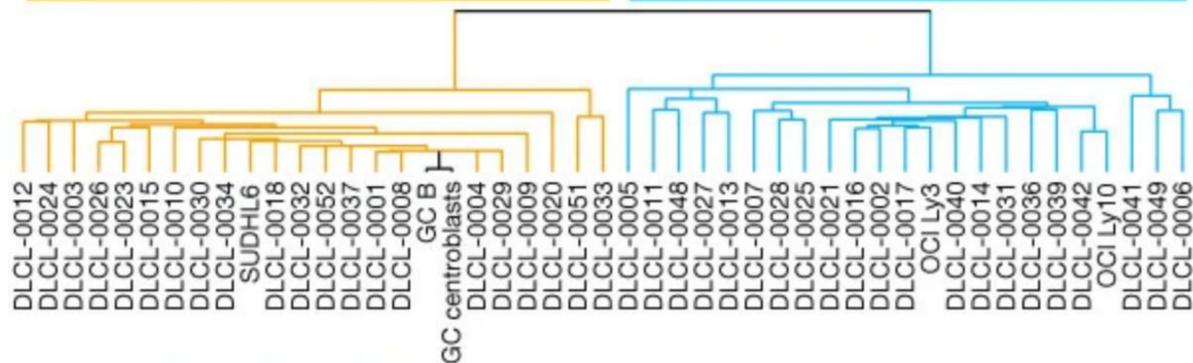
The young side of LYMPHOMA

gli under 40 a confronto



GC B-like DLBCL

Activated B-like DLBCL



> Nature. 2000 Feb 3;403(6769):503-11. doi: 10.1038/35000501.

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

A A Alizadeh¹, M B Eisen, R E Davis, C Ma, I S Lossos, A Rosenwald, J C Boldrick, H Sabet, T Tran, X Yu, J I Powell, L Yang, G E Marti, T Moore, J Hudson Jr, L Lu, D B Lewis, R Tibshirani, G Sherlock, W C Chan, T C Greiner, D D Weisenburger, J O Armitage, R Warnke, R Levy, W Wilson, M R Grever, J C Byrd, D Botstein, P O Brown, L M Staudt

CELL OF ORIGIN (COO)

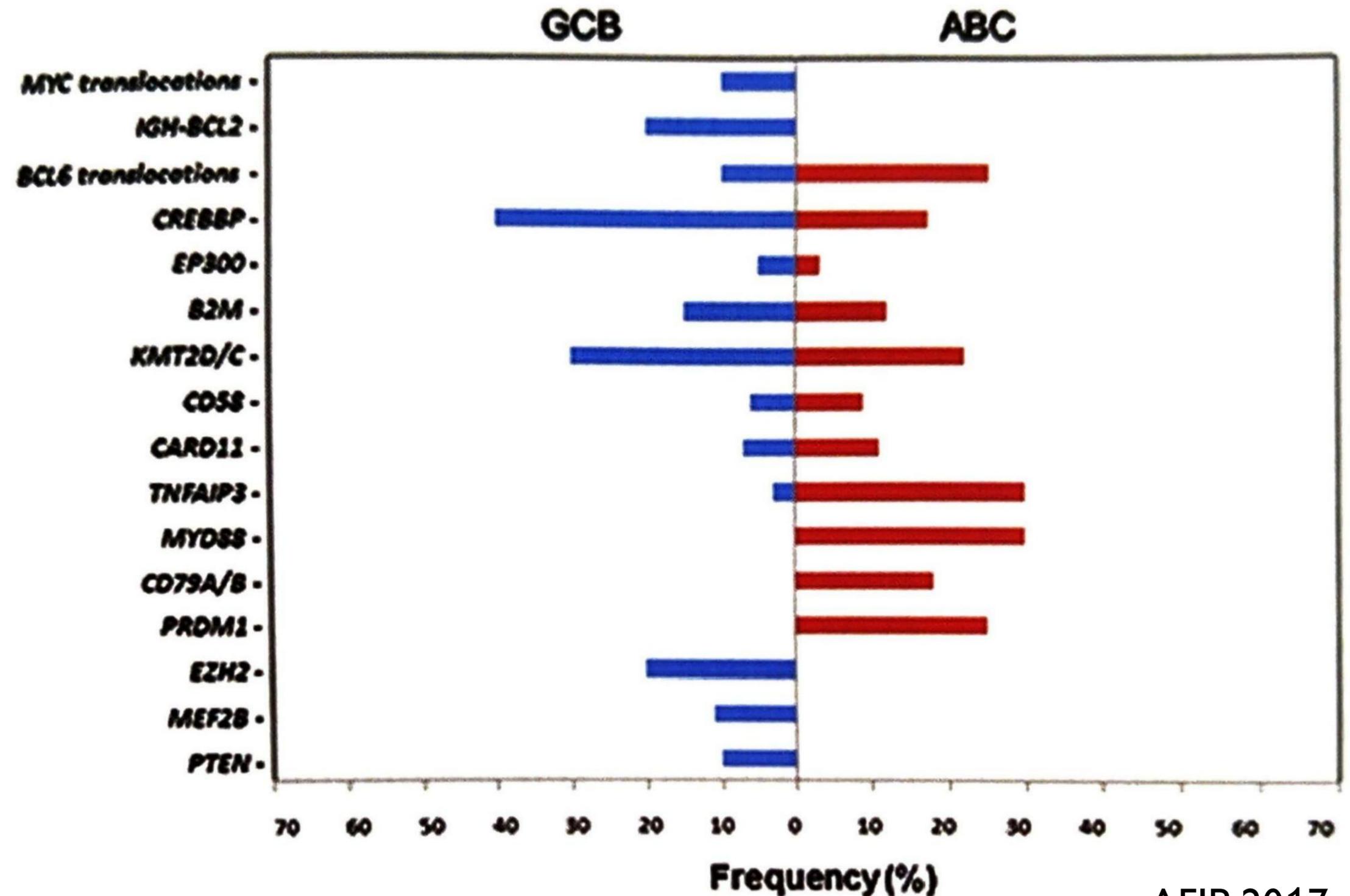
Le alterazioni geniche correlano con la classificazione COO.

GCB:

- modificazioni istone,
- B-cell homing,
- inattivazione CDK2NA e CDKN2B.

ABC:

- attivazione pathway NF-kB (CD79A/B, CARD11, MALT1, BCL10, TNFAIP3, MYD88).

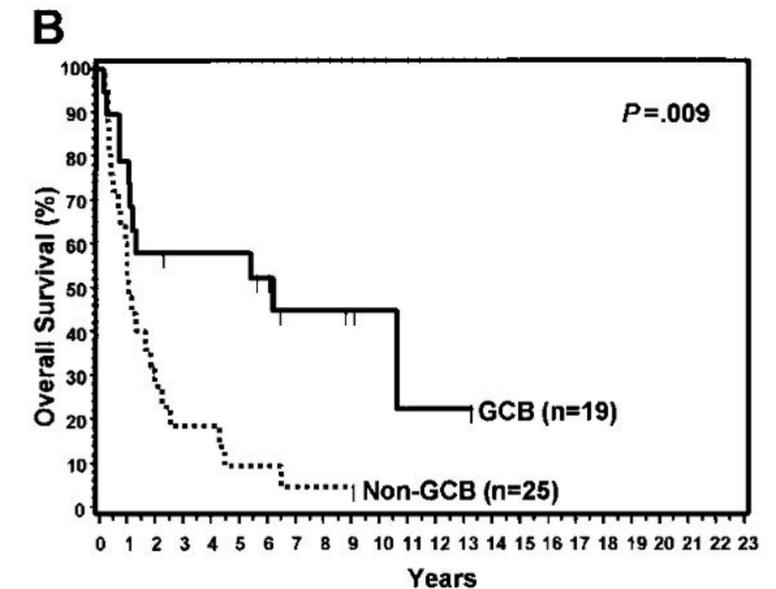
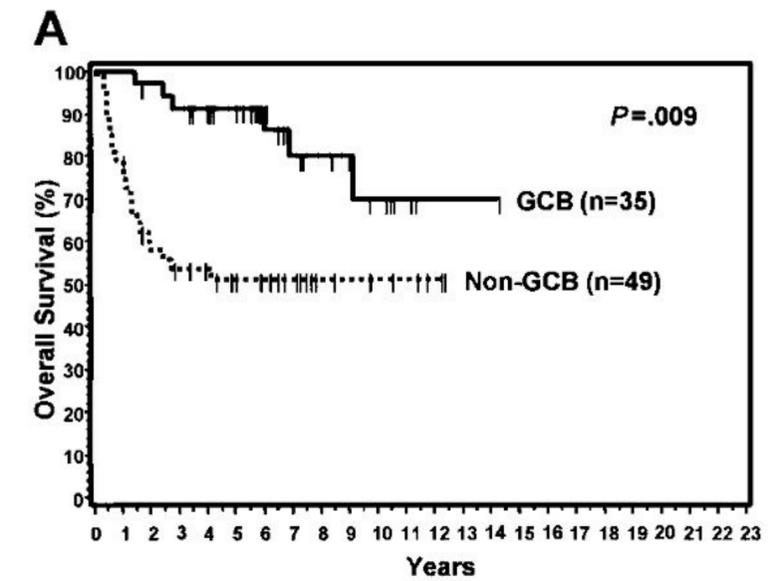
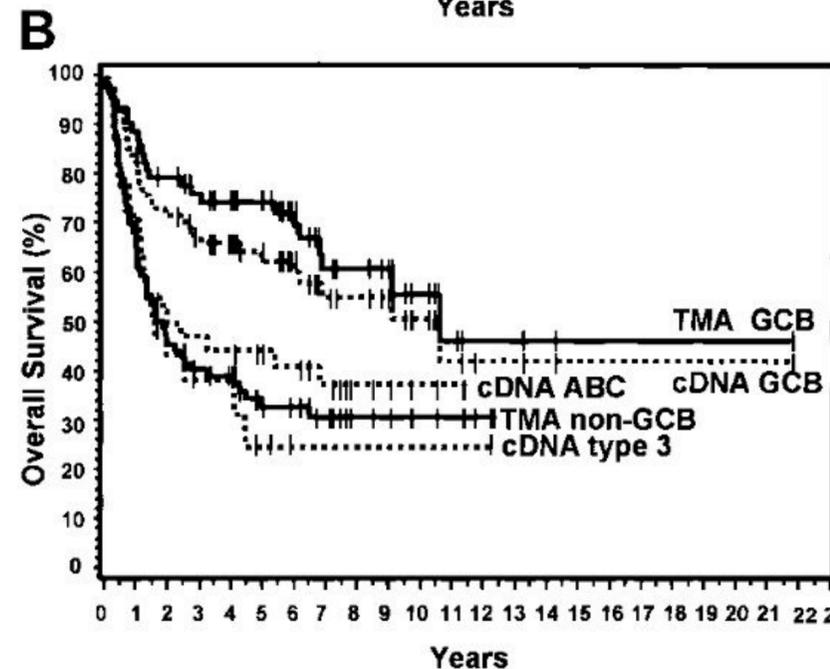
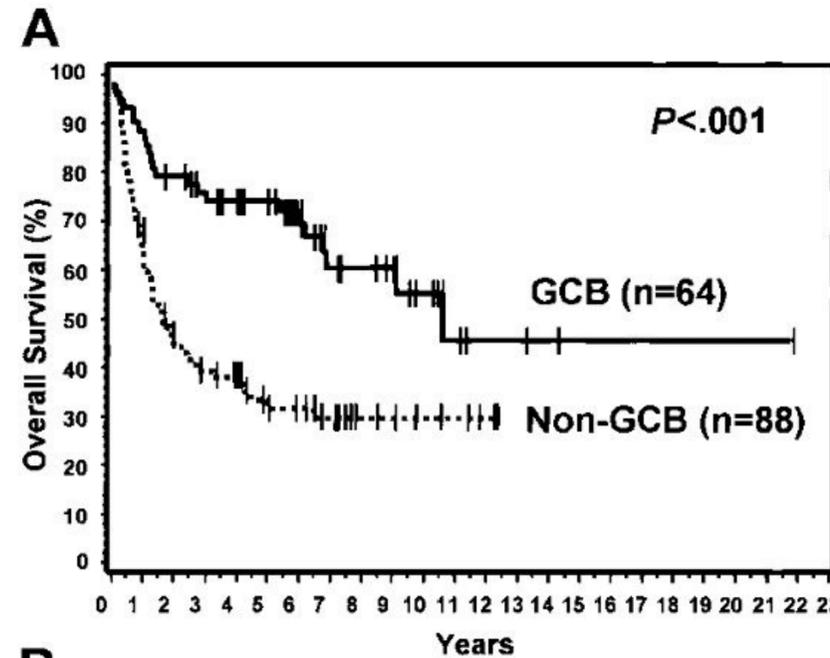


AFIP 2017

LINFOMA DIFFUSO A GRANDI CELLULE B, NAS

Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray

Christine P Hans¹, Dennis D Weisenburger, Timothy C Greiner, Randy D Gascoyne, Jan Delabie, German Ott, H Konrad Müller-Hermelink, Elias Campo, Rita M Braziel, Elaine S Jaffe, Zenggang Pan, Pedro Farinha, Lynette M Smith, Brunangelo Falini, Alison H Banham, Andreas Rosenwald, Louis M Staudt, Joseph M Connors, James O Armitage, Wing C Chan

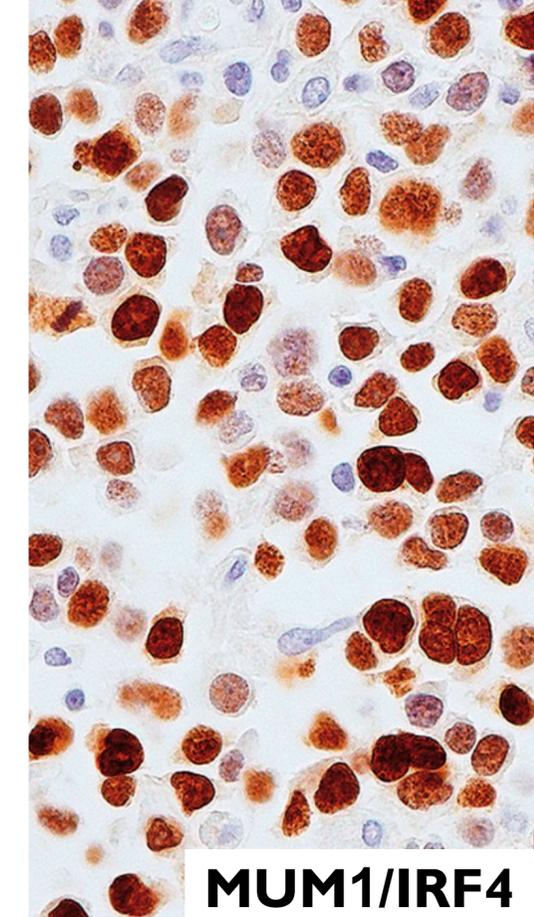
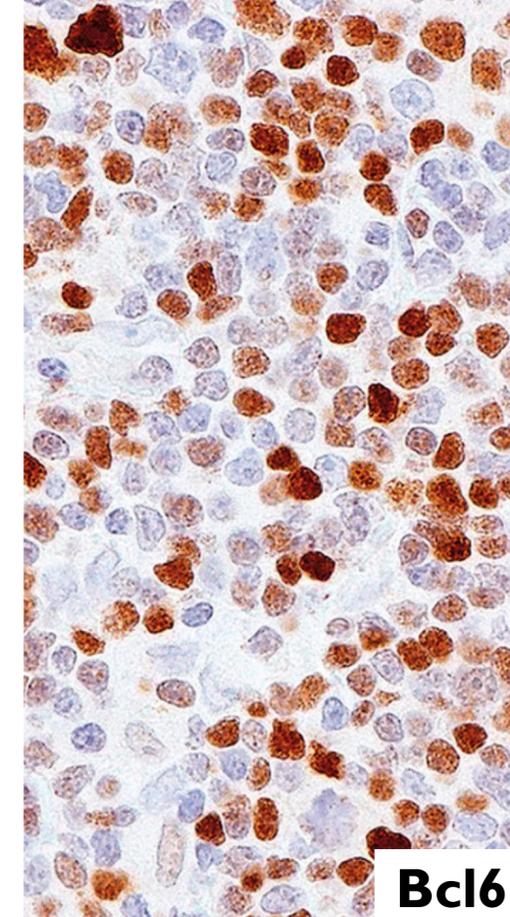
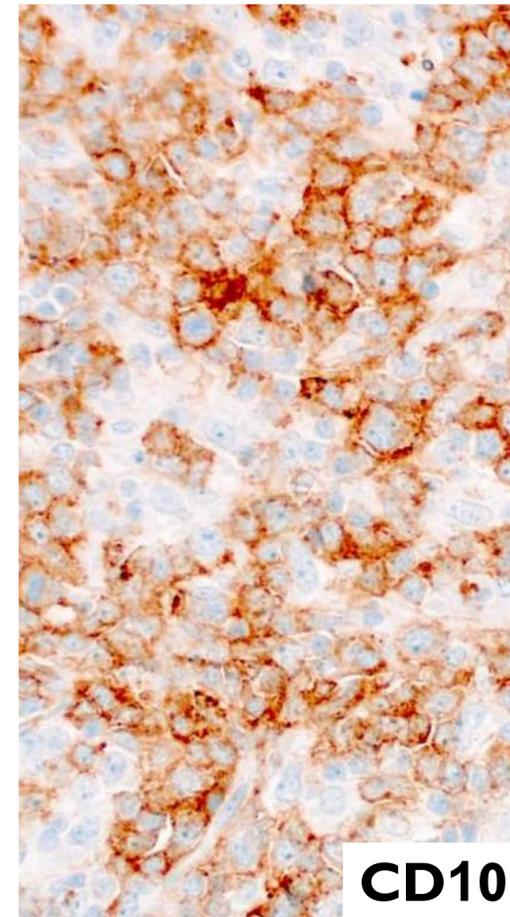
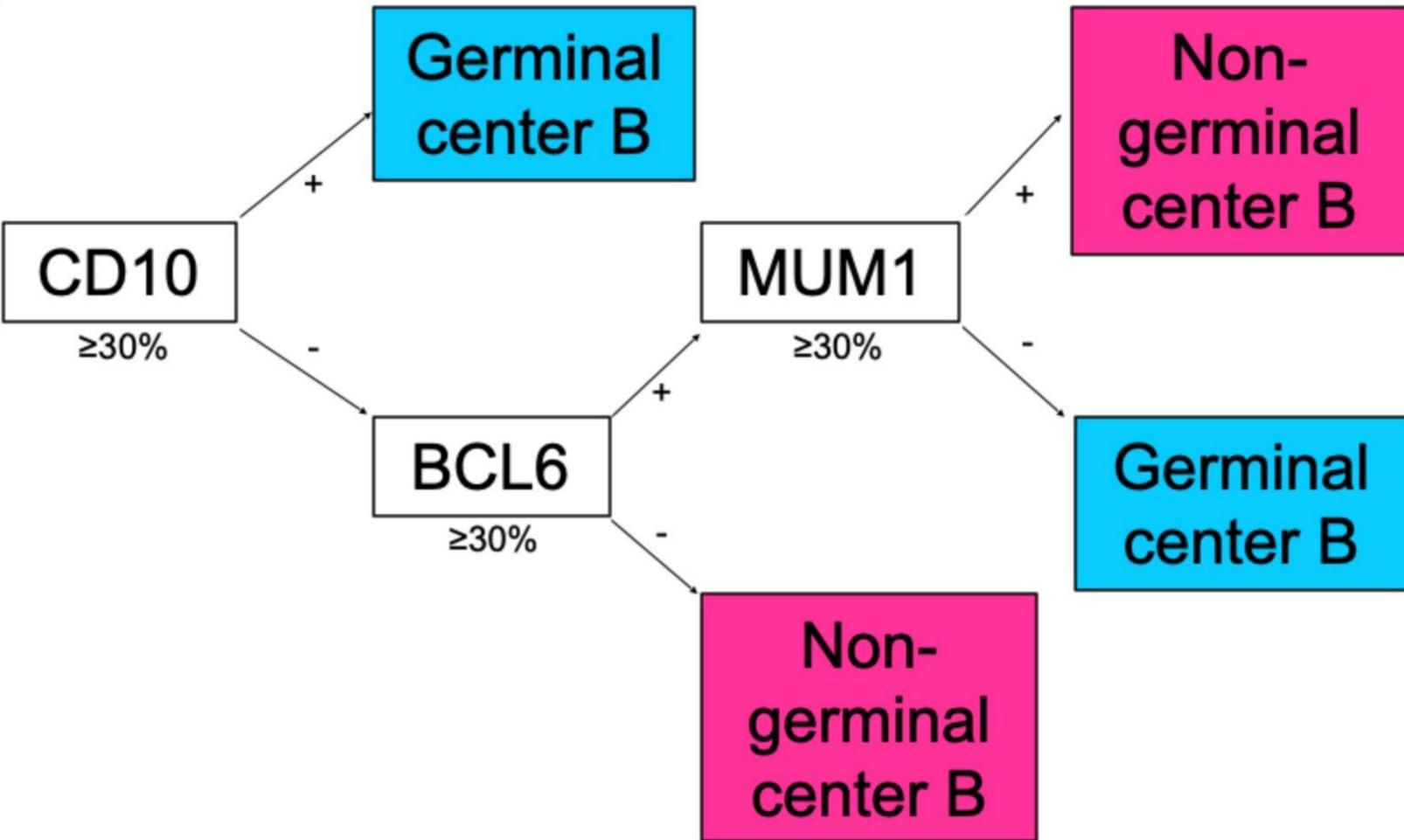


IPI 0-2

IPI 3-5

Figure 7. Relationship between IPI scores and TMA classification. (A) OS curves of patients with low IPI scores (0-2) by TMA classification of GCB versus non-GCB. (B) Patients with high IPI scores (3-5) by TMA classification.

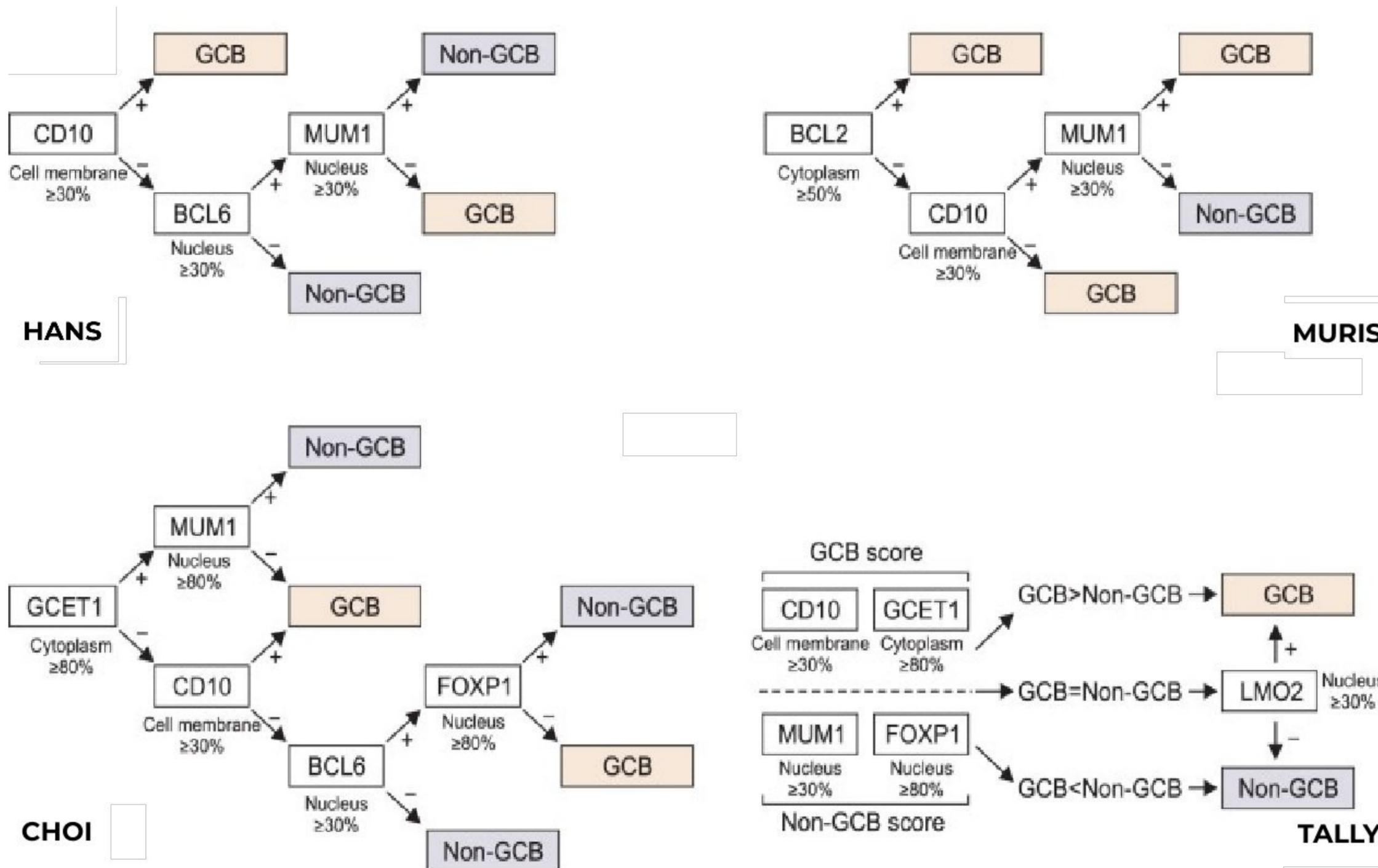
LINFOMA DIFFUSO A GRANDI CELLULE B, NAS



ALGORITMO DI HANS

- Sottotipo *germinal centre B-cell*
- Sottotipo *non germinal centre B-cell*

LINFOMA DIFFUSO A GRANDI CELLULE B, NAS

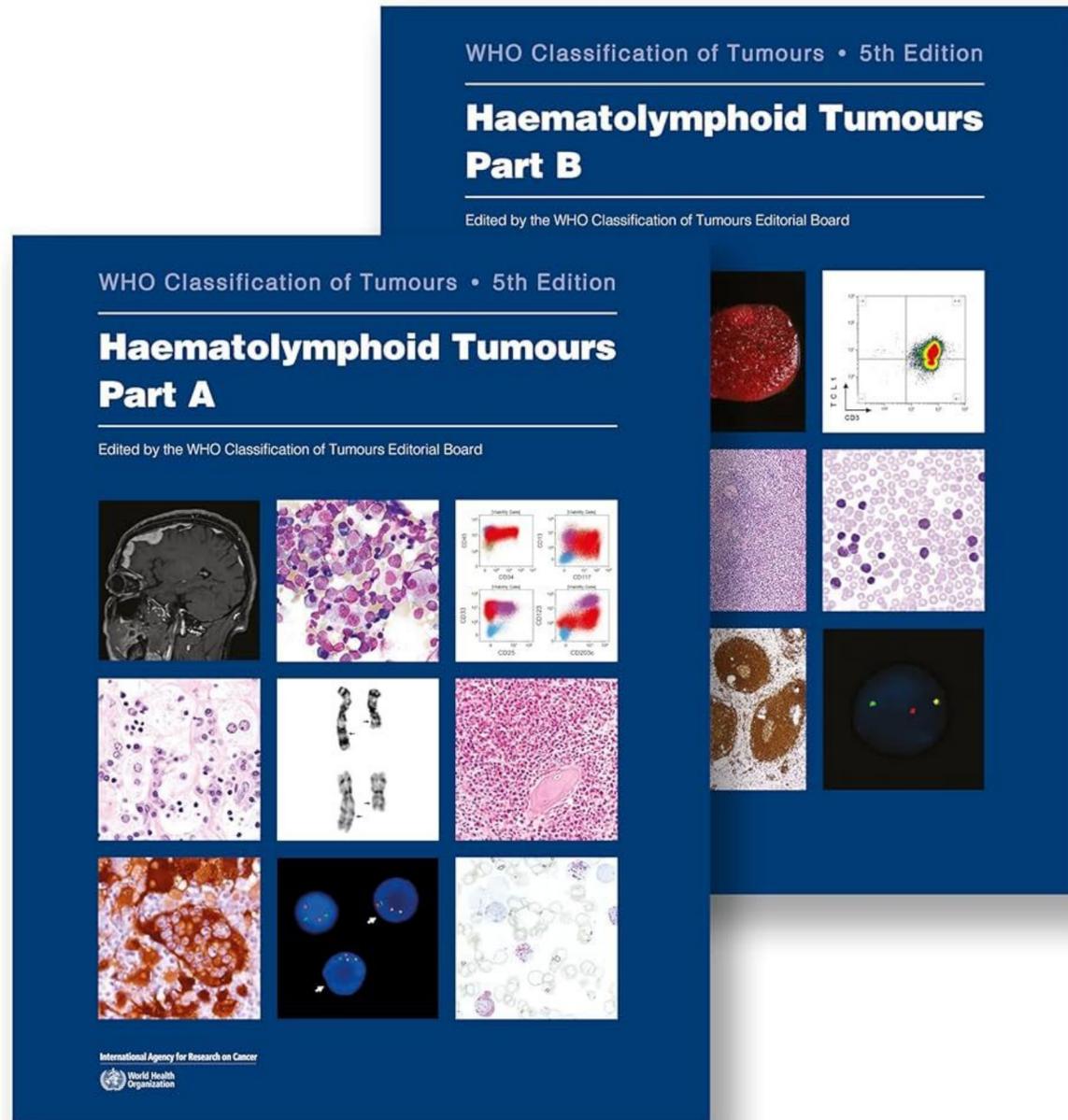


L'APPROCCIO DICOTOMICO POTREBBE ESSERE TROPPO SEMPLICISTICO

1. **Prognosi sfavorevole per una parte di tumori GCB (es. doppio hit).**
2. **Buona risposta in alcuni tumori non-GBC (20-30%).**
3. **Gruppi GCB e non-GBC geneticamente eterogenei, con ampio numero di mutazioni di singolo gene, amplificazioni, delezioni geniche/cromosomiche, traslocazioni e inversioni cromosomiche, alterazioni *copy number*.**

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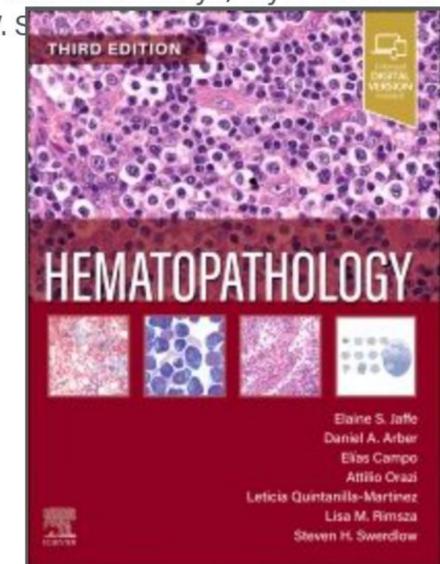
ICC 2022



SPECIAL REPORT | SEPTEMBER 15, 2022

The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

Elias Campo, Elaine S. Jaffe, James R. Cook, Leticia Quintanilla-Martinez, Steven H. Swerdlow, Kenneth C. Anderson, Pierre Brousset, Lorenzo Cerroni, Laurence de Leval, Stefan Dirnhofer, Ahmet Dogan, Andrew L. Feldman, Falko Fend, Jonathan W. Friedberg, Philippe Gaulard, Paolo Ghia, Steven M. Horwitz, Rebecca L. King, Gilles Salles, Jesus San-Miguel, John F. Seymour, Steven P. Treon, Julie M. Vose, Emanuele Zucca, Ranjana Advani, Stephen Ansell, Wing-Yan Au, Carlos Barrionuevo, Leif Bergsagel, Wing C. Chan, Jeffrey I. Cohen, Francesco d'Amore, Andrew Davies, Brunangelo Falini, Irene M. Ghobrial, John R. Goodlad, John G. Gribben, Eric D. Hsi, Brad S. Kahl, Won-Seog Kim, Shaji Kumar, Ann S. LaCasce, Camille Laurent, Georg Lenz, John P. Leonard, Michael P. Link, Armando Lopez-Guillermo, Maria Victoria Mateos, Elizabeth Macintyre, Ari M. Melnick, Franck Morschhauser, Shigeo Nakamura, Marina Narbaitz, Astrid Pavlovsky, Stefano A. Pileri, Miguel Piris, Barbara Pro, Vincent Rajkumar, Steven T. Rosen, Birgitta Sander, Laurie Sehn, Margaret A. Shipp, Sonali M. Smith, Louis M. Staudt, Catherine Thieblemont, Thomas Tousseyn, Wyndham H. Wilson, Tadashi Yoshino, Pier-Luigi Zinzani, Martin Dreyling, David W. S. Zelenetz



LINFOMA DIFFUSO A GRANDI CELLULE B, NAS

WHO 2017

- Variante centroblastica
- Variante immunoblastica
- Variante anaplastica

- Sottotipo *germinal-centre B-cell*
- Sottotipo *activated B-cell*

WHO 2022

Sottotipi morfologici

- Centroblastico
- Immunoblastico
- Anaplastico

Sottotipi molecolari

- *Germinal-centre B-cell*
- *Activated B-cell*

Sottotipo genetico

- **Con riarrangiamento di MYC e BCL6**

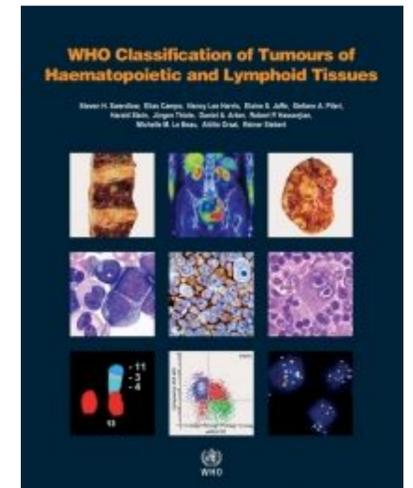
ICC 2022

- Sottotipo *germinal-centre B-cell*
- Sottotipo *activated B-cell*

LINFOMA B DI ALTO GRADO

Gruppo di linfomi aggressivi a cellule B mature che, per ragioni biologiche e cliniche, non devono essere classificati come linfoma diffuso a grandi cellule B, NAS, o come linfoma di Burkitt.

WHO 2017



Due sottotipi:

**A. LINFOMA B DI ALTO GRADO,
CON RIARRANGIAMENTO di
MYC e BCL2 e/o BCL6**

**B. LINFOMA B DI ALTO GRADO,
NON ALTRIMENTI SPECIFICATO**

A. LINFOMA B DI ALTO GRADO, CON RIARRANGIAMENTO di MYC e BCL2 e/o BCL6

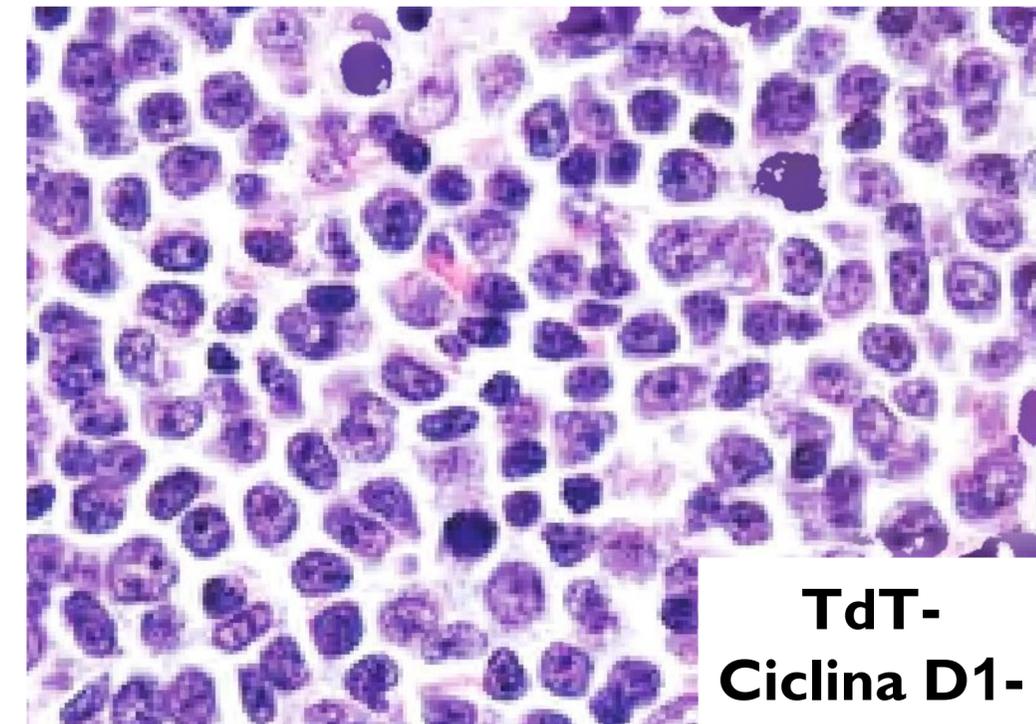
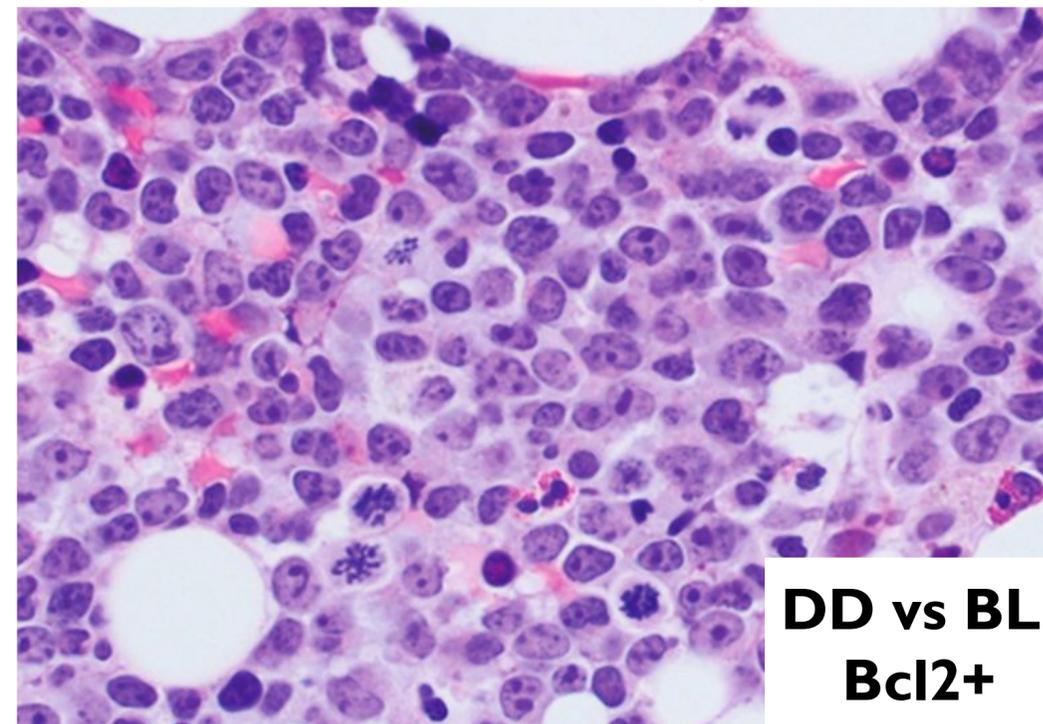
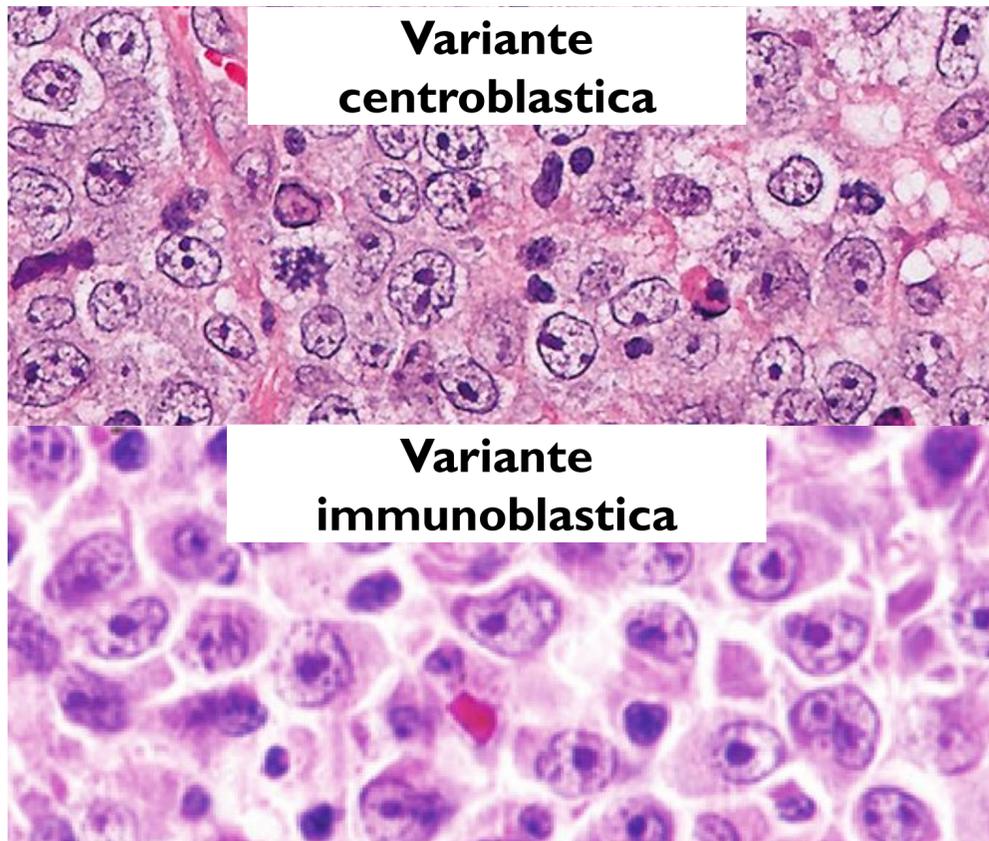
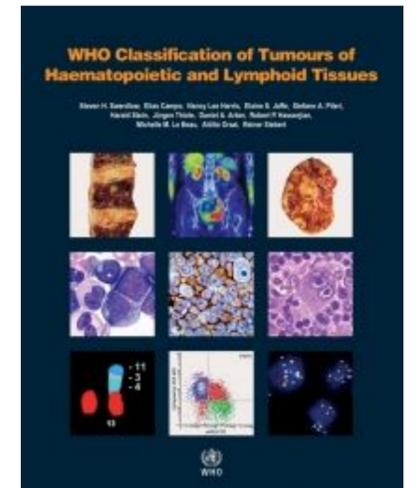
Comprende quasi tutti i linfomi B con riarrangiamento MYC (8q24) + BCL2 (18q21) e/o BCL6 (3q27): *double-hit* o *triple-hit*.

Simile a linfoma diffuso a grandi cellule B (DLBCL), NAS (~50%).

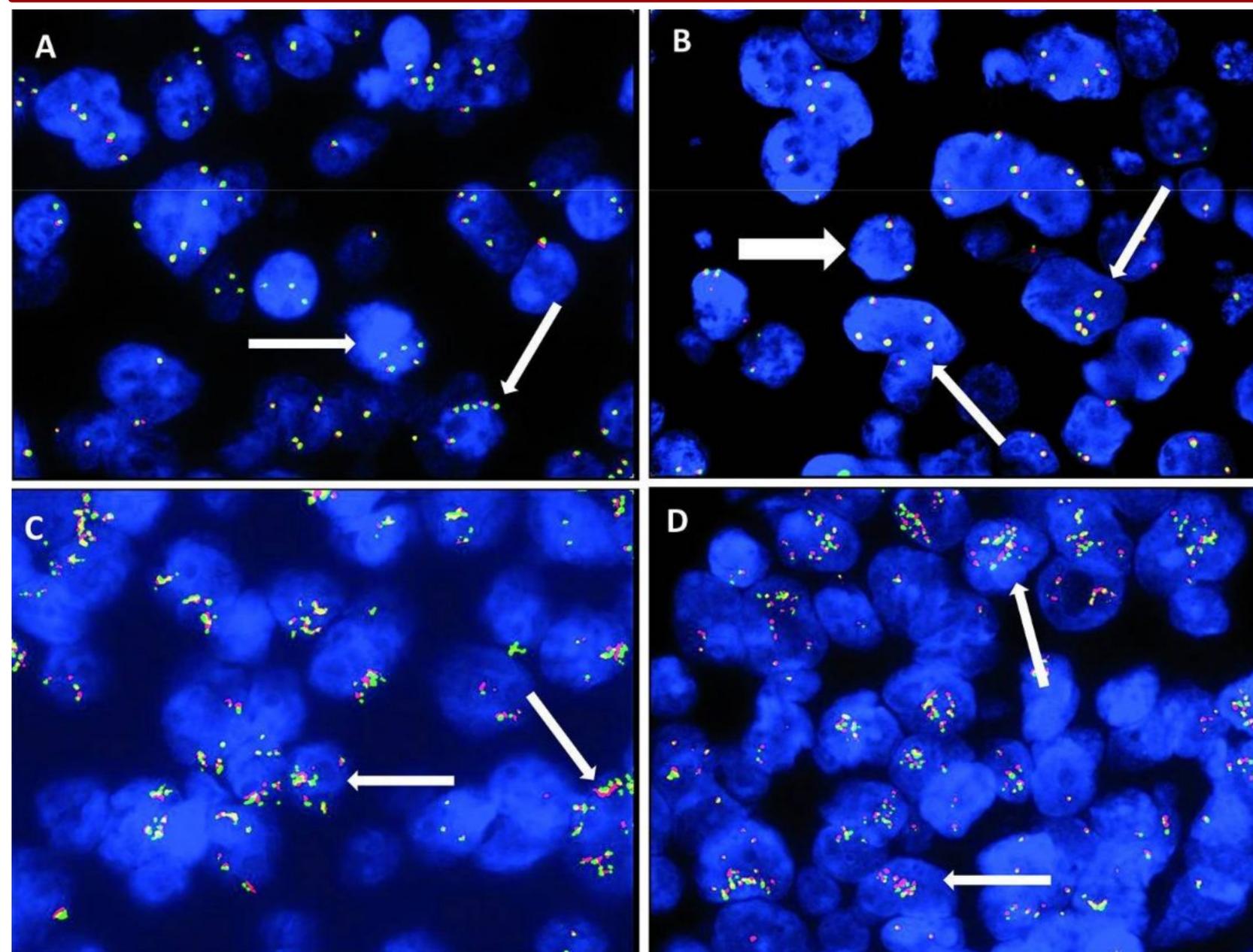
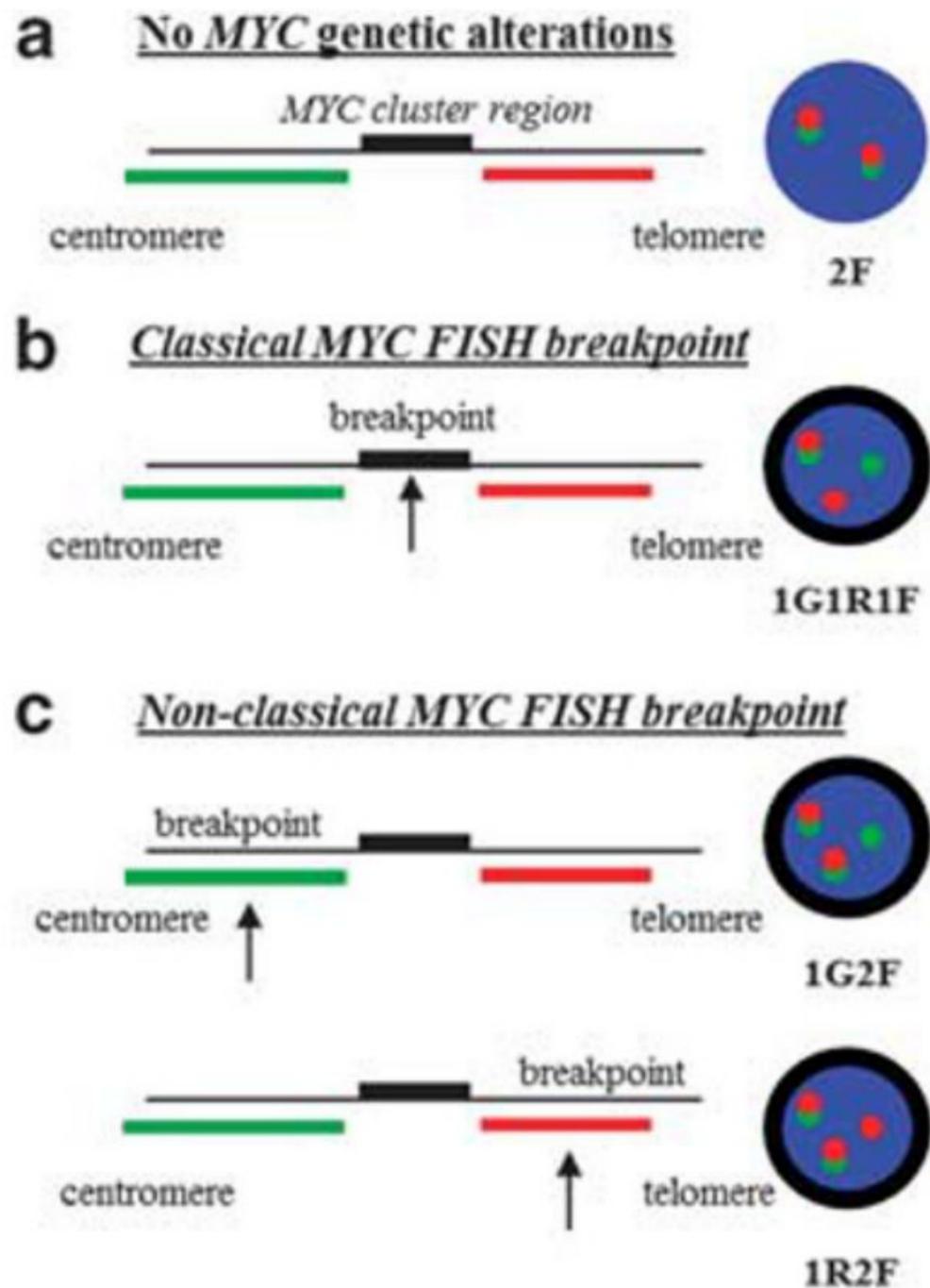
Caratteristiche sia di DLBCL che di linfoma di Burkitt (BL) (ex linfoma B inclassificabile con caratteristiche intermedie tra DLBCL e BL).

Blastoide (simile a linfoma linfoblastico e variante blastoide del linfoma mantellare).

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La presenza di aumento del numero di copie/amplificazione o mutazioni somatiche, senza un riarrangiamento, non è sufficiente per far rientrare un linfoma in questa categoria.



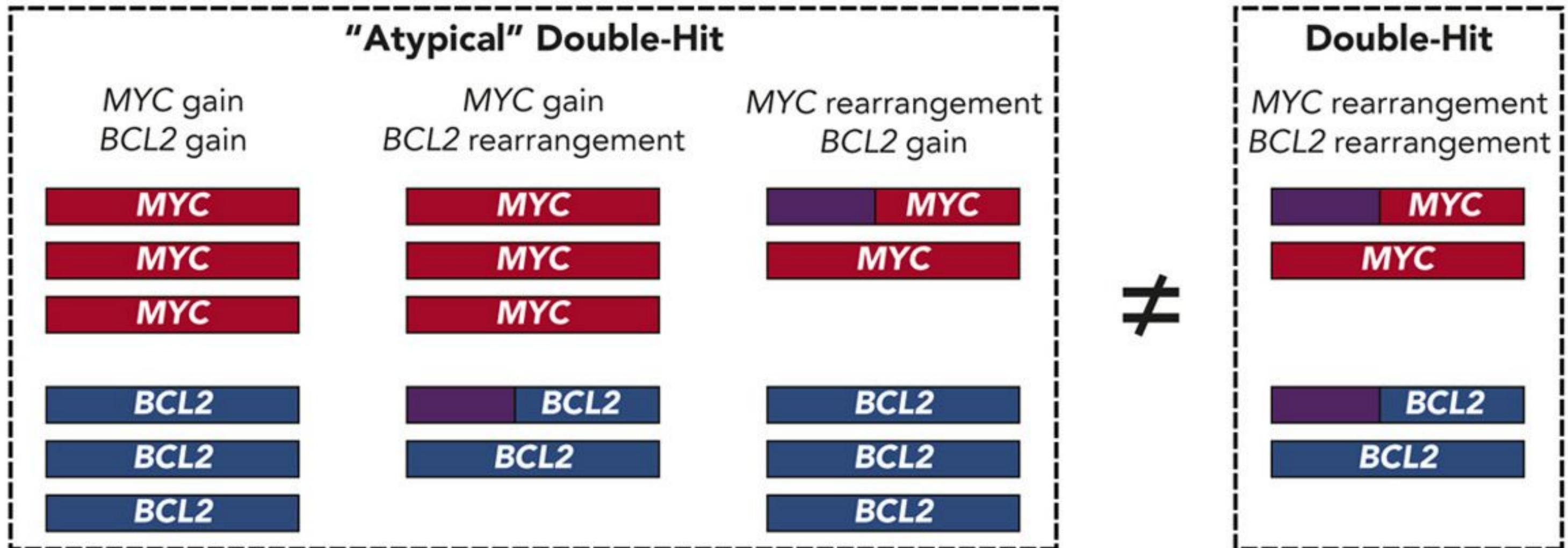
Aumento numero di copie di MYC.

Amplificazione di MYC.

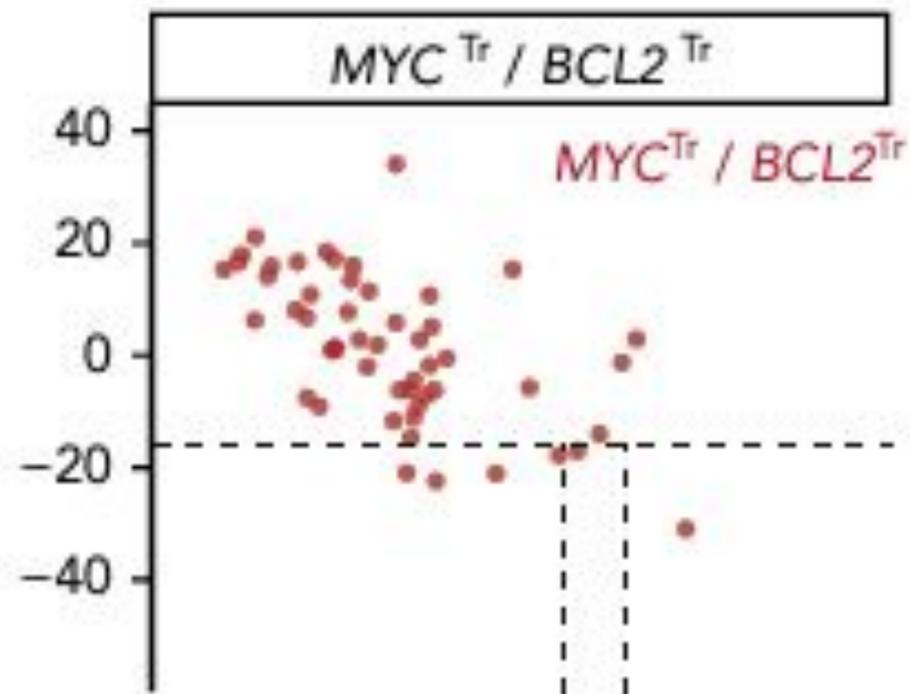
> Blood. 2021 Apr 22;137(16):2196-2208. doi: 10.1182/blood.2020007193.

The impact of MYC and BCL2 structural variants in tumors of DLBCL morphology and mechanisms of false-negative MYC IHC

Brett Collinge^{1 2}, Susana Ben-Neriah¹, Lauren Chong¹, Merrill Boyle¹, Aixiang Jiang^{1 2}, Tomoko Miyata-Takata¹, Pedro Farinha^{1 2}, Jeffrey W Craig^{1 2}, Graham W Slack^{1 2}, Daisuke Ennishi¹, Anja Mottok¹, Barbara Meissner¹, Elizabeth A Chavez¹, Alina S Gerrie^{1 3}, Diego Villa^{1 3}, Ciara Freeman¹, Kerry J Savage^{1 3}, Laurie H Sehn^{1 3}, Ryan D Morin^{4 5}, Andrew J Mungall⁴, Randy D Gascoyne^{1 2}, Marco A Marra^{4 6}, Joseph M Connors^{1 3}, Christian Steidl^{1 2}, David W Scott^{1 2 3}



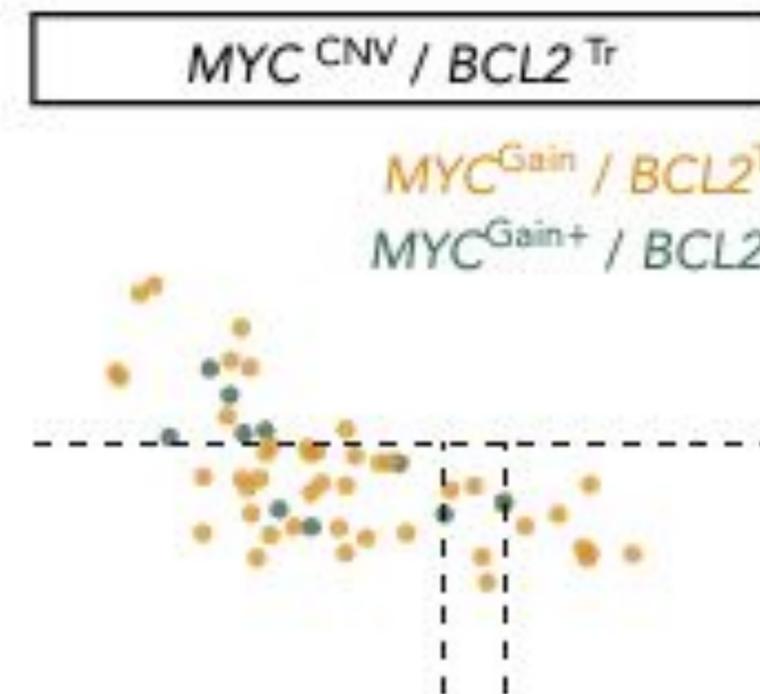
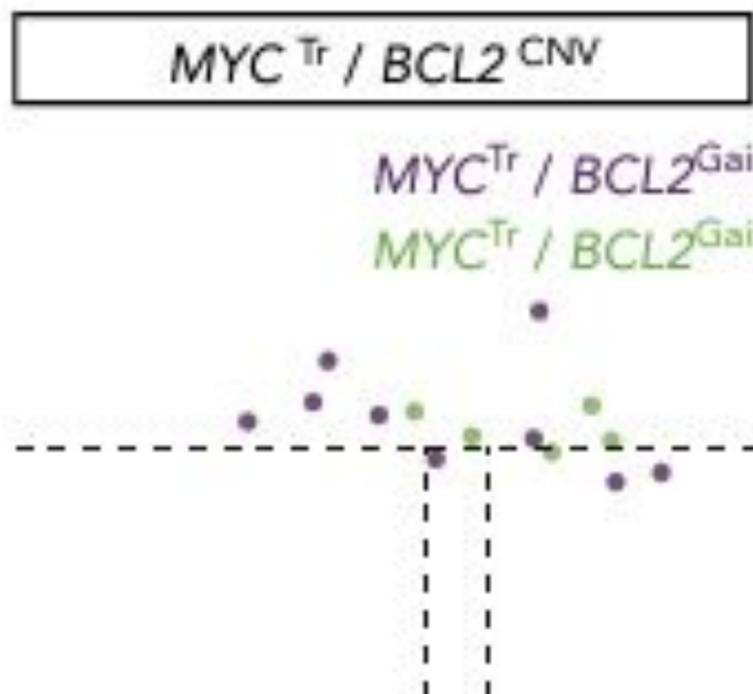
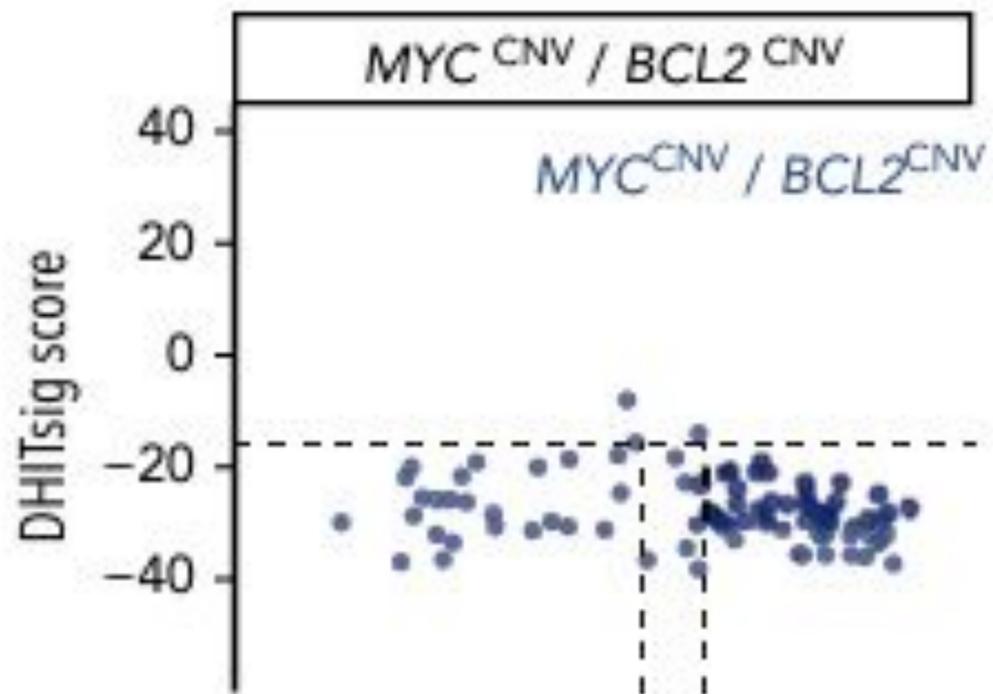
HGBL-DH/TH-BCL2



Linfomi B doppio *hit* “atipici” presentano espressione genica diversa da veri doppio *hit*.



Atypical Double-Hit



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gli under 40 a confronto

[Haematologica](#). 2020 May; 105(5): 1369–1378. Prepublished online 2019

Aug 8. doi: [10.3324/haematol.2019.223891](https://doi.org/10.3324/haematol.2019.223891)

PMCID: PMC7193495 | PMID: [31399522](https://pubmed.ncbi.nlm.nih.gov/31399522/)

An increase in *MYC* copy number has a progressive negative prognostic impact in patients with diffuse large B-cell and high-grade lymphoma, who may benefit from intensified treatment regimens

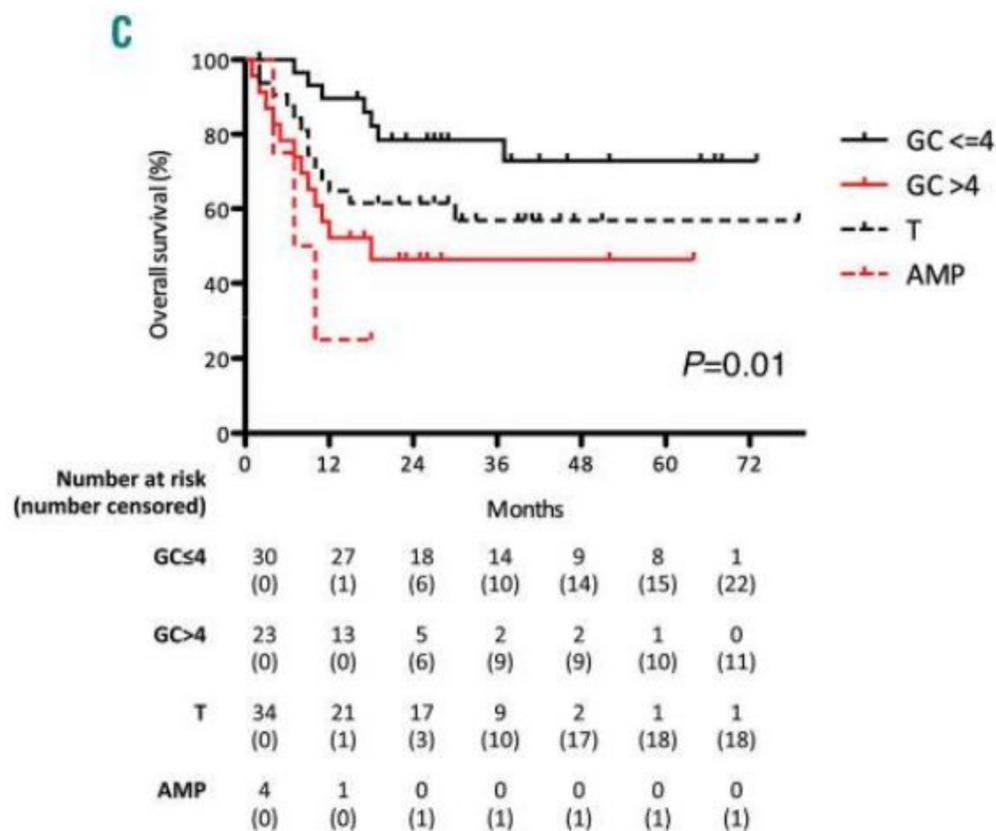
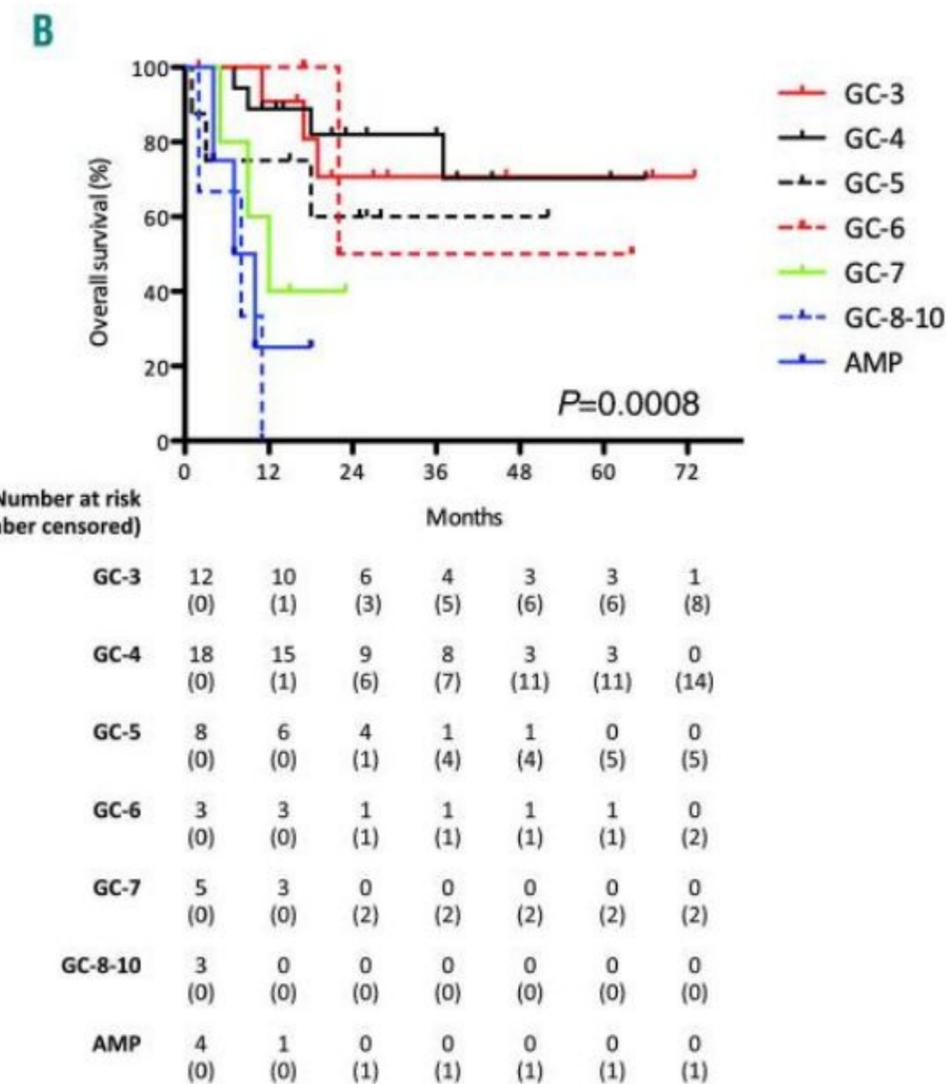
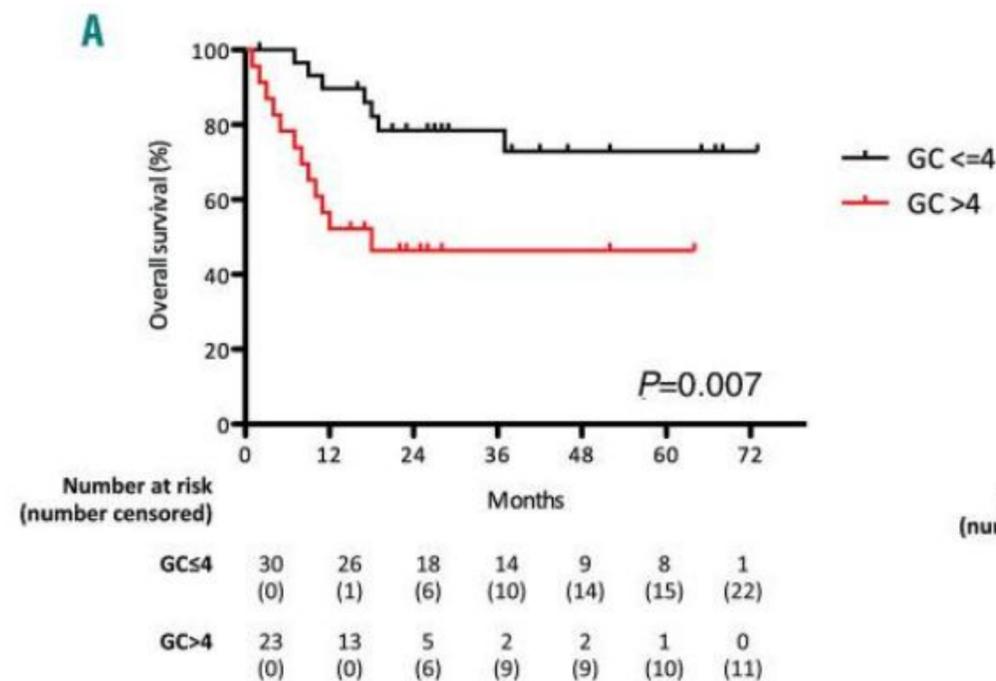
[Francesca Schieppati](#),^{1,*} [Piera Balzarini](#),^{2,*} [Simona Fisogni](#),²

[Alessandro Re](#),¹ [Chiara Pagani](#),¹ [Nicola Bianchetti](#),¹ [Lorenzo Micheli](#),²

[Angela Passi](#),¹ [Samantha Ferrari](#),¹ [Adriana Maifredi](#),¹ [Chiara Bottelli](#),¹

[Rossella Leopaldo](#),¹ [Vilma Pellegrini](#),² [Fabio Facchetti](#),² [Giuseppe Rossi](#),¹

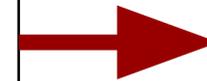
and [Alessandra Tucci](#)¹



WHO 2022

LINFOMA DIFFUSO A GRANDI CELLULE B/LINFOMA DI ALTO GRADO, CON RIARRANGIAMENTO di MYC e BCL2

LINFOMA DI ALTO GRADO, CON RIARRANGIAMENTO di MYC e BCL6



LINFOMA DIFFUSO A GRANDI CELLULE B, NON ALTRIMENTI SPECIFICATO

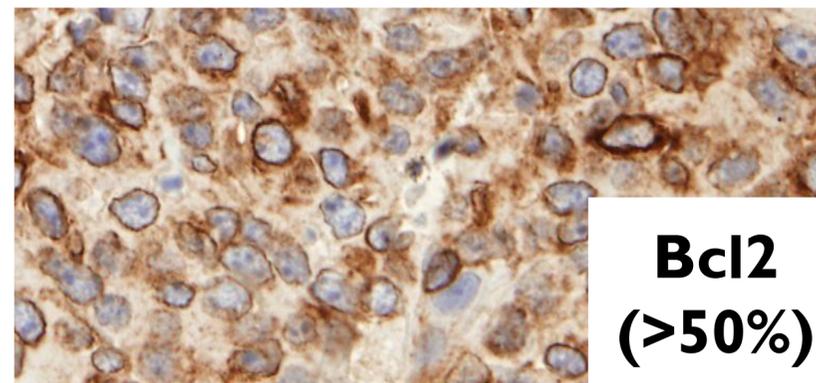
ICC 2022

LINFOMA B DI ALTO GRADO, CON RIARRANGIAMENTO di MYC e BCL2 (con o senza riarrangiamento di BCL6)

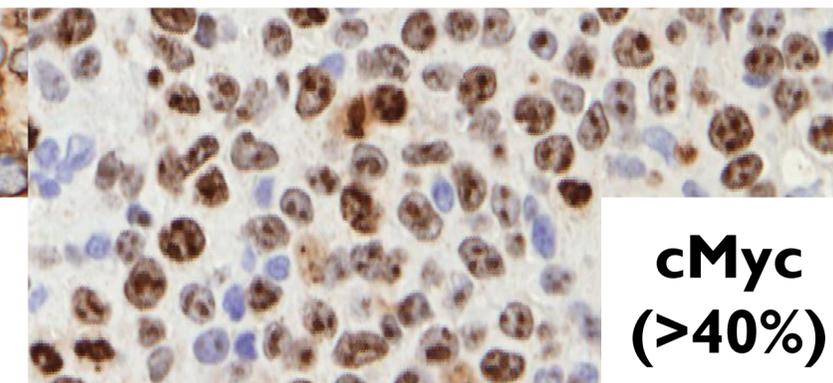
LINFOMA B DI ALTO GRADO, CON RIARRANGIAMENTO di MYC e BCL6*

***Provvisoria**

LINFOMA DIFFUSO A GRANDI CELLULE B, NAS, DOPPIO ESPRESSORE cMyc/Bcl2

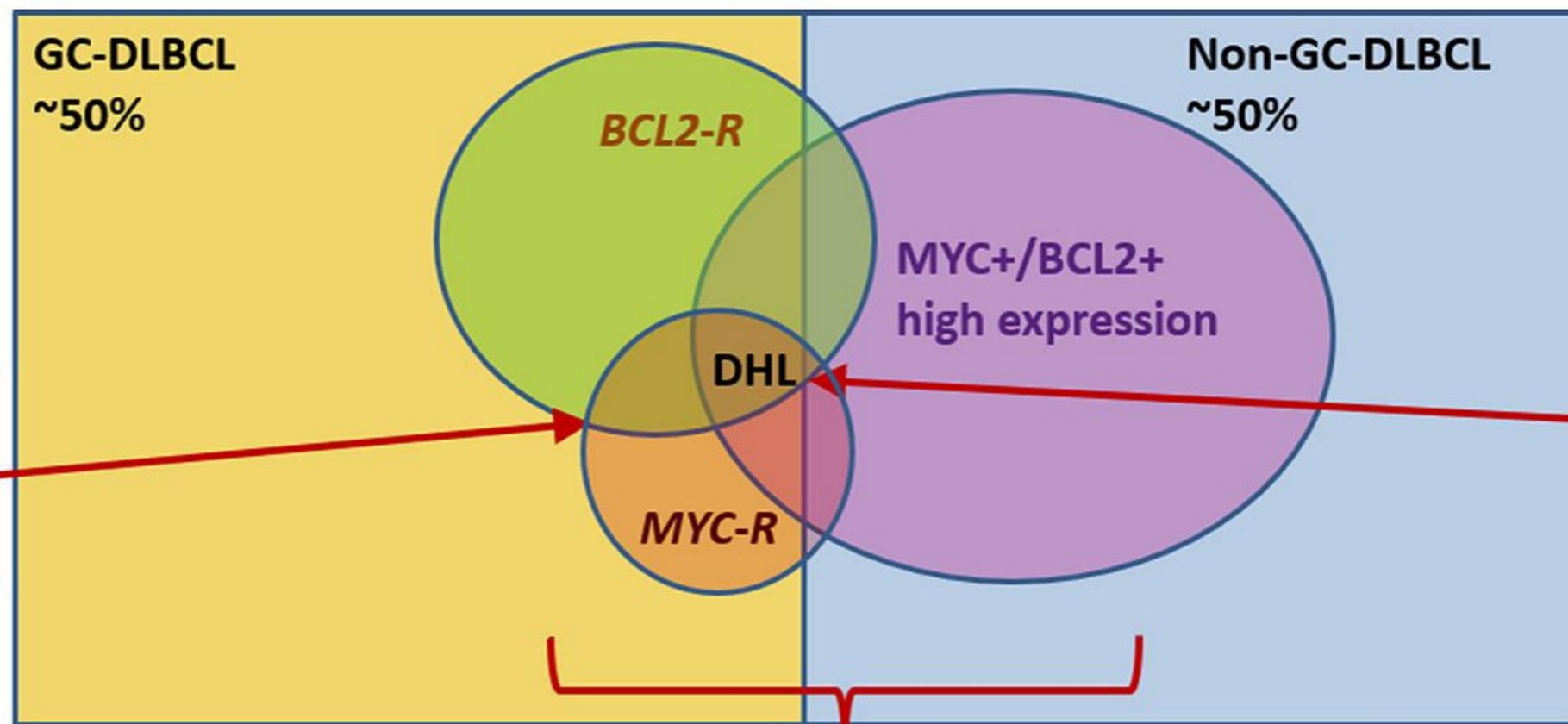


Bcl2 (>50%)



cMyc (>40%)

Non rappresenta una categoria diagnostica.



20% Double-Hit lymphoma are MYC and BCL2 protein NEGATIVE

Only 5-20% of Double-Expressor lymphomas are Double-Hit

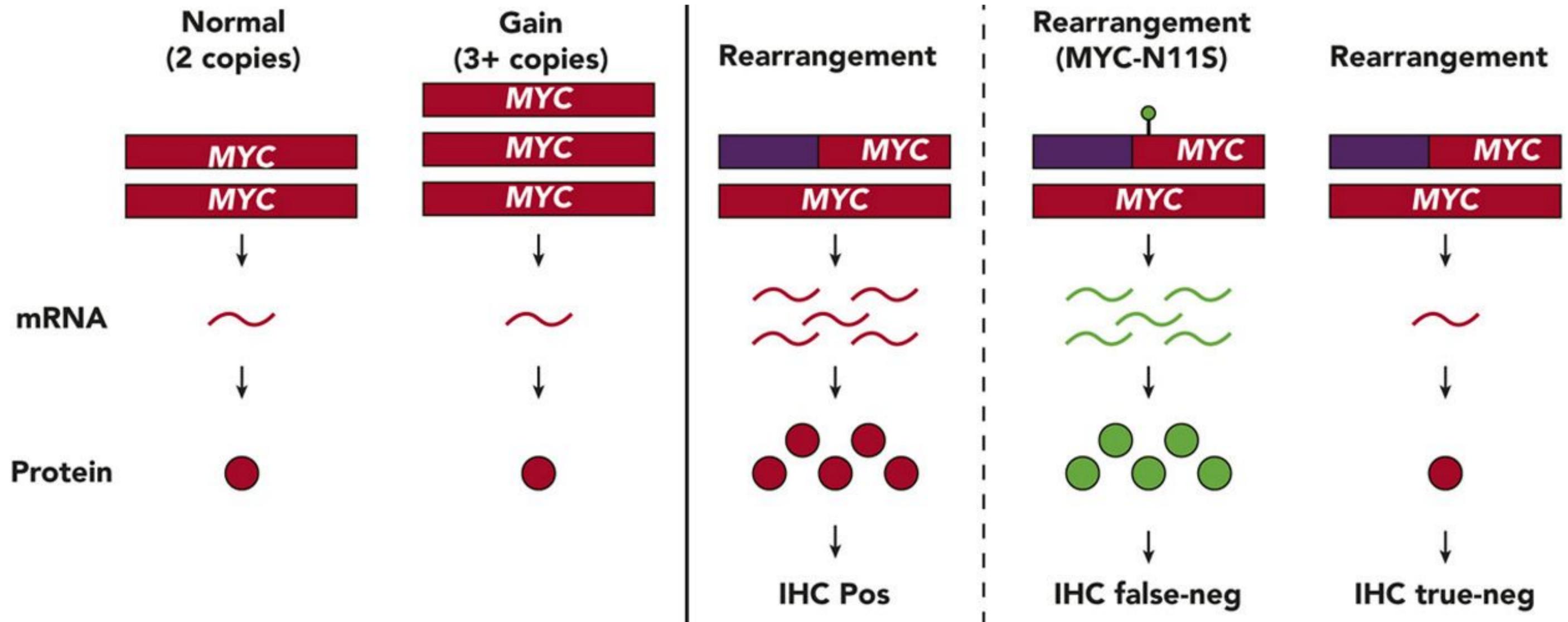
Variable expression and rearrangement rates according to Cell of Origin

Wight et al., Prognostication of diffuse large B-cell lymphoma in the molecular era: moving beyond the IPI. Blood Rev. 2018 Sep;32(5):400-415

> *Blood*. 2021 Apr 22;137(16):2196-2208. doi: 10.1182/blood.2020007193.

The impact of MYC and BCL2 structural variants in tumors of DLBCL morphology and mechanisms of false-negative MYC IHC

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Prognostication of diffuse large B-cell lymphoma in the molecular era: moving beyond the IPI

Joel C. Wight ^{a1}, Geoffrey Chong ^{a1}, Andrew P. Grigg ^{a b1},
Eliza A. Hawkes ^{a b c}

Available online 26 March 2018, Version of Record 5 September 2018.

Table 3. Significance of up-regulation of MYC, BCL2 and BCL6.

Marker	Significance
Lone MYC protein expression (IHC)	Probably not significant
Lone BCL2 protein expression (IHC)	Poor prognosis by univariate analysis in some studies, likely worse in ABC subtype disease
Lone BCL6 protein expression (IHC)	Probably favourable, confounded by COO correlation
MYC and BCL2 co-expression (IHC)	Poor prognosis, independent of IPI and COO. Controversy exists over what constitutes "positive" staining
Lone MYC translocation	Conflicting data. Prognostic significance may be dependent on the "second hit" when TP53, BCL2 and BCL6 all considered.
Lone BCL2 translocation	In GCB subtype has a poor prognosis independent of IPI
Lone BCL6 translocation	Insufficient data
MYC translocation with BCL2 or BCL6 translocation	"Double-hit" lymphoma, biologically distinct from DLBCL. Poor prognosis.

LINFOMA DIFFUSO A GRANDI CELLULE B, DOPPIO ESPRESSORE cMyc/Bcl2

Risk Factor	IPI	B Symptoms	BMI	B2M	L:M Ratio	Low Vitamin D	Concordant BM	Bulk	Plasma PD-L1	Tumour PD-L1	Non-GC (IHC)	Non-GC (GEP)	BCL2 IHC	MYC IHC	BCL2 FISH	MYC FISH	DE DLBCL	TP53 mutant	MTV	siL-2R	Low T3 syndrome	TK level	CD30 -	CD37-	CD5+	HLA-DR-	Type 2 stromal sig	High dominant TCR	↓T cell: checkpoint	Sequence variations
B Symptoms	Green	Grey	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Green	Blue	Orange	Orange	Orange	Orange	Orange	Blue	Blue	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange
BMI	Green	Green	Grey	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange
B2M	Green	Green	Orange	Grey	Green	Orange	Green	Green	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Green	Green	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange
Lymphocyte: Monocyte Ratio	Green	Green	Orange	Orange	Grey	Orange	Orange	Orange	Green	Orange	Green	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	
Low Vitamin D level	Green	Orange	Orange	Orange	Orange	Grey	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	
Concordant BM involvement	Green	Orange	Orange	Orange	Orange	Grey	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	
Bulk	Blue	Orange	Orange	Orange	Orange	Orange	Orange	Grey	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	
Plasma PD-L1 levels	Green	Orange	Orange	Orange	Green	Orange	Green	Orange	Grey	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	
PD-L1 positive tumour	Green	Green	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Grey	Green	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	
Non-GC subtype (IHC determined)	Blue	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Grey	Orange	Blue	Blue	Blue	Blue	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	
Non-GC subtype (GEP determined)	Green	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Grey	Orange	Green	Green	Green	Green	Blue	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	
Lone BCL2 expression by IHC	Green	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Grey	Green	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Green	Orange	Orange	Orange	Orange	
Lone MYC expression by IHC	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Grey	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	
Lone BCL2-R by FISH	Green	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Grey	Green	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	
Lone MYC-R by FISH	Blue	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Grey	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	
Double-expressor DLBCL	Green	Green	Orange	Orange	Orange	Orange	Green	Green	Orange	Orange	Green	Green	Green	Green	Green	Green	Grey	Green	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	

INDICE DI PROLIFERAZIONE

L'espressione immunohistochimica di Ki-67/MIB1 variabile:

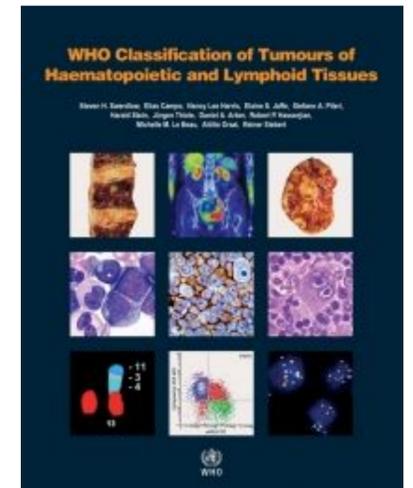
- nei casi simili a BL, 80-95%;
- nei casi con morfologia DLBCL, può essere ingannevolmente basso (<30%).

L'indice di proliferazione non può essere utilizzato per selezionare i casi per FISH di MYC.

LINFOMA B DI ALTO GRADO

Gruppo di linfomi aggressivi a cellule B mature che, per ragioni biologiche e cliniche, non devono essere classificati come linfoma diffuso a grandi cellule B, NAS, o come linfoma di Burkitt.

WHO 2017



Due sottotipi:

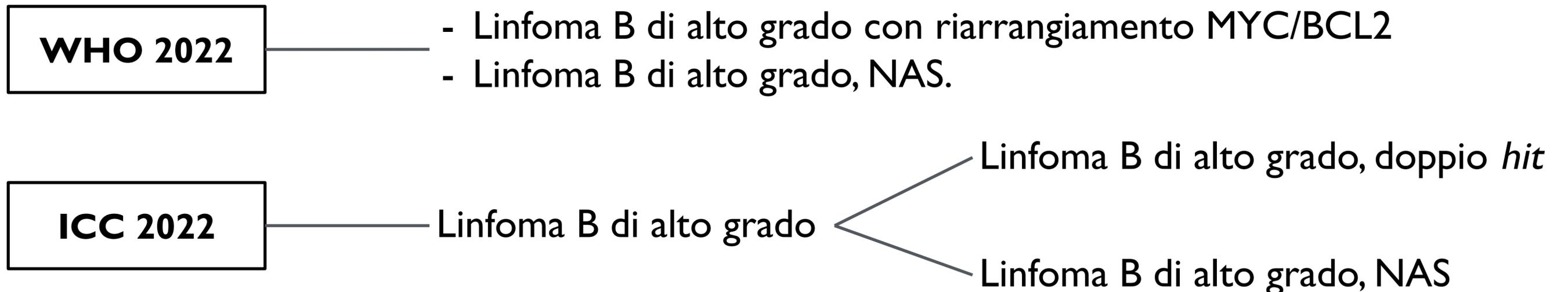
**A. LINFOMA B DI ALTO GRADO,
CON RIARRANGIAMENTO di
MYC e BCL2 e/o BCL6**

**B. LINFOMA B DI ALTO GRADO,
NON ALTRIMENTI SPECIFICATO**

**B. LINFOMA B DI ALTO GRADO,
NON ALTRIMENTI SPECIFICABILE**

Categoria eterogenea di linfomi aggressivi a cellule B mature composti da **cellule intermedie** o **blastoidi** che non soddisfa i criteri diagnostici per DLBCL e BL, privo di riarrangiamento di MYC e BCL2 (e/o BCL6).

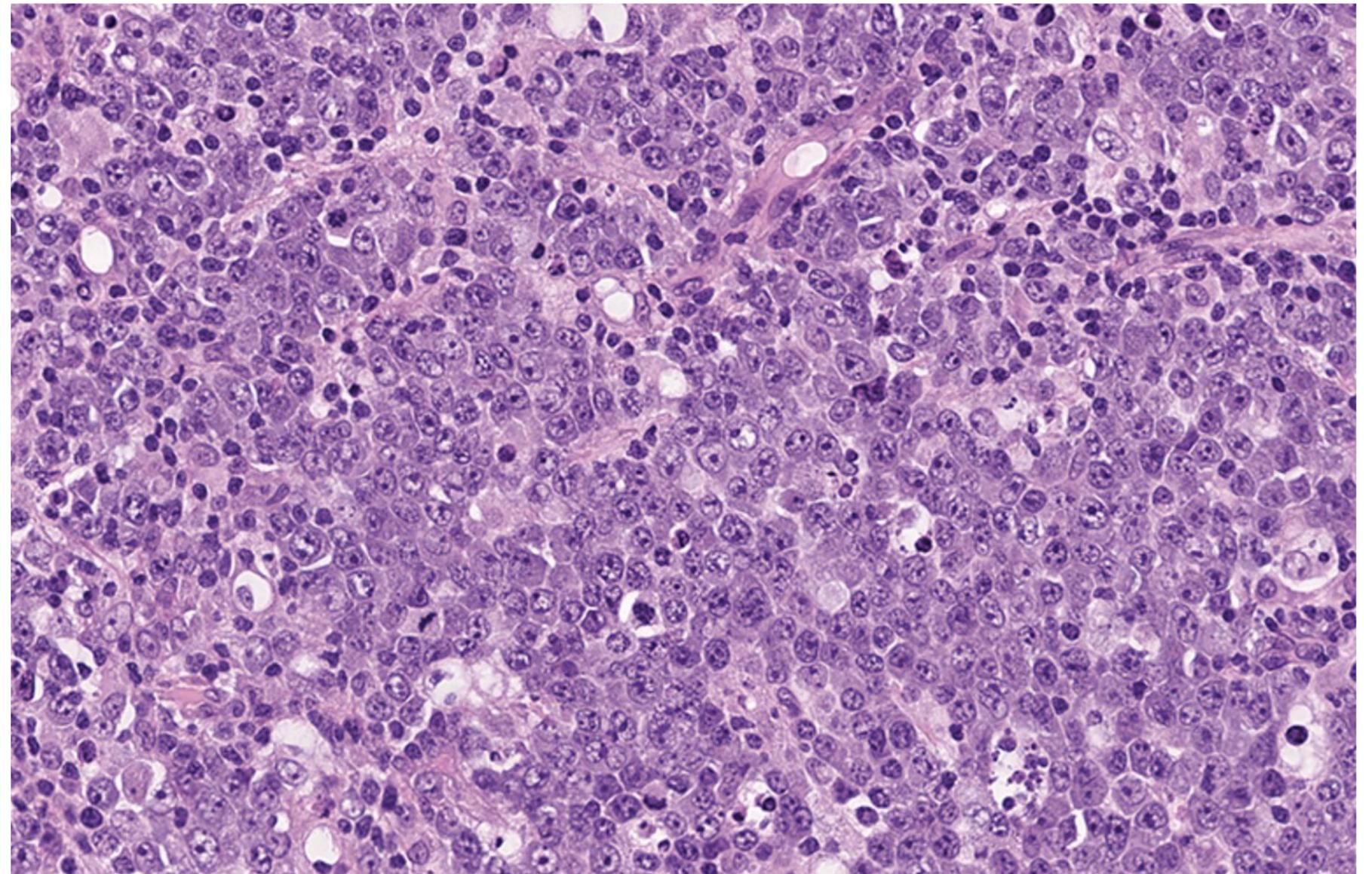
Casi rari: diagnosi solo quando non è possibile classificare con sicurezza un caso come DLBCL o BL.



B. LINFOMA B DI ALTO GRADO, NON ALTRIMENTI SPECIFICABILE

Morfologicamente:

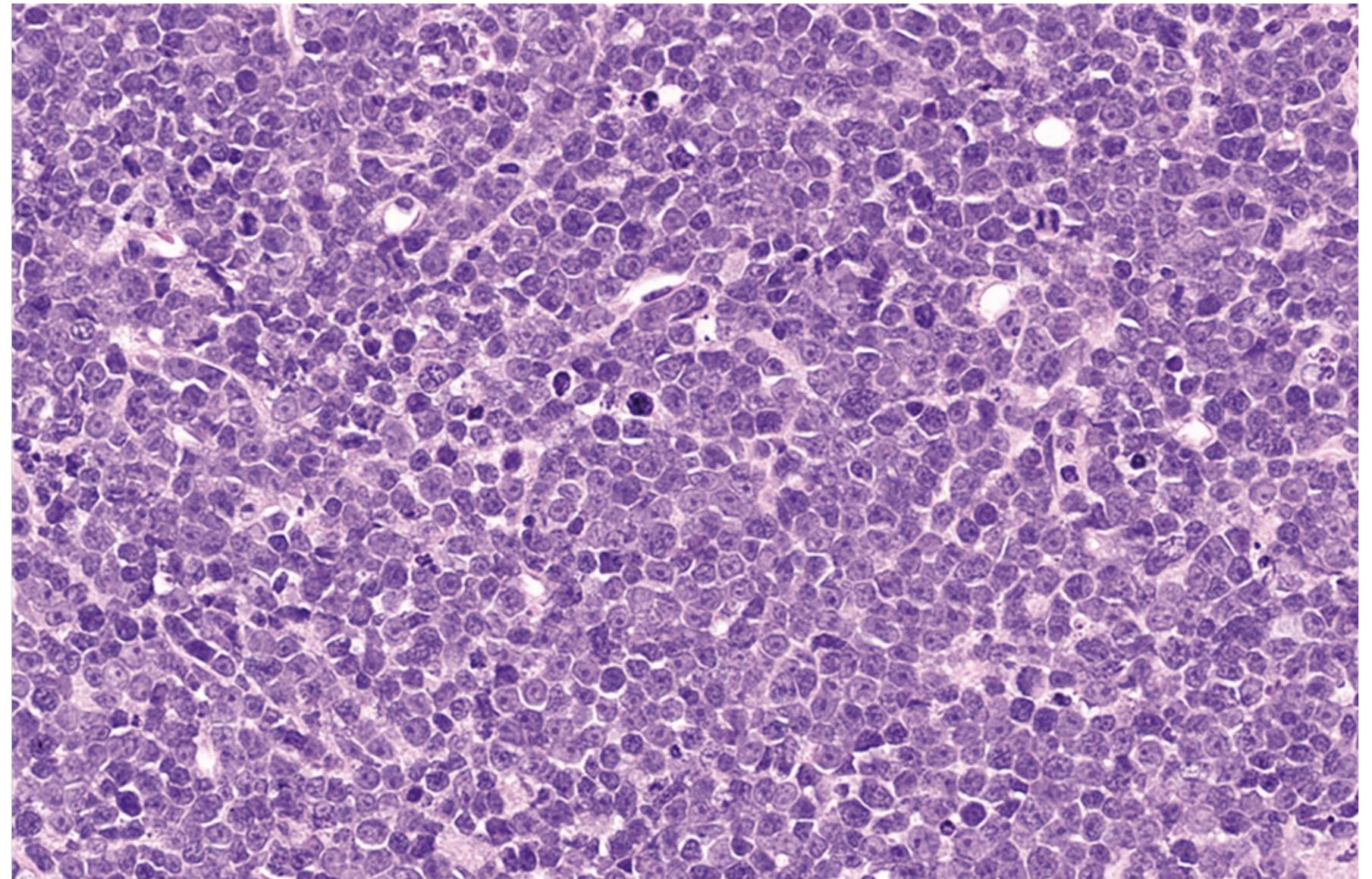
- **cellule intermedie**, di medie dimensioni con pochissimi piccoli linfociti frammentati e nessuna reazione stromale o fibrosi; possibili macrofagi “a cielo stellato” oltre a numerose figure mitotiche e apoptosi elevata;



B. LINFOMA B DI ALTO GRADO, NON ALTRIMENTI SPECIFICABILE

Morfologicamente:

- variante **blastoide** caratterizzata da cellule di dimensioni da piccole-intermedie con un piccola rima citoplasmatica, contorni nucleari rotondi, nucleoli poco evidenti e cromatina finemente dispersa.



ESPRESSIONE GENICA

J Clin Oncol. 2019 Jan 20; 37(3): 202–212.

PMCID: PMC6338391

Published online 2018 Dec 3. doi: [10.1200/JCO.18.01314](https://doi.org/10.1200/JCO.18.01314)

PMID: [30523719](https://pubmed.ncbi.nlm.nih.gov/30523719/)

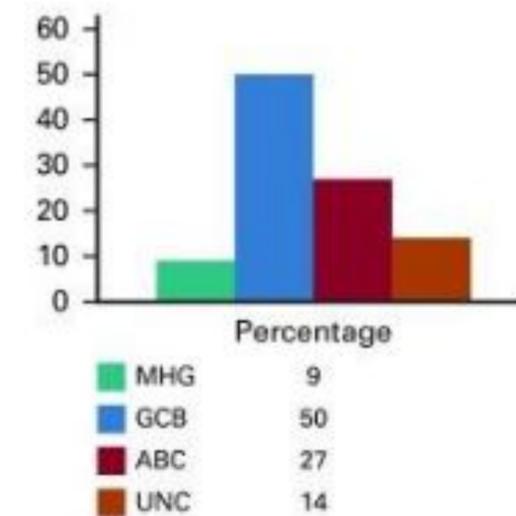
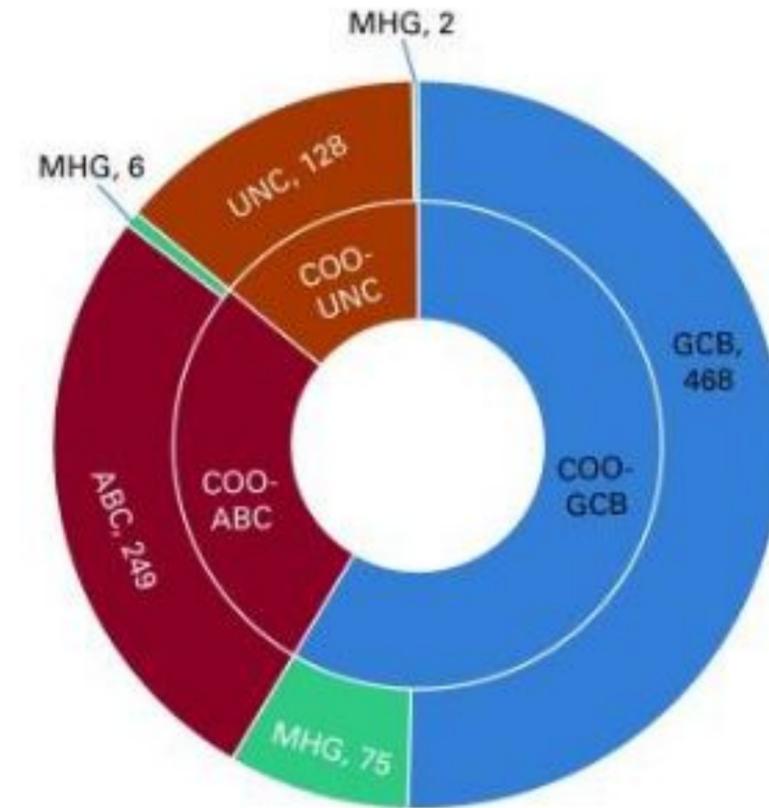
Molecular High-Grade B-Cell Lymphoma: Defining a Poor-Risk Group That Requires Different Approaches to Therapy

[Chulin Sha](#), PhD,¹ [Sharon Barrans](#), PhD,² [Francesco Cucco](#), PhD,³ [Michael A. Bentley](#), DPhil,¹ [Matthew A. Care](#), PhD,¹ [Thomas Cummin](#), MD,⁴ [Hannah Kennedy](#), PhD,³ [Joe S. Thompson](#), MPhil,³ [Rahman Uddin](#), MSc,¹ [Lisa Worrillow](#), PhD,² [Rebecca Chalkley](#), MPhil,² [Moniek van Hoppe](#), MSc,² [Sophia Ahmed](#), PhD,¹ [Tom Maishman](#), PhD,⁴ [Josh Caddy](#), BSc,⁴ [Anna Schuh](#), MD,⁵ [Christoph Mamot](#), MD,⁶ [Catherine Burton](#), MD,² [Reuben Tooze](#), PhD,¹ [Andrew Davies](#), PhD,⁴ [Ming-Qing Du](#), PhD,³ [Peter W.M. Johnson](#), MD,⁴ and [David R. Westhead](#), DPhil¹

Molecular high-grade group (MHG)

Sottogruppo a prognosi sfavorevole all'interno del sottotipo GCB della convenzionale COO.

Oltre ai casi MYC/BCL2-DH, include casi con prognosi sfavorevole senza doppio *hit*, non facilmente identificati con altri metodi.



J Clin Oncol. 2019 Jan 20; 37(3): 190–201.

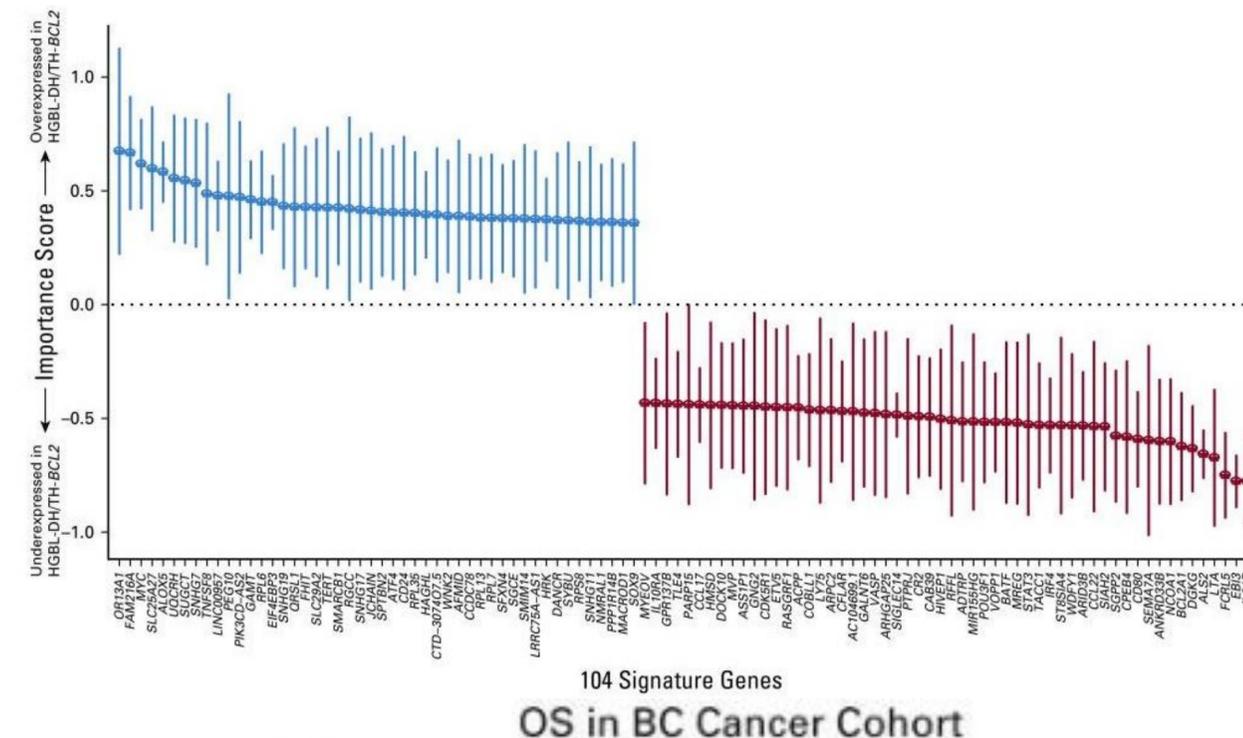
Published online 2018 Dec 3. doi: [10.1200/JCO.18.01583](https://doi.org/10.1200/JCO.18.01583)

PMCID: PMC6804880

PMID: [30523716](https://pubmed.ncbi.nlm.nih.gov/30523716/)

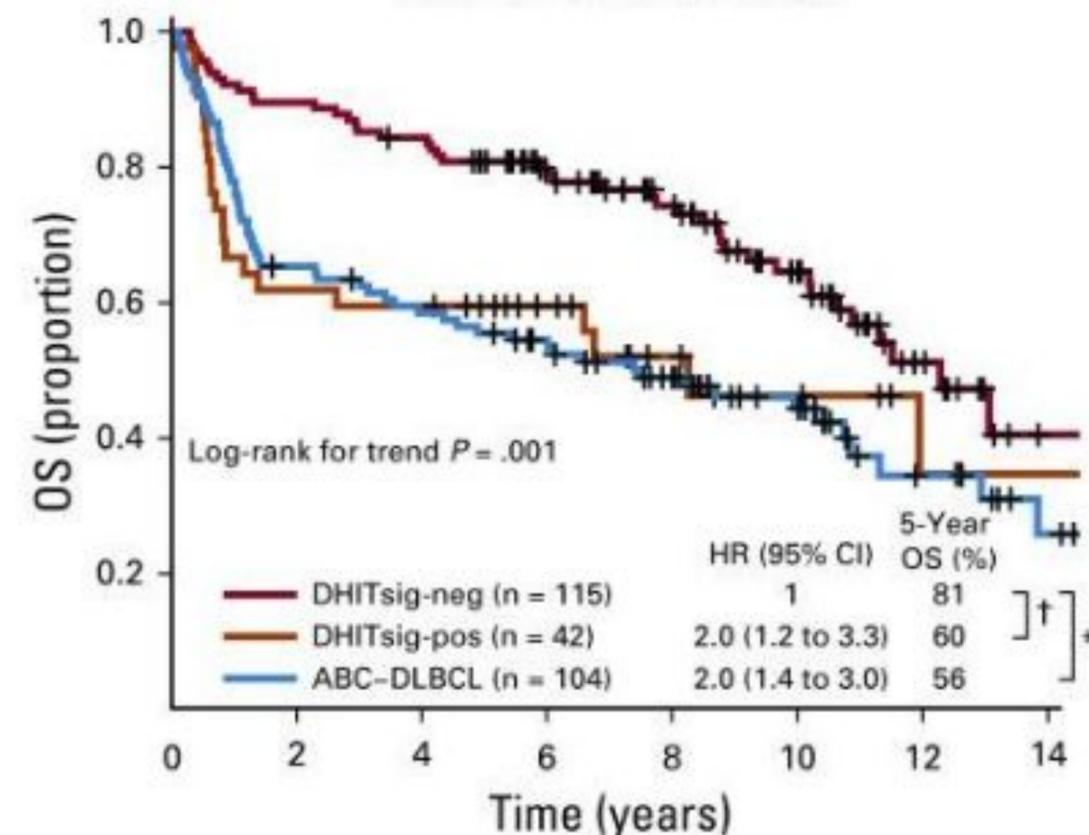
Double-Hit Gene Expression Signature Defines a Distinct Subgroup of Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma

[Daisuke Ennishi](#), PhD,¹ [Aixiang Jiang](#), MSc,^{1,2} [Merrill Boyle](#), BSc,¹ [Brett Collinge](#), BSc,¹ [Bruno M. Grande](#), BSc,² [Susana Ben-Neriah](#), MSc,¹ [Christopher Rushton](#), BSc,² [Jeffrey Tang](#), BSc,² [Nicole Thomas](#), BSc,² [Graham W. Slack](#), MD,¹ [Pedro Farinha](#), PhD,¹ [Katsuyoshi Takata](#), MD,¹ [Tomoko Miyata-Takata](#), MD,¹ [Jeffrey Craig](#), PhD,¹ [Anja Mottok](#), PhD,³ [Barbara Meissner](#), PhD,¹ [Saeed Saberi](#), PhD,⁴ [Ali Bashashati](#), PhD,⁴ [Diego Villa](#), MD,¹ [Kerry J. Savage](#), MD,¹ [Laurie H. Sehn](#), MD,¹ [Robert Kridel](#), PhD,⁵ [Andrew J. Mungall](#), PhD,⁶ [Marco A. Marra](#), PhD,⁶ [Sohrab P. Shah](#), PhD,⁴ [Christian Steidl](#), MD,¹ [Joseph M. Connors](#), MD,¹ [Randy D. Gascoyne](#), MD,¹ [Ryan D. Morin](#), PhD,² and [David W. Scott](#), PhD¹

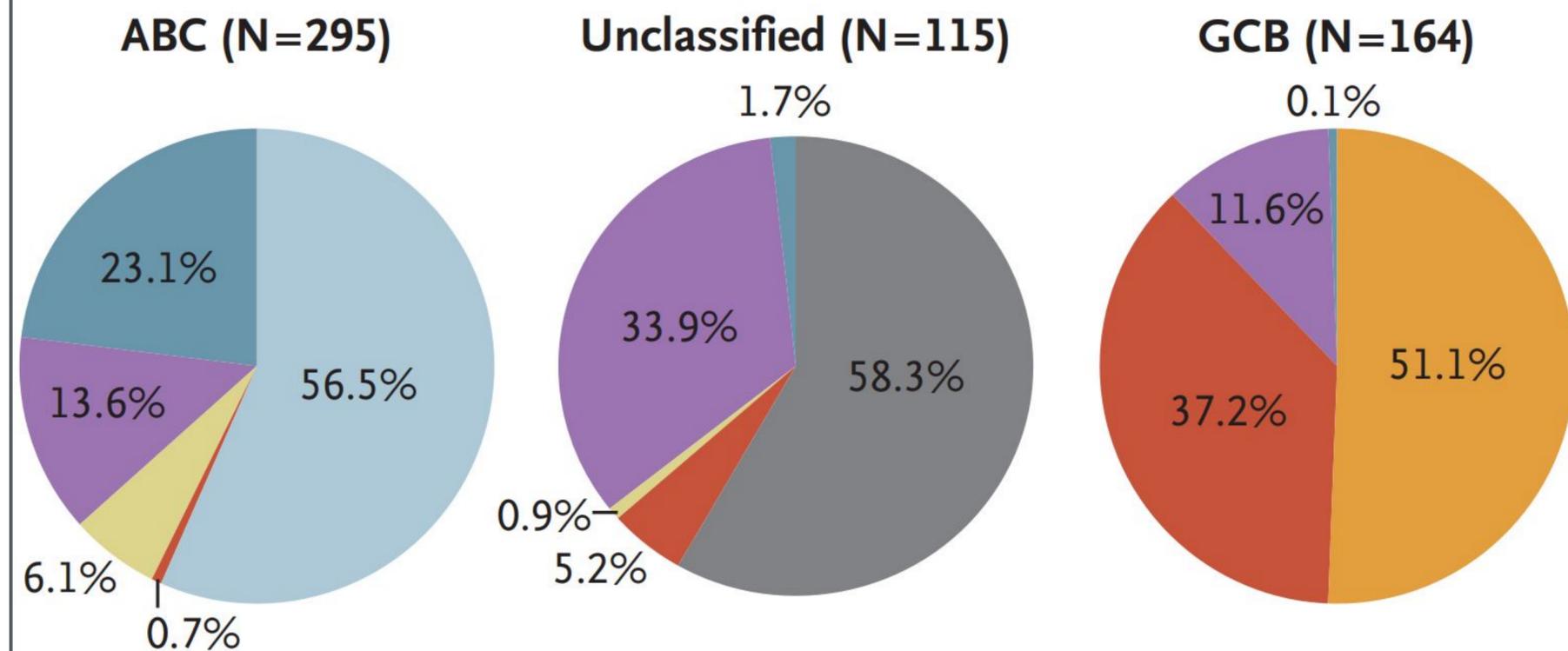


Double-hit signature (DHITsig)

- 27% dei GCB-DLBCL rientra nel gruppo DHITsig;
- solo metà con riarrangiamenti di MYC e BCL2 (HGBL-DH/TH-BCL2).



■ MCD ■ BN2 ■ N1 ■ EZB
■ Other ABC ■ Other GCB ■ Other unclassified



- **MCD** (mutazioni di MYD88 e CD79B): sottogruppo ABC, risposta a Ibrutinib nei linfomi refrattari, in particolare SNC.
- **BN2** (traslocazione BCL6 e mutazioni NOTCH2): sottogruppo inclassificabile, attivazione NK-kB, responsivo a inibitori di BTK.
- **N1** (mutazioni NOTCH1)
- **EZB** (mutazioni EZH2 e traslocazioni BCL2): sottogruppo GCB.

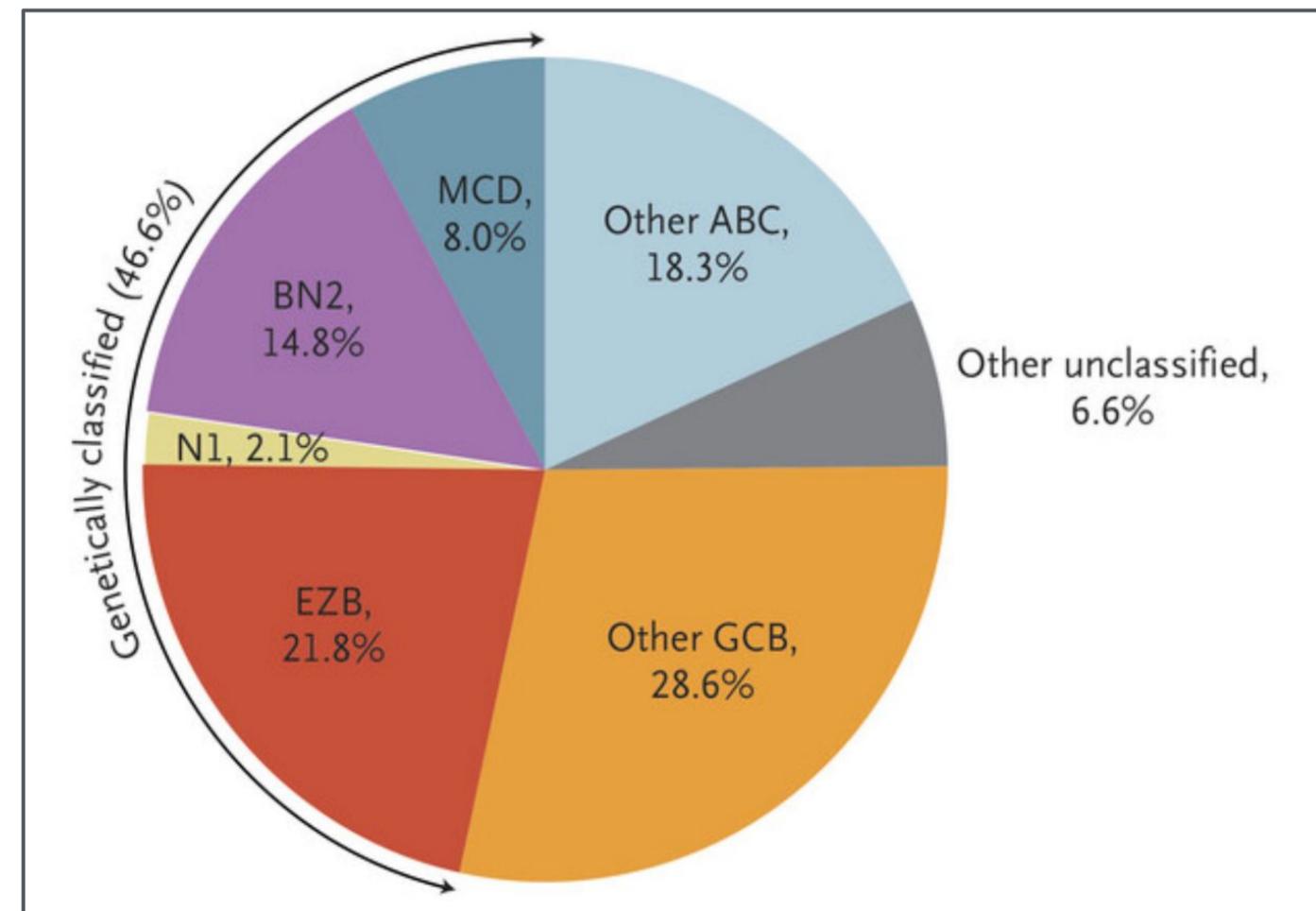
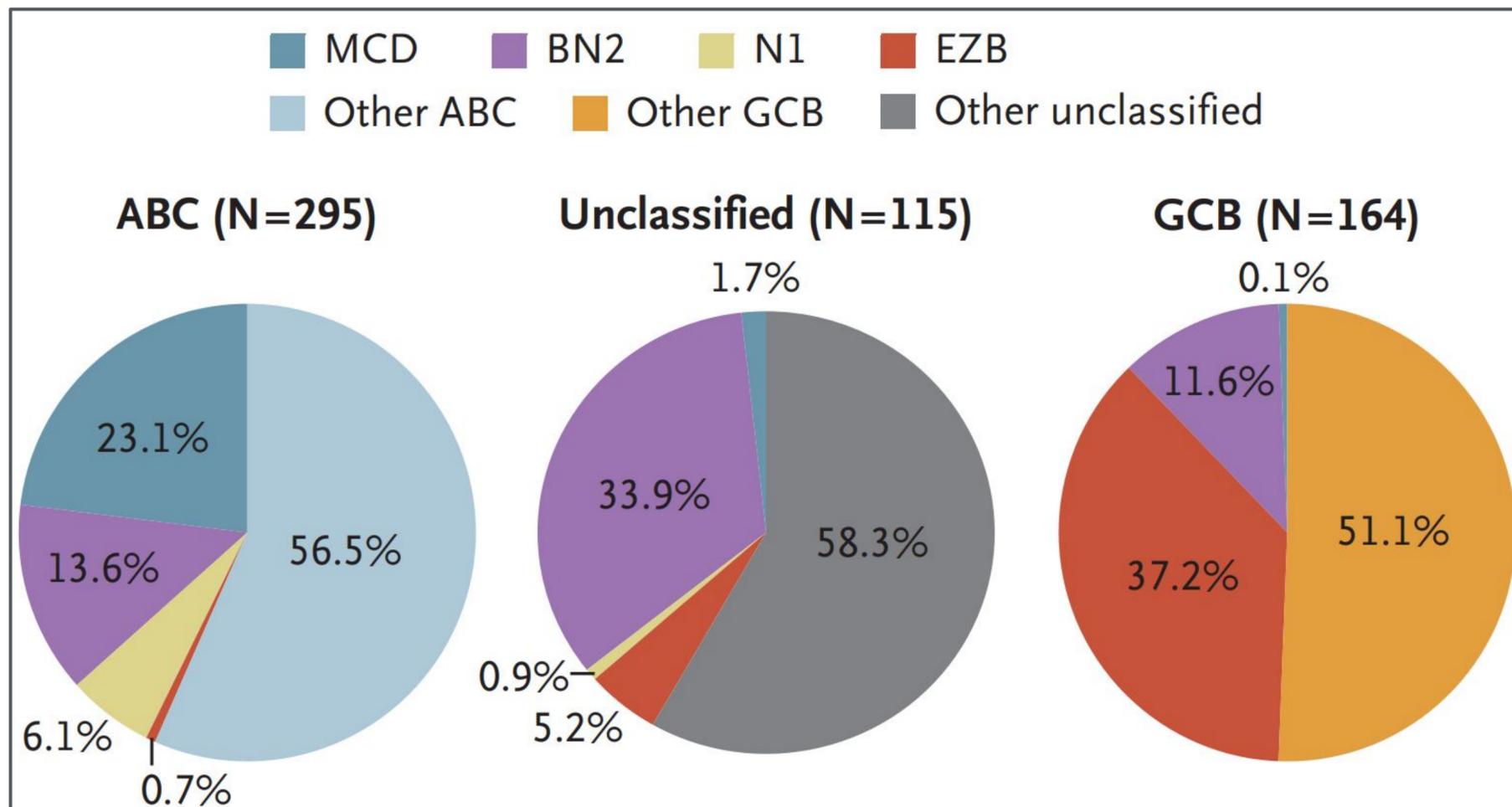
Prognosi EZB/BN2 >> MCD/N1

Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma

Authors: Roland Schmitz, Ph.D., George W. Wright, Ph.D., Da Wei Huang, M.D., Calvin A. Johnson, Ph.D., James D. Phelan, Ph.D., James Q. Wang, Ph.D., Sandrine Roulland, Ph.D., [+32](#), and Louis M. Staudt, M.D., Ph.D. [Author Info & Affiliations](#)

Published April 11, 2018 | N Engl J Med 2018;378:1396-1407 | DOI: 10.1056/NEJMoa1801445 | [VOL. 378 NO. 15](#)

**Identificazione di 4 sottotipi
genetici di DLBCL con
caratteristiche genotipiche,
epigenetiche e cliniche distinte.**



Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma

Authors: Roland Schmitz, Ph.D., George W. Wright, Ph.D., Da Wei Huang, M.D., Calvin A. Johnson, Ph.D., James D. Phelan, Ph.D., James Q. Wang, Ph.D., Sandrine Roulland, Ph.D., [+32](#), and Louis M. Staudt, M.D., Ph.D. [Author Info & Affiliations](#)

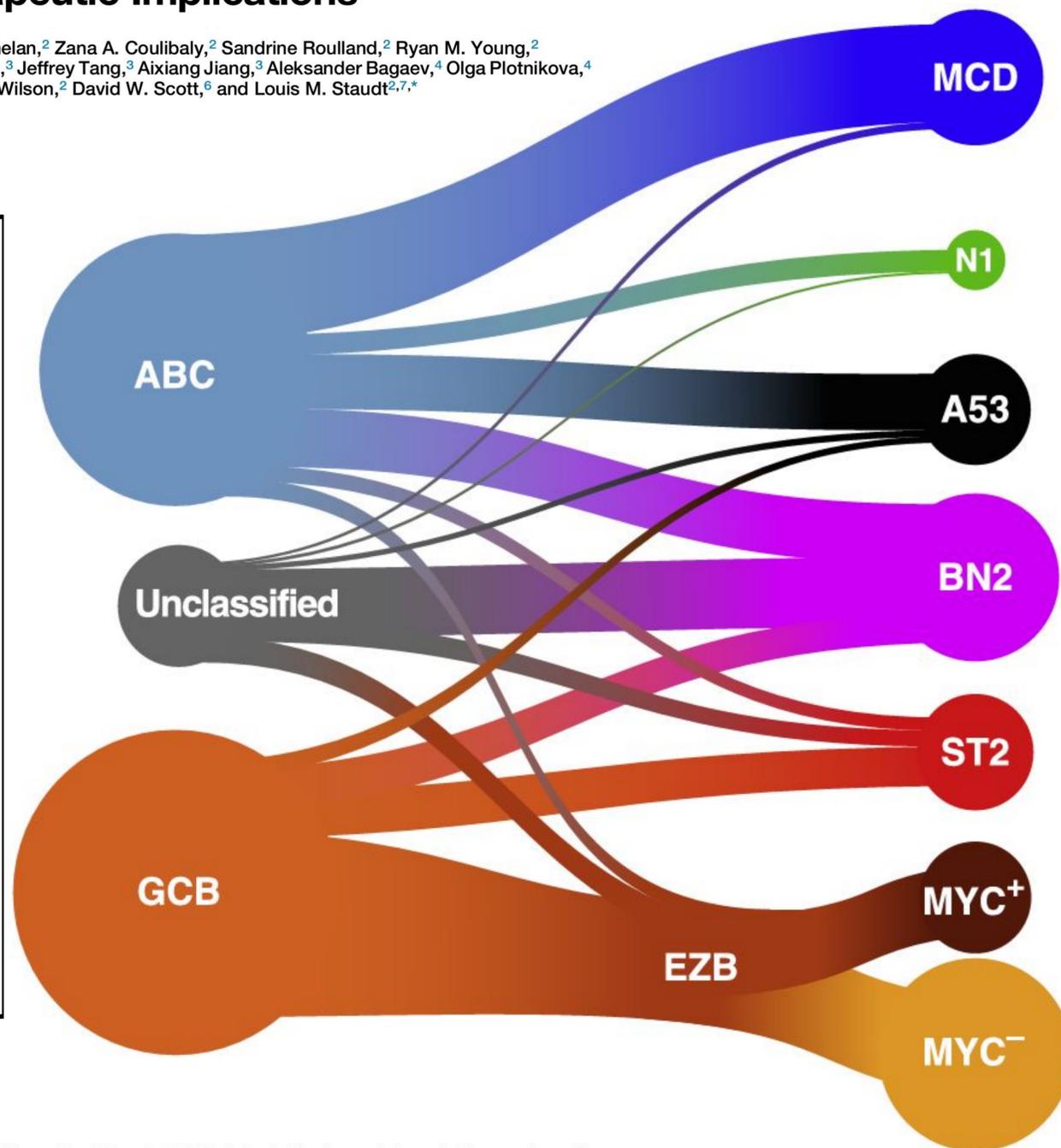
Published April 11, 2018 | N Engl J Med 2018;378:1396-1407 | DOI: 10.1056/NEJMoa1801445 | [VOL. 378 NO. 15](#)

Identificazione di 4 sottotipi genetici di DLBCL con caratteristiche genotipiche, epigenetiche e cliniche distinte.

A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications

George W. Wright,¹ Da Wei Huang,² James D. Phelan,² Zana A. Coulbaly,² Sandrine Roulland,² Ryan M. Young,² James Q. Wang,² Roland Schmitz,² Ryan D. Morin,³ Jeffrey Tang,³ Aixiang Jiang,³ Aleksander Bagaev,⁴ Olga Plotnikova,⁴ Nikita Kotlov,⁴ Calvin A. Johnson,⁵ Wyndham H. Wilson,² David W. Scott,⁶ and Louis M. Staudt^{2,7,*}

LymphGen
Sette sottotipi genetici sulla base di pathway onocogenica, espressione genica, microambiente tumorale, tassi di sopravvivenza e potenziali bersagli terapeutici.



Prevalence	5-yr overall survival	Genetic themes	Genetically related lymphomas	Gene expression signatures	Potential therapeutic targets
8.7%	40% (All) 37% (ABC)	My-T-BCR-dependent NF-κB Immune evasion-MHC class I Cell survival - <i>BCL2</i> expression Altered B cell differentiation G1-S cell cycle/p53 checkpoint BCR: IgM >> IgG; IgV _H 4-34 ⁺⁺	Primary extranodal DLBCL Transformed WM	B cell activation NF-κB IRF4 Myc Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 BCL2-BCLX _L -MCL1 JAK1 IRAK4 IRF4
1.7%	27% (All) 22% (ABC)	NOTCH1 signaling Altered B cell differentiation BCR: IgM > IgG	NOTCH1-mutant CLL	NOTCH Quiescence Plasma cell T cell-myeloid-FDC	NOTCH1 Immune checkpoints
5.8%	63% (All) 33% (ABC) 100% (GCB)	<i>TP53</i> inactivation/DNA damage Aneuploidy Immune evasion - <i>B2M</i> loss BCR: IgM >> IgG; IgV _H 4-34 ⁺⁺	-	p53 Immune low	BCR-dep. NF-κB
13.3%	67% (All) 76% (ABC) 100% (GCB) 38% (UC)	NOTCH2 signaling Altered B cell differentiation BCR-dependent NF-κB Immune evasion - <i>CD70</i> loss Proliferation - Cyclin D3 BCR: IgM >> IgG; IgV _H 4-34 ⁺⁺	MZL Transformed MZL	B cell activation NF-κB NOTCH Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 BCL2 NOTCH2
6.4%	84% (All) 81% (GCB)	JAK/STAT3 signaling NF-κB activation <i>P2RY8</i> - <i>GNA13</i> inactivation Altered B cell differentiation BCR: IgG >> IgM	NLPHD THRLBCL	GC B cell PI3K signaling JAK2 signaling Glycolysis Stromal	PI3 kinase JAK2
5.9% (MYC ⁺) 17.6% (MYC ⁻)	48% (MYC ⁺) 82% (MYC ⁻)	Chromatin modification Anti-apoptosis PI3 kinase signaling <i>S1PR2</i> - <i>GNA13</i> inactivation Altered T _{FH} interactions MYC (EZB-MYC ⁺) BCR: IgG > IgM	FL Transformed FL BL (EZB-MYC ⁺)	GC LZ (MYC ⁻) GC IZ (MYC ⁺) BCL6 (MYC ⁺) TCF3 (both) T _{FH} cells (MYC ⁻) Stromal (MYC ⁻) Immune low (MYC ⁺)	PI3 kinase mTORC1 EZH2 BCL2-MCL1

High-grade B-cell lymphoma (HGBL)-NOS is clinicopathologically and genetically more similar to DLBCL/HGBL-DH than DLBCL

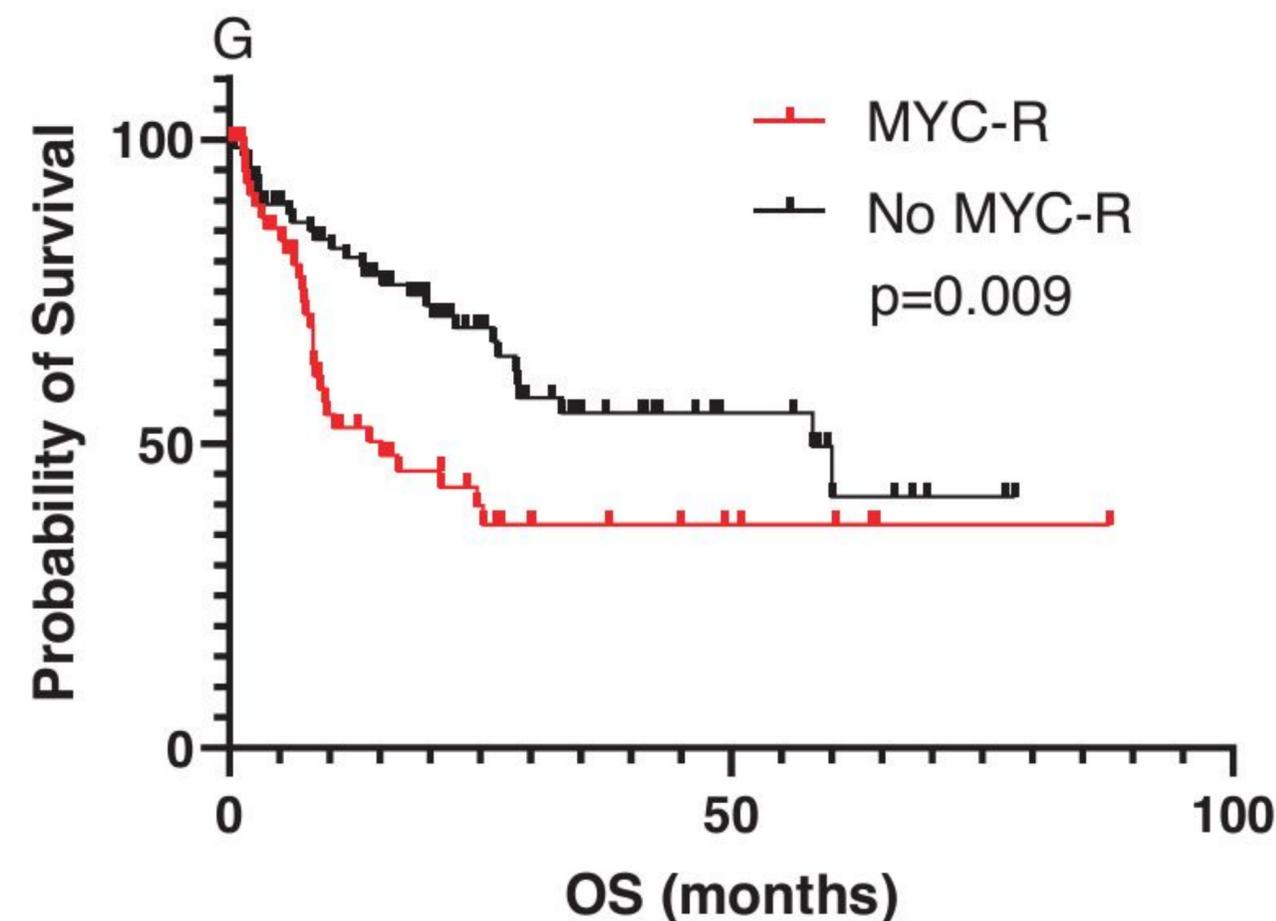
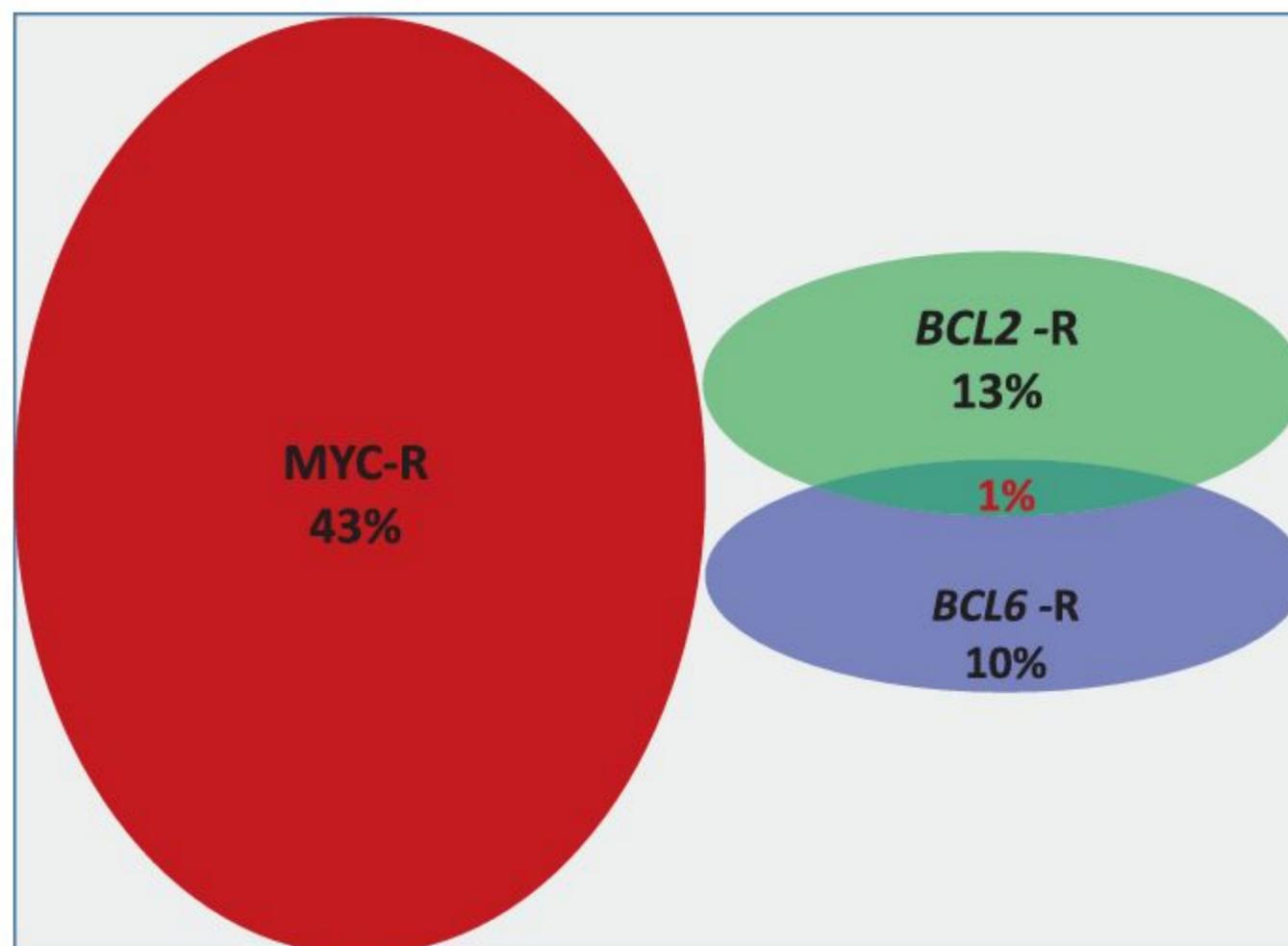
[Shaoying Li](#) , [Lianqun Qiu](#), [Jie Xu](#), [Pei Lin](#), [Chi Young Ok](#), [Guilin Tang](#), [Timothy J. McDonnell](#), [M. James](#)

[You](#), [Mahsa Khanlari](#), [Roberto N. Miranda](#) & [L. Jeffrey Medeiros](#)

Leukemia 37, 422–432 (2023) | [Cite this article](#)

- 75% di HGBL-NOS MYC-R era DH-like-Sig+.
- Prognosi peggiore nei HGBL-NOS con MYC-R, simile ai pazienti DLBCL/HGBL-DH; senza MYC-R, OS simile ai pazienti DLBCL.

HGBL-NOS



[Leukemia](#). 2020; 34(5): 1329–1341.

PMCID: PMC7192846

Published online 2019 Dec 16. doi: [10.1038/s41375-019-0691-6](https://doi.org/10.1038/s41375-019-0691-6)

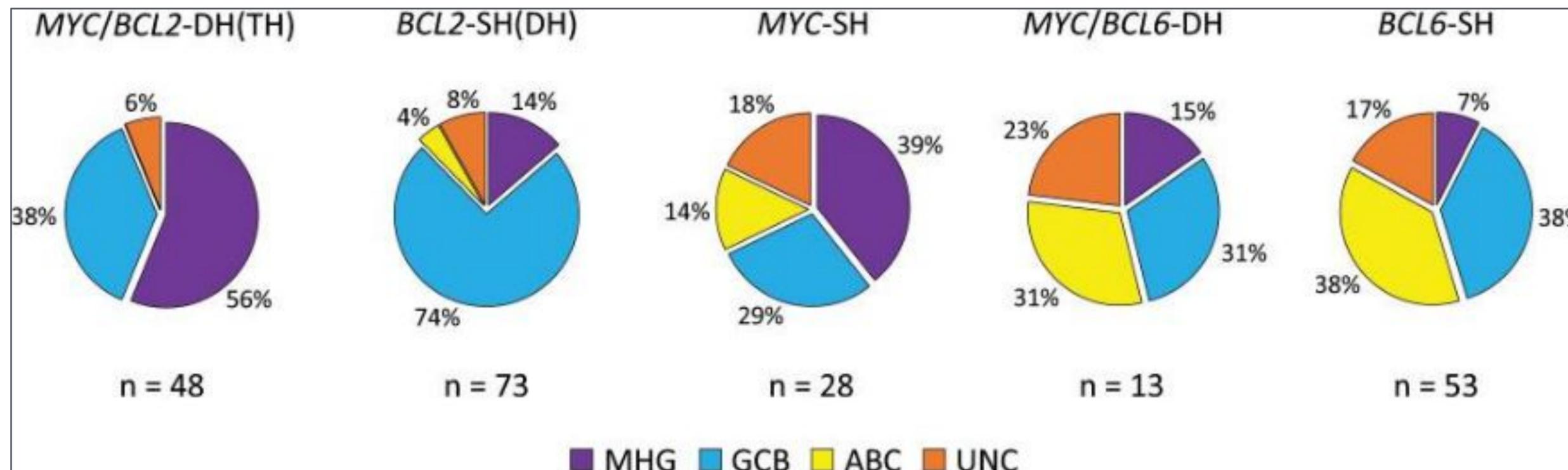
PMID: [31844144](https://pubmed.ncbi.nlm.nih.gov/31844144/)

Distinct genetic changes reveal evolutionary history and heterogeneous molecular grade of DLBCL with *MYC/BCL2* double-hit

[Francesco Cucco](#),^{#1} [Sharon Barrans](#),^{#2} [Chulin Sha](#),^{#3} [Alexandra Clipson](#),¹ [Simon Crouch](#),⁴ [Rachel Dobson](#),¹ [Zi Chen](#),¹ [Joe Sneath Thompson](#),¹ [Matthew A. Care](#),³ [Thomas Cummin](#),⁵ [Josh Caddy](#),⁵ [Hongxiang Liu](#),⁶ [Anne Robinson](#),⁶ [Anna Schuh](#),⁷ [Jude Fitzgibbon](#),⁸ [Daniel Painter](#),⁴ [Alexandra Smith](#),⁴ [Eve Roman](#),⁴ [Reuben Tooze](#),² [Catherine Burton](#),² [Andrew J. Davies](#),⁵ [David R. Westhead](#),^{#3} [Peter W. M. Johnson](#),^{#5} and [Ming-Qing Du](#)^{✉#1}

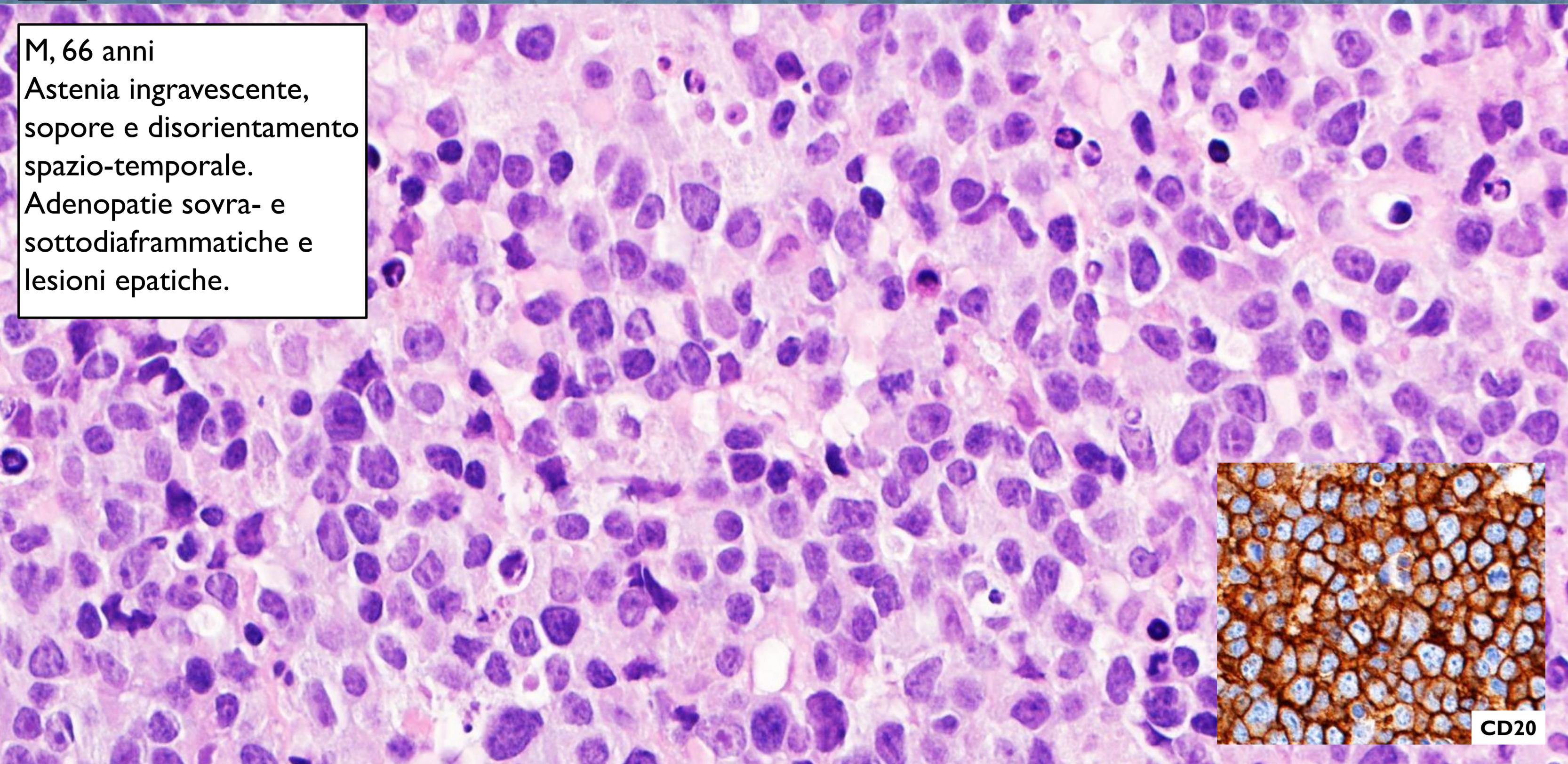
- Il profilo mutazionale di DLBCL con *MYC/BCL2*-DH o *BCL2*-SH suggerisce la loro derivazione dal linfoma follicolare.

- **HGBCL-DH-BCL6** gruppo eterogeneo: dati a supporto di una biologia distinta meno convincenti.



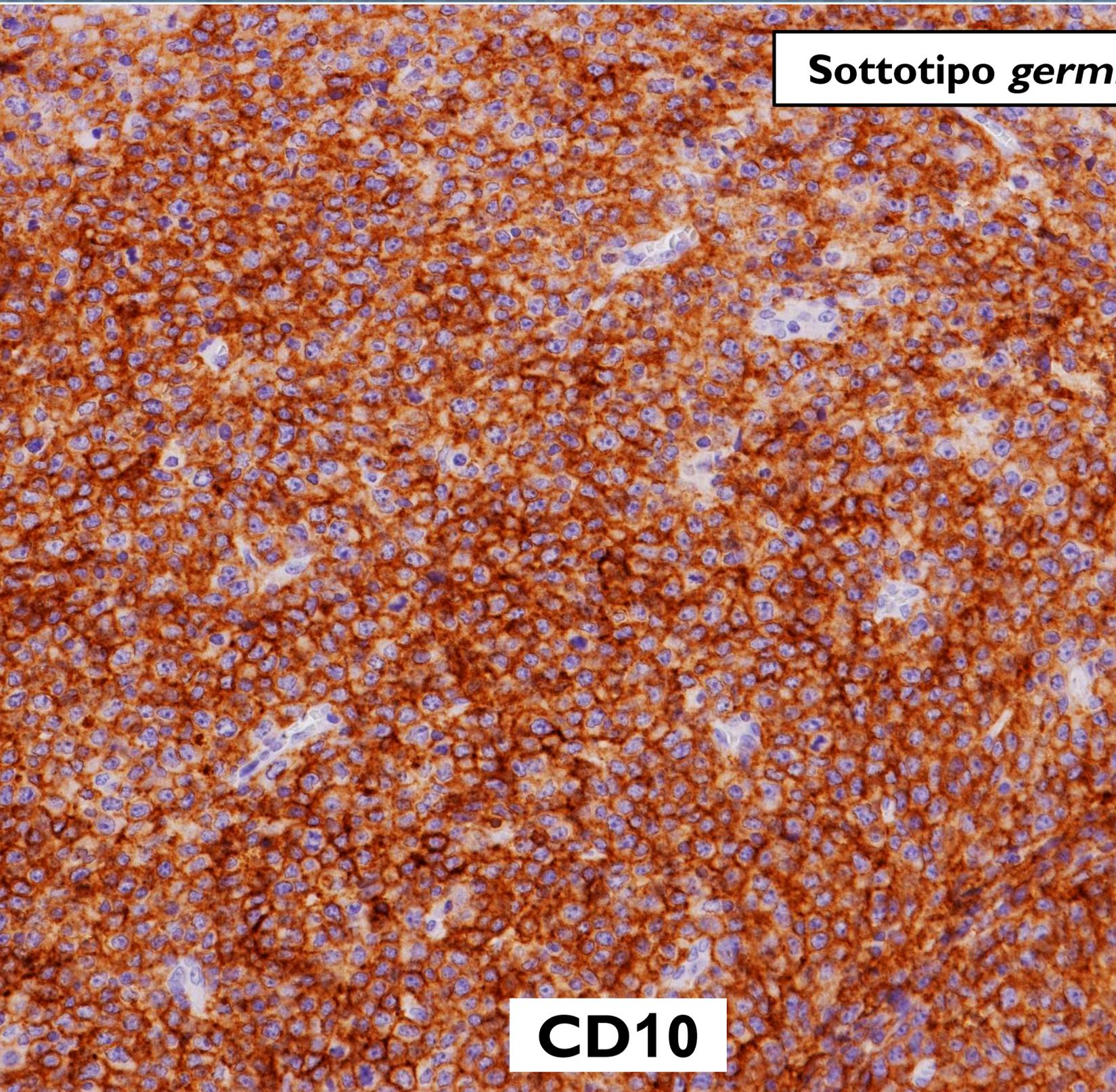
CASI CLINICI

M, 66 anni
Astenia ingravescente,
sopore e disorientamento
spazio-temporale.
Adenopatie sovra- e
sottodiaframmatiche e
lesioni epatiche.

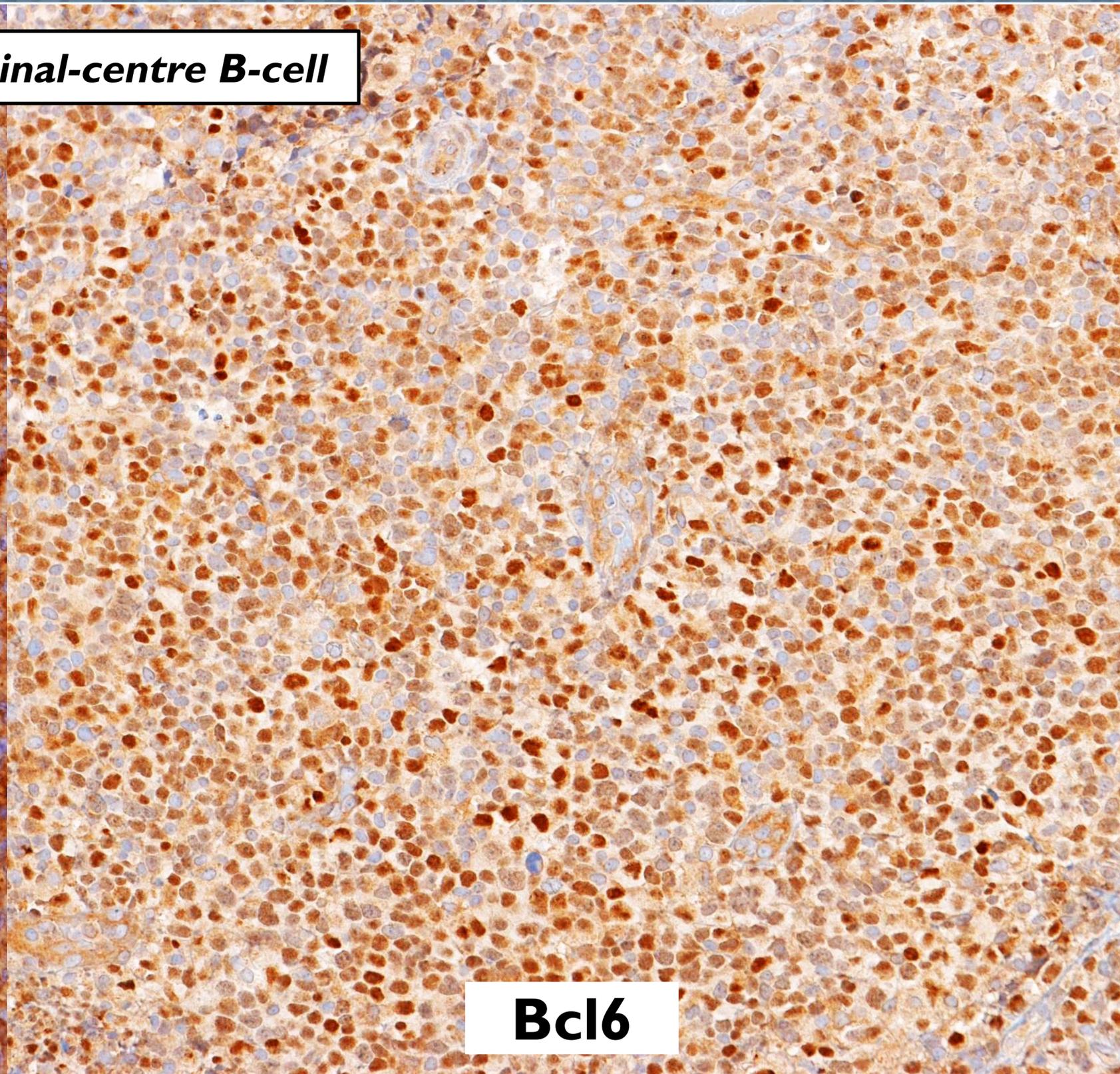


CD20

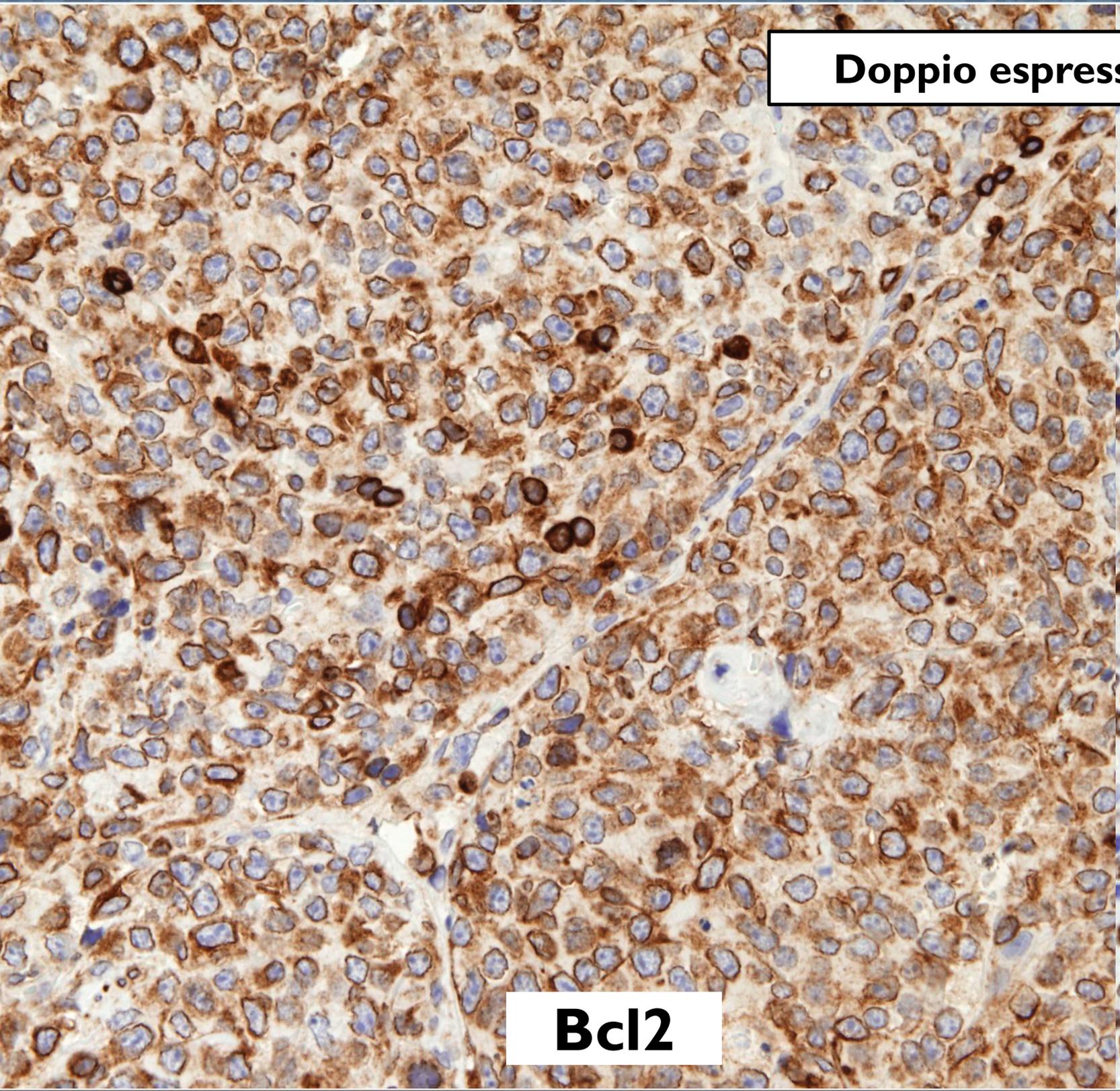
Sottotipo *germinal-centre B-cell*



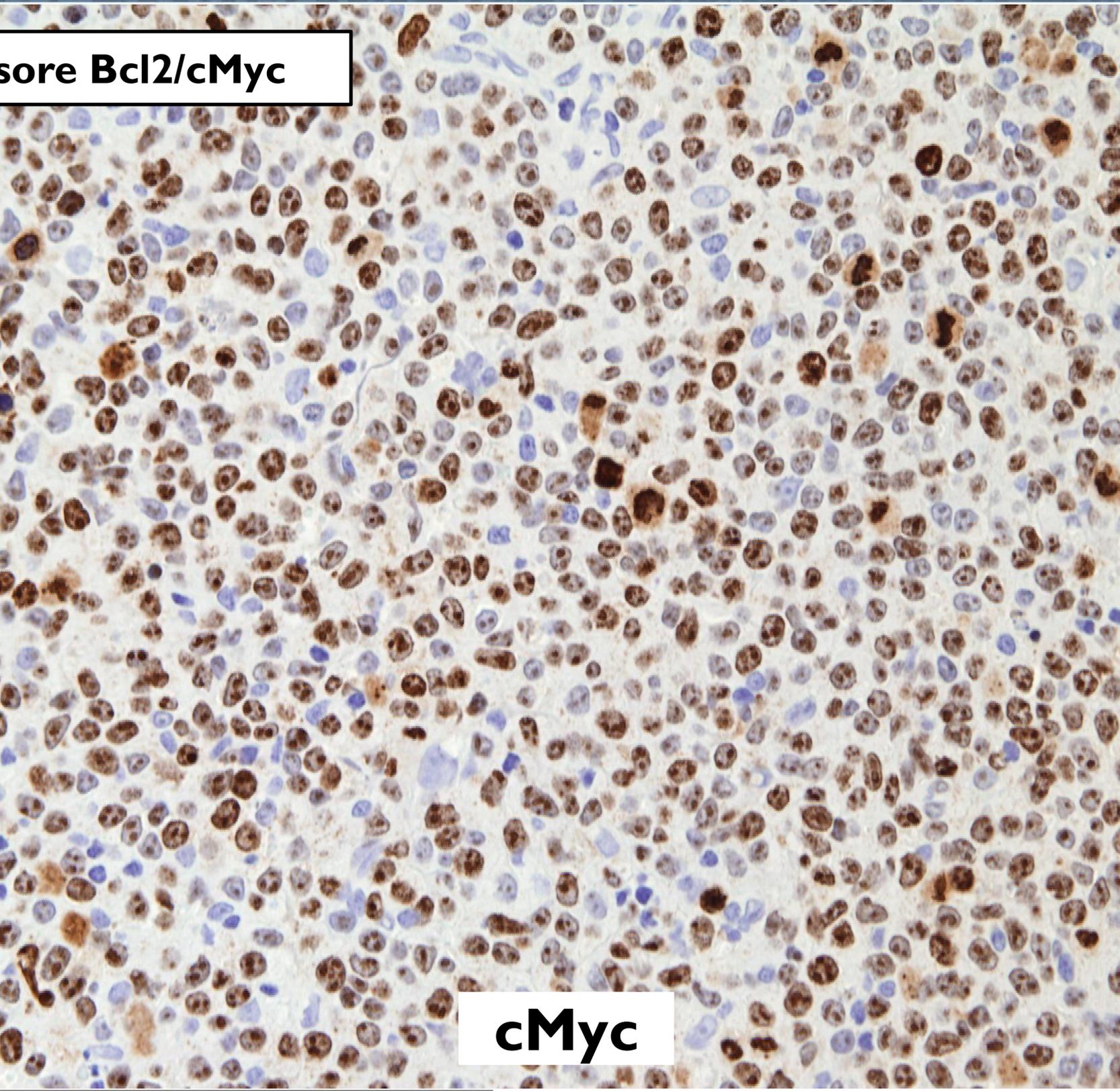
CD10



Bcl6



Bcl2



cMyc

Doppio espressore Bcl2/cMyc

DIAGNOSI PRELIMINARE

Linfoma non Hodgkin B, a cellule di grande taglia, doppio espressore Bcl2/cMyc.

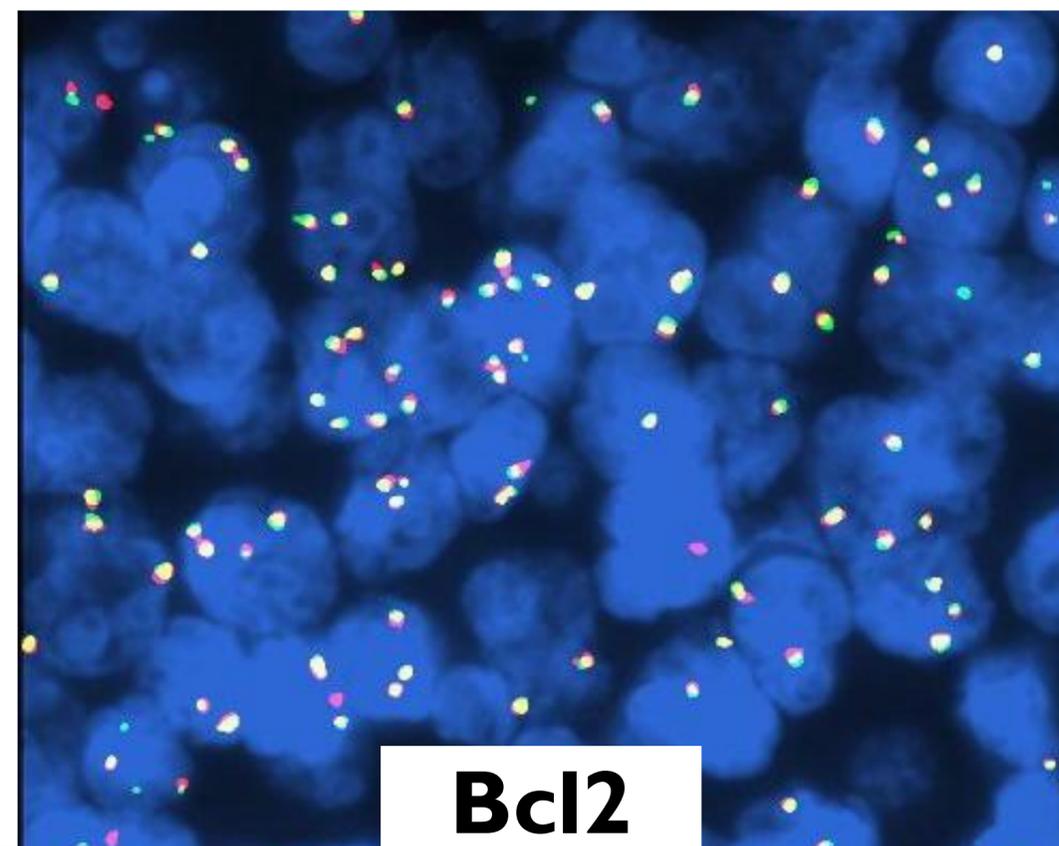
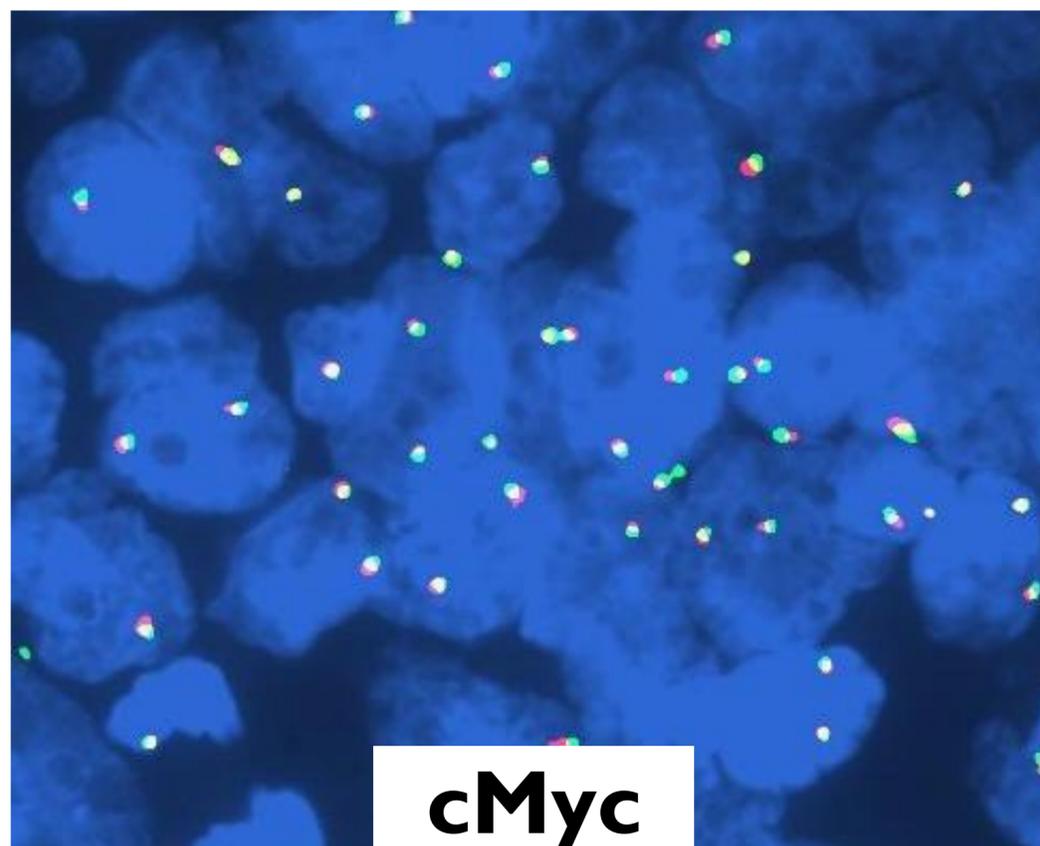
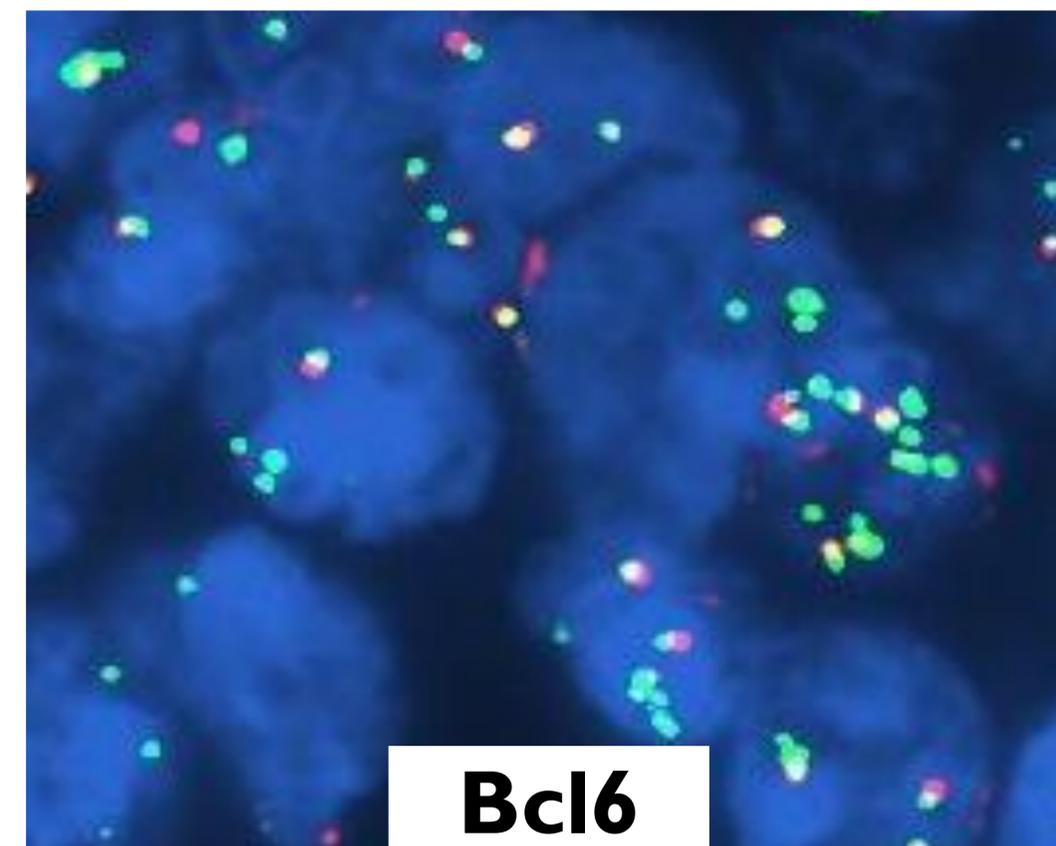
Nota: per una corretta classificazione, necessaria integrazione con studio FISH di cui seguirà integrazione diagnostica.

Analisi genica mediante tecnica FISH

Si segnalano più copie del gene **BCL2** (3-7RV/nucleo) con aspetto di tipo cluster in una frazione degli elementi.

NEGATIVA

Pattern anomali (1RV+9V, 2RV+3V, 2RV+2V, 2RV+1V con aspetto a cluster) ad indicare anomalie complesse.

**Bcl2****cMyc****Bcl6**

DIAGNOSI FINALE

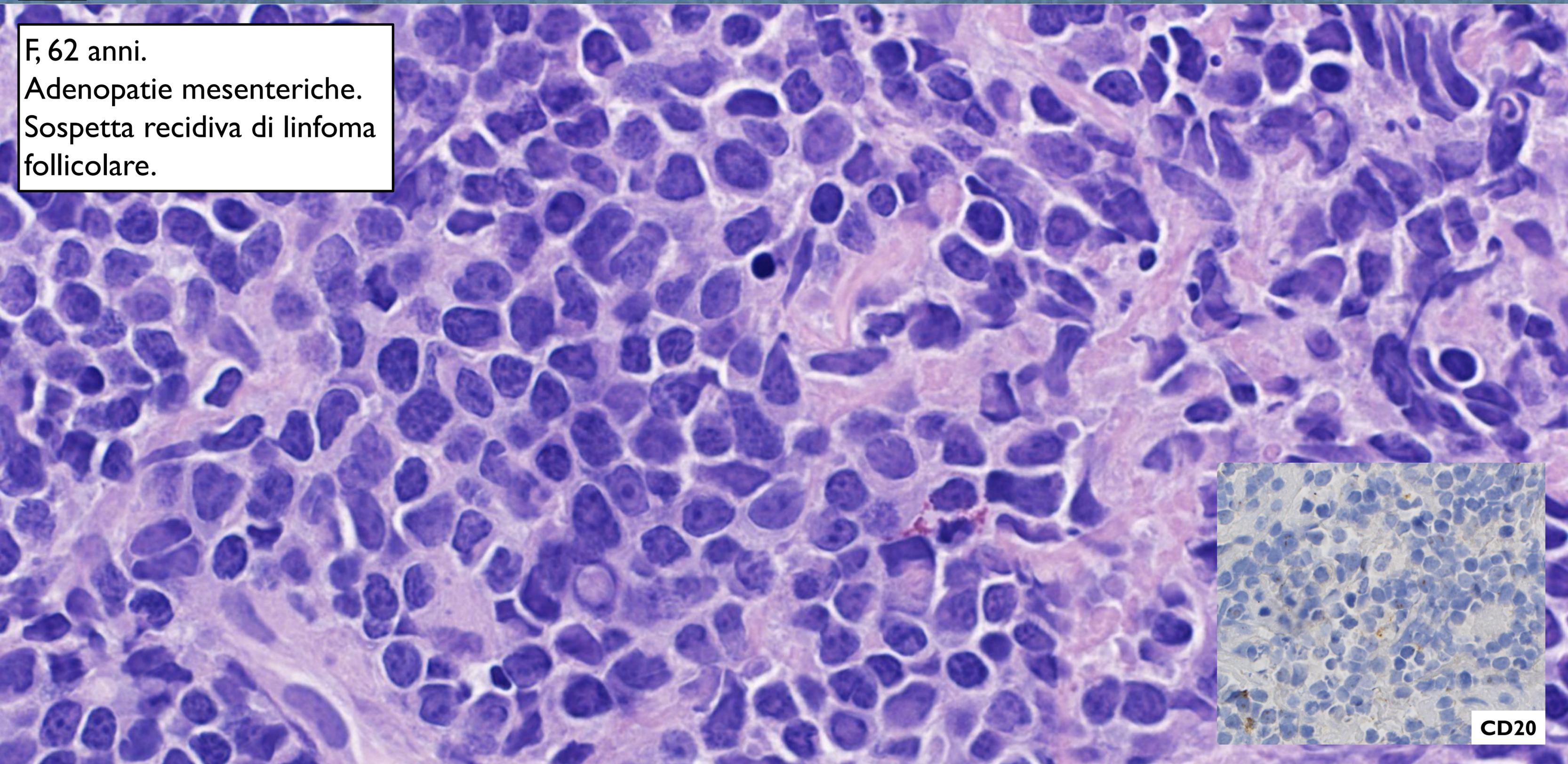
Linfoma non Hodgkin B, diffuso a grande cellule, non altrimenti specificato.

#2

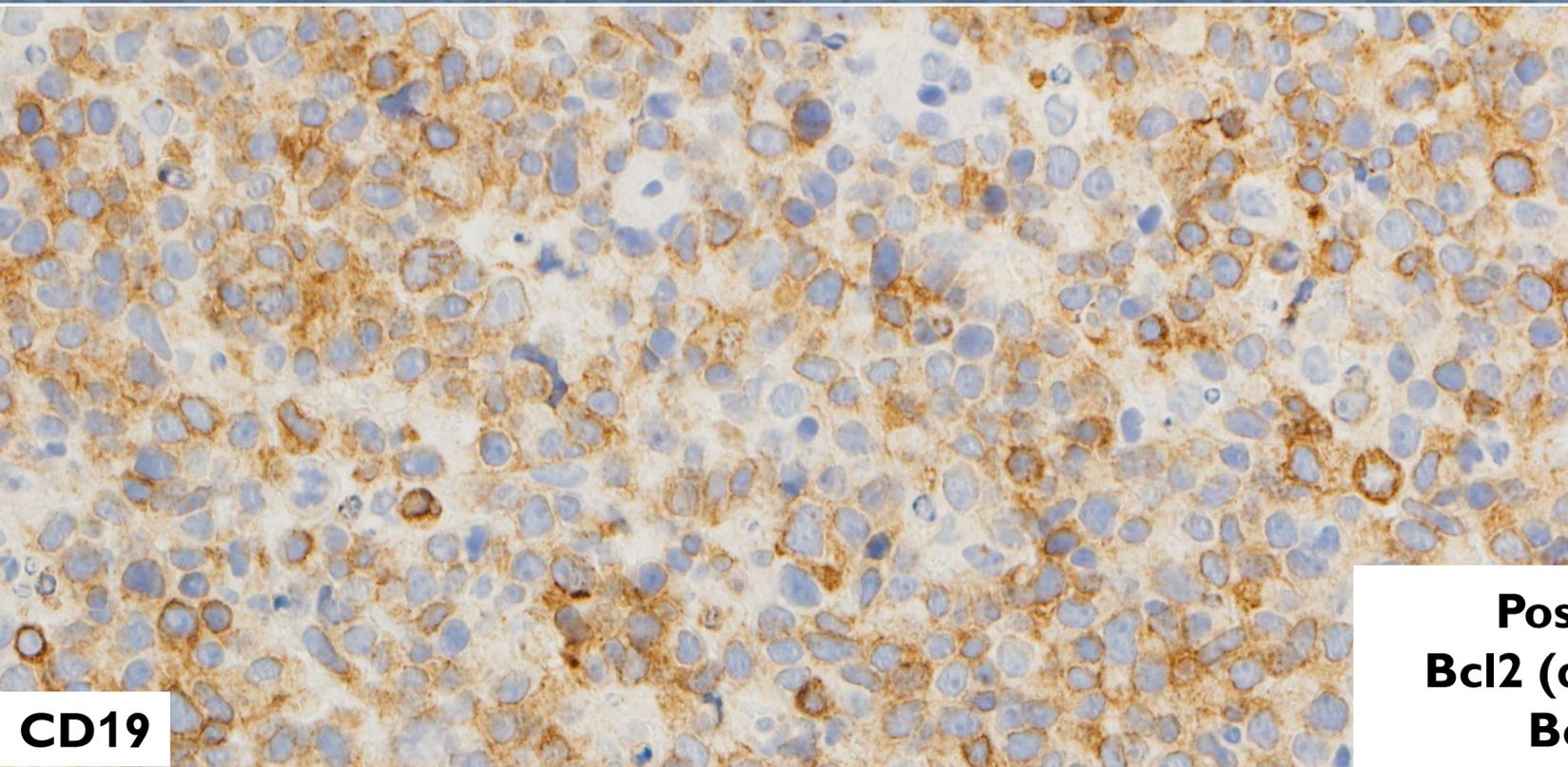
The young side of LYMPHOMA

gli under 40 a confronto

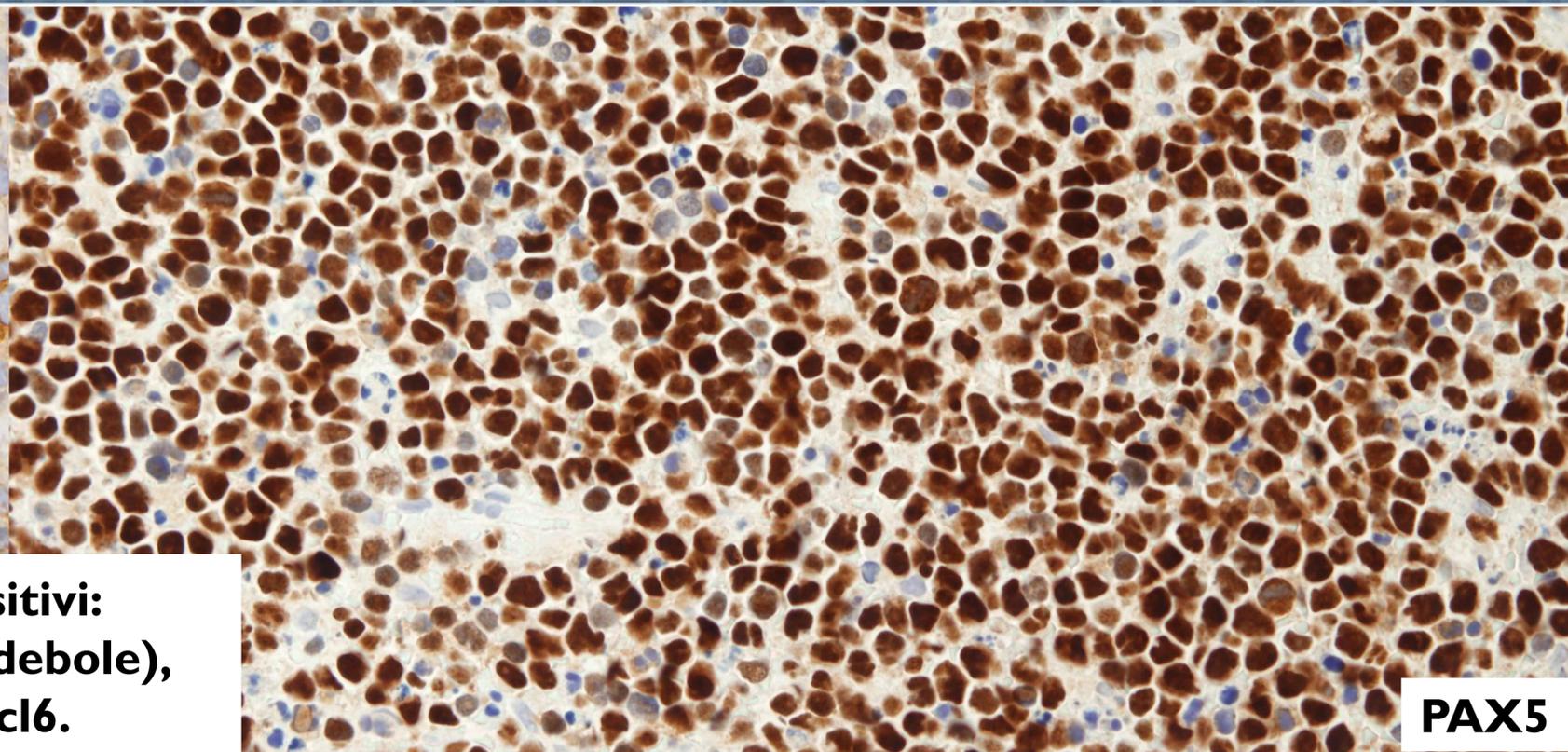
F, 62 anni.
Adenopatie mesenteriche.
Sospetta recidiva di linfoma
follicolare.



CD20

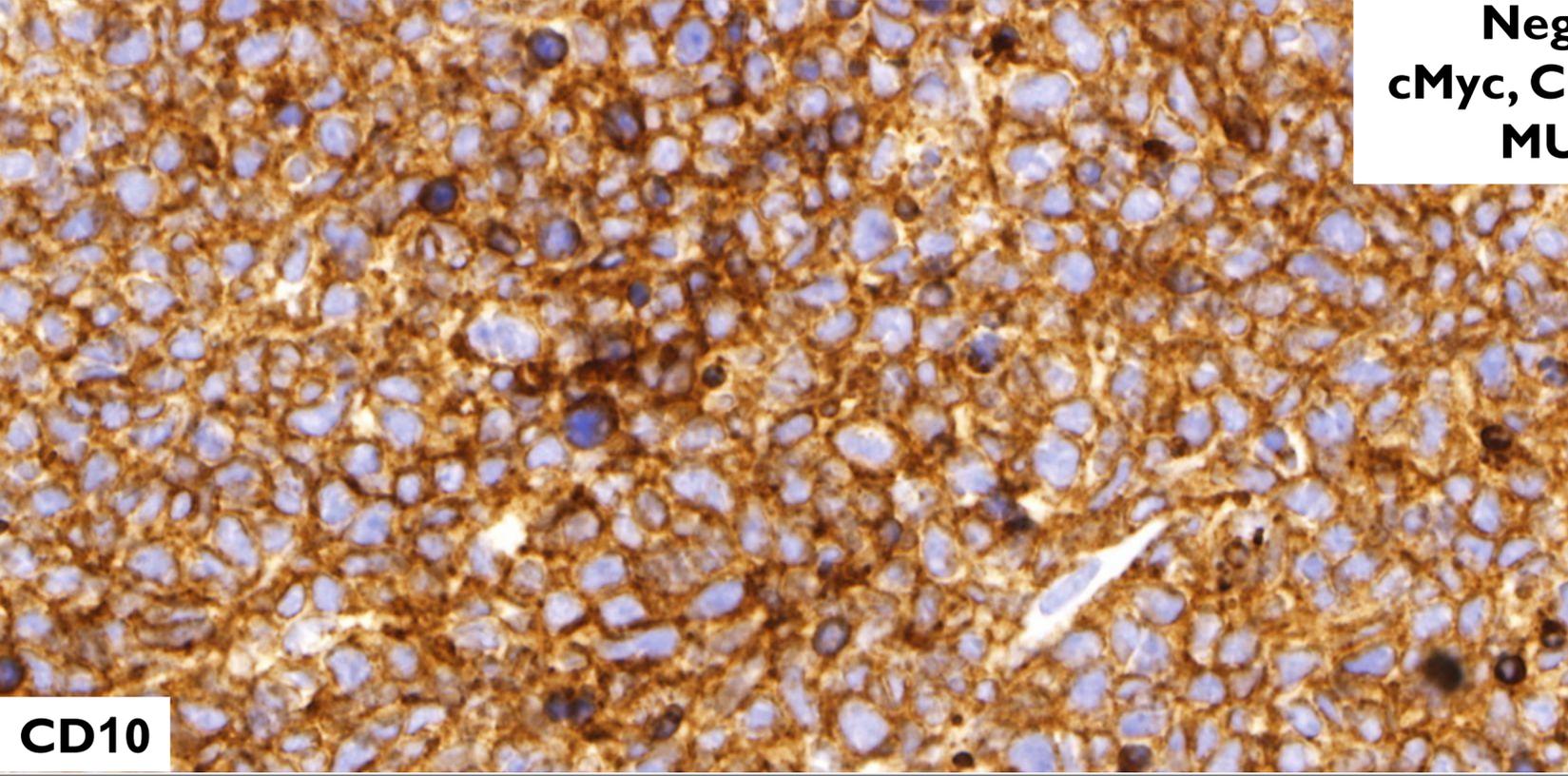


CD19

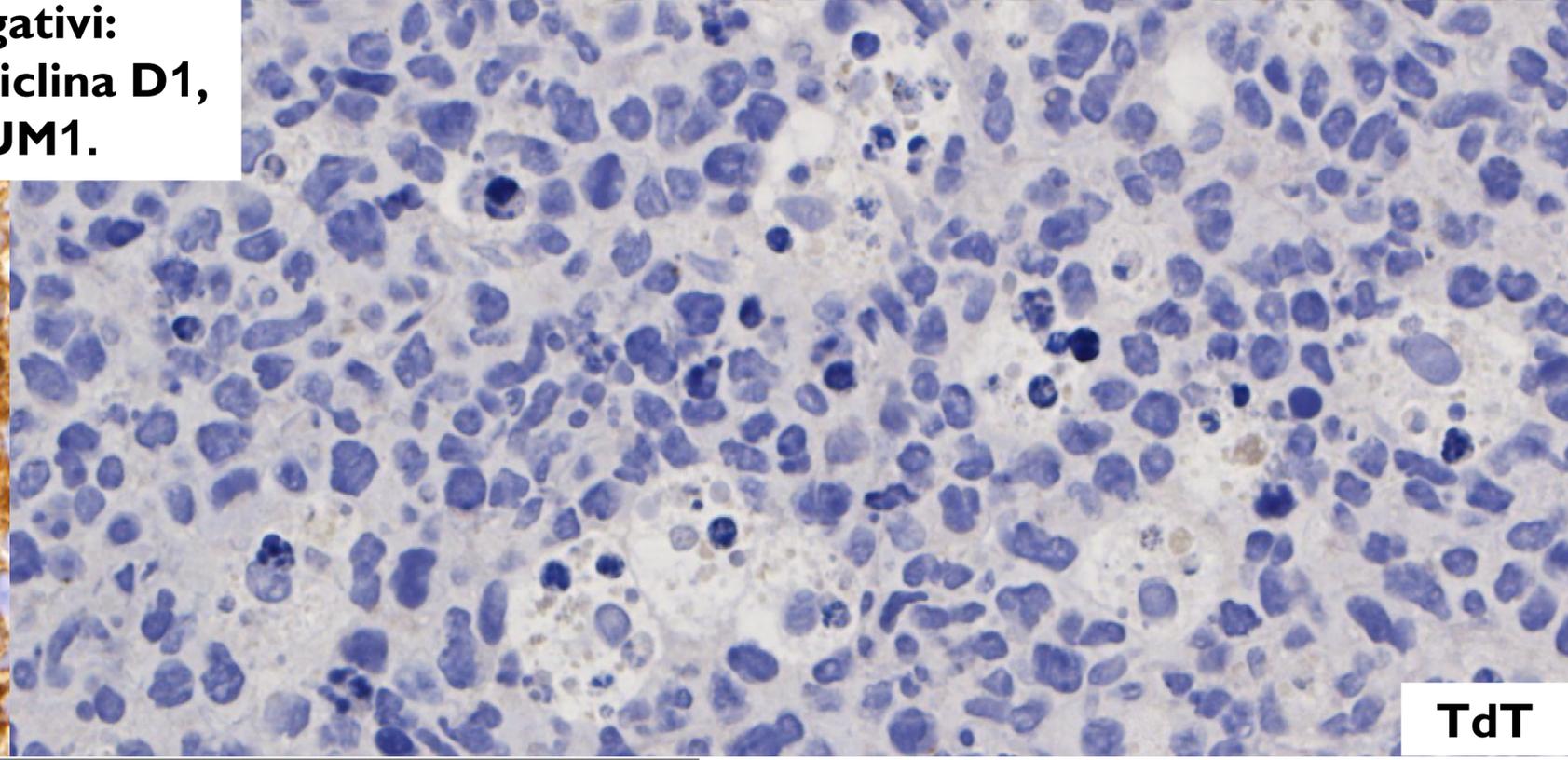


PAX5

Positivi:
Bcl2 (debole),
Bcl6.
Negativi:
cMyc, Ciclina D1,
MUM1.



CD10



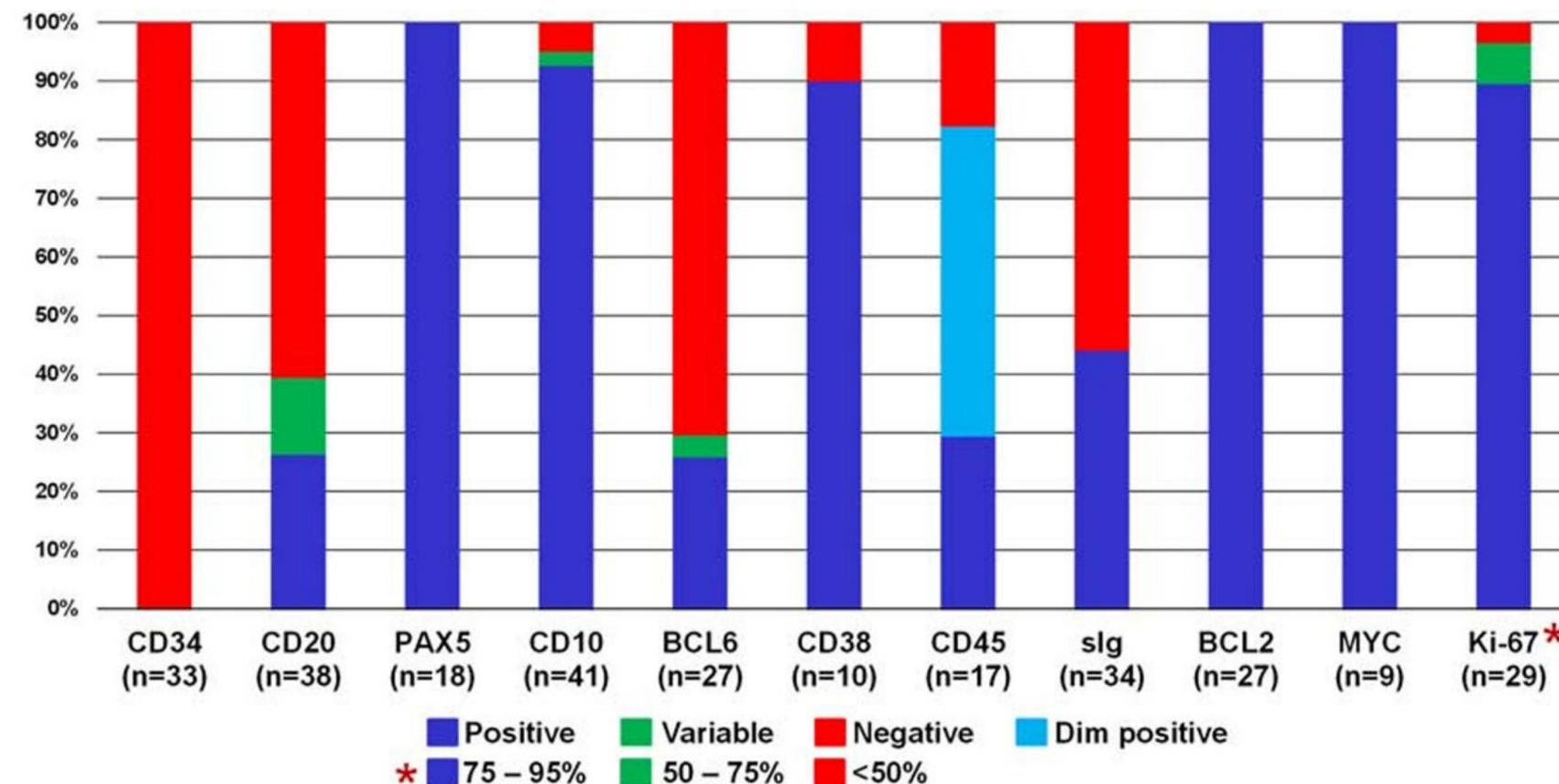
TdT

Mutational Landscape of TdT⁺ Large B-cell Lymphomas Supports Their Distinction From B-lymphoblastic Neoplasms

A Multiparameter Study of a Rare and Aggressive Entity

Shweta Bhavsar, MD,* Yen-Chun Liu, MD, PhD, MS,† Sarah E. Gibson, MD,† Erika M. Moore, MD,† and Steven H. Swerdlow, MD†

Am J Surg Pathol • Volume 46, Number 1, January 2022



Spesso con riarrangiamento dei geni MYC e BCL2 (raramente BCL6)

Subtype(s)

DLBCL/HGBCL-MYC/BCL2 without BCL6 rearrangement; DLBCL/HGBCL-MYC/BCL2 with BCL6 rearrangement; DLBCL/HGBCL-MYC/BCL2 (with or without BCL6 rearrangement) with TdT expression

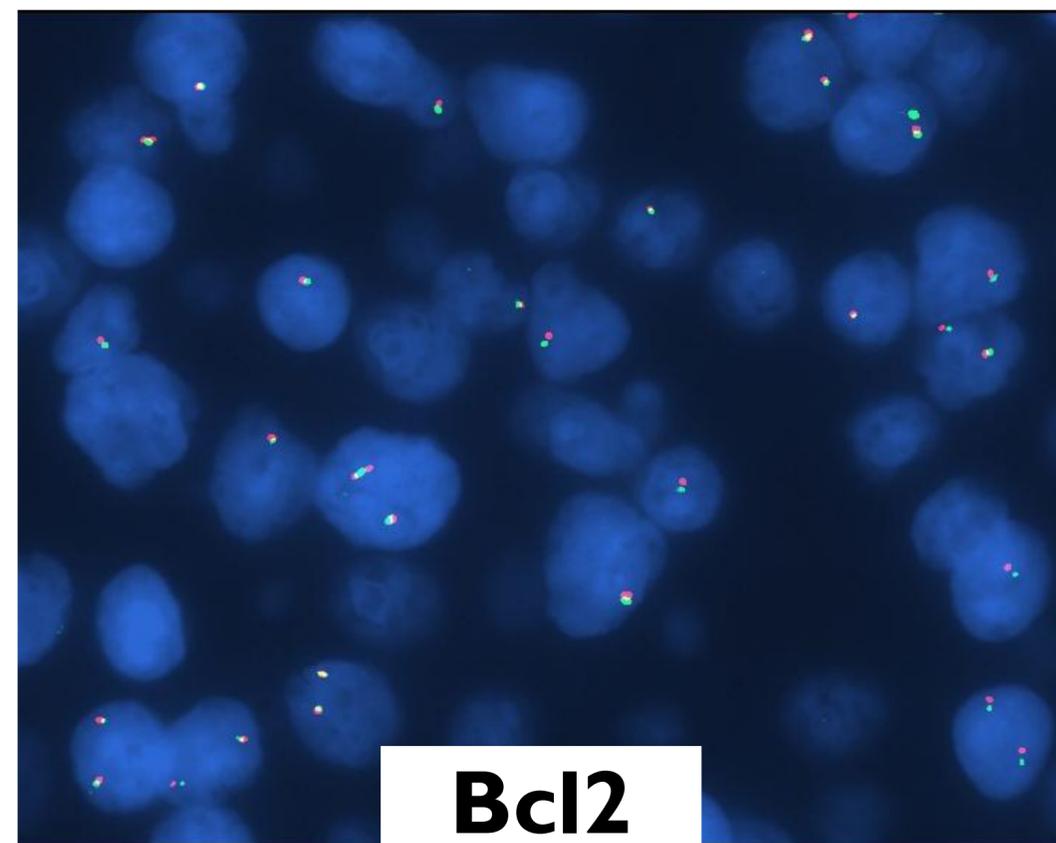
WHO 2022



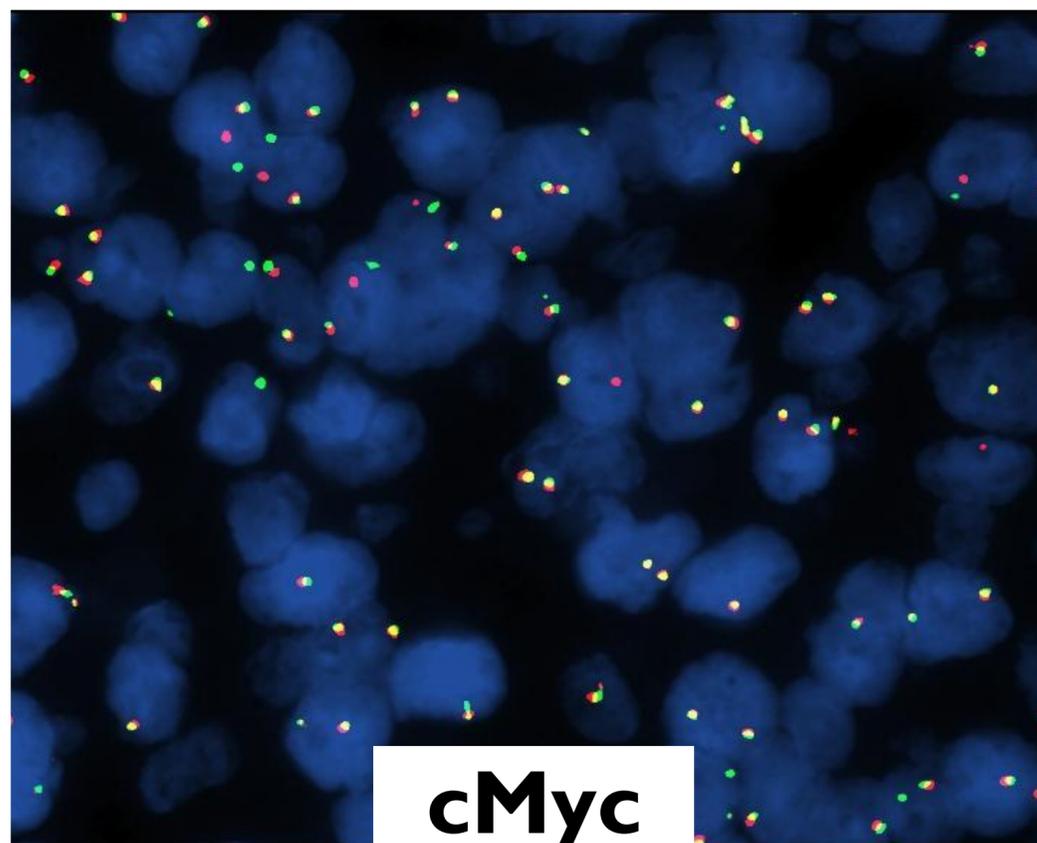
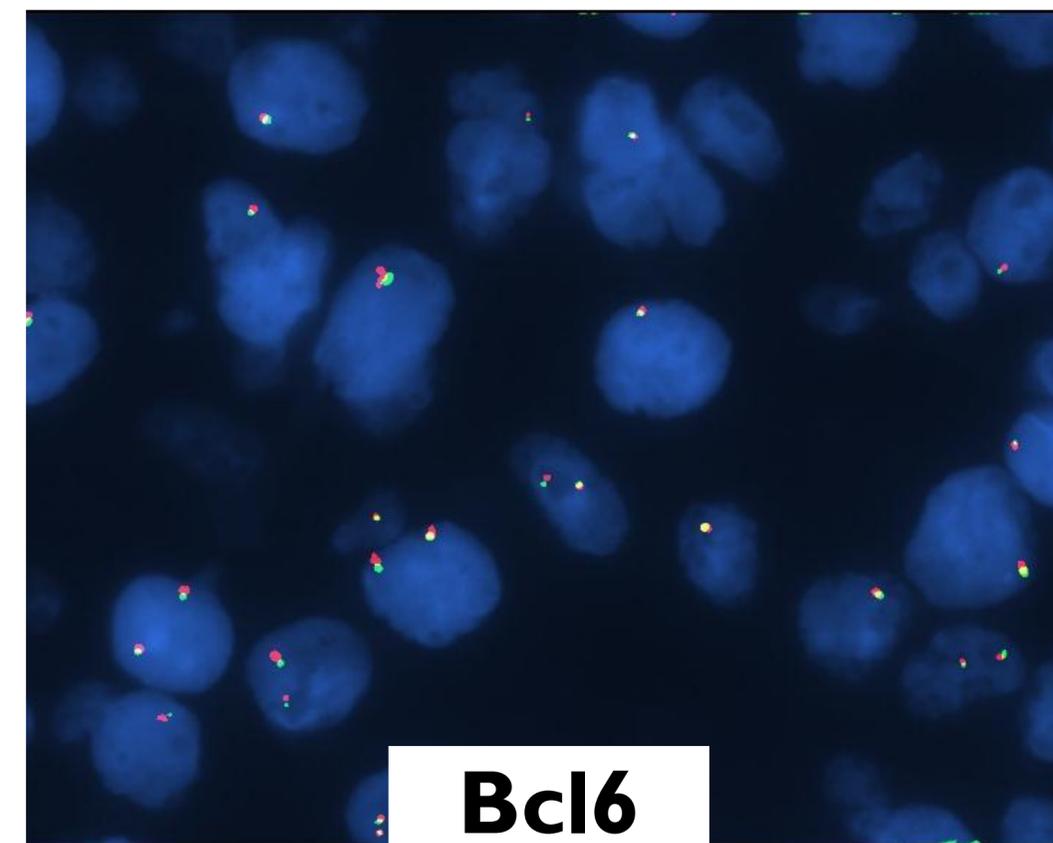
Analisi genica mediante tecnica FISH

Positiva in microfoci complessivamente
<<5% della complessiva popolazione
neoplastica.

NEGATIVA

**Bcl2**

NEGATIVA

**cMyc****Bcl6****DIAGNOSI FINALE**

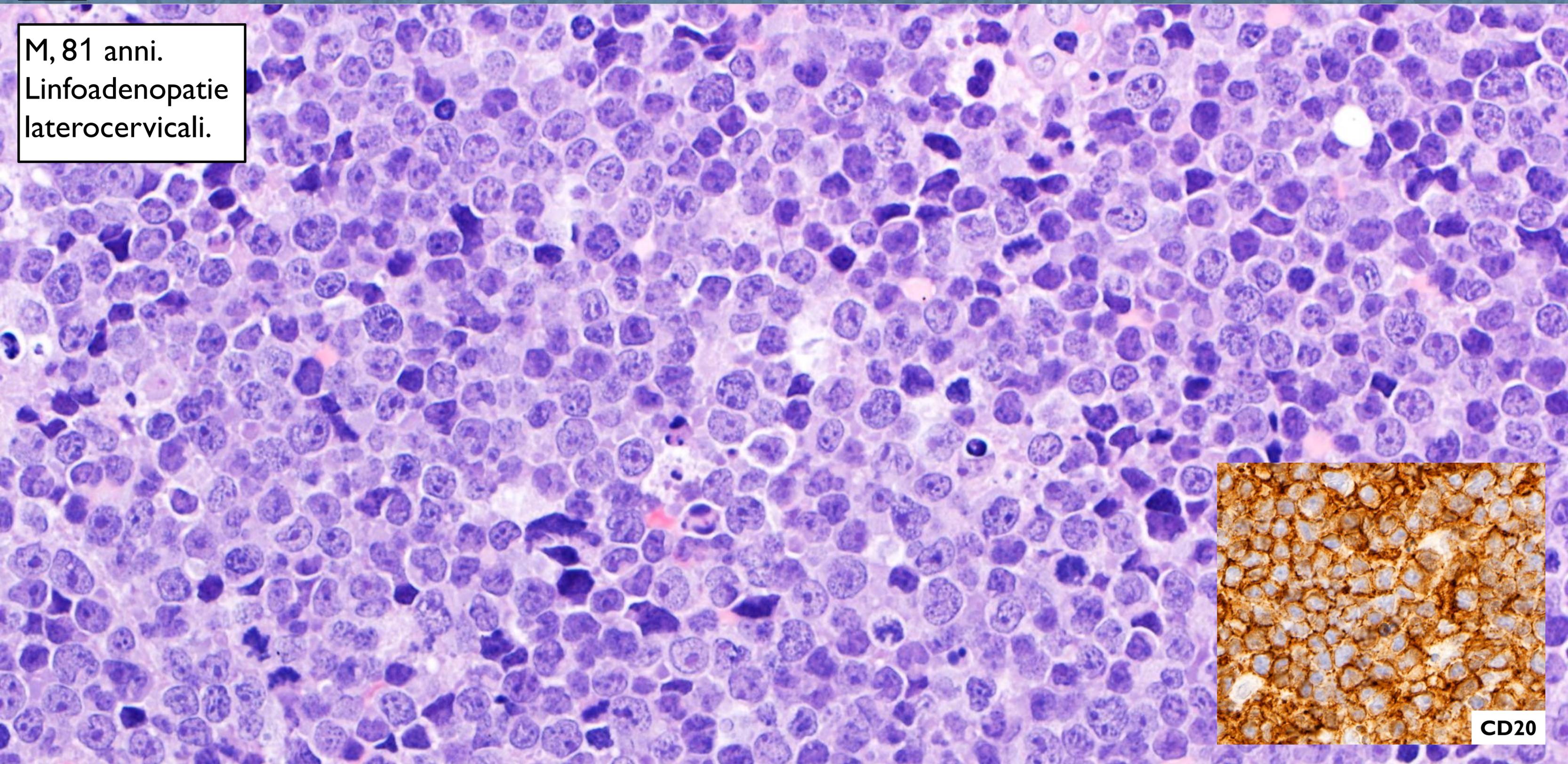
Linfoma non Hodgkin B, di alto grado, non altrimenti specificabile.

#3

The young side of LYMPHOMA

gli under 40 a confronto

M, 81 anni.
Linfoadenopatie
laterocervicali.

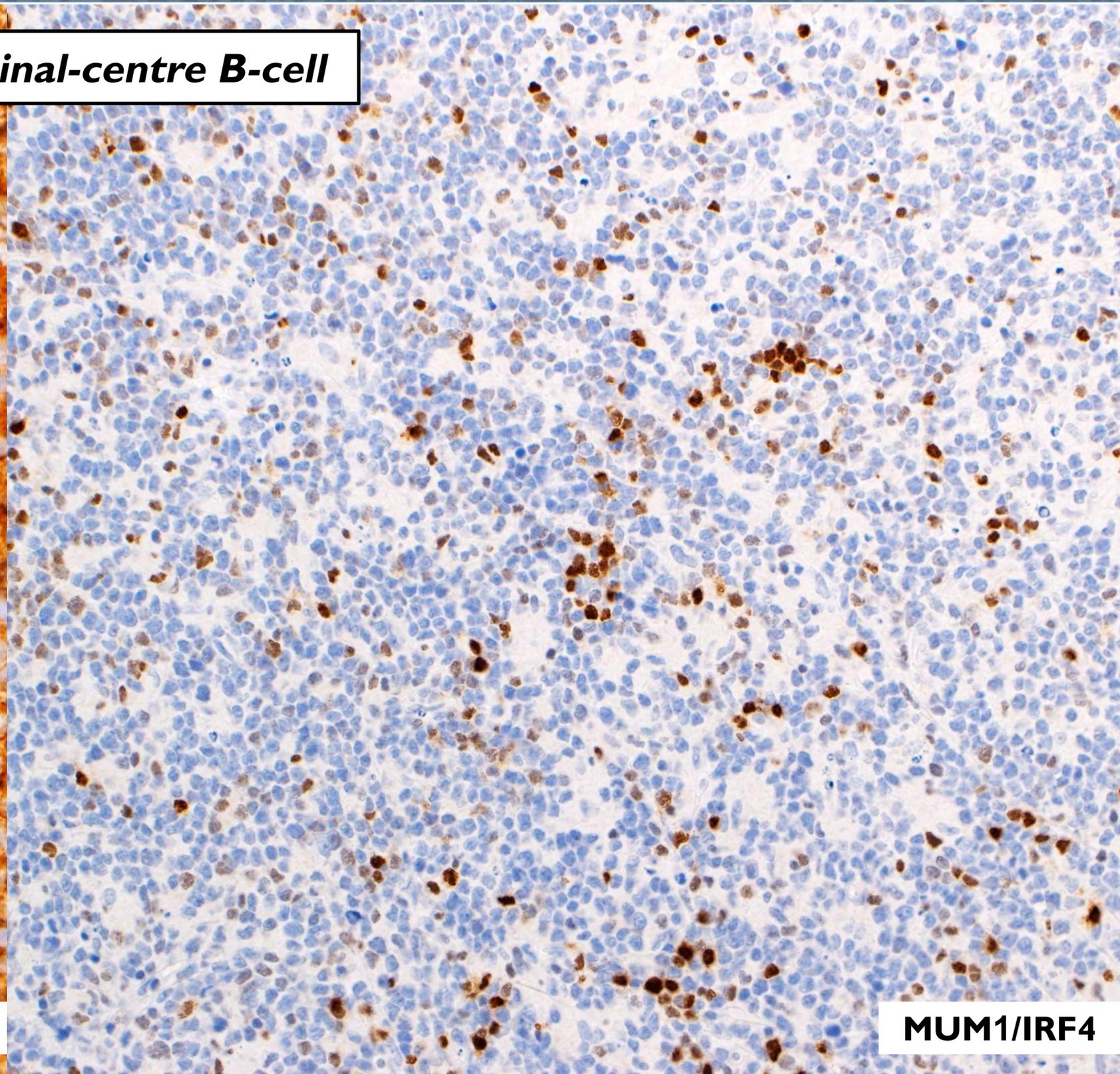


CD20

Sottotipo *germinal-centre B-cell*

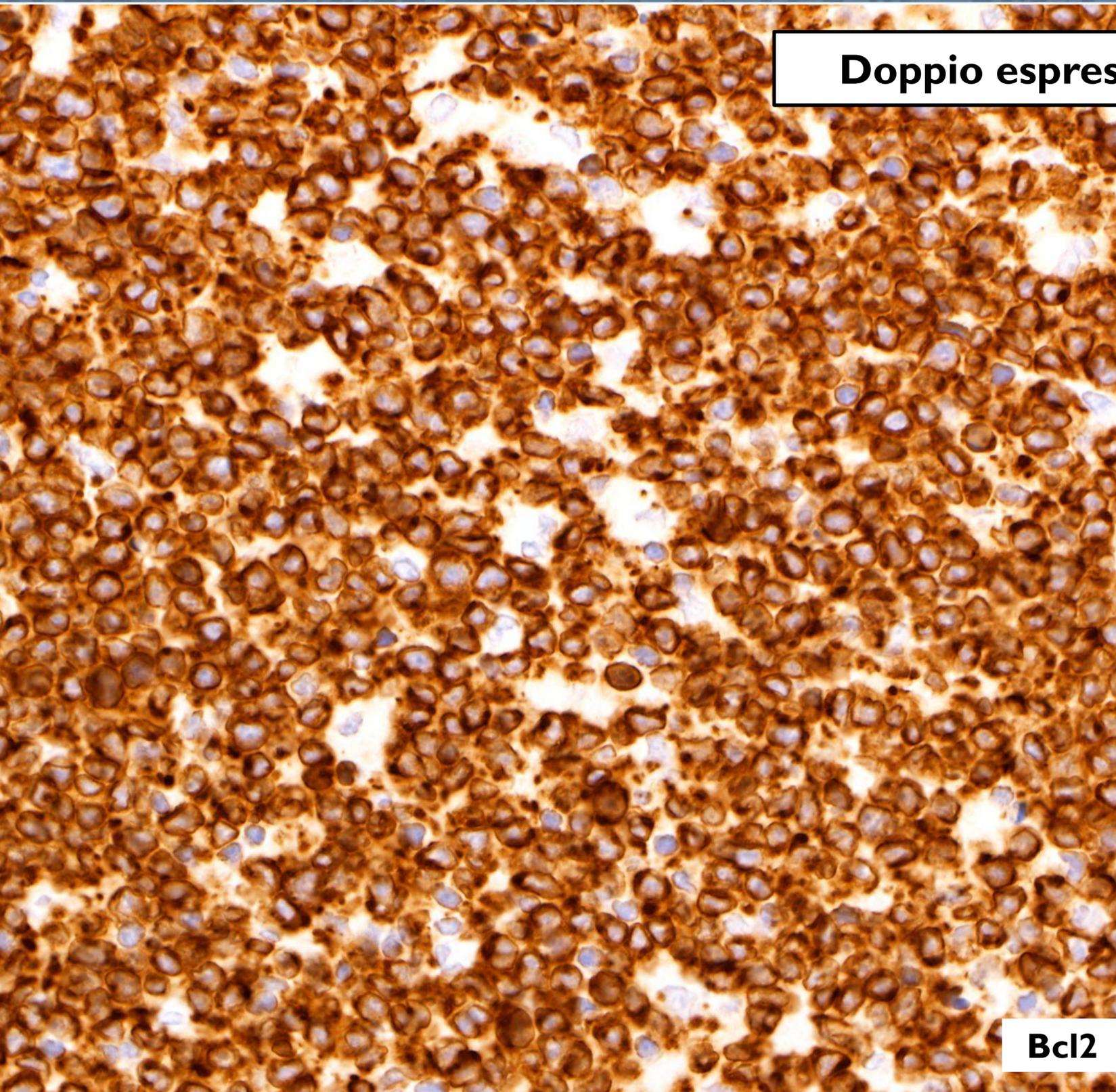


CD10

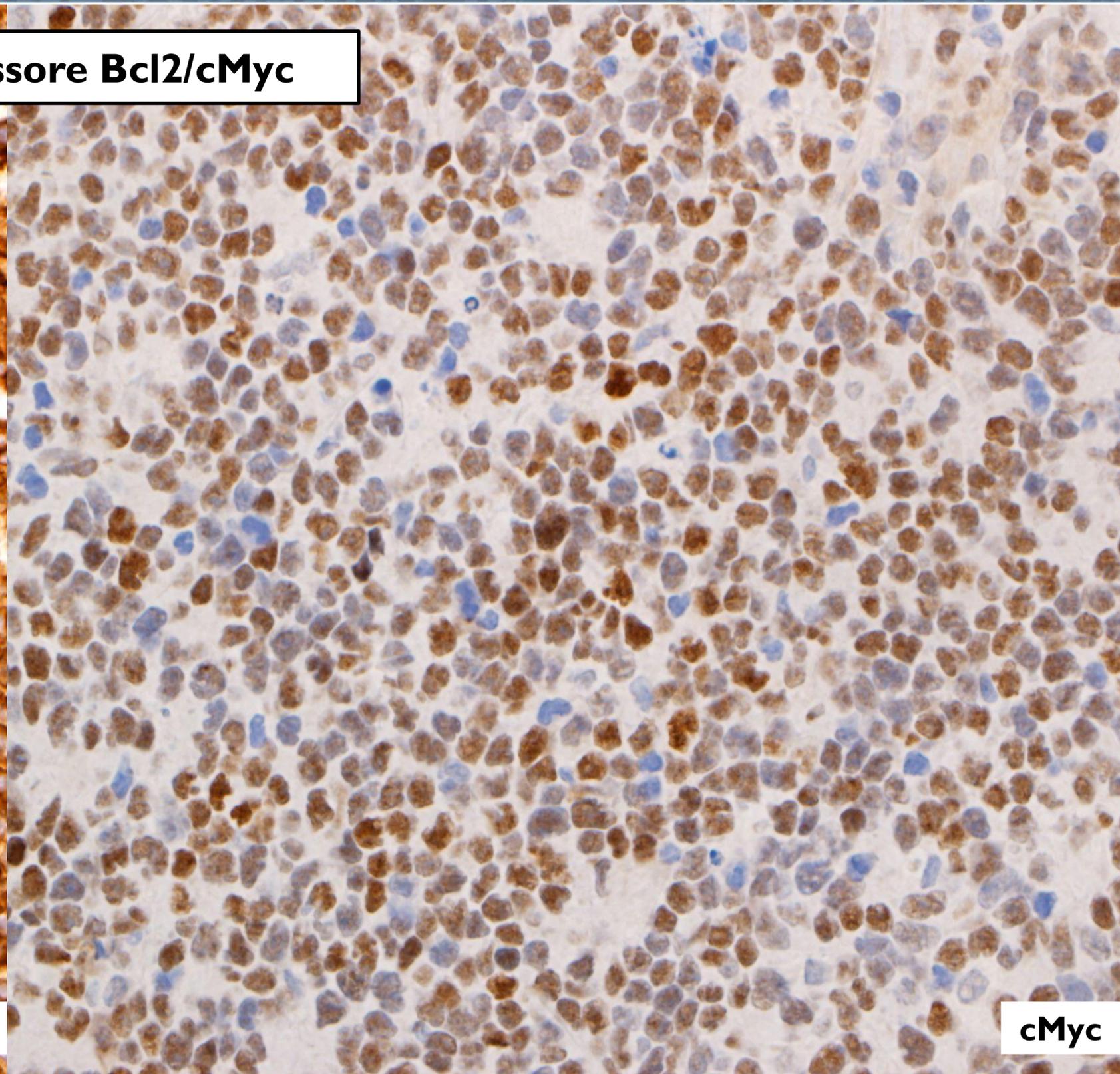


MUM1/IRF4

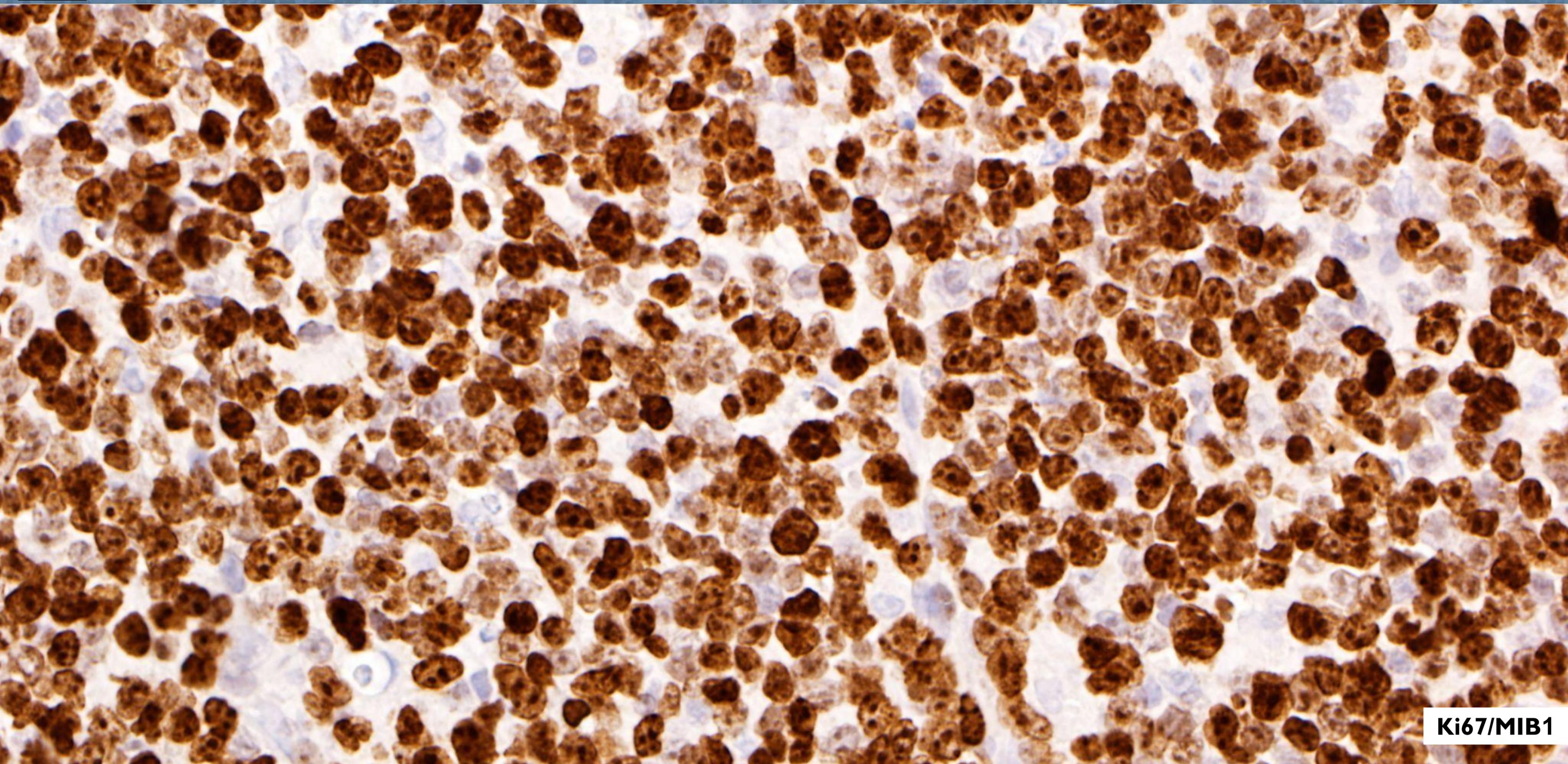
Doppio espressore Bcl2/cMyc



Bcl2



cMyc

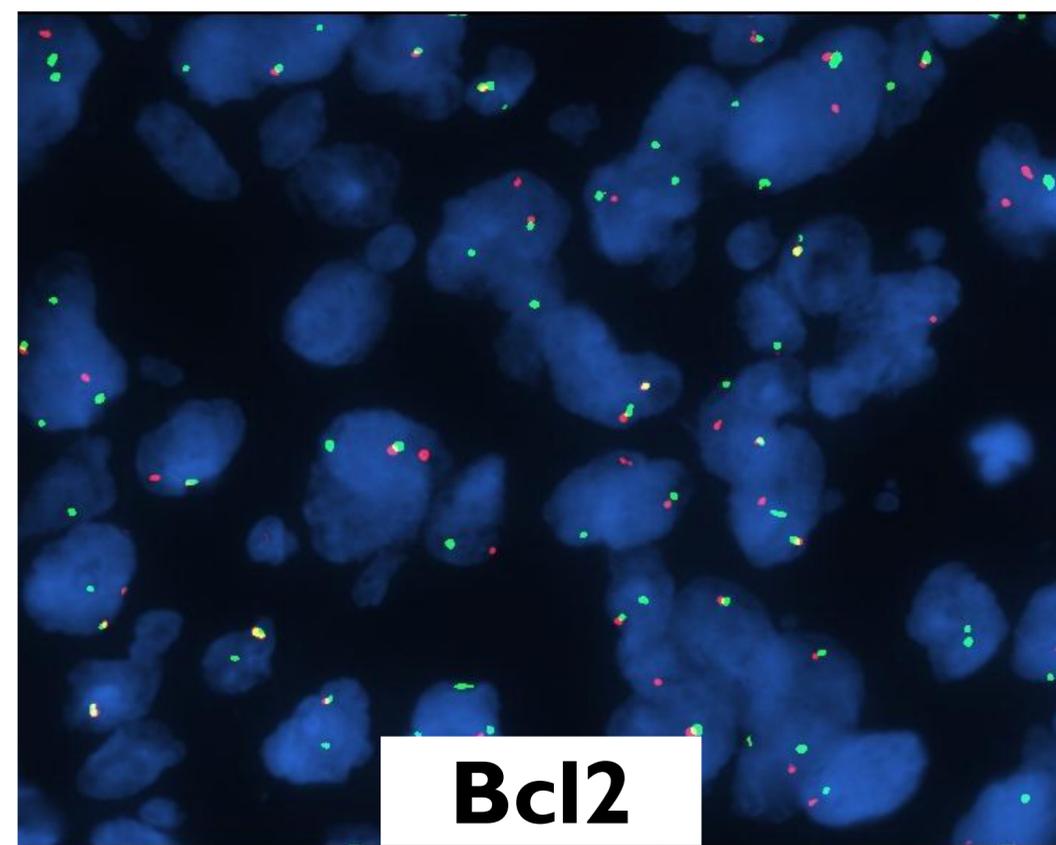
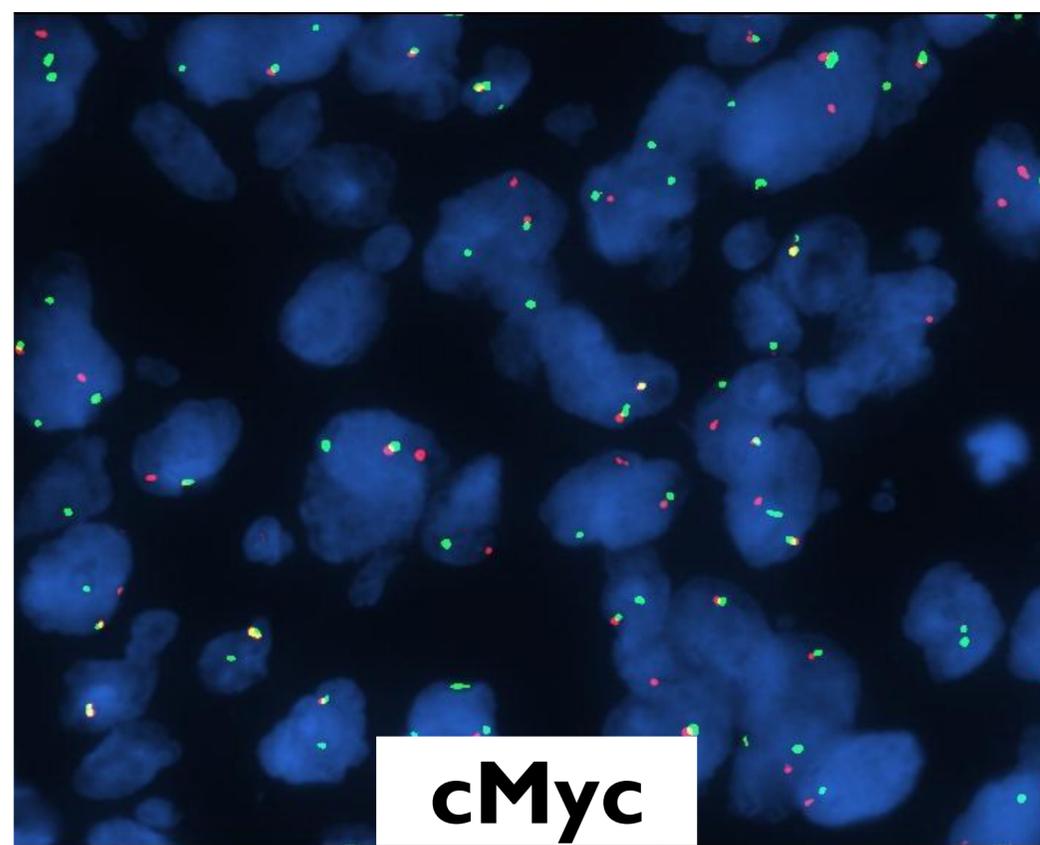
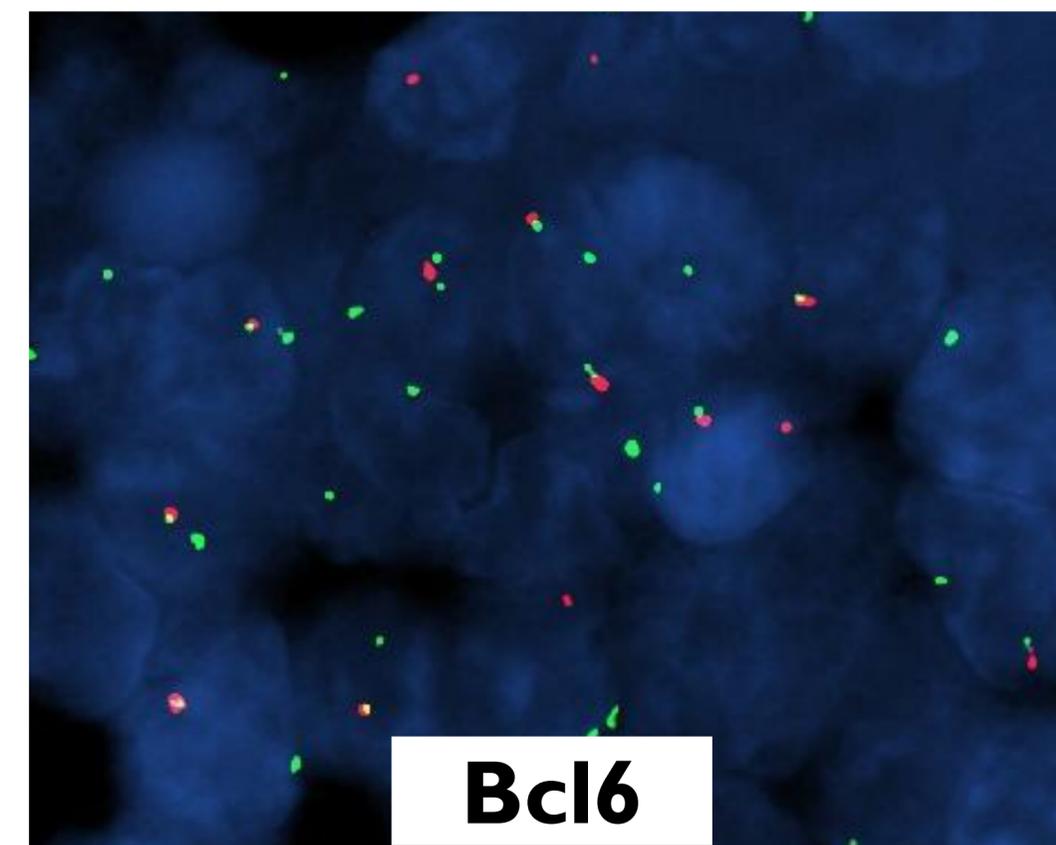


Ki67/MIB1

DIAGNOSI PRELIMINARE

Linfoma non Hodgkin B, di alto grado NOS, doppio espressore Bcl2/cMYC.

Nota: è in corso l'analisi del riarrangiamento dei geni cMYC, BCL2 e BCL6 tramite tecnica FISH, al fine di poter definire con maggiore esattezza la natura di questo linfoma "ad alto grado".

Analisi genica mediante tecnica FISH**POSITIVA****POSITIVA****POSITIVA**

DIAGNOSI FINALE**Linfoma non Hodgkin B, di alto grado, "triplo-hit" (WHO 2017)****Linfoma diffuso a grandi cellule
B/linfoma di alto grado, con
riarrangiamento di cMYC e BCL2
(WHO 2022)****Linfoma B di alto grado, con
riarrangiamento di MYC e BCL2
(con riarrangiamento di BCL6)
(ICC 2022)**

ALGORITMO DIAGNOSTICO

MORFOLOGIA

**TAGLIA
CELLULARE**
Piccola? Media?
Grande?

MORFOLOGIA
Centroblasti?
Immunoblasti?
Blastoide?

IMMUNOFENOTIPO

MARCATORI DI ORIGINE
CD3 CD5 CD20
INDICE PROLIFERATIVO
Ki67/MIB1

ALGORITMO DI HANS
CD10 Bcl6 MUM1/IRF4
DOPPIO ESPRESSORE?
cMyc Bcl2
INFEZIONI
EBV/EBER

EVENTUALI
Altri marcatori B
Ciclina D1 SOX11
TdT
ORF73/HHV8

ANALISI GENICA FISH: MYC, BCL2, BCL6

CHI ESEGUE LA RICHIESTA?

OGNI CASO È A SÉ PER PROBLEMATICHE AMMINISTRATIVE

L'esperienza di ASST Spedali Civili di Brescia (ospedale SSN)

- Paziente ricoverato: richiesta dal patologo a completamento diagnostico e spesa caricata sul ricovero.
- In generale, se la FISH serve a completamento diagnostico la può richiedere il Patologo, meglio se il paziente ha già l'esenzione.
- Se il paziente ha eseguito escissione del linfonodo come ambulatoriale (MAC) e non ha ancora l'esenzione: la FISH viene prescritta dall'Ematologo quando il referto istologico è firmato e l'esenzione è fatta.
Nel frattempo si potrebbe andare avanti con la procedura (taglio sezioni) consapevoli che arriverà richiesta (accordo tra clinico e patologo).
- Paziente anziano o con comorbidità e la terapia potrebbe non cambia in base alla FISH: prestazione non necessaria.
- **In generale, dal momento che ora la FISH serve per fare DD tra DLBCL e HGBCL-DH-TH, lo scopo è diagnostico e il patologo è autorizzato a richiedere la FISH; dal momento che la spesa è significativa (rimborso Regione Lombardia 2024: 300 euro/test) l'accordo tra clinico e patologo diventa cruciale per evitare spese SSN inutili.**