**Supplemental Methods**

***Cohort description***

This study was conducted in accordance with the Declaration of Helsinki after obtaining informed patient consent form for participation to biological studies. Tumor specimens were collected from DLBCL patients treated in Grenoble Alpes University Hospital and Daniel Hollard Institute from January 2011 to December 2018. Patient cohort was established based on the following inclusion criteria: *de novo* DLBCL tumors, excluding all patients with previous history of lymphoma. Primitive cerebral DLBCLs, DLBCL leg-type and Primary Mediastinal B-cell Lymphoma were also excluded because of their particular pathological and biological presentations. IHC analysis of CYCLIN D1 and SOX11 were performed for CD5-positive DLBCL to exclude mantle cell lymphoma and Richter’s transformation. First-line treatment had to be R-CHOP or R-CHOP like (at least 3 cycles realized, median treatment time = 106 days, 95%CI 93-168). Tissues had to be Formalin-Fixed Paraffin-Embedded (FFPE) (AFA fixation was excluded to avoid IHC bias) and enough residual material had to be available to build Tissue Micro Array (TMA). Biological and clinical data were collected for each patient, including gender, age, IPI score, Ann Arbor stage, serum Lactate Dehydrogenase (LDH) level, therapeutic scheme and survival data with a long-term follow-up. DLBCLs were classified according to the WHO classification between GC or non-GC status using the Hans algorithm.

***Tissue Micro-array***

Five TMA blocks were built from FFPE blocks for each patient. TMA was composed of four 6µm cores (Alphametrix) for each sample to avoid artifacts caused by technical sampling; non-tumor samples were also included as internal positive control (testis). A visual inspection was performed after Hematoxylin and Eosin (H&E) staining to check for the presence of tumor cells and to exclude cores with fibrotic or necrotic changes. A detailed spreadsheet file was used for each TMA, specifying the tumor identity of each spot.

***Immunohistochemistry***

Immunohistochemical analyses were performed on 4-μm sections from TMA blocks using fully automated (baking, deparaffinization, cell conditioning and staining, IHC, counter stain and titration) Benchmark Ultra ROCHE Diagnostic System (Ventana, n°4802). Rabbit polyclonal anti-CYCLON antibody (HPA 041117, Atlas antibodies) was used in a Ventana Cell Conditioning 2 retrieval solution (citrate pH6) for 44 min and incubated for 60 minutes at 37°C, at a 1:50 dilution (final concentration of 6µg/ml). The Ventana UltraView Universal DAB Detection Kit was used followed by Hematoxylin (8 minutes) and Bluing Reagent (4minutes) staining as a nuclear counterstain. IHC staining was blindly semi-quantitatively scored by two different pathologists, using a scale from 1 to 4 according to positive cells rate (1 [1-25%], 2 [26-50%] and 3 [51-75%] and 4 [76-100%] and a scale from 1 to 3 depending on the staining intensity (1=weak, 2=medium, 3=strong). Discordant cases were the subject of a joint proofreading. A morphological examination was also performed to determine the different CYCLON staining patterns (negative, pan-nuclear, nucleolar or extra-nucleolar).

***Assessing the reliability of cell number and staining intensity scores using intraclass correlation (ICC) coefficients.***

To assess homogeneity between repeated measurements of cell number (positive cells rate) and staining intensity among TMA tissue cores, a one-way random effect model was assumed. Each DLBCL case being scored independently by a different set of 4 cores, it was of interest to determine the extent of the agreement of the scores between cores. The one-way random effect model posits that there are no systematic differences in scores due to cores. Therefore, the effects due to cores and possibly due to core-and-DLBCL interaction cannot be separated from random error and the DLBCL sample under examination is the only random effect in this model. For CYCLON staining, the estimated ICC between scores was 0.87 (95% CI, 0.82 – 0.91) for the percentage of positive cells, and 0.85 (95% CI, 0.79-0.89) for cell staining intensity. A one-sided F test confirmed that every ICC was different from zero, with p<0.001. Collectively, the ICC data demonstrated inter-core consistency of CYCLON staining.

***Multinomial models assessing the relationship between CYCLON staining pattern and cell staining intensity, and the relationship between clinical outcomes and CYCLON staining pattern.***

A first multinomial logit regression model was fitted for the categorical variable CYCLON staining pattern (negative, pan-nuclear, nucleolar or extra-nucleolar) assuming that the staining patterns had no natural ordering and were independent of one another, with staining intensity score as predictor of the model. Standard errors of model coefficients were based on robust variance accounting for correlation of intensity core scores within patients. The coefficients of the model were exponentiated and interpreted as relative risk ratio, which is the probability of a given staining intensity score to be associated with nucleolar or extra-nucleolar CYCLON staining pattern outcome over the probability to be associated with diffuse staining pattern outcome, the base reference outcome of the model. A second multinomial logit regression model was fitted for the categorical variable clinical outcomes (primary refractory disease, relapse, full response) assuming that clinical outcomes had no natural ordering and were independent of one another, with CYCLON staining pattern as predictor of the model. Standard errors of model coefficients were based on variance estimates given by the inverse of the negative Hessian matrix. The coefficients of the model were exponentiated and interpreted as relative risk ratio, which is the probability of a given CYCLON staining pattern to be associated with primary refractory disease or relapse over the probability to be associated full remission, the base reference outcome of the model. Model coefficients were compared with a standard Wald test.

***Silver (Ag) staining of Nucleolar Organizers Regions (AgNOR)***

Nucleoli were stained using the previously described AgNOR protocol [1](#_ENREF_1). Histological sections of 3-μm thick were cut from TMA blocks the day before the staining and were manually deparaffinized. Two solutions were used: 2% gelatin (solution A) dissolved in ultrapure water, to which formic acid was added to make a 1% final solution and 50% silver nitrate (solution B) in ultrapure water. The staining solution was obtained by rapidly mixing one volume of solution A with two volumes of solution B. Slides were pretreated with citrate buffer for 20 minutes at 120°C before incubation for 13 min in the staining solution at room temperature and in the dark to avoid direct light exposure during silver-staining. After staining, the slides were washed, dehydrated and mounted.

***Fluorescence in situ hybridization (FISH)***

FISH was performed using FFPE tissues, with 4-μm sections mounted on slides. All samples were tested with *MYC, BCL2* and *BCL6* break-apart FISH probes using respectively the ZytoLight ® SPEC *MYC* Dual Color Break Apart Probe, the ZytoLight ® SPEC *BCL2* Dual Color Break Apart Probe and the ZytoLight ® SPEC *BCL6* Dual Color Break Apart Probe. Furthermore, a Vysis LSI *IGH/MYC/CEP* 8 Tri-Color Dual Fusion Probe Kit was used to determine if *IGH* was the partner gene of *MYC* rearrangement. At least 100 tumor nuclei were analyzed for each sample. Nuclei were counterstained with DAPI/Vectashield® (Vektor Laboratories, Burlingame, CA, USA) and were analyzed with a Leica CytoVision GSL10 FISH fluorescence capture system® (Leica, Nanterre, France) under a 63x oil immersion objective. Signals were enumerated with the CytoVision imaging system® (Leica). A cut-off value of 10% of the cells showing rearrangement was selected to validate rearrangement for a specimen.

***Targeted NGS sequencing***

DNA was extracted from 3 to 5 FFPE core biopsies/per case by QIAsymphony DSP DNA Mini Kit (Qiagen). DNA quality was assessed by TapeStation (Agilent) and quantified by Qubit (ThermoFisher). Targeted sequencing was performed by a capture approach covering 51 genes that present mutations in DLBCL, Follicular Lymphoma and Chronic Lymphocytic Leukemia. This panel is based on the 34-genes panel developed for DLBCL by the French Lymphoma Study Association [2](#_ENREF_2) that was extended to include additional genes of interest for diagnosis, prognosis and theranostic requirements in routine diagnostic workup of mature lymphoid neoplasms [3](#_ENREF_3), as well as genes of interest for research purpose. Detailed gene list are presented in Supplemental Table 5. Libraries were prepared by standard procedures using 50 ng of DNA and KAPA HyperPlus kit (Roche). Libraries were purified, quantified and barcoded before being submitted to Illumina sequencing by NextSeq 500/550 Mid Output Kit V2 (300 cycles) on a Nextseq 550 Illumina sequencer. Somatic mutation calling was performed using a custom sequence alignment, variant caller and annotation pipeline, as described [4](#_ENREF_4). Somatic mutations that affected protein coding regions (non-synonymous), and at exon splice site junctions were retained for analysis. KMT2D analysis was not performed because of high background noise at this gene locus in sequencing data.

***Statistics***

Specific overall survival (SOS) and progression free survival (PFS) were assessed by Kaplan‐Meier analyses and Cox regression. The starting point for time-to-event analysis was the date of the pathological diagnosis. SOS was defined as time to disease-related death and PFS as the time to disease progression with censoring at date of last contact. Patients without any event at the time of the last follow-up were censored. The proportional-hazards assumption of the Cox models was checked on the basis of Schoenfeld residuals after Cox model fitting. The fit of the Cox models was assessed using Harrell’s concordance index which is defined as the probability that predictions and outcomes are concordant. Prediction accuracy of multivariate models was evaluated by using time-dependent receiver operating characteristic (ROC) curves and corresponding areas under time-dependent ROC curves (AUCs). All statistical analyses were performed using Stata 16.1 (Stata Corporation) or JPM 10 (SAS).

**Supplemental References**

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3. Sujobert P, Le Bris Y, de Leval L, et al. The Need for a Consensus Next-generation Sequencing Panel for Mature Lymphoid Malignancies. Editorial. *HemaSphere*. Feb 2019;3(1):e169.

4. Burlet B, Ramla S, Fournier C, et al. Identification of novel, clonally stable, somatic mutations targeting transcription factors PAX5 and NKX2-3, the epigenetic regulator LRIF1, and BRAF in a case of atypical B-cell chronic lymphocytic leukemia harboring a t(14;18)(q32;q21). *Cold Spring Harbor molecular case studies*. Feb 2021;7(1)