XXV Congreso de la SEAP-SEC-SEPAF, Zaragoza, Mayo 2011

# Linfomas B Maduros Agresivos, panel diagnóstico básico y diagnostico diferencial de entidades intermedias.

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Rticc Red Temática de Investigación Cooperativa en Cáncer

FUNDACIÓN aecc INVESTIGACIÓN CONTRA EL CÁNCER

# Linfoma de Burkitt.

## DIAGNÓSTICO

**ESENCIAL*:**

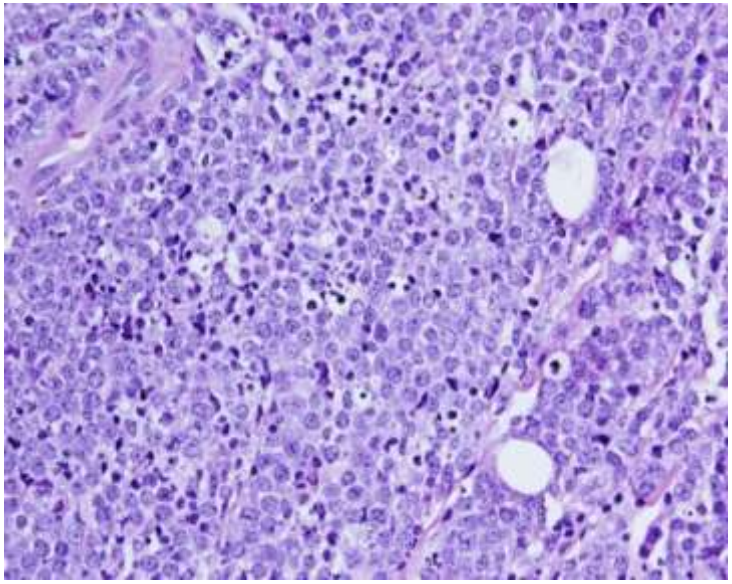
- Revisión hematopatológica de las preparaciones con al menos un bloque de parafina representativo de la lesión. Rebiopsia si el material no es diagnóstico.
- PAAF o biopsias con aguja fina de forma aislada no son suficientes para el diagnóstico inicial de linfoma. En ocasiones si la lesión no es accesible a la biopsia incisional o excisional la combinación de PAAF y biopsia con aguja fina junto con técnicas suplementarias (IHQ, citometría de flujo, PCR para reordenamientos de IgH y/o TCR y FISH para los reordenamientos principales puede ser suficiente).
- Estudio fenotípico adecuado:
- FFPE: CD45 (ALC), CD20, CD3, CD10, Ki-67, BCL2, BCL6, TdT.
- CF: CD45, CD20, CD3, CD5, CD19, CD10, TdT, K/L.
- Citogenética o FISH: C-MYC, BCL2, BCL6.

**ÜTILES EN DETERMINADAS CIRCUNSTANCIAS:**

- ISH para EBV-EBER.
- Molecular para detectar reordenamientos de IgH.

**Adaptado de NCCN Guidelines Version 1.2011*

# Linfoma de Burkitt.



- **BL:** morfología típica de LB con fenotipo **LB (CD10pos, bcl6pos, bcl2neg, TdTneg, Ki67 100%)** + reordenamientos de C-MYC (8-15% neg). Correlación clínico-patológica.
- Bcl2 puede ser positivo en casos que por el resto de criterios morfológicos y fenotípicos se clasificarían como LB. Si la expresión de BCL2 es intensa es preciso buscar traslocaciones de BCL2 (LB con rasgos intermedios entre LB y LBDCG, “”double hit”).

  El fenotipo de LB expandido incluye TCL1pos, CD44neg, C-MYCn pos y VPREB-3 pos). Estos, junto con CD10pos y Ki67 100% son marcadores de traslocación de C-MYC aunque no sustituyen la necesidad de testar CMYC por FISH/cariotipo.

# Linfoma del manto

## DIAGNÓSTICO

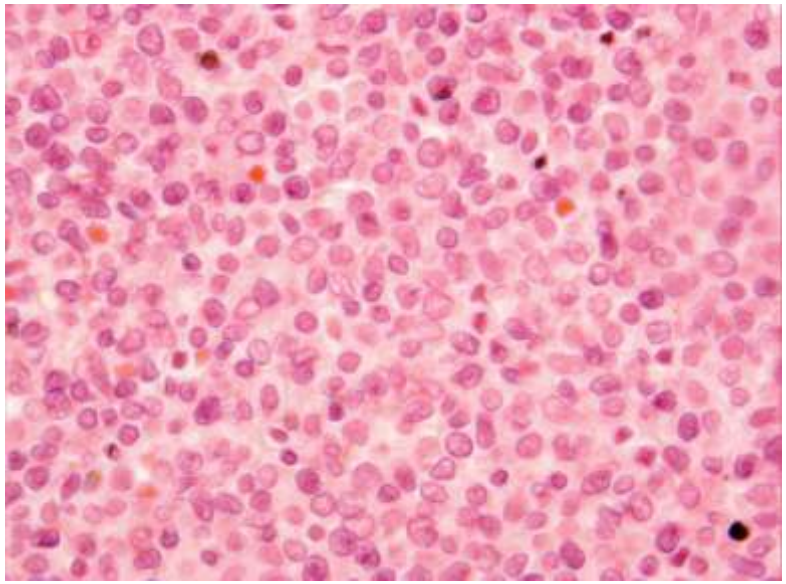
**ESENCIAL:**

- Revisión hematopatológica de las preparaciones con al menos un bloque de parafina representativo de la lesión. Rebiopsia si el material no es diagnóstico.
- PAAF o biopsias con aguja fina de forma aislada no son suficientes para el diagnóstico inicial de linfoma. En ocasiones si la lesión no es accesible a la biopsia incisional o excisional la combinación de PAAF y biopsia con aguja fina junto con técnicas suplementarias (IHQ, citometría de flujo, PCR para reordenamientos de IgH y/o TCR y FISH para los reordenamientos principales puede ser suficiente).
- Estudio fenotípico adecuado:
- FFPE: CD20, CD3, CD5, ciclinaD1, CD23, CD10, Ki-67, BCL2, BCL6.
- CF: CD20, CD3, CD5, CD19, CD23, CD10, K/L.

**ÜTILES EN DETERMINADAS CIRCUNSTANCIAS:**

- Citogenética o FISH (reordenamientos de CiclinaD1, BCL2, panel CLL).
- Molecular para detectar reordenamientos de IgH/BCL1.

# Linfoma del manto



- **MCL:** morfología típica de MCL con fenotipo MCL (CD20pos, CD5pos, ciclinaD1pos, CD43pos, CD23neg/$_{pos}$, CD10neg/$_{pos}$).
- SOX11 puede ser de utilidad en casos ciclinaD1 negativos (convencionales y blastoides; MCL indolente: SOX11 negativo/parcialmente positivo).
- Morfología pleomorfa y débil/heterogénea expresión de ciclinaD1 sugiere DLBCL. FISH para ciclinaD1 (ausencia de reordenamientos de ciclinaD1 en DLBCL).

# Linfoma B Difuso de Células Grandes

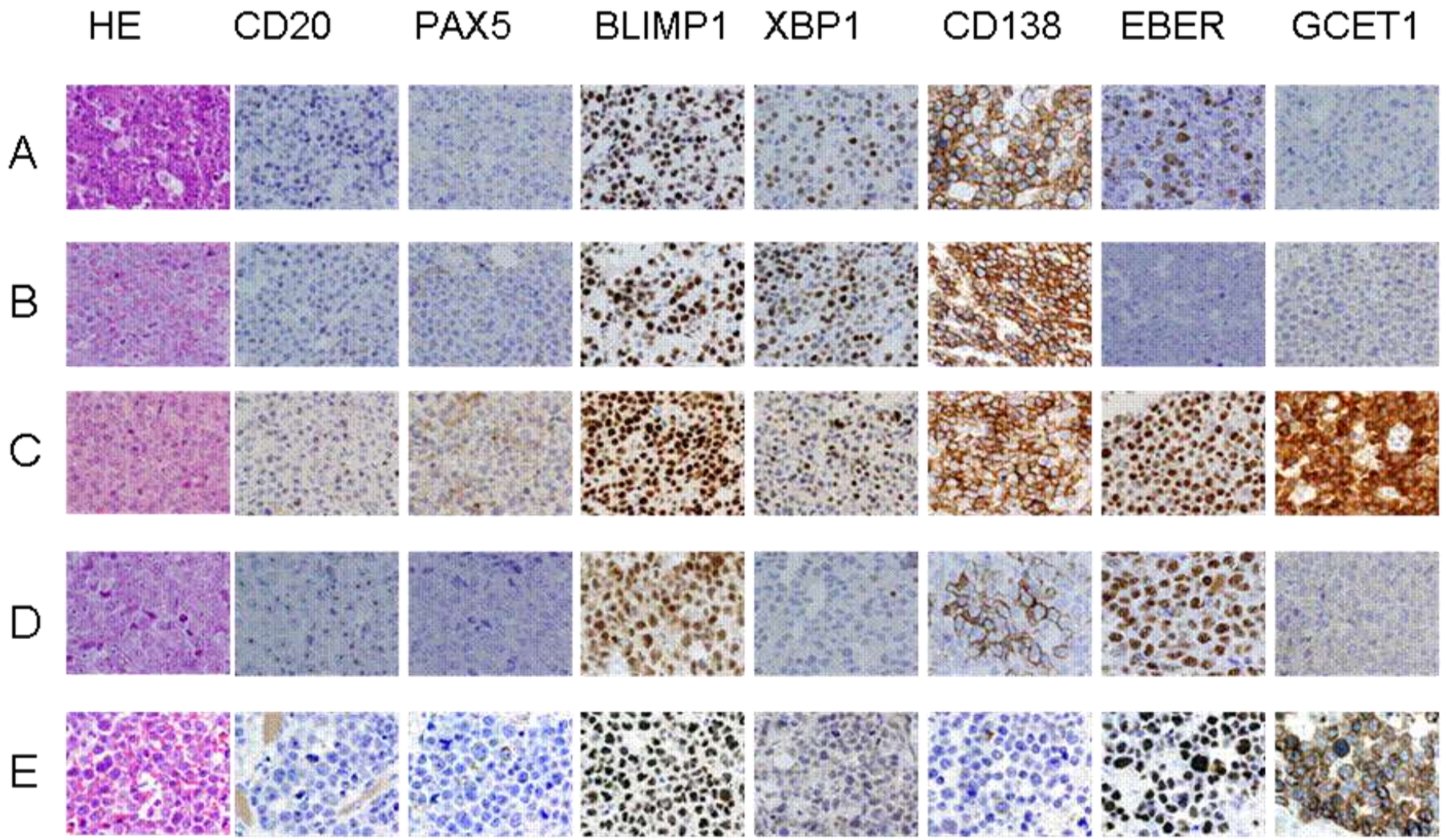
## DIAGNÓSTICO

**ESENCIAL:**

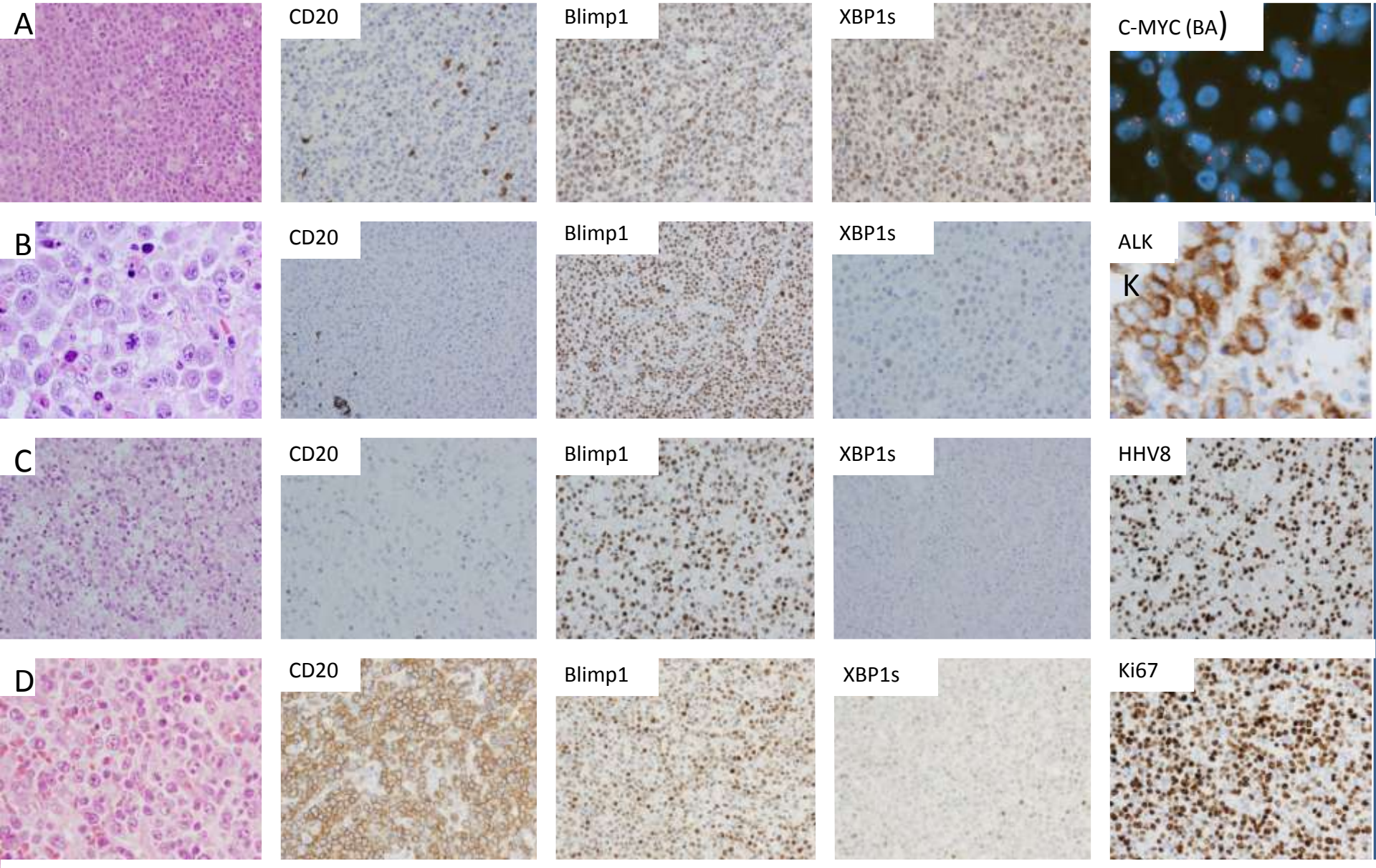
- Revisión hematopatológica de las preparaciones con al menos un bloque de parafina representativo de la lesión. Rebiopsia si el material no es diagnóstico.
- PAAF o biopsias con aguja fina de forma aislada no son suficientes para el diagnóstico inicial de linfoma. En ocasiones si la lesión no es accesible a la biopsia incisional o excisional la combinación de PAAF y biopsia con aguja fina junto con técnicas suplementarias (IHQ, citometría de flujo, PCR para reordenamientos de IgH y/o TCR y FISH para los reordenamientos principales puede ser suficiente).
- Estudio fenotípico adecuado:
- FFPE: CD45 (ALC), CD20, CD3, CD10, Ki-67, BCL2, BCL6, MUM1.
- CF: CD45, CD20, CD3, CD5, CD19, CD10, K/L.

**ÜTILES EN DETERMINADAS CIRCUNSTANCIAS:**

- Subclasificación por subtipos: EBV-LMP1/ISH para EBV-EBER, ALK, K/L, CD138, Blimp1, XBP1, HHV-8, CD30, CD23, MAL1, TRAF1, c-REL.
- Subclasificación en variantes moleculares (GC-ABC). Marcadores de mal pronóstico:p53.
- Citogenética o FISH: C-MYC, BCL2, BCL6, MALT1.
- Molecular para detectar reordenamientos de IgH, BCL2.

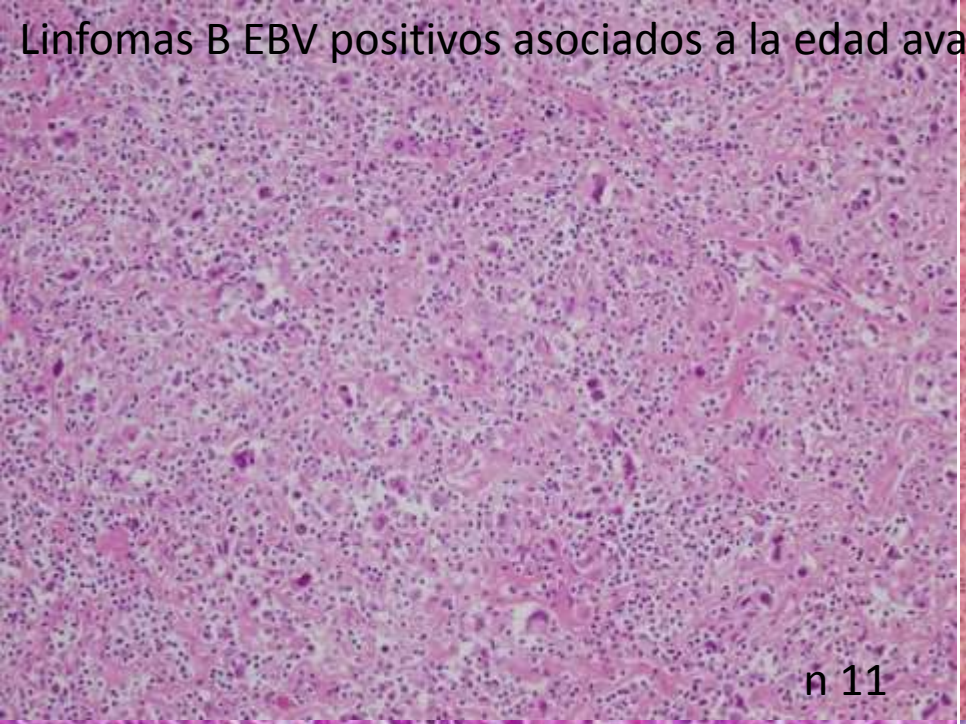


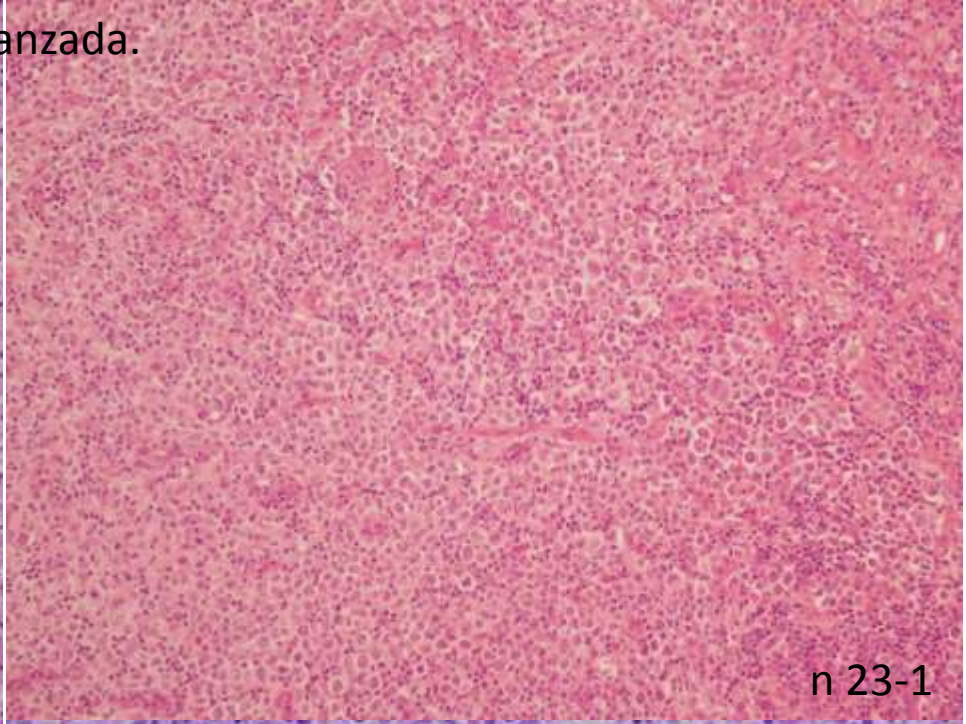

Linfomas Plasmablásticos.

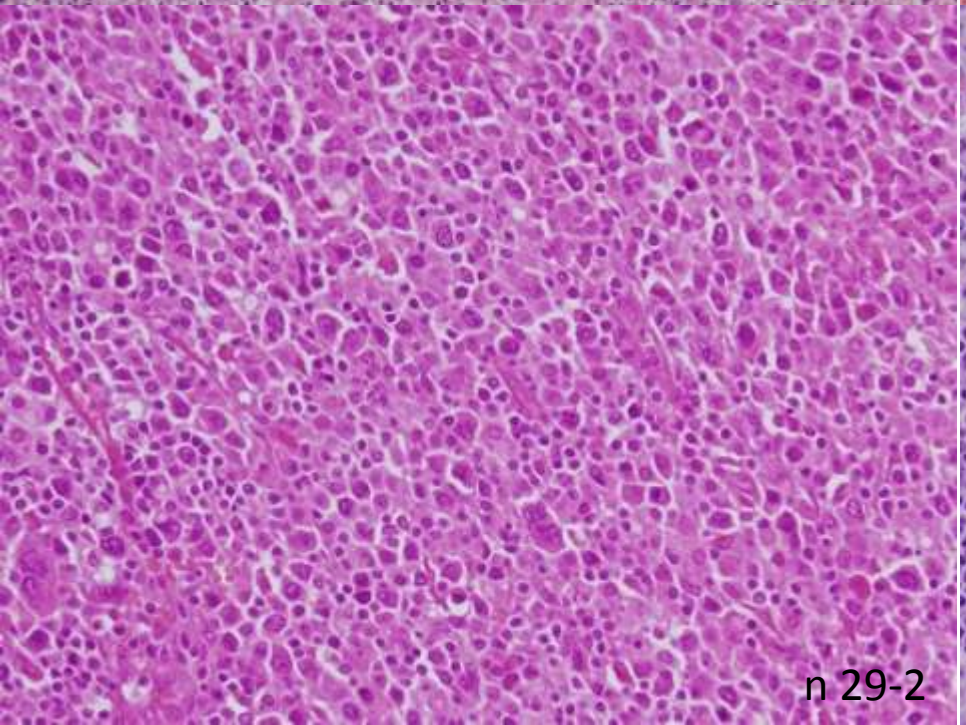


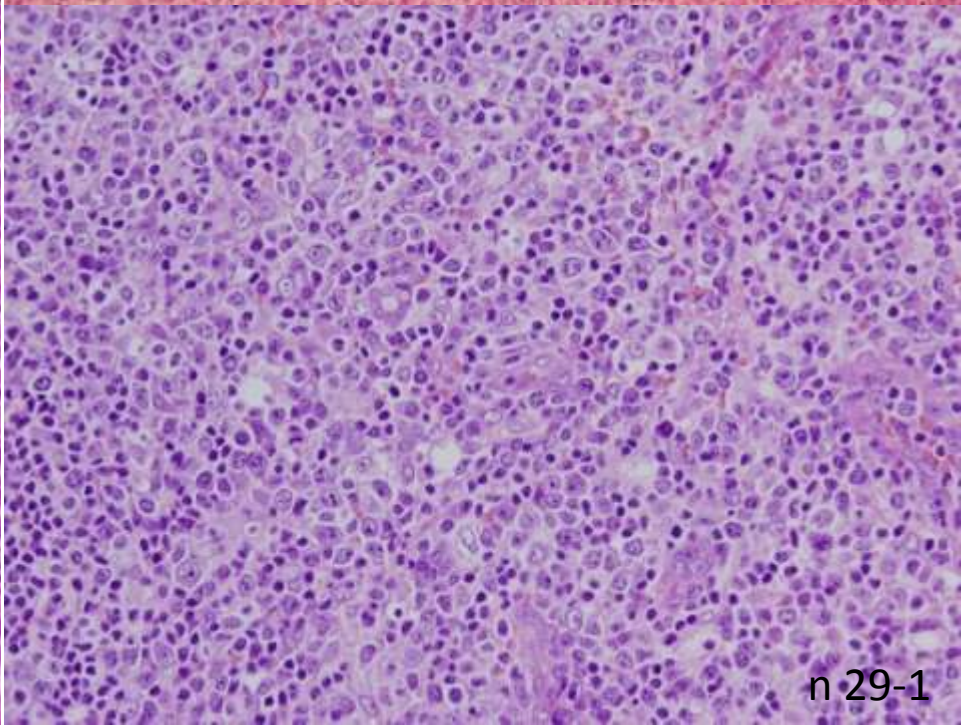

Linfomas de Células Grandes con Diferenciación Plasmablástica.

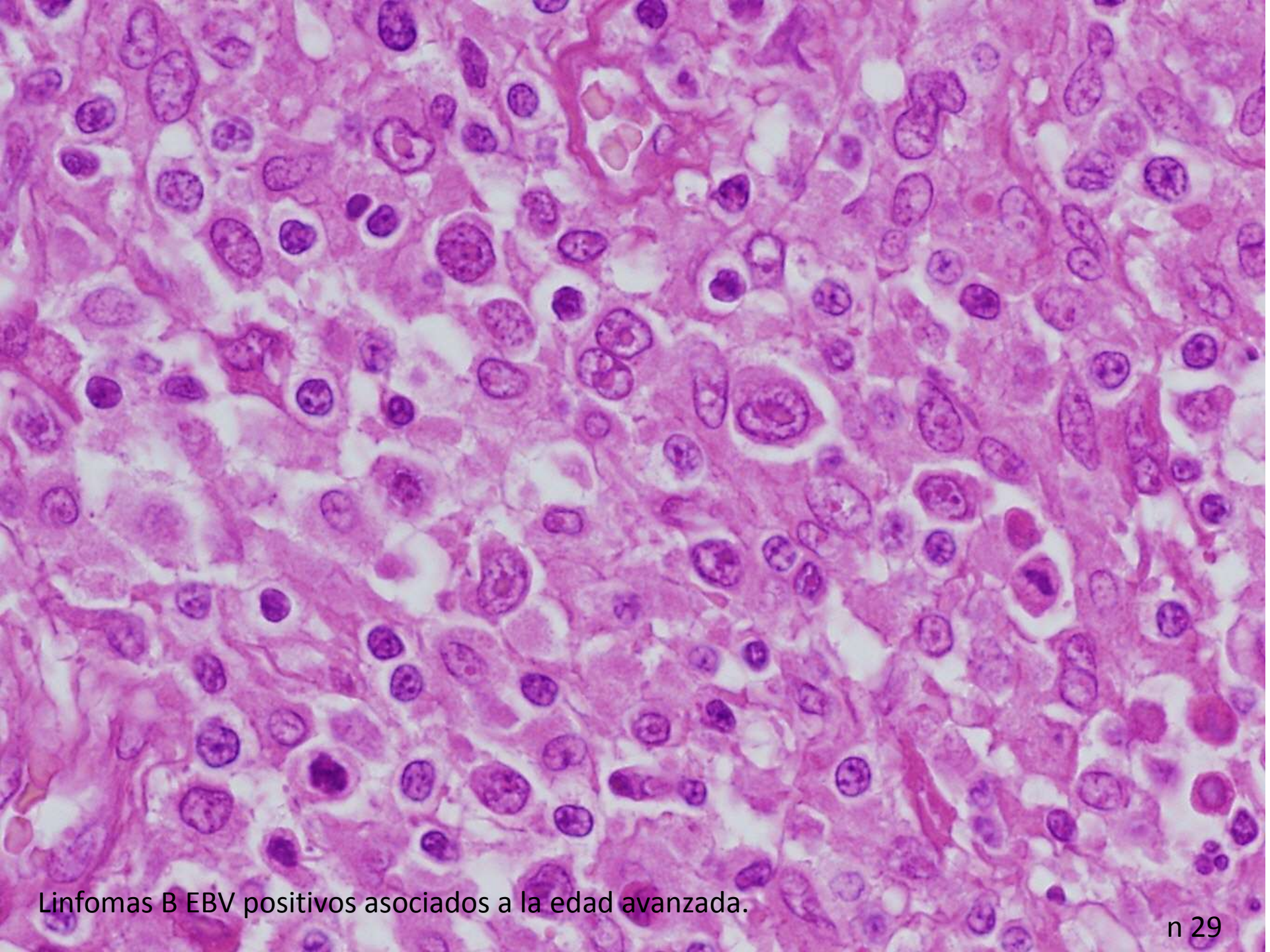
Linfomas B EBV positivos asociados a la edad avanzada.



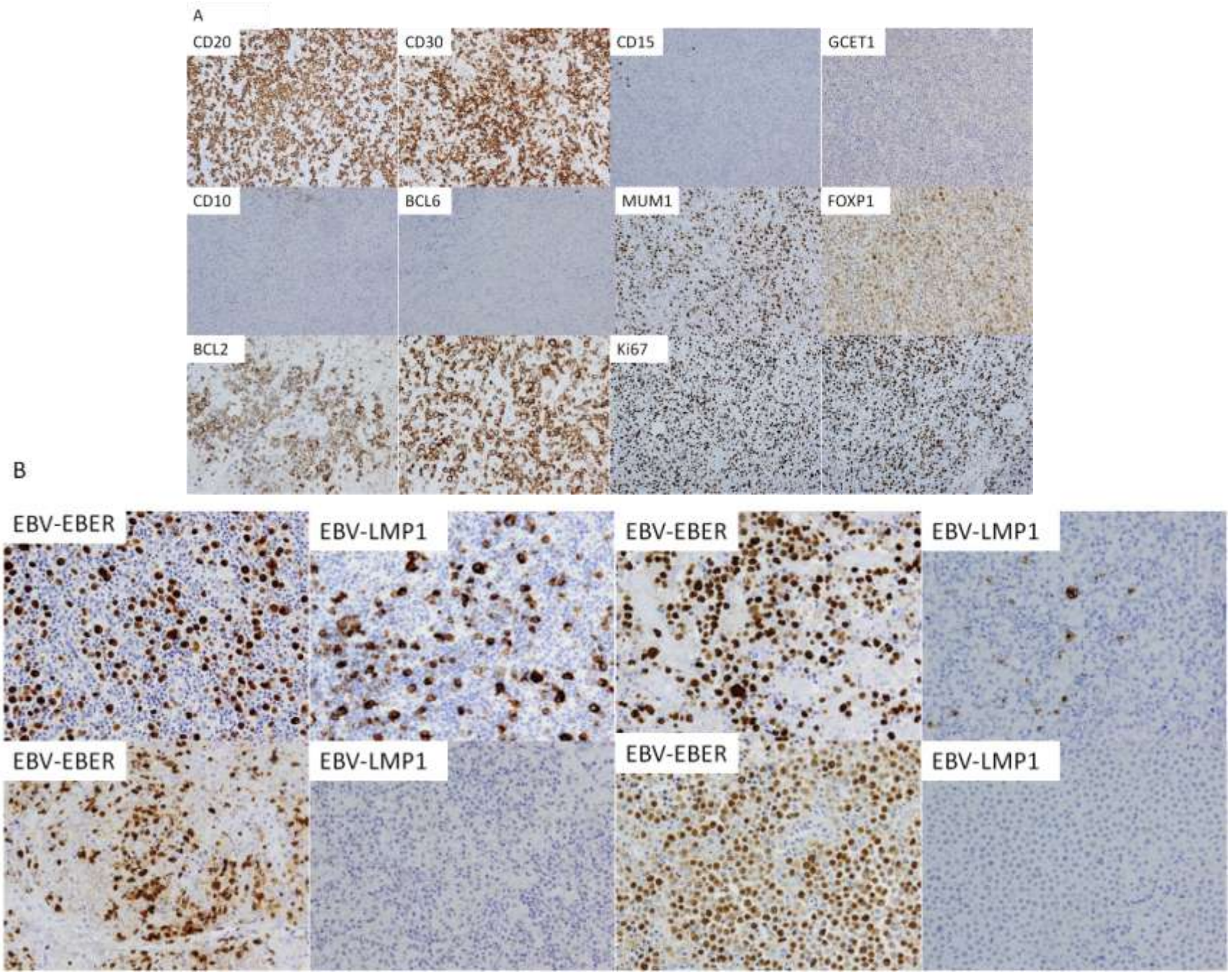



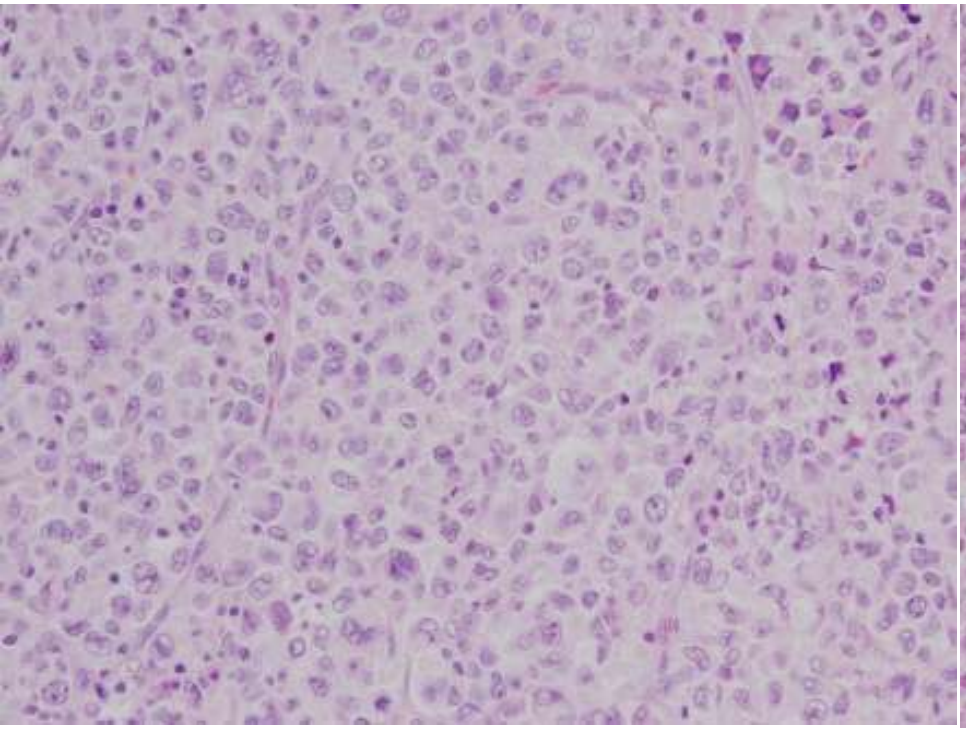
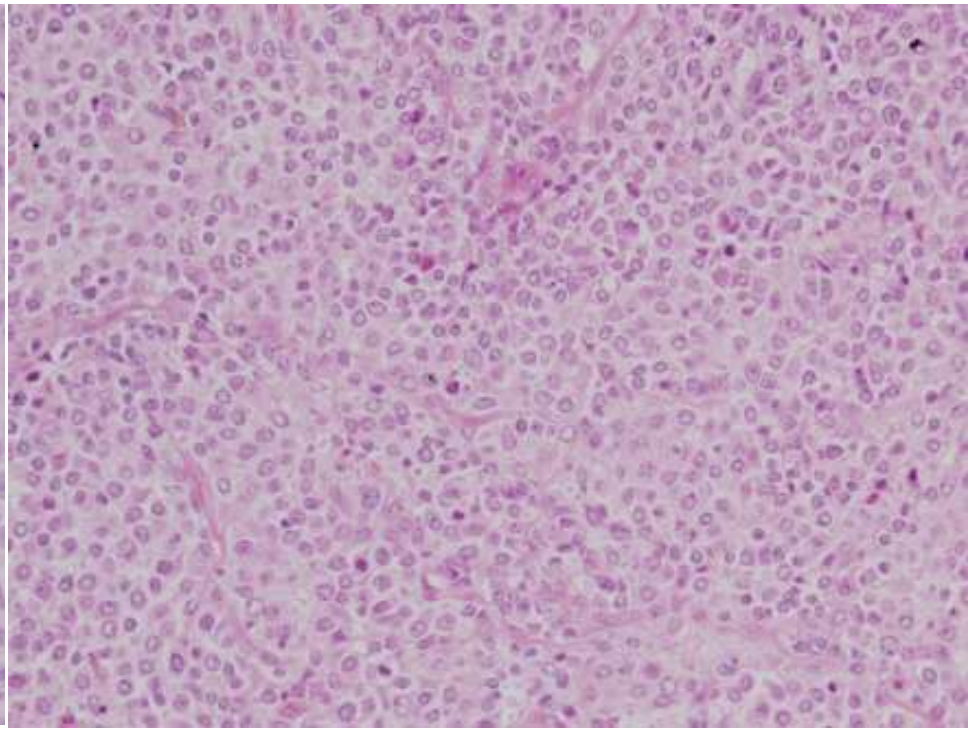



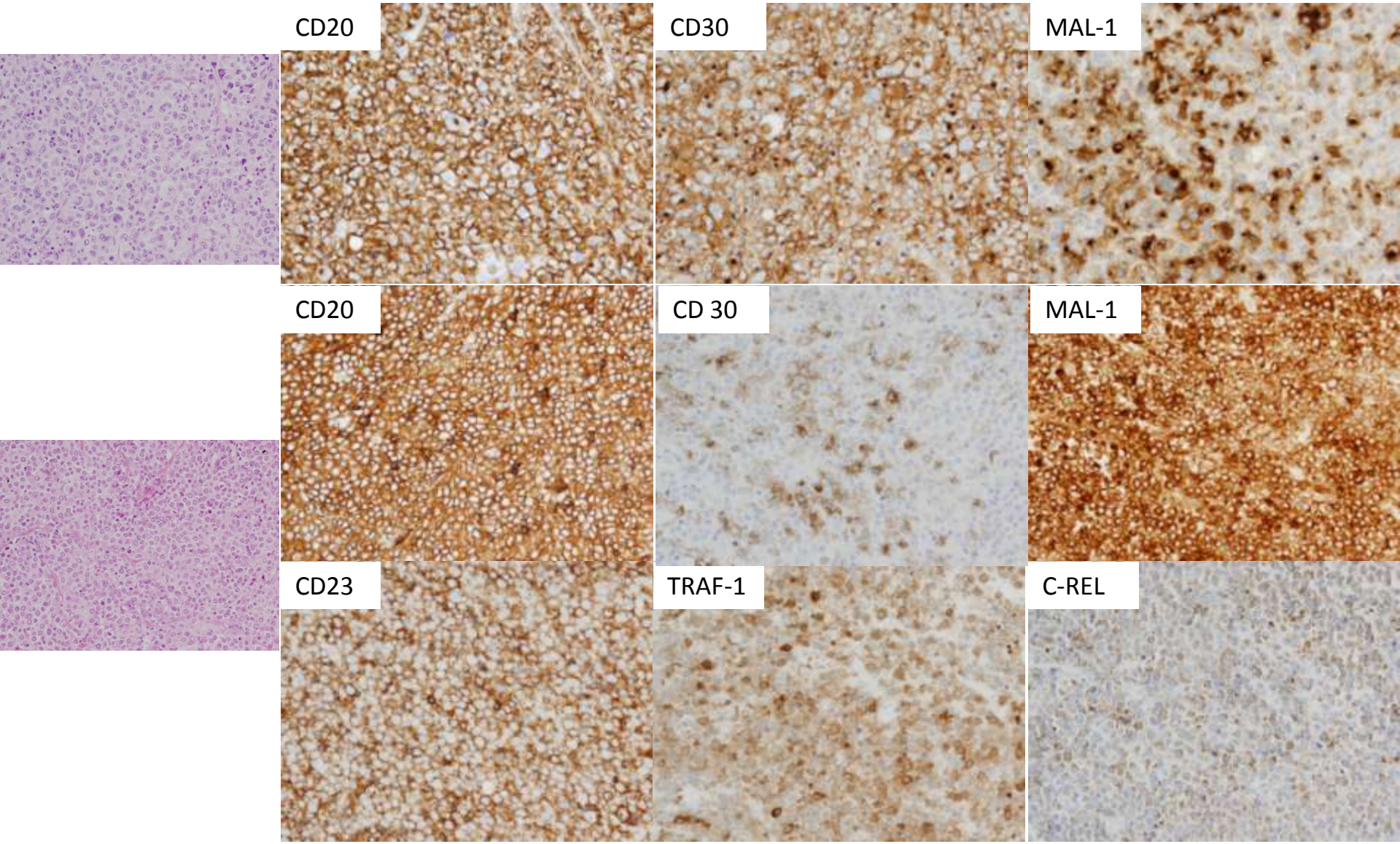


Linfomas B EBV positivos asociados a la edad avanzada.

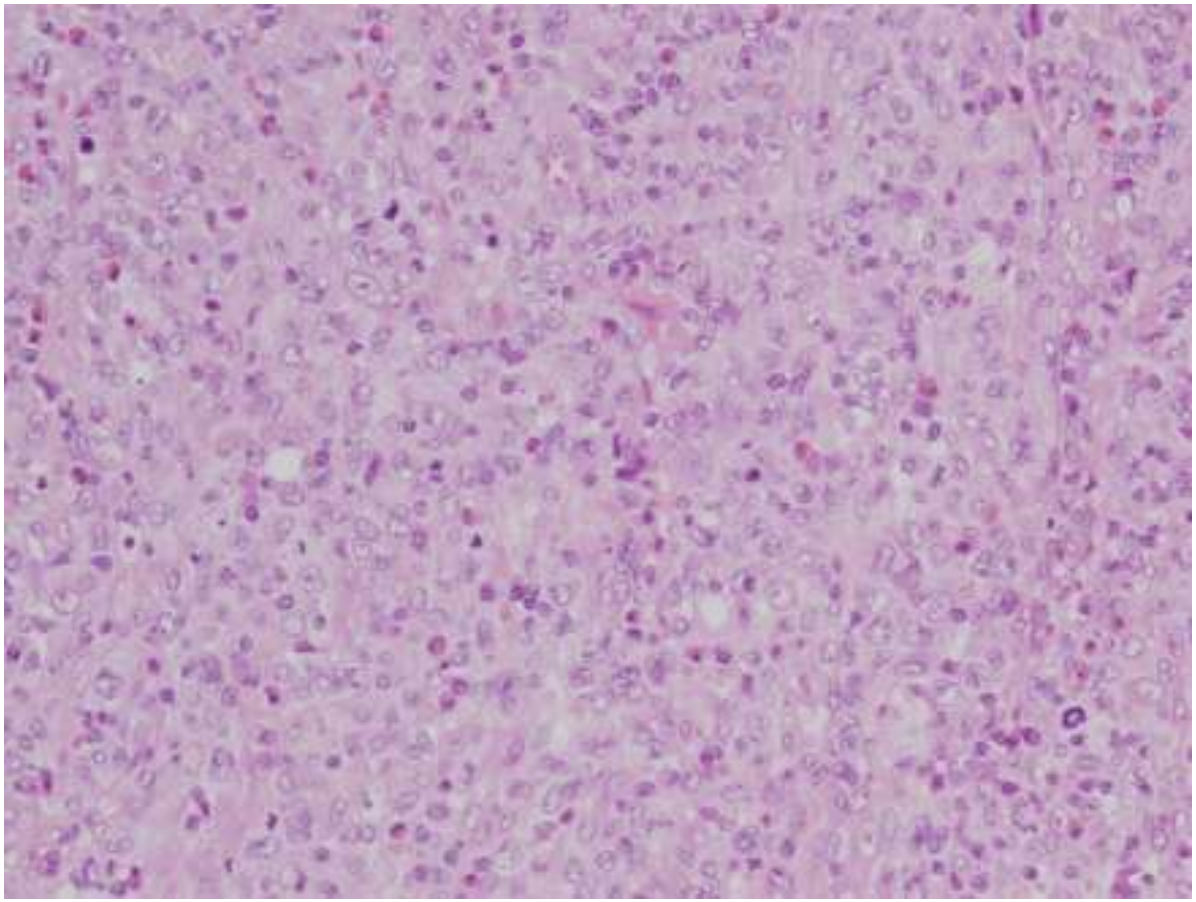


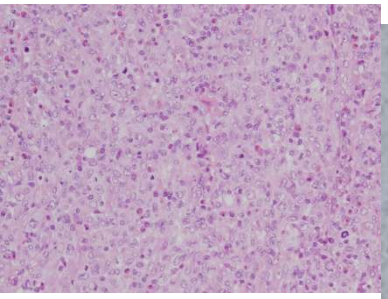

Linfomas B EBV positivos asociados a la edad avanzada.

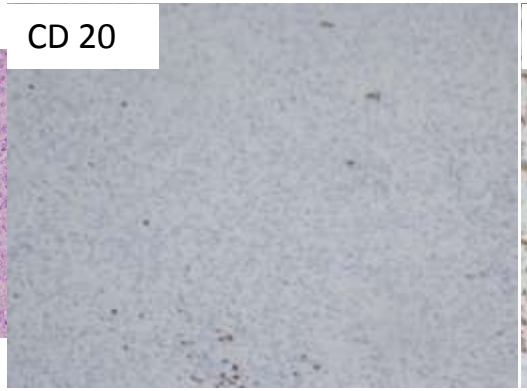



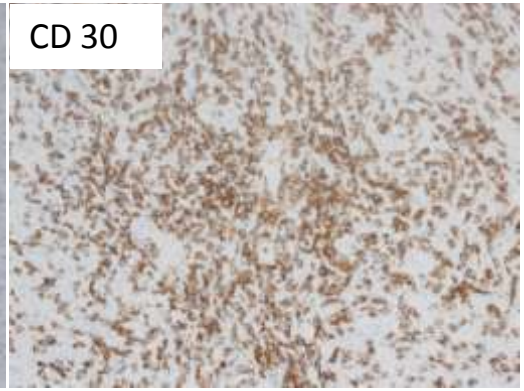


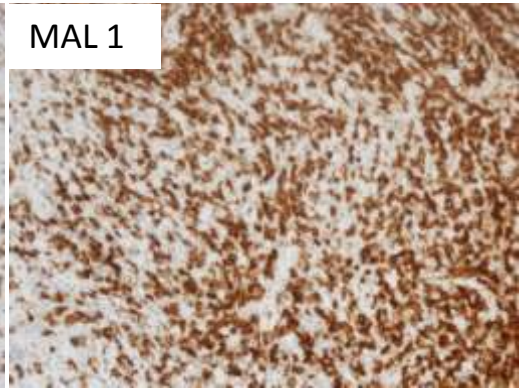

Linfomas B primarios mediastínicos.

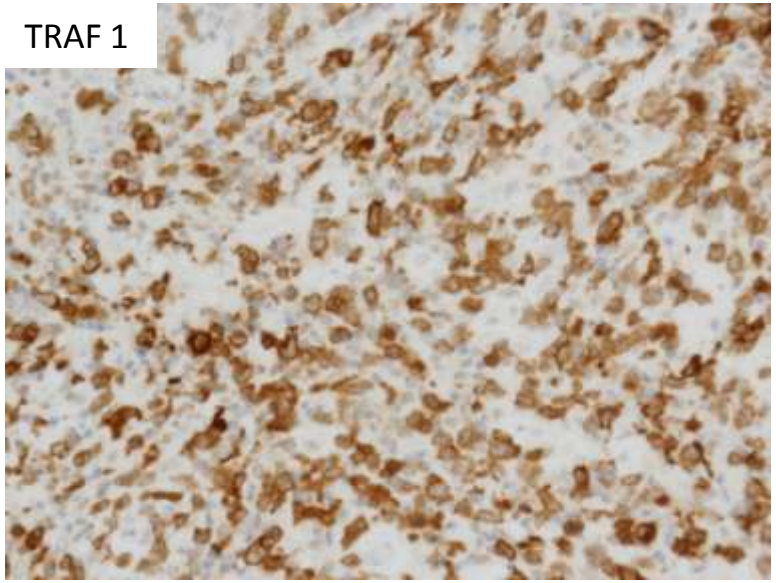


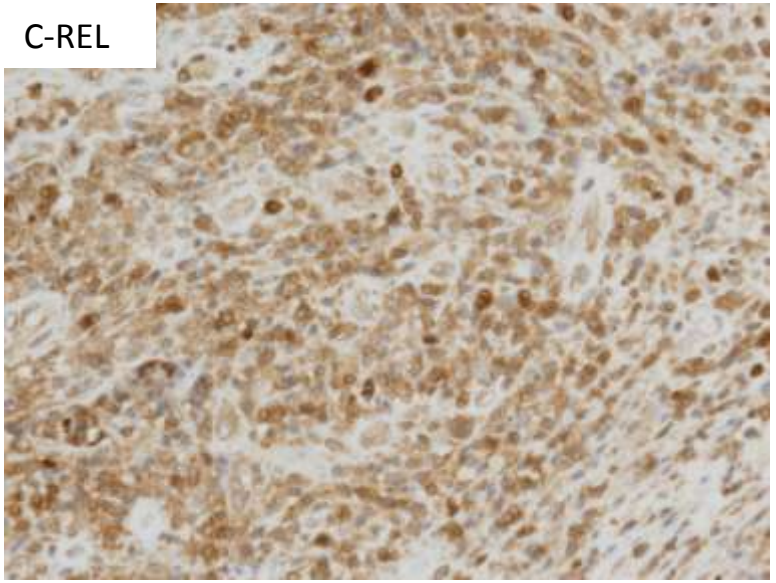





Linfomas B con rasgos intermedios entre LHC y LBCG.

# Expression of TRAF1 and Nuclear c-Rel Distinguishes Primary Mediastinal Large Cell Lymphoma From Other Types of Diffuse Large B-cell Lymphoma

*Scott J. Rodig, MD, PhD,* Kerry J. Savage, MD,† Ann S. LaCasce, MD,‡ Andrew P. Weng, MD, PhD,§ Nancy L. Harris, MD,‖ Margaret A. Shipp, MD,‡ Eric D. Hsi, MD,¶ Randy D. Gascoyne, MD,§ and Jeffery L. Kutok, MD, PhD**

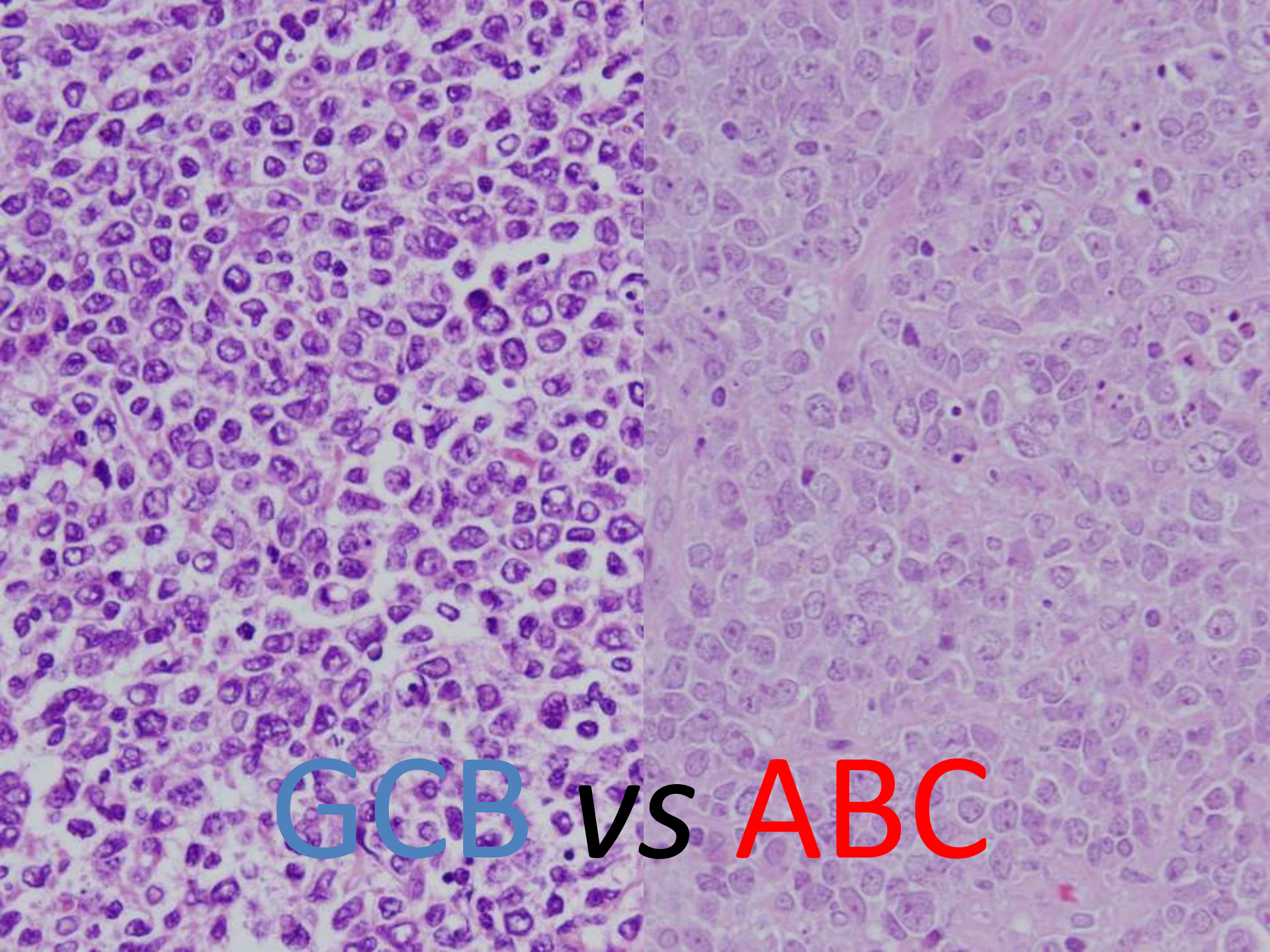
**TABLE 3.** Combined Expression of Nuclear c-Reland TRAF1 in PMLBCL versus Other DLBCLs

| Diagnosis | Total Cases | No. Nuclear c-Rel + and TRAF1 + Cases (%) | No. Nuclear c-Rel − and TRAF1 + Cases (%) | No. Nuclear c-Rel + and TRAF1 − Cases (%) | No. Nuclear c-Rel − and TRAF1 − Cases (%) | Institutional Origin |
|---|---|---|---|---|---|---|
| PMLBCL | 13 | 9 (70) | 2 (15) | 2 (15) | 0 (0) | BWH/BWH |
| DLBCL | 31 | 2 (6) | 0 (0) | 10 (32) | 19 (61) | BWH/MGH |
| PMLBCL | 13 | 6 (46) | 3 (23) | 2 (15) | 2 (15) | BCCA |
| DLBCL | 125 | 1 (0.8) | 13 (10) | 15 (12) | 96 (77) | BCCA |
| PMLBCL | 19 | 9 (47) | 4 (21) | 1 (5) | 5 (26) | CC |
| DLBCL | 0 | N/A | N/A | N/A | N/A | CC |
| PMLBCL total | 45 | 24 (53) | 9 (20) | 5 (11) | 7 (16) | Combined |
| DLBCL total | 156 | 3 (2) | 13 (8) | 25 (16) | 115 (74) | Combined |

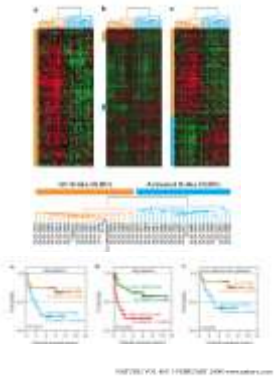
**TABLE 4.** Sensitivity and Specificity of c-Rel and TRAF1 for PMLBCL versus Other DLBCLs

| Antigen (Localization) | Sensitivity (%)* | Specificity (%)* |
|---|---|---|
| c-Rel alone (nuclear) | 65 | 82 |
| TRAF1-positive alone (cytoplasmic) | 62 | 88 |
| c-Rel(nuclear) and TRAF1 positive | 53 | 98 |

*For PMLBCL.


GCB vs ABC

# Los subtipos biologicos de DLBCL tienen un impacto en el pronóstico en pacientes tratados con RCHOP? y pueden tener un valor en la elección de la terapia.



Nuevo contexto clínico: Quimio-Immunoterapia con Rituximab (R-CHOP)

EVIDENCIA A FAVOR

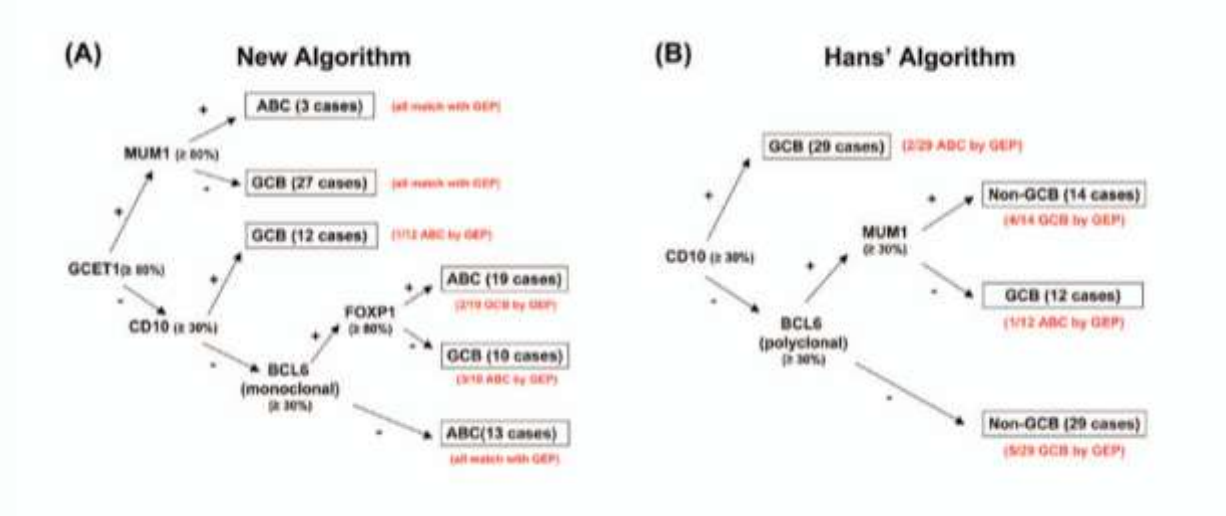
- Choi et al CCR 2009.
-Meyer et al JCO2010.
-Montes-Moreno et al, Blood 2011

EVIDENCIA EN CONTRA

- Ott et al, Blood 2010
-Gutierrez-García et al Blood 2011
-Salles et al, Blood 2011

| PUBLICACIÓN | NUMERO DE PACIENTES Y TIPO DE SERIE | ALGORITMO/S UTILIZADO/S | IMPACTO CLINICO | Comentarios |
|---|---|---|---|---|
| Choi et al. CCR 2009 | 84 (CHOP) + 63 (R-CHOP) (multicentrica, retrospectiva) | Hans y Choi | GCB (87% vivos a los 3 a) vs ABC (44%) p < 0.001 | 93% concordancia con GEP |
| Meyer et al JCO 2010 | 262 R-CHOP (& CHOP-like), (multicéntrica, retrospectiva) | Hans, Choi, Hans*, Choi*, Muris, Nyman, | Choi & Tally, mayor concordancia con GEP (87 y 93%). Todos los algoritmos con efecto pronóstico | |
| Ott et ak, Blood 2010 | 179 (CHOP) + 173 (R-CHOP), multicentrica. Ensayo clínico RICOVER 60 | Hans* | ns OS, EFS | IB morphology |
| Gutierrez-García et al. Blood 2011 | 157 (R-CHOP) (multicentrica, retrospectiva) | Hans, Choi, Muris, Colomo, Tally | ns OS, PFS | GEP predictor. |
| Montes-Moreno et al. Blood 2011 | 240 (R-CHOP & CHOP-like) (multicentrica, retrospectiva) | Choi | GCB (81% vivos a los 2 años) vs ABC (69%) p <0.05 | |
| Salles et al. | 1514 (RCHOP 347p, CHOP 289p, Early CHOP 878p) (multicéntrica procedente de Ecs) | Hans, BCL2, Ki67, HLA-DR, CD5 | ns OS en R-CHOPp, ni CHOPp, sólo significativo en Early CHOPp | Indice combinado BCL2+Ki67+IPI |

**Los subtipos biologicos de DLBCL tienen un impacto en el pronóstico en pacientes tratados con RCHOP?** y pueden tener un valor en la elección de la terapia.




*Imaging, Diagnosis, Prognosis*

**A New Immunostain Algorithm Classifies Diffuse Large B-Cell Lymphoma into Molecular Subtypes with High Accuracy**

William W.L. Choi,[1] Dennis D. Weisenburger,[1] Timothy C. Greiner,[1] Miguel A. Piris,[4] Alison H. Banham,[5] Jan Delabie,[6] Rita M. Braziel,[7] Huimin Geng,[1] Javeed Iqbal,[1] Georg Lenz,[8] Julie M. Vose,[2] Christine P. Hans,[1] Kai Fu,[1] Lynette M. Smith,[3] Min Li,[1] Zhongfeng Liu,[1] Randy D. Gascoyne,[10] Andreas Rosenwald,[11] German Ott,[11,12] Lisa M. Rimsza,[13] Elias Campo,[14] Elaine S. Jaffe,[9] David L. Jaye,[15] Louis M. Staudt,[8] and Wing C. Chan[1]

**Clin Cancer Res 2009;15(17) September 1, 2009**

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

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

**Table 2.** Results for Each Algorithm Adjusted for IPI

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

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

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

**Table 1.** Antibodies and Conditions Used for Immunohistochemistry

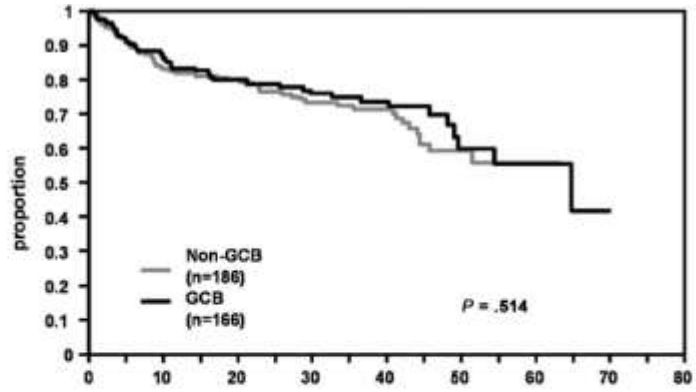
| Antibody | Manufacturer | Dilution | Antibody Incubation Time (minutes) | Antigen Retrieval |
|---|---|---|---|---|
| GCET1 | Gift* | 1:1 | 30 | EDTA 10 minutes |
| CD10 | Ventana | RTU | 32 | CC1 |
| BCL6 | Dako | RTU | 30 | FLEX |
| MUM1 | Dako | 1:800 | 20 | FLEX |
| FOXP1 | Gift† | 1:80 | 30 | EDTA 30 minutes |
| LMO2 | Santa Cruz | 1:100 | 30 | CC1 |

Abbreviations: RTU, ready to use; CC1, cell conditioning solution for antigen unmasking (Ventana); FLEX, Envision Flex high pH visualization system (Dako); EDTA 10 minutes, 1 mmol/L EDTA, pH 8.0, 10 minutes at 115°C; EDTA 30 minutes, 1 mmol/L EDTA, pH 8.0, 30 minutes at 95°C; Santa Cruz, Santa Cruz Biotechnology, Santa Cruz, CA.

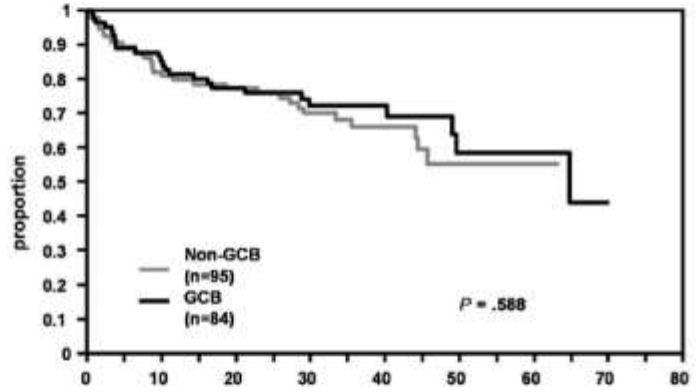
*Kindly donated by Miguel Piris, Lymphoma Group, Molecular Pathology Program, Spanish National Cancer Center, Madrid, Spain.

†Kindly donated by Alison Banham, Nuffield Department of Clinical Laboratory Sciences, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom.

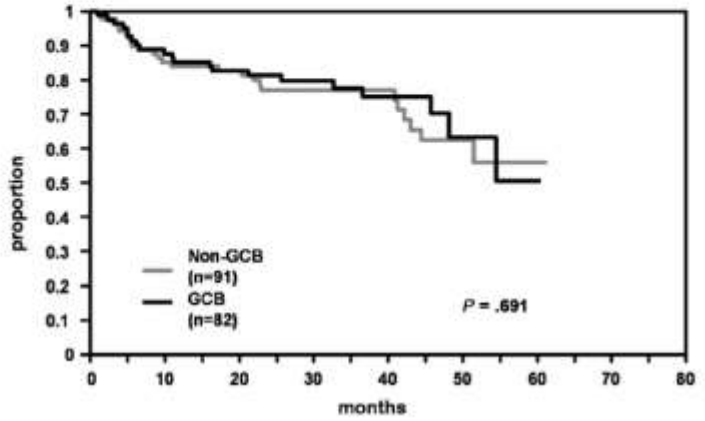
all patients:

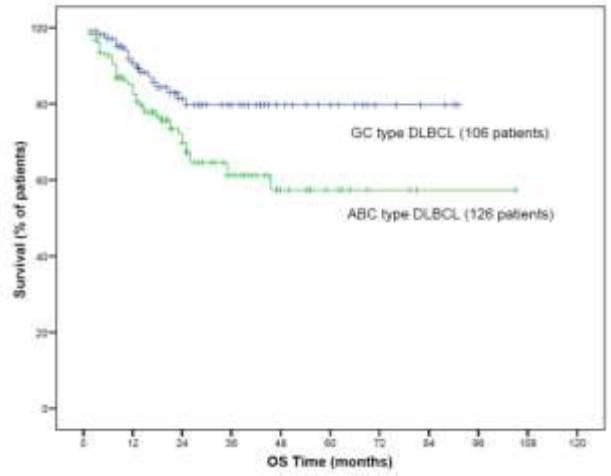



patients treated without Rituximab:

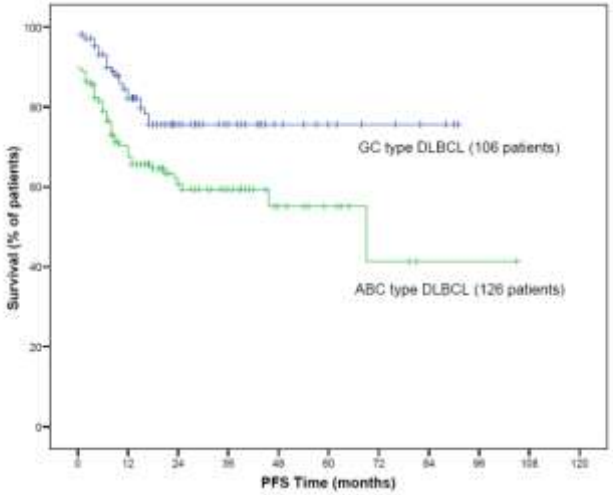



patients treated with Rituximab:






| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| GC type DLBCL | | | | | | | | | | | |
| Number of patients at risk | 106 | 79 | 50 | 32 | 15 | 10 | 5 | 3 | 0 | 0 | 0 |
| ABC type DLBCL | | | | | | | | | | | |
| Number of patients at risk | 126 | 95 | 59 | 33 | 12 | 7 | 3 | 1 | 0 | 0 | 0 |




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| GC type DLBCL | | | | | | | | | | | |
| Number of patients at risk | 106 | 71 | 42 | 25 | 11 | 7 | 5 | 3 | 0 | 0 | 0 |
| ABC type DLBCL | | | | | | | | | | | |
| Number of patients at risk | 126 | 75 | 47 | 29 | 11 | 7 | 3 | 1 | 1 | 0 | 0 |

**Confirmation of the predictive capacity of COO classification based on immunohistochemistry.**

Immunohistochemistry was performed in all 240 cases with available FFPE tissue. Most cases (232/240) could be classified into GC or ABC subtypes according to previously published algorithms [12]. One-hundred and six cases were classified as GC type (46%) and 126 as ABC type (54%). The estimated 2-year OS for ABC type DLBCL cases was 69.8% ± 4.5, significantly worse than for GC type DLCBL patients (81.4% ± 4.3; $p < 0.05$). Differences were also found for PFS (60.7% ± 4.7 for ABC type compared with 75.6% ± 4.6 for GC type; $p < 0.05$ (see **SFigure 1**).

*Blood 2011*

# Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: a study from the Lunenburg Lymphoma Biomarker Consortium

Gilles Salles, Daphne de Jong, Wanling Xie, Andreas Rosenwald, Mukesh Chhanabhai, Philippe Gaulard, Wolfram Klapper, Maria Calaminici, Birgitta Sander, Christoph Thorns, Elias Campo, Thierry Molina, Abigail Lee, Michael Pfreundschuh, Sandra Horning, Andrew Lister, Laurie H. Sehn, John Raemaekers, Anton Hagenbeek, Randy D. Gascoyne and Edie Weller

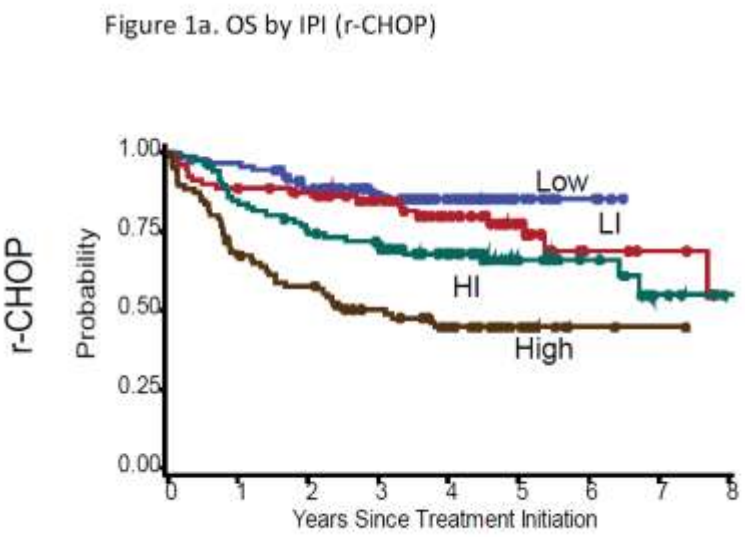
**Table 2.** Optimal cutpoints of immunohistochemical markers to predict OS in patients of r-CHOP. When optimal cutpoints were not determined using the r-CHOP series, the e-CHOP cut-points are presented. Results obtained from applying the cutpoints to the all cohorts are shown.

| Marker | Optimal cut-point selected | Rituximab-CHOP | | Early-CHOP | | Control-CHOP | |
|---|---|---|---|---|---|---|---|
| | | HR** (95% CI) | Log rank P-value | HR** (95% CI) | Log rank P-value | HR** (95% CI) | Log rank P-value |
| BCL2 | ≤ 75% vs. > 75% | 1.4 (0.9,2.2) | .09 | 1.7 (1.4,2.1) | <.0001 | 1.6 (1.1,2.3) | .02 |
| BCL6 | No staining vs staining | 1.1 (0.5,2.7) | .76 | 1.7 (1.3,2.3) | .0003 | 2.9 (1.7,5.0) | <.0001 |
| CD5 | ≤ 75% vs. > 75% | 2.4 (1.3,4.3) | 0.003 | 1.6 (1.2,2.2) | 0.004 | 1.0 (0.6,1.9) | 0.9 |
| CD10 | Negative vs. Positive | 1.1 (0.8,1.7) | .56 | 1.2 (0.9, 1.5) | .17 | 1.4 (1.0,2.0) | .06 |
| HLA-DR | Negative vs. Positive | 1.3 (0.7,2.4) | .36 | 1.6 (1.2,2.1) | .001 | 1.3 (0.8,1.9) | .33 |
| Ki67 | ≤ 75% vs. > 75% | 1.8 (1.1,2.9) | .02 | 0.8 (0.7,1.0) | .11 | 1.0 (0.6,1.5) | .86 |
| MUM1 | ≤ 75% vs. > 75% | 1.4 (0.8,2.3) | .22 | 1.3 (1.0,1.7) | .03 | 1.5 (1.0,2.4) | .06 |

*The number of the 1514 patients scored for BCL2, BCL6, CD5, CD10, HLA-dr, Ki67, MUM1, are 1306, 985, 1366, 1344, 1377, 1138, 1249, respectively

** Reference groups: ≤75% for BCL2, CD5, MUM1 and Ki67, any staining for BCL6, positive for CD10 and HLA-DR,

Figure 1a. OS by IPI (r-CHOP)




*prepub en Blood Mayo 2011*

Figure 4a. OS by GCB(adjusted): r-CHOP

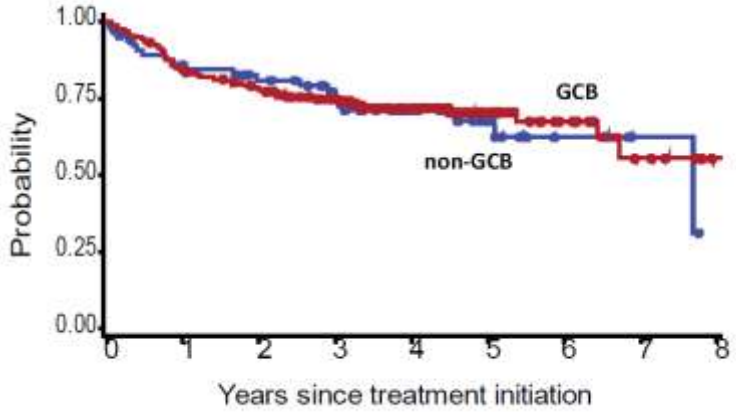



Figure 4b. OS by GCB(adjusted): c-CHOP

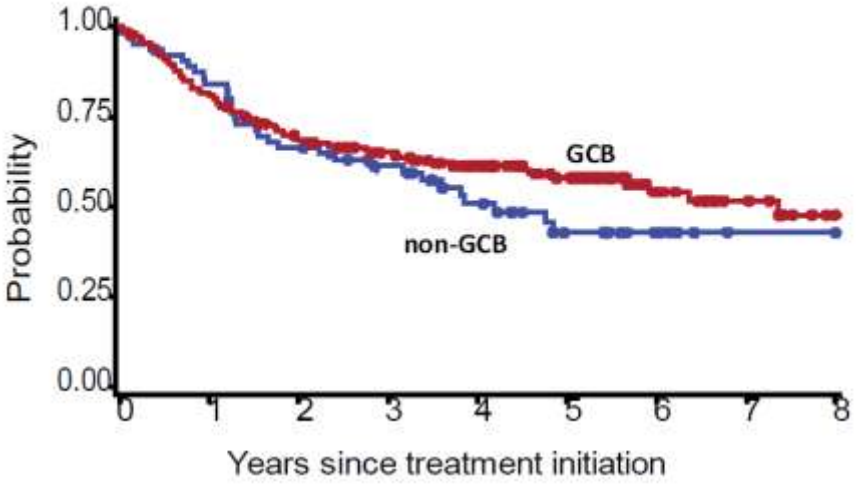
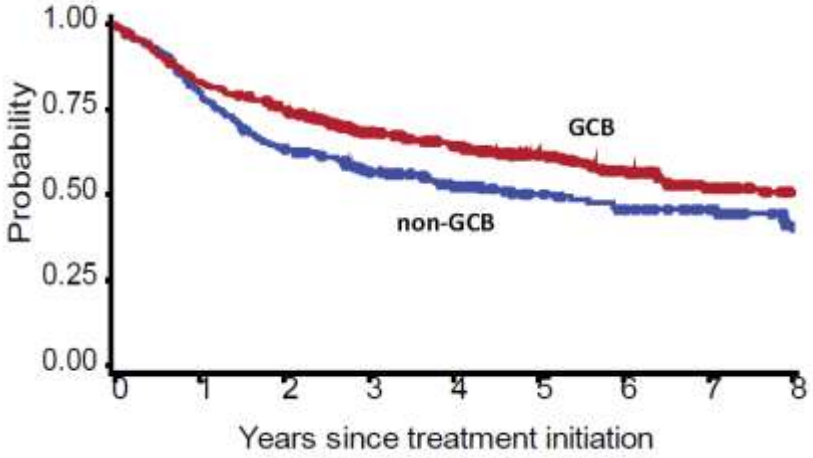



Figure 4c. OS by GCB(adjusted): e-CHOP




*Salles et al. Blood 2011*

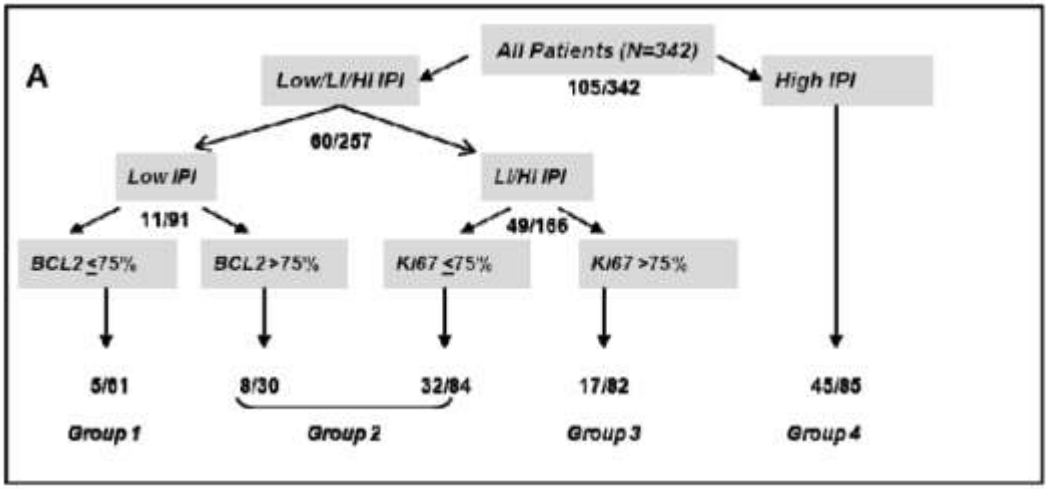
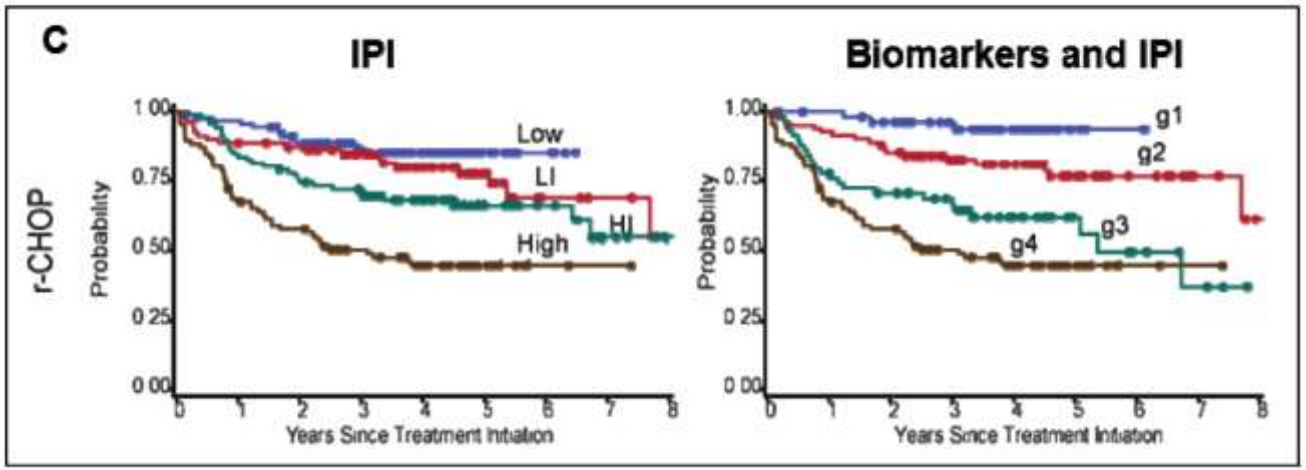



Figure 5 panel B

| | Cox PH Regression Model Results | | | |
|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 |
| N. and % of patients | 56 (20) | 84 (30) | 58 (20) | 86 (30) |
| 4-year OS (%) | 94 | 81 | 62 | 45 |
| HR without imputation (95% CI) | 1 | 3.6 (1.1, 12) | 8.4 (2.5, 28) | 13 (3.9, 41) |
| HR with imputation (95% CI) | 1 | 2.1 (0.8, 5.7) | 4.5 (1.8, 12) | 7.5 (3,19) |

Figure 5 panel C




*Salles et al. Blood 2011*

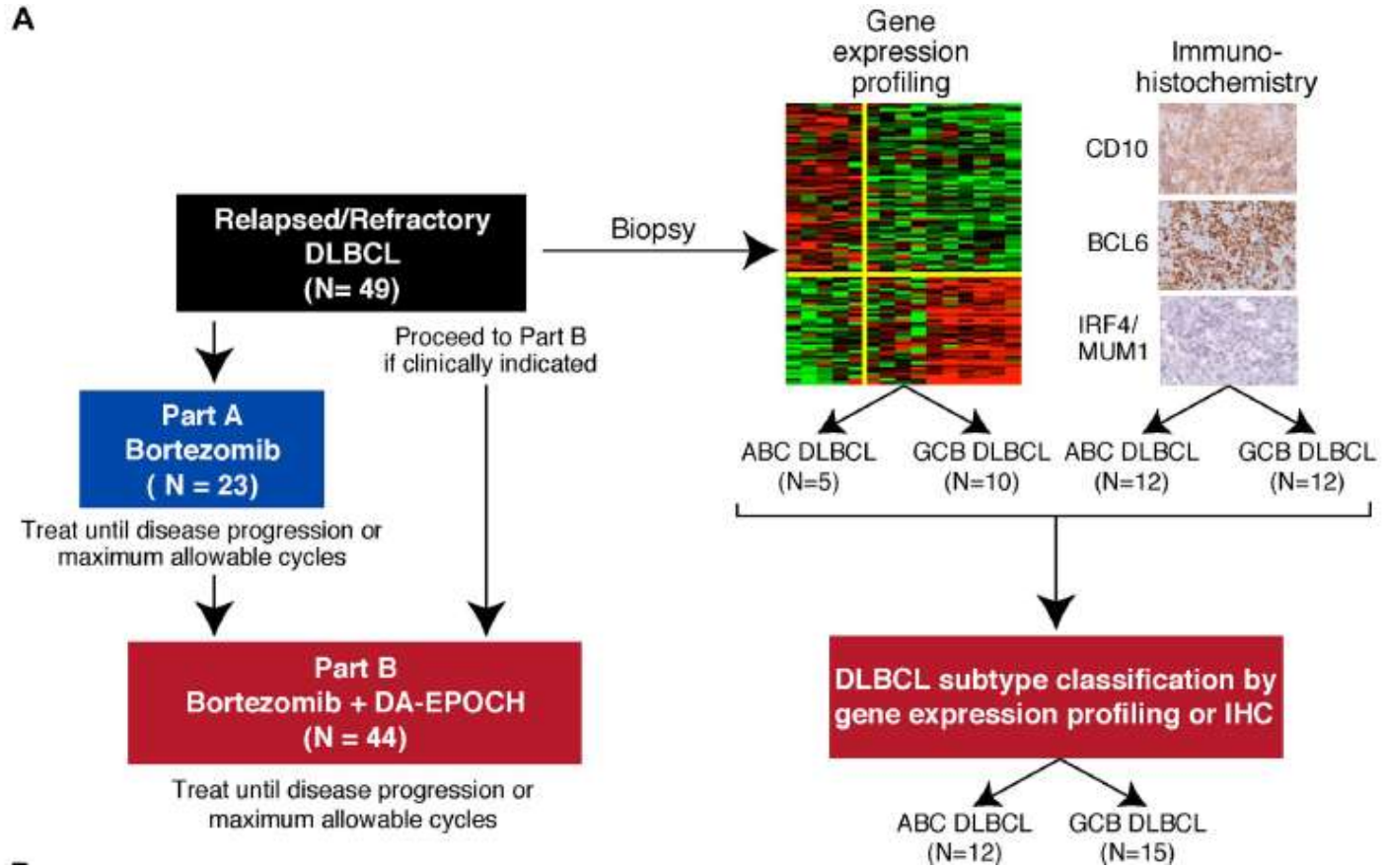
**Los subtipos biologicos de DLBCL ¿**tienen un impacto en el pronóstico en pacientes tratados con RCHOP? y **pueden tener un valor en la elección de la terapia?.**

blood

2009 113: 6069-6076
Prepublished online Apr 20, 2009;
doi:10.1182/blood-2009-01-199679

**Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma**

Kieron Dunleavy, Stefania Pittaluga, Myron S. Czuczman, Sandeep S. Dave, George Wright, Nicole Grant, Margaret Shovlin, Elaine S. Jaffe, John E. Janik, Louis M. Staudt and Wyndham H. Wilson



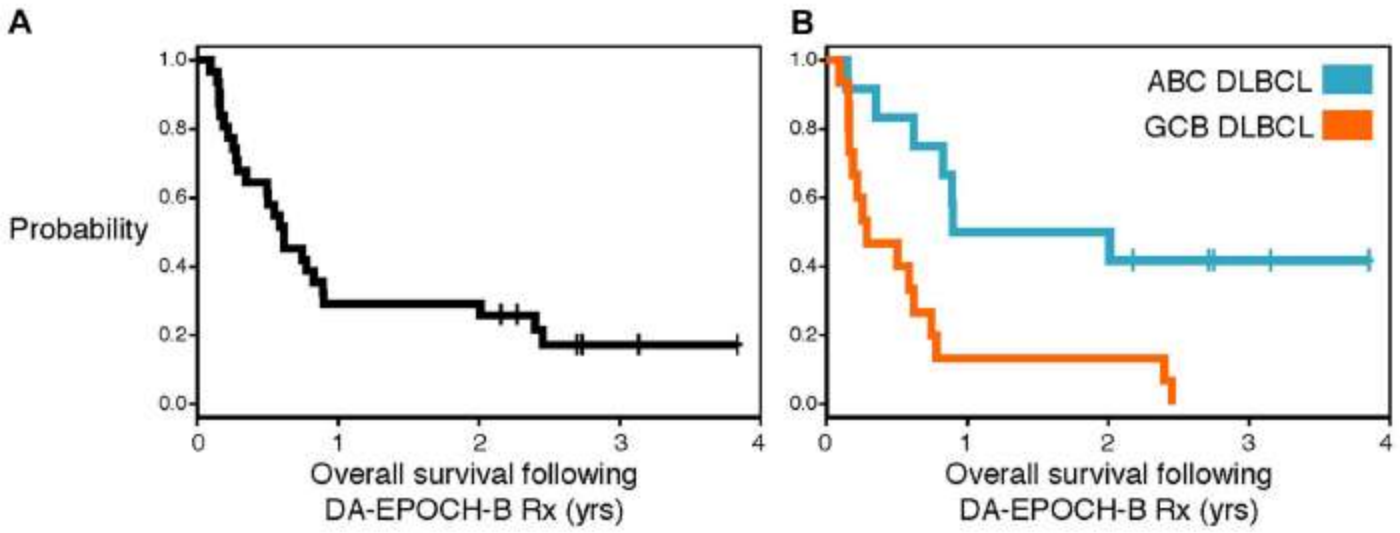
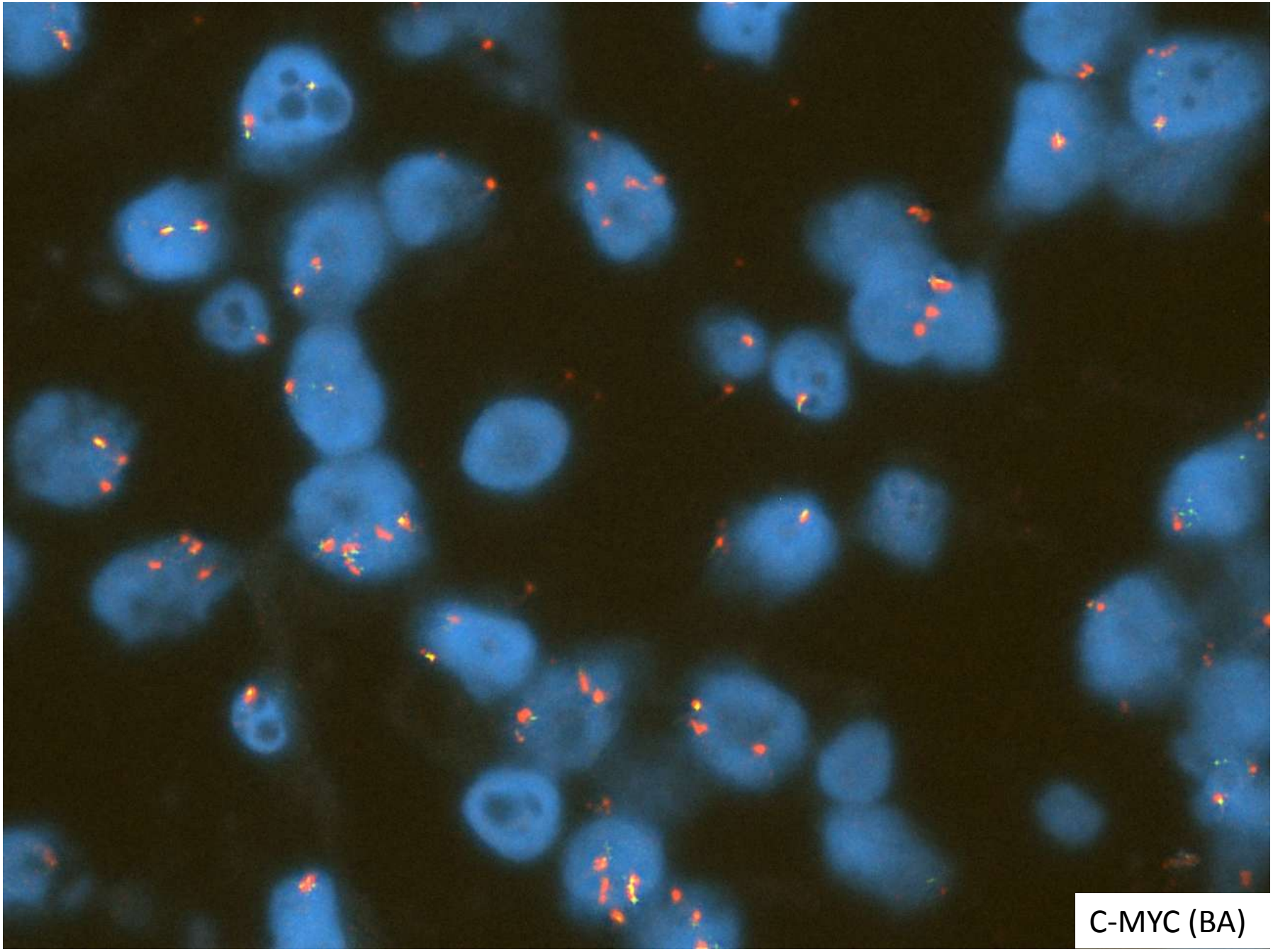



**Table 3. DA-EPOCH-B overall response and by molecular subtype**

| Treatment group | n (%) | Response, n (%) | | | *P** |
|---|---|---|---|---|---|
| | | Complete | Partial | None | |
| All patients | 44 | 8 (18) | 7 (16) | 29 (66) | |
| DLBCL (de novo)† | 31 (70) | 7 (23) | 6 (19) | 18 (58) | .63 |
| **Molecular subtypes‡** | 27 | 6 (22) | 6 (22) | 15 (56) | |
| ABC DLBCL | 12 (44) | 5 (41.5) | 5 (41.5) | 2 (17) | |
| GCB DLBCL | 15 (56) | 1 (6.5) | 1 (6.5) | 13 (87) | < .001 |

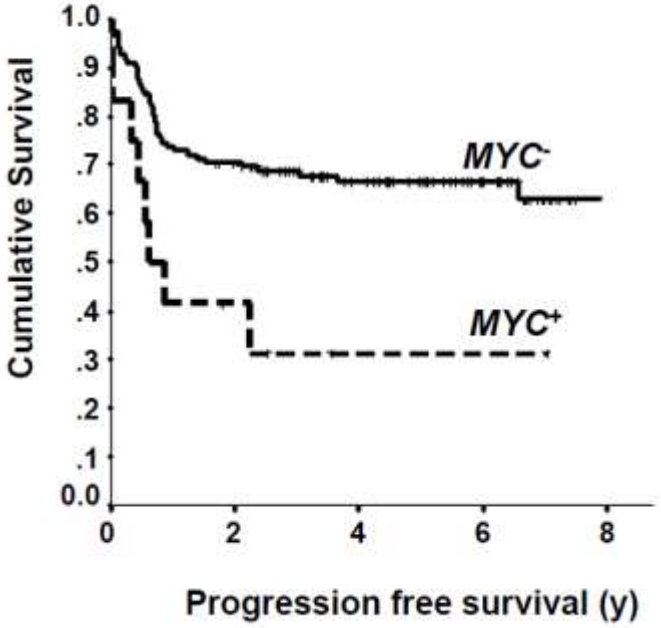
*Fisher exact test.
†Excluding primary mediastinal B-cell lymphomas (PMBL).
‡All de novo DLBCL except PMBL with microarray or immunohistochemical determination of molecular subtype.

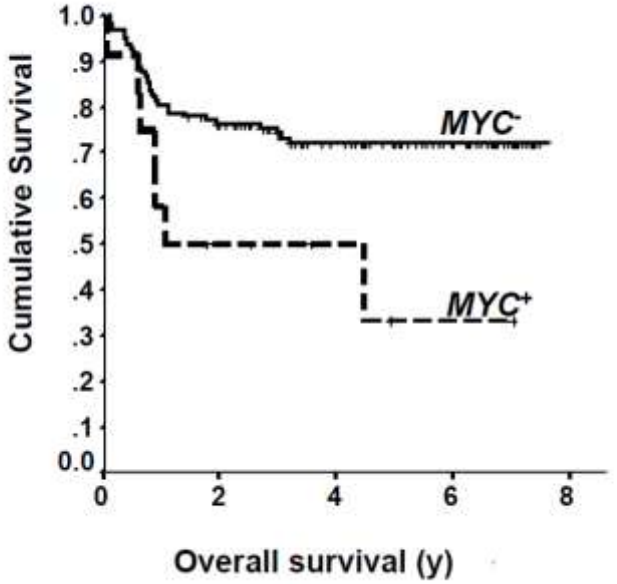
*Dunleavy et al. Blood 2009*


C-MYC (BA)

# MYC gene re-arrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy

Kerry J. Savage, Nathalie A. Johnson, Susana Ben-Neriah, Joseph M. Connors, Laurie H. Sehn, Pedro Farinha, Douglas E. Horsman and Randy D. Gascoyne




MYC+ shorter time to CNS relapse.

*Blood 2009*

# Rearrangement of *MYC* Is Associated With Poor Prognosis in Patients With Diffuse Large B-Cell Lymphoma Treated in the Era of Rituximab

*Sharon Barrans, Simon Crouch, Alex Smith, Kathryn Turner, Roger Owen, Russell Patmore, Eve Roman, and Andrew Jack*

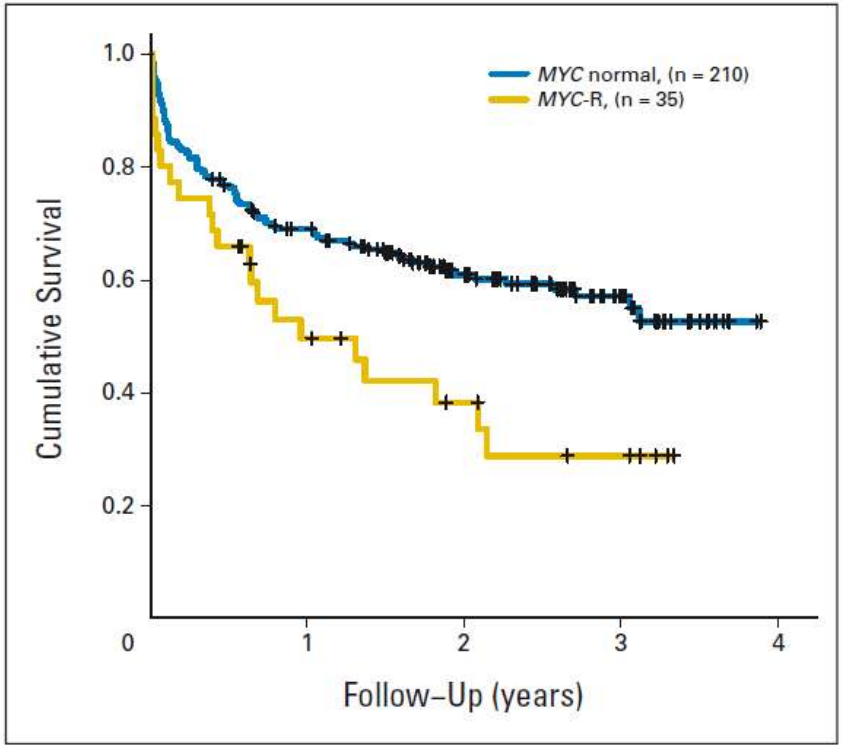



**Fig 2.** Univariate Kaplan-Meier analysis of overall survival in the *MYC* rearrangement (*MYC*-R) versus nonrearranged patients. Patients with rearrangement of *MYC* have a significantly inferior outcome compared to those without (hazard ratio, 2.03; 95% CI, 1.15 to 3.58). The probability of survival at 2 years was 0.35 in the *MYC* rearrangement group versus 0.61 for all others, based on n = 240 patients with *MYC* data and clinical follow-up.

**Table 2.** Model Coefficients/Hazard Multipliers of the Model Produced by Analysis of Patients With Diffuse Large B-Cell Lymphoma Who Had Complete Data (n = 176) and in All Patients After Multiple Imputation (N = 303)

| Parameter | Coefficient | SE | Hazard Ratio | 95% CI |
|---|---|---|---|---|
| Age | | | | |
| Complete data | 0.04 | 0.01 | 1.04 | 1.01 to 1.06 |
| Multiple imputation | 0.05 | 0.01 | 1.05 | 1.03 to 1.07 |
| Age-removed IPI | | | | |
| Intermediate | | | | |
| Complete data | 1.08 | 0.30 | 2.95 | 1.65 to 5.27 |
| Multiple imputation | 0.69 | 0.21 | 1.99 | 1.31 to 3.03 |
| High | | | | |
| Complete data | 1.74 | 0.31 | 5.67 | 3.08 to 10.45 |
| Multiple imputation | 1.19 | 0.22 | 3.30 | 2.13 to 5.12 |
| *MYC* rearranged | | | | |
| Complete data | 0.71 | 0.29 | 2.03 | 1.15 to 3.58 |
| Multiple imputation | 0.52 | 0.24 | 1.68 | 1.05 to 2.69 |

Abbreviation: IPI, International Prognostic Index.

*JCO 2010*

# B-cell Lymphomas With Concurrent *IGH-BCL2* and *MYC* Rearrangements Are Aggressive Neoplasms With Clinical and Pathologic Features Distinct From Burkitt Lymphoma and Diffuse Large B-cell Lymphoma

*Matija Snuderl, MD,*† Olga K. Kolman, MD,*† Yi-Bin Chen, MD,‡ Jessie J. Hsu, AM,§‖ Adam M. Ackerman,‡ Paola Dal Cin, PhD,†¶ Judith A. Ferry, MD,*† Nancy Lee Harris, MD,*† Robert P. Hasserjian, MD,*† Lawrence R. Zukerberg, MD,*† Jeremy S. Abramson, MD,‡ Ephraim P. Hochberg, MD,‡ Hang Lee, PhD,§ Alfred I. Lee, MD, PhD,‡ Christiana E. Toomey, BS,‡ and Aliyah R. Sohani, MD*†*

*Am J Surg Pathol* • Volume 34, Number 3, March 2010

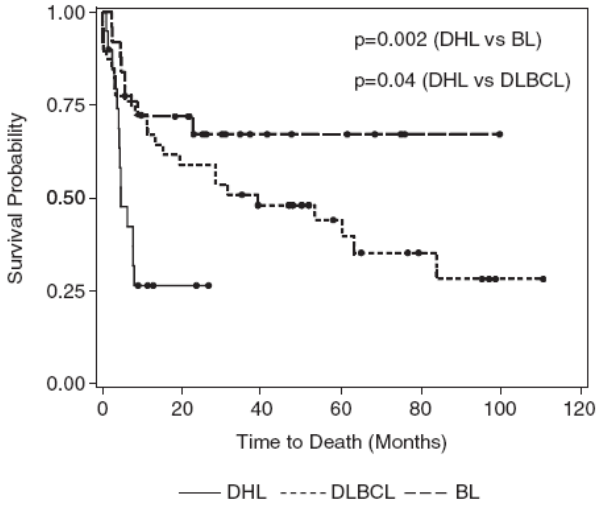



**FIGURE 1.** Kaplan-Meier overall survival distributions for double-hit lymphoma, Burkitt lymphoma, and IPI-matched diffuse large B-cell lymphoma patients, Black circles denote patients who were alive at the time of last follow-up. BL indicates Burkitt lymphoma; DHL, double-hit lymphoma; DLBCL, diffuse large B-cell lymphoma.

**TABLE 4.** Comparison of Pathologic Characteristics Between Double-Hit Lymphoma Cases and Burkitt Lymphoma Controls

| | DHL (n = 20) | BL (n = 25) | *P* |
|---|---|---|---|
| Light chain expression* | | | NS |
| Absent (%) | 5/18 (28) | 2/13 (15) | |
| κ (%) | 3/18 (17) | 6/13 (46) | |
| λ (%) | 10/18 (56) | 5/13 (38) | |
| CD10 expression (%) | 17/19 (89) | 21/23 (91) | NS |
| Bcl6 expression (%) | 17/19 (89) | 22/24 (92) | NS |
| CD10 or Bcl6 expression (%) | 20/20 (100) | 24/24 (100) | NS |
| Bcl2 expression (%) | 18/18 (100)† | 1/24 (4)‡ | < 0.0001 |
| Mum1 expression (%) | 8/19 (42) | 1/24 (4) | 0.006 |
| Ki-67 proliferation index < 95% (%) | 15/20 (75) | 0/24 (0) | < 0.0001 |
| EBER expression (%) | 0/19 (0) | 8/24 (33)§ | 0.006 |
| Complex karyotype (3 or more abnormalities) (%) | 11/11 (100) | 3/6 (50) | 0.03 |
| Median number of cytogenetic abnormalities (range) | 9 (5-20) | 2.5 (2-6) | 0.0009 |
| *MYC* partner | | | 0.001 |
| *IGH* (%) | 0/11 (0) | 5/6 (83) | |
| *IGL* (%) | 9/11 (82) | 1/6 (17) | |
| Unknown (%) | 2/11 (18) | 0/6 (0) | |

*Surface light chain expression was determined by flow cytometry in all DHL and BL cases.
†The single DHL case that was negative for Bcl2 expression with clone 124 but positive with clone C-2 (case 3) had a t(14;18) by karyotype.
‡The single Bcl2+ BL case showed no BCL2 rearrangement by FISH.
§Among 8 EBER+ BL cases, 4 arose in HIV+ adults.
BL indicates Burkitt lymphoma; DHL, double-hit lymphoma; EBER, Epstein-Barr virus encoded RNA; IGH, immunoglobulin heavy chain gene; IGL, immunoglobulin λ light chain gene.

# RESUMEN/CONCLUSIONES.

-Primer panel de HE e IHQ básica que oriente el diagnóstico, accesible en la mayoría de los centros. Control de calidad IHQ.
-Deseable confirmación diagnóstica por centro de referencia antes de indicar terapia.
-Paneles “avanzados” y técnicas de citogenética molecular en casos seleccionados.

-Papel y panel de subclasificación molecular de DLBCL basado en IHQ a debate en pacientes tratados con R-CHOP: Se precisa mayor evidencia antes de aplicar en la rutina en la determinación del pronóstico y, desde luego, en la seleccion de terapias alternativas a R-CHOP. Preciso testar algoritmos ampliados en condiciones de IHQ óptimas y series clínicas prospectivas/ensayos clínicos. Necesidad de nuevos marcadores más robustos.

- FISH para C-MYC en DLBCL, alto valor pronóstico: Linfomas Intermedios entre BL y DLBCL y DLBCL con alta sospecha de reordenamientos de C-MYC (CD10pos con proliferación >90% con o sin rasgos Burkitt-like) deben recibir terapias más intensivas.