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ORIGINAL RESEARCH

Characteristics and Management of *TP53*-Mutated Diffuse Large B-Cell Lymphoma Patients

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Background/Aim: TP53 mutation is recognized as a negative prognostic factor for patients with diffuse large B-cell lymphoma (DLBCL). Here, we present the characteristics of *TP53*^{mut} DLBCL patients following investigation of the effect of a treatment approach on survival of *TP53*^{mut} DLBCL patients.

Methods: A total of 44 DLBCL patients with *TP53*^{mut} and treated with an R-CHOP regimen were included for analysis. Patients who failed to achieve a complete response (CR) to initial treatment or relapsed in the first 6 months after initial CR were deemed to have primary refractory disease.

Results: Among 44 patients harboring *TP53* mutations who underwent upfront R-CHOP or R-CHOP–like treatment, 21 (47.7%) had limited-stage and 23 (52.3%) presented advanced-stage disease. Apart from the seven patients receiving upfront surgical resection, 37 had measurable disease under the R-CHOP regimen, with 59.1% (n=26) developing primary refractory disease. Seven limited-stage patients after early complete resection and one with residue resection remained event-free at median follow-up of 37 months. Multivariate analysis revealed that elevated baseline lactate dehydrogenase (LDH), extranodal involvement (two or more), Ann Arbor stage, and locoregional treatment (surgery or radiation therapy) were independent indicators for progression-free survival (PFS). After adjustment for baseline LDH and extranodal involvement, adding locoregional treatment including surgery and radiation to the R-CHOP regimen significantly improved PFS (p=0.008) and overall survival (p=0.017) in limited-stage *TP53*^{mut} DLBCL patients compared to R-CHOP–only treatment.

Conclusion: This study presents the characteristics of *TP53*-mutated DLBCL and implies a potential benefit of locoregional treatment in limited-stage DLBCL patients with *TP53* mutations.

Keywords: diffuse large B-cell lymphoma, *TP53*, surgery, survival, clinical benefit

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid malignancy in non-Hodgkin's lymphoma (NHL). Up to 50% of DLBCL patients can be cured with rituximab plus cyclophosphamide, hydroxydaunorubicin, Oncovin (vincristine) and prednisone (R-CHOP) chemotherapy, considered the standard first-line treatment,[1–3] while the rest develop refraction or relapse and usually have poor prognosis. According to the literature, relapsed or refractoryDLBCL can be defined as nonachievement of complete response (CR), lacking response, or partial response in <6 months.[4–7] Compared to other DLBCL patients, refractory patients have median overall survival (OS) <12 months with R-CHOP treatment.[8–10] Therefore, identifying new clinical

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procedures to benefit DLBCL patients at higher risk of developing primary refraction under R-CHOP regimens is of great urgency.

TP53 mutation occurs in 20%–25% of DLBCL patients, and has been identified as one of the most frequently mutated genes in both germinal center Bcell (GCB) and activated B-cell subtypes in DLBCL patients.[11–14] *TP53* mutation is associated with p53 overexpression, where the protein plays an important role in cell death, DNA repair, transcription, metabolism, apoptosis, and autophagy.[12] Dysfunction of p53 is observed in many malignant tumors.[15–19] In DLBCL, *TP53* mutation has been identified as an unfavorable prognostic factor for patients under a CHOP or R-CHOP treatment regimen.[12,20–25] In a study of 102 DLBCL patients, the CR rate was significantly higher in patients missing *TP53*^{mut}.[25] The prognostic impact of *TP53*^{mut} was further investigated in a study with 506 de novo DLBCL patients, and the results showed *TP53*^{mut} was an independent predictor of OS and progression-free survival (PFS) in patients treated with an R-CHOP regimen.[23] The prognostic impact of *TP53*^{mut} was further confirmed in the RICOVER 60 trial, suggesting the use of *TP53*^{mut} for prognostication and treatment stratification.[24]

In lymphomas other than DLBCL, *TP53* mutation has been identified as an independent prognostic indicator of OS under current standard care in young patients with mantle-cell lymphoma.[26] It has also been confirmed that *TP53*^{mut} is correlated with low response rate to immunochemotherapy in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) patients,[27,28] and ibrutinib is a preferred treatment approach for CLL/SLL patients with *TP53* mutation.[29,30] Despite reports about the prognostic impact of *TP53* mutation in DLBCL patients, no clinical procedures are available to seek better patient outcomes.[31] Here, we conducted an analysis of 44 *TP53*^{mut} DLBCL patients treated with R-CHOP to identify clinical features and explore the potential benefit of different treatment approaches.

Methods

Patients and Samples

A series of 214 patients diagnosed with DLBCL according to the World Health Organization classification of tumors of hematopoietic and lymphoid tissue (2008)[32] were enrolled retrospectively between January 2013 and December 2018 at the Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, and Suzhou Municipal Hospital. Inclusion criteria were pathologically confirmed DLBCL, treatment with R-CHOP or R-CHOP–like regimen, validated for DNA extraction, HIV-negative. Driven by the purpose of identifying genetic high-risk subtypes, most patients in that series presented with advanced-stage and high-risk disease according to the revised international prognostic index (R-IPI; part of the study has been published).[25] Retrospectively selected from that cohort, patients harboring *TP53* mutations were enrolled in the present study. Clinical data were collected and analyzed: sex, age, Ann Arbor stage, Eastern Cooperative Oncology Group performance status, extranodal involvement, B symptoms, lactate dehydrogenase (LDH), bulky disease, R-IPI, first-line treatment, salvage treatment, response to treatment, and survival. GCB and non-GCB were determined by immunohistochemistry (IHC) using anti-CD10, MUM1, and BCL6 antibodies (Fuzhou Maixin Biotech). IHC staining for p53 expression was performed using MX008 mAb (MXB Biotechnologies). Response was assessed according to International Working Group criteria. The study was approved by the Institutional Review Board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College (NCC2018JJJ-004), and was performed in accordance with the ethical standards of the institutional committee and the Declaration of Helsinki.

Genomic DNA Extraction and *TP53* Sequencing

Formalin-fixed, paraffin-embedded (FFPE) tissue samples were collected from the enrolled patients. Genomic DNA was extracted using the QIAamp DNA FFPE tissue kit (Qiagen). DNA concentrations were measured using Qubit dsDNA assay (Life Technologies). We then performed DNA fragmentation with an M220 focused ultrasonicator (Covaris, Woburn, MA, USA), followed by end repair, phosphorylation, and adaptor ligation. Fragments of 200–400 bp were selected by AMPure beads (Agencourt AMPure XP kit; Beckman Coulter, Brea, CA, USA). Subsequently, hybridization with capture-probe baits, hybrid selection with magnetic beads, and PCR amplification were performed. Two capture probes were chosen: one with 413 genes frequently mutated in DLBCL patients, and the other consisting of 112 genes common to lymphoma and hematologic malignancies. There were in total 100 genes overlapping between these two panels, and *TP53* was one of them. A high-sensitivity DNA assay was implemented in order to ensure sufficient DNA yield. Indexed samples were sequenced using a NextSeq 500

sequencer (Illumina, Hayward, CA, USA) with pair-end reads.

After removal of terminal adaptor sequences and low-quality data, reads were mapped to the reference human genome (hg19) and aligned using a Burrows–Wheeler 0.7.10 (Broad Institute). Local alignment optimization, variant calling, and annotation were performed using GATK 3.2 and MuTect (both from Broad Institute, Cambridge, MA, USA) and VarScan (Genome Institute, Washington University, USA). Loci with a depth <100 were filtered out by the VarScan filter pipeline. At least five supporting reads were required for insertions/deletions, and eight for single-number variations in tissue samples. The average sequencing depth for all targeted regions was 1,402×. Selected exons of *TP53* in two panels were analyzed. In accordance with the Exome Aggregation Consortium, 1000 Genomes Project, ESP6500SI-V2, and dbSNP databases, variants with frequency >0.1% were categorized as single-nucleotide polymorphisms and excluded from further analysis. The remaining variants were annotated with ANNOVAR and SnpEff v3.6 software. TopHat2 (Center for Computational Biology, Johns Hopkins University and Genome Sciences Department, University of Washington, USA) and Factera 1.4.3 were utilized for DNA translocation analysis.

Statistical Analysis

PFS in this study was defined as time from therapy start to documented disease progression, relapse, or death. OS referred to the interval between the date of initial treatment and date of death or last follow-up. Patients who failed to achieve CR to initial treatment or relapsed in the first 6 months after initial CR were deemed to have primary refractory disease. Fisher's exact and χ^2 tests were conducted to assess associations between *TP53* and clinical characteristics. OS and PFS were calculated using the Kaplan–Meier method, and log-rank tests were used to compare time-to-event curves between groups. Prognostic indicators were evaluated by Cox proportional-hazard regression. $P<0.05$ was set as the threshold for significance. All these analyses were conducted with R version 3.0.2 (http://www.R-project.org) and SPSS 22.0.

Results

TP53 Variants and p53 Expression

TP53 mutations were found in tumor samples from 47 of 214 (22%) patients. All detected genomic mutations are listed in Supplemental Table S1. In total, 54 mutations were found in *TP53*^{mut} patients, of which 41 (87.2%) had a single *TP53* mutation, five (10.6%) presented two mutations, and one had three mutations. Alterations were most commonly observed in exon 5 (n=20, 42.6%), followed by exon 6 (n=11, 23.4%), exon 7 (n=11, 23.4%), and exon 8 (n=6, 12.8%). Overall, 41 (87.2%) patients had mutations located in the DNA-binding domain (DBD) of *TP53*. We were only able to perform IHC staining of p53 in 18 patients with available tissue samples. Based on the cutoff rate of 10%, 16 were determined positive. Twelve patients with p53 overexpression were identified by a cutoff of 50%. For case 11 and case 45, both were negative with p53 and detected with R196 stop gained and A248 frameshift.

Clinical and Pathological Characteristics in *TP53*-Mutated DLBCL

Among 44 patients harboring *TP53* alterations who underwent upfront R-CHOP or R-CHOP–like treatment, 21 (47.7%) were men and 23 (52.3%) women. Median age at diagnosis was 56 (range 18–82) years, and 28 (63.6%) were aged <60 years. Determined by Hans algorithm, 27.3% (12 of 44) were categorized as GCB and 68.2% (30 of 44) non-GCB. Subtype classification for two patients was missing, due to insufficient tissue samples. Among *TP53*^{mut} patients, 21 (47.7%) had limited stage and 23 (52.3%) advanced stage. Overall, 30 patients had extranodal involvement and four had extranodal involvement of two or more. The other 14 patients had nodular involvement only. IHC-based coexpression of Myc and BCL2 was positive in ten (26.3%) of 38 patients with cutoff values of ≥40% and ≥50%, respectively. Based on the R-IPI, eight (19%), 21 (50%), and 13 (31%) patients were classified as very good, good, and poor, respectively. Clinical features of *TP53*^{mut} DLBCL patients are detailed in Table 1.

Treatment Response and Survival Analysis of *TP53*-Mutated DLBCL Patients

For patients with limited-stage disease (n=21), 13 (61.9%) received locoregional treatment (five [22.7%] radiotherapy and eight [36.4%] surgical resection) in a front-line setting. Seven (33.3%) patients (four primary intestinal DLBCL, two primary Waldeyer's ring DLBCL, and one primary testicular DLBCL) had complete resection before receiving immunochemotherapy. One patient with primary

Table 1 Clinical Features of 44 Patients with *TP53*-mutated DLBCL

	n (%)
Sex	
Male	21 (47.7)
Female	23 (52.3)
Age	
Median, years (range)	56 (18–82)
<60 years	28 (63.6)
Myc–BCL2 double-expression#	10 (26.3)
Cell of origin (Han's algorithm)	
GCB	12 (27.3)
Non-GCB	30 (68.2)
NA	2 (4.5)
Disease involvement	
Extranodal involvement	30 (68.2)
Nodular involvement alone	14 (31.8)
Ann Arbor stage	
I/II	21 (47.7)
III–IV	23 (52.3)
Elevated LDH*	23 (60.5)
IPI	
0	8 (19.0)
1–2	21 (50.0)
3–5	13 (31.0)
Treatment	
Chemotherapy + surgery	8 (18.2)
Chemotherapy + radiotherapy	5 (11.4)
Chemotherapy alone	31 (70.5)

Notes: #38 patients had undergone both Myc and BCL2 immunohistochemistry; *38 patients had available LDH-baseline records.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; IPI, International Prognostic Index; GCB, germinal center B cell–; GCB, germinal centre B-cell-like; NA, not available.

intestinal DLBCL had residual disease resection after six cycles of R-CHOP (Figure 1). All patients with complete resection stayed event-free till the last follow-up date, with a median follow-up of 37 months.

Apart from the seven patients that received upfront surgical resection, 37 had measurable disease on R-CHOP, with 25 (67.6%) responsive to initial R-CHOP treatment (14 [37.8%] CR, 11 [29.7%] partial response). A total of 12 (32.4%) patients developed refraction to R-CHOP treatment (Figure 1). Among the 44 patients treated with R-CHOP, 59.1% (n=26) developed primary refraction, with 22 (50.0%) failing to achieve CR to initial treatment and four (9.1%) relapsing in the first 6 months after initial CR. Noticeably, among these primary refractory patients, a 51-year old woman had a most aggressive disease course and succumbed to disease progression in the second month following diagnosis. It is worth mentioning that she had a concurrent *CDKN2A* frameshift in addition to the *TP53* mutation.

With median follow-up of 15.5 months, median PFS and OS were 9 (95% CI 4.9–13.1) months and 46 (95% CI 11.2–80.8) months in the 44 R-CHOP–treated patients harboring *TP53* mutations (Figure 2A and B). On univariate analysis, LDH (elevated vs normal, 6.5 vs not reached [NR] months p=0.001), disease stage (limited vs advanced, NR vs 6.2 months; p=0.005) and extranodal involvement (0-1 vs ≥2, 12.5 vs 6.0 months; p=0.017) were correlated with PFS. However, no survival difference was observed between different *TP53* subtypes (DBD vs non-DBD, 8 months vs NA; p=0.389) and no factor was identified to be significantly correlated with OS.

Locoregional Treatment in Limited-Stage Patients

We further analyzed the impact of locoregional treatment in the limited-stage subset (n=21), and found locoregional treatment was correlated with PFS (yes vs no, NR vs 6 months; p<0.001) and OS (yes vs no, NR vs 18 months; p=0.008). After adjustment for baseline LDH and extranodal involvement, adding locoregional treatment to immunochemotherpy was associated with longer PFS (HR 0.092, 95% CI 0.016–-0.543; p=0.008) and OS (HR 0.032, 95% CI 0.002–0.535; p=0.017).

Discussion

We analyzed clinical features of *TP53*^{mut} DLBCL patients and found a high occurrence of primary refraction. Although surgical resection is not recommended as the standard of care for DLBCL patients, this study demonstrates an improved outcome for *TP53*^{mut} patients with locoregional intervention involving surgery and radiotherapy. We were able to identify 22% of DLBCL patients harboring *TP53* mutations, similar to previous studies.[11,12,33] Additionally, 89% of *TP53* mutations were located in exons 5–8 in DBD and showed no statistically significant difference for DBD versus non-DBD mutations in relationship to poor prognosis, as previously reported.[23, 34,35] Both *TP53* mutation and accumulation of wild-type p53 led to readings of IHC-determined overexpression. A cutoff >50% was used for stratification of DLBCL patients.[23] Among 18 *TP53*^{mut} patients in our study, 16 had p53 overexpression and 12 were over the cutoff of 50%. Two

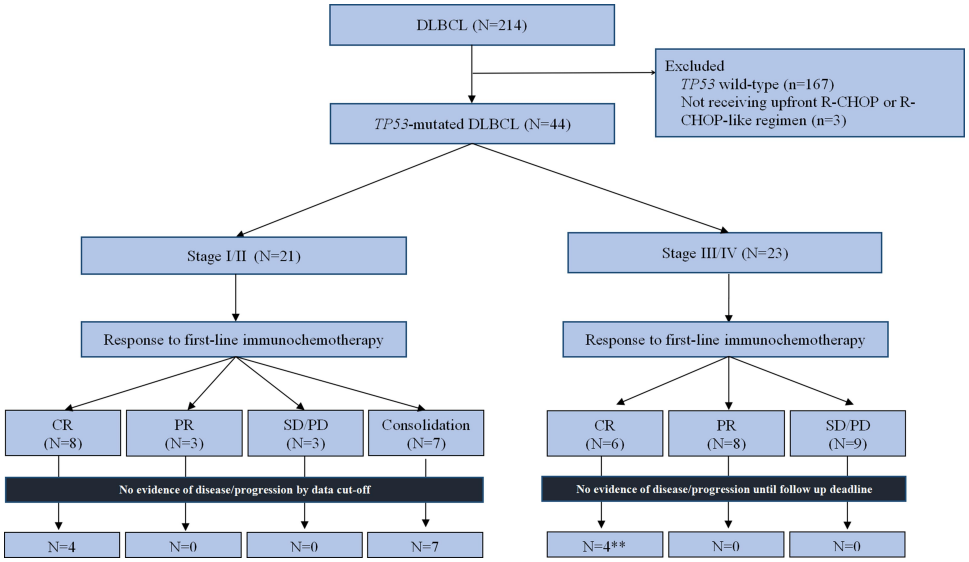

Figure 1 Patient disposition and response to frontline treatment and survival status in 44 DLBCL patients with *TP53* mutation.
Note: Consolidation refers to receipt of upfront surgical resection and subsequent R-CHOP regimen.

TP53^{mut} patients were p53 IHC-negative, which may relate to the spot of mutation (one frameshift and one stop gain). They both progressed in the first month of R-CHOP treatment.

TP53 mutation was associated with unfavorable response to standard treatment and resulted in short survival for many solid tumors and hematologic malignancies.[36–38] Abundant evidence shows the function of *TP53* mutations is varied depending on the cell type, differentiation state, stress conditions, and tissue microenvironment.[39] In this study, 59.1% (n=26) of *TP53*^{mut} DLBCL patients developed primary refractory disease, much higher than general population,[40–42] indicating *TP53* mutations correlated with unfavorable response to R-CHOP. Promoting cell-cycle arrest and apoptosis are two major functions of p53, while the absence of p53 can promote accumulation and permit survival of aneuploid cells. In CLL, evidence suggests *TP53* mutations are associated with resistance to alkylator- and nucleoside-analogue treatment, resulting in a chemotherapy-resistant phenotype. Actually, in *TP53*^{mut} CLL, the poor response to conventional chemotherapy has facilitated the development of targeted therapies, such as ibrutinib, optimizing clinical practice for this population.

Efforts in exploring optimal treatment have also been made in *TP53*^{mut} DLBCL. Of the *TP53*^{mut} DLBCL patients in the RICOVER-60 trial, eight cycles of CHOP or R-CHOP failed to improve patient outcome over six cycles.[24] The present study focused on the impact of locoregional treatment, including radiotherapy and surgical intervention, in patients with limited-stage DLBCL. Although surgical resection is not recommended as a routine approach in DLBCL treatment, benefits of surgical resection have been reported in primary gastrointestinal DLBCL.[43] Here, we are the first to report the impact of locoregional treatment in patients with *TP53*^{mut} DLBCL, a molecular subgroup carrying unfavorable prognosis. We identified the possible clinical benefit of adding a locoregional procedure in limited-stage *TP53*^{mut} DLBCL patients, and propose that a combination of systemic and locoregional measures could contribute to overcoming the chemotherapy-resistant phenotype of *TP53*^{mut} DLBCL.

This study's retrospective nature, limited sample size, and lack of incorporation of other prognostic indicators[44–47] may have introduced bias, and thus the results should be interpreted with caution. Nevertheless, considering the curability of DLBCL, the frequency of *TP53* mutations in DLBCL, and the proportion of primary refraction, we believe our findings could provide some hints for optimizing treatment for *TP53*^{mut} DLBCL. Further studies are warranted to prospectively explore individualized treatment for this population with poor prognosis. In summary, we conclude that primary refractory disease is common in DLBCL patients with *TP53* mutations receiving R-CHOP treatment. A combination of locoregional treatment and R-CHOP chemotherapy could provide additional clinical benefit to limited-stage DLBCL patients with *TP53* mutations.

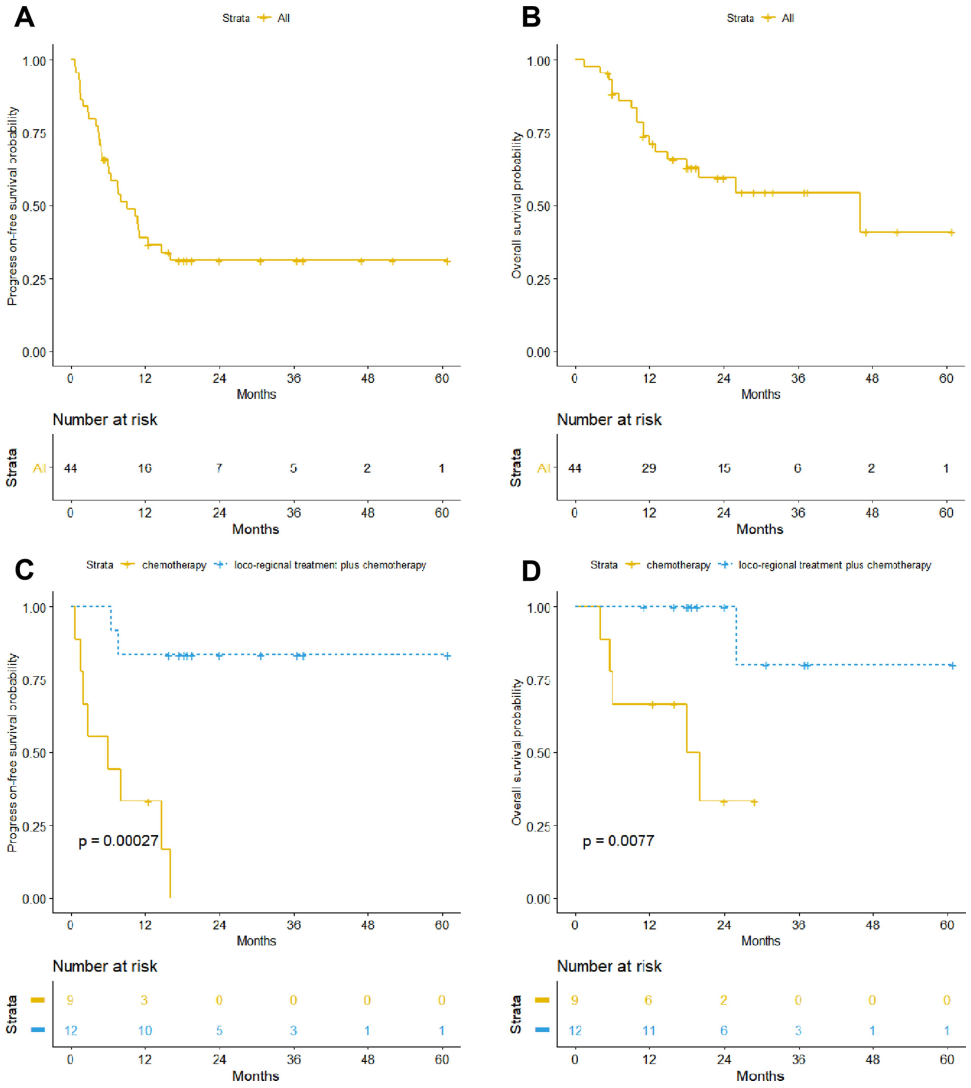

Figure 2 (**A**) Progression-free survival and (**B**) overall survival of *TP53*-mutated DLBCL treated with R-CHOP regimen. Locoregional treatment was associated with (**C**) progression-free survival and (**D**) overall survival.
Abbreviation: R-CHOP, rituximab plus cyclophosphamide, hydroxydaunorubicin, Oncovin (vincristine), and prednisone.

Code Availability

Not available.

Abbreviations

DLBCL, diffuse large B-cell lymphoma; CR, complete response; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; PFS, progression-free survival; OS, overall survival; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin's lymphoma; GCB, germinal centre Bcell; LDH, lactate dehydrogenase; R-IPI, revised International Prognostic Index; IHC, immunohistochemistry; FFPE, formalin-fixed, paraffin-embedded; DBD, DNA-binding domain.

Data-Sharing Statement

The data set used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Ethical Approval

All patients provided written informed consent. The protocol was approved by the institutional review boards of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (NCC2018JJJ-004).

Consent to Participate

Consent to publish has been obtained from the participants to report individual patient data.

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Disclosure

XHD and YTY are employees of Geneplus Beijing. JL is an employee of Burning Rock Biotech. The aforementioned authors report no other potential conflicts of interest in this work. All other authors declare no conflicts of interest.

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