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ORIGINAL ARTICLE

Positron emission tomography-adapted therapy in low-risk diffuse large B-cell lymphoma: results of a randomized, phase III, non-inferiority trial

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Abstract

Background: The current standard of care for non-bulky diffuse large B-cell lymphoma (DLBCL) patients with an International Prognostic Index (IPI) of 0 is four cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) but whether the same efficacy can be achieved with reduced chemotherapy regimen of four cycles for non-bulky DLBCL patients with an IPI of 1 remains unclear. This study compared four cycles versus six cycles of chemotherapy in non-bulky low-risk DLBCL patients with negative interim positron emission tomography with computed tomography (PET-CT, Deauville 1-3), irrespective of age and other IPI risk factors (IPI 0-1).

Methods: This was an open-label, randomized, phase III, non-inferiority trial. Patients aged 14-75 years with newly diagnosed low-risk DLBCL, according to IPI, achieving PET-CT confirmed complete response (CR) after four cycles of

Abbreviations: aaIPI, age-adjusted IPI; ABC, activated B-cell-like; CAR-T, chimeric antigen receptor T-cell; CNS, central nervous system; COO, cell-of-origin; CR, complete response; DEL, double-expressor lymphoma; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FFPE, formalin-fixed paraffin-embedded; GCB, germinal center B-cell-like; HBV, hepatitis B virus; HR, hazard ratio; IPI, International prognostic index; IQR, interquartile range; LDH, lactate dehydrogenase; OS, overall survival; PET-CT/PET, ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography; R, rituximab; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; WES, whole exome sequencing; WGS, whole genome sequencing; 95% CI, 95% confidence interval.

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R-CHOP were randomized (1:1) between four cycles of rituximab (4R-CHOP+4R arm) or two cycles of R-CHOP plus two cycles of rituximab (6R-CHOP+2R arm). The primary endpoint was 2-year progression-free survival (PFS), conducted in the intention-to-treat population. Safety was assessed in patients with at least one cycle of assigned treatment. The non-inferiority margin was -8%.

Results: A total of 287 patients were included in the intention-to-treat analysis, the median follow-up was 47.3 months, and the 2-year PFS rate was 95% (95% confidence interval [CI], 92% to 99%) and 94% (95% CI, 91% to 98%) for the 4R-CHOP+4R and 6R-CHOP+2R arm. The absolute difference in 2-year PFS between the two arms was 1% (95% CI, -5% to 7%), supporting the non-inferiority of 4R-CHOP+4R. Grade 3-4 neutropenia was lower in the last four cycles of rituximab alone in the 4R-CHOP+4R arm (16.7% versus 76.9%), with decreased risk of febrile neutropenia (0.0% versus 8.4%) and infection (2.1% versus 14.0%).

Conclusions: For newly diagnosed low-risk DLBCL patients, interim PET-CT after four cycles of R-CHOP was effective in identifying patients with Deauville 1-3 who would have a good response and Deauville 4-5 patients who might have high-risk biological features or develop resistance. Reducing the standard six cycles to four cycles of chemotherapy had comparable clinical efficacy and fewer adverse events in low-risk, non-bulky DLBCL with interim PET-CT confirmed CR.

KEYWORDS

diffuse large B-cell lymphoma, low-risk, positron emission tomography, randomized phase III trial

1 | BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of non-Hodgkin lymphoma with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) immunochemotherapy as the standard of care in first-line treatment [1]. The international prognostic index (IPI) is widely applied in clinical practice based on age, serum lactate dehydrogenase (LDH), performance status, Ann Arbor stage, and extranodal involvement, categorizing DLBCL into four risk groups: low (0-1 points), low-intermediate (2 points), high-intermediate (3 points) and high risk (4-5 points), with estimated 3-year progression-free survival (PFS) rate of 86%, 75%, 64% and 53%, respectively [2]. More recently, considered as robust endpoints, PFS at 24 months (PFS24) and PFS at 12 months (PFS12) are significantly associated with durable remission and increased risk for early death in DLBCL, respectively [3, 4]. The MInT study showed that young DLBCL patients (aged $\leq$ 60 years) with IPI = 0 and without bulky disease (maximum lymphoma diameter < 7.5 cm) have a very favorable prognosis with a 3-year PFS rate of 95%, an event-free survival (EFS) rate of 89%, and an overall survival (OS) rate of 98% when treated with six cycles of R-CHOP-like regimens [5]. The FLYER study focused on young DLBCL patients with age-adjusted IPI (aaIPI) of 0 (age $\leq$ 60 years, normal LDH, Eastern Cooperative Oncology Group [ECOG] performance status 0-1, and stage I-II) and indicated that four cycles of R-CHOP plus two cycles of rituximab are non-inferior to six cycles of R-CHOP (3-year PFS rate 96% versus 94% and 3-year EFS rate 89% versus 89%) [6]. However, whether reducing chemotherapy to four cycles is effective and safe in low-risk DLBCL patients with one risk factor (IPI = 1) has not been answered. Therefore, we aimed to evaluate the potential role of four cycles of R-CHOP on durable remission in all patients with low-risk DLBCL, irrespective of age and other IPI risk factors.

Interim ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography (interim ^{18}F-FDG-PET-CT, interim PET hereafter) has a high negative predictive value for the disease progression of DLBCL [7] and may also function as a useful tool in PFS24 prediction. The HOVON-84 study presented evidence that interim PET after four cycles of R-CHOP had a predictive value of PFS24 (negative interim PET versus positive, 2-year PFS

rate 84% versus 61%, $P < 0.001$) [8]. Interim PET after three cycles of R-CHOP was also proven to be highly predictive of outcome (negative interim PET versus positive, 5-year PFS rate 72.6% versus 39.3%, $P < 0.001$) [9]. In the PETAL trial, CD20-positive aggressive non-Hodgkin lymphoma patients with positive interim PET after two cycles of R-CHOP had a 2-year PFS rate of 46.1% and EFS rate of 36.7%, significantly lower than those with negative interim PET (2-year PFS rate of 79.4% and EFS rate of 75.6%, $P < 0.001$). Moreover, outcome prediction by interim PET was independent of IPI [10]. Therefore, interim PET should be further investigated in each IPI risk group, particularly in low-risk DLBCL.

In addition, biological alterations confer inferior survival in DLBCL patients [11]. DLBCL is divided into three molecular subtypes based on cell-of-origin (COO): germinal center B-cell-like (GCB), activated B-cell-like (ABC), and unclassified [12], which is further translated into an immunohistochemistry-based classification as GCB and non-GCB [13]. The overexpression of both BCL2 and MYC, termed double-expressor lymphoma (DEL) [14], and high proliferation index (high Ki67) [15] are predictors of poor clinical outcomes upon R-CHOP treatment. Besides, *TP53* mutations showed a significantly worse prognosis under conventional immunochemotherapy, autologous stem-cell transplantation, and CD19-chimeric antigen receptor T-cell (CAR-T) [16–18]. Whether these adverse prognostic factors are equally predictive in low-risk DLBCL has not been specifically explored.

In the present study, we performed an open-label, randomized, phase III, non-inferiority trial to compare the efficacy and safety of four cycles of R-CHOP plus four cycles of rituximab to six cycles of R-CHOP plus two cycles of rituximab in low-risk DLBCL patients achieving complete response (CR) confirmed by PET-CT after four cycles of R-CHOP. We aimed to reduce chemotherapy to four cycles in all low-risk patients, including those with one IPI risk factor (IPI = 1) and identify patients with potential high-risk features through interim PET evaluation. In addition, we investigated the prognostic impact of clinical characteristics and biological alterations in this low-risk population.

2 | METHODS

2.1 | Study design and participants

This investigator-initiated study was a two-arm, open-label, randomized, non-inferiority phase III trial. Eligible patients were 14-75 years; had previously untreated biopsy-confirmed DLBCL according to the 2008 World Health Organization classification; had no more than one risk factor according to IPI, as well as an ECOG performance status of 0 or 1, and had no bulky disease, defined by a tumor < 7.5 cm in diameter; achieved CR after four cycles of standard R-CHOP regimen (assessed by PET-CT). The Deauville 5-point scale was used, using uptake in the mediastinum and liver as reference points, with Deauville 1-3 considered as CR. Exclusion criteria were previous chemotherapy or stem-cell transplantation; previous history of malignancy; uncontrollable cardio-cerebrovascular, coagulative, autoimmune, or serious infectious disease; primary cutaneous or central nervous system (CNS) DLBCL; impaired cardiac, liver, renal and hematological functions; other uncontrollable medical condition that may interfere the participation of the study; pregnancy or lactation; HIV infection; hepatitis B virus (HBV) DNA positive; and inability to comply to the protocol for mental or other unknown reasons. This study was approved by the Review Board of Shanghai Ruijin Hospital with informed consent obtained from all patients in accordance with the Declaration of Helsinki.

2.2 | Randomization and masking

Randomization was done in a 1:1 ratio using computer-assisted permuted-block randomization with a block size of four. Eligible patients were randomly assigned after achieving CR upon four cycles of R-CHOP to receive either four cycles of rituximab (4R-CHOP+4R arm) or two cycles of R-CHOP plus two cycles of rituximab (6R-CHOP+2R arm). Investigators and patients were not masked to treatment assignment.

2.3 | Procedures

R-CHOP consisted of rituximab 375 mg/m^2 intravenously on day 1, cyclophosphamide 750 mg/m^2, epirubicin 70 mg/m^2, and vincristine 1.4 mg/m^2 (maximum dose, 2 mg) intravenously on day 2, plus prednisone 60 mg/m^2 (maximum dose, 100 mg) orally once daily on day 2-6. Rituximab was given at the same dose as monotherapy. The cycles were repeated every 21 days. To exclude CNS involvement, lumbar puncture was mandatory in patients with involvement of the nasal or paranasal sinuses, adrenal gland, breast, bone marrow, uterus and ovaries, or testis. Prophylaxis for CNS relapse was given to patients with testicular and breast involvement, consisting of intrathecal methotrexate, 10 mg per dose and cytosine arabinoside, 50 mg per dose, administered during the first four cycles. Prophylactic radiotherapy to the contralateral testis was given to patients with testicular involvement. No radiotherapy was administered to other sites. The use of granulocyte

colony-stimulating factor (including pegylated recombinant human granulocyte colony-stimulating factor) for the prophylaxis of neutropenia was determined at the discretion of the investigators.

Response was evaluated at the end of treatment, based on a PET-CT scan according to the Lugano criteria for non-Hodgkin lymphoma, using the Deauville 5-point scale. Deauville 1-3 was considered CR [19]. Follow-up examination was repeated every three months during the first year, six months during the second year, and subsequent every year. Follow-up examinations included a clinical examination, laboratory analysis, and contrast-enhanced neck, thorax, abdomen and pelvis CT.

All diagnoses were confirmed by experienced pathologists of Shanghai Ruijin Hospital. The Hans classification was used to identify the COO profile (the GCB subtype and non-GCB subtype), with 30% cutoff values for CD10, BCL6, and MUM-1 by immunohistochemistry. DEL was defined as > 50% for BCL2 and ≥ 40% for MYC, as previously described [14]. Fluorescence in situ hybridization analysis for rearrangements of BCL2, BCL6 and MYC was performed to exclude double-hit lymphoma or triple-hit lymphoma.

2.4 | Outcomes

PFS at two years was the primary endpoint, in which PFS was defined as the time from randomization until disease progression, relapse or death from any cause. The key secondary endpoint was OS at two years, in which OS was defined as the time from randomization until death from any cause. Other secondary endpoints were CR rate and safety. Adverse events were graded in accordance with the National Cancer Institute Common Terminology Criteria of Adverse Events, version 4.0.

2.5 | DNA sequencing

DNA sequencing was performed on 256 patients with available tumor samples to detect genetic aberrations. Genomic DNA was extracted from frozen tumor tissue by a QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) or from formalin-fixed paraffin-embedded (FFPE) tumor tissue by a GeneRead DNA FFPE Tissue Kit (Qiagen), based on the manufacturer's guidelines. Whole exome sequencing (WES) data from 44 patients and whole genome sequencing (WGS) data from 9 patients have been reported in our previous manuscript about extranodal DLBCL [20]. Two hundred and three patients with FFPE tumor tissue or frozen tumor tissue were analyzed by targeted sequencing of 55 lymphoma-associated genes using the methods defined in the supporting information of our previous study [20]. Sequencing data have been deposited on https://www.biosino.org/node in project OEP001143.

2.6 | Statistical analysis

This trial aims to assess the efficacy of four cycles of R-CHOP plus four cycles of rituximab compared to six cycles of R-CHOP plus two cycles of rituximab. We hypothesized a 2-year PFS rate of 94% for the 6R-CHOP+2R arm and no difference between groups. With a prespecified non-inferiority margin of -8% [21, 22] and a 4% dropout rate, 290 patients were required to reach a power of 80% at a significance level of 2.5% (one-sided). Analyses were performed in the intention-to-treat population. PFS and OS endpoints were analyzed with the Kaplan-Meier method. To demonstrate non-inferiority, the difference between the 2-year PFS rate of the 4R-CHOP+4R arm versus the 6R-CHOP+2R arm and the two-sided 95% confidence interval (CI) using the Newcombe-Wilson method with continuity correction were calculated [23], and whether it lies entirely on the positive side of the prespecified non-inferiority margin of -8% was established. Safety was assessed in all patients who received at least one cycle of assigned treatment. Characteristics of patients between treatment regimens were compared by $\chi 2$ tests (Fisher's exact test was adopted, if necessary). The significance level was two-sided at 0.05. Continuous variables were analyzed using a parametric test (student's t-test) or a nonparametric test (Wilcoxon signed-rank test) according to the situation. Response and relapse rates are presented with 95% CIs. Hazard ratio (HR) was estimated by Cox proportional hazard regression model in univariate analysis. In exploratory analyses, we performed subgroup analysis according to age, serum LDH, Ann Arbor stage, extranodal involvement, COO profile, and DEL status and explored the prognostic value of gene mutations. The associations between clinical and pathological characteristics with PFS24 and PFS12 were also evaluated by $\chi 2$ tests (Fisher's exact test was adopted, if necessary). EFS was analyzed, which was defined as the time from randomization until any treatment failure or discontinuation of treatment for any reason (e.g., disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death) [24]. Besides, characteristics between patients with negative interim PET (achieving interim CR, i.e., with Deauville 1-3) and patients with positive interim PET (not achieving CR, i.e., with Deauville 4-5) were also compared. Statistical analyses were done with SPSS, version 22, and R, version 4.2.1. This trial is registered at ClinicalTrials.gov, number NCT02752815.

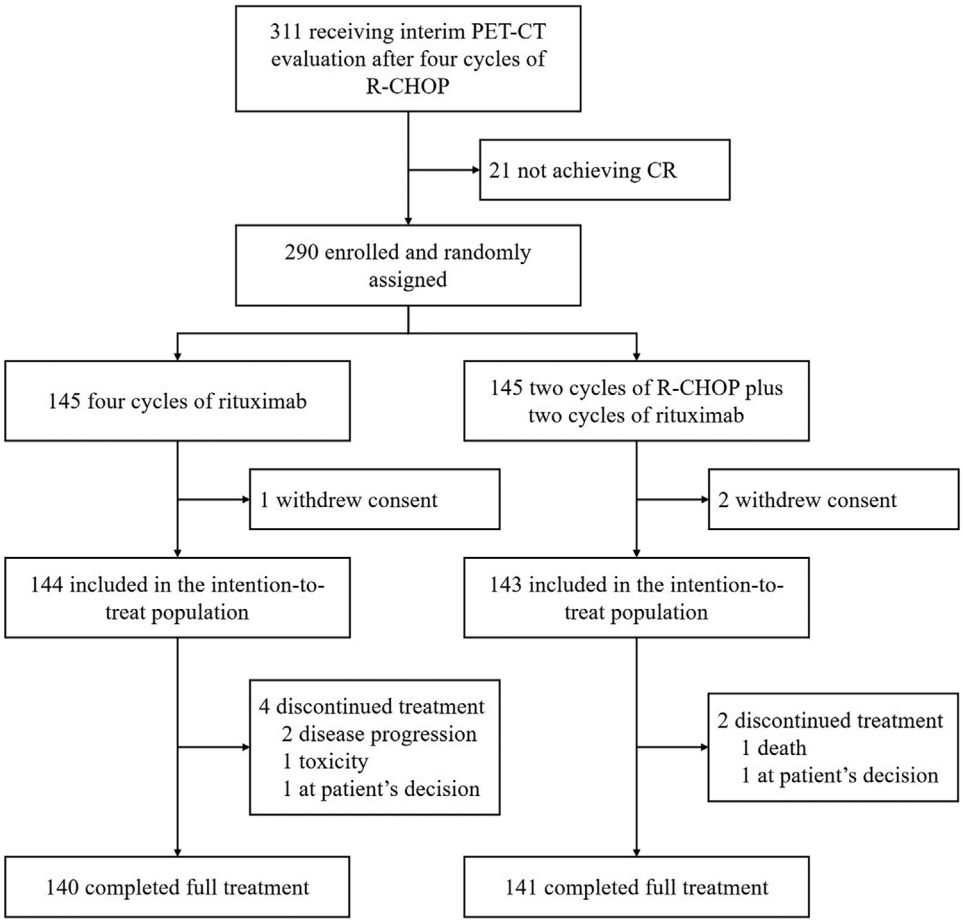

FIGURE 1 CONSORT diagram of the study. From June 14, 2016, to October 30, 2020, 311 patients were screened, of whom 290 were randomized. Two hundred eighty-seven patients were included in the intention-to-treat analysis, with 144 in the 4R-CHOP+4R arm and 143 in the 6R-CHOP+2R arm. Abbreviations: CR, complete response. PET-CT, 18F-fluorodeoxyglucose positron emission tomography with computed tomography; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

3 | RESULTS

From June 14, 2016, to October 30, 2020, 311 patients who received four cycles of R-CHOP and interim PET were screened, among whom 21 patients failed to meet the inclusion criteria due to positive interim PET. Two hundred and ninety patients were enrolled and randomly assigned to either additional four cycles of rituximab (4R-CHOP+4R arm, $n = 145$) or two cycles of R-CHOP plus two cycles of rituximab (6R-CHOP+2R arm, $n = 145$). With one patient in the 4R-CHOP+4R arm and two in the 6R-CHOP+2R arm withdrawing informed consent, 287 patients were included in the intention-to-treat analysis (Figure 1). Baseline characteristics were well-balanced across the two treatment arms (Table 1). The median age at baseline was 55 years of the whole cohort (range 18-75 years). In all 287 patients, 50.9% had one risk factor according to IPI, 30.3% were older than 60 years, and 47.4% had extranodal involvement. Reference pathology was performed in all 287 patients and diagnosed as CD20+ DLBCL.

The data cutoff for the present analyses was October 30, 2022. The median follow-up time for PFS was 47.3 months (interquartile range [IQR] 36.5-62.2 months), during which 19 (6.6%) patients had disease progression and 7 (2.4%) patients died. One hundred and forty patients in the 4R-CHOP+4R arm and 141 patients in the 6R-CHOP+2R arm completed the treatment. The reasons for treatment termination of 4 patients in the 4R-CHOP+4R arm were disease progression, toxicity, and personal decision, and the reasons for 2 patients in the 6R-CHOP+2R arm were death from severe pulmonary infection and personal decision. Protocol deviations occurred in 1 patient in the 4R-CHOP+4R arm and 3 patients in the 6R-CHOP+2R arm (2 rituximab deviations and 2 chemotherapy deviations). Fifteen patients with testicular involvement were enrolled (6 patients in the 4R-CHOP+4R arm and 9 in the 6R-CHOP+2R arm). Prophylactic radiotherapy to the

TABLE 1 Baseline demographic and disease characteristics (intention-to-treat population).

Characteristics	Four cycles of R-CHOP plus four cycles of rituximab ($n = 144$)	Six cycles of R-CHOP plus two cycles of rituximab ($n = 143$)	*P* value
Gender			0.440
Female	71 (49.3%)	64 (44.8%)	
Male	73 (50.7%)	79 (55.2%)	
Age			0.984
Median (IQR)	55 (44-62)	55 (46-62)	
Range	18-75	25-74	
> 60 years	47 (32.6%)	40 (28.0%)	0.390
Serum LDH > ULN	22 (15.3%)	23 (16.1%)	0.851
ECOG performance status			0.888
0	122 (84.7%)	122 (85.3%)	
1	22 (15.3%)	21 (14.7%)	
Ann Arbor Stage			0.685
I	73 (50.7%)	74 (51.7%)	
II	66 (45.8%)	60 (42.0%)	
III	3 (2.1%)	6 (4.2%)	
IV	2 (1.4%)	3 (2.1%)	
Extranodal involvement	62 (43.1%)	74 (51.7%)	0.140
IPI			0.860
0	70 (48.6%)	71 (49.7%)	
1	74 (51.4%)	72 (50.3%)	
B-symptoms	14 (9.7%)	16 (11.2%)	0.685
Cell of origin according to Hans			0.518
GCB	62 (43.1%)	67 (46.9%)	
Non-GCB	82 (56.9%)	76 (53.1%)	
BCL2-MYC double expression			0.772
Yes	25 (17.4%)	23 (16.1%)	
No	119 (82.6%)	120 (83.9%)	
BCL2 rearrangement			0.610
Yes	1 (0.7%)	3 (2.1%)	
No	143 (99.3%)	140 (97.9%)	
BCL6 rearrangement			0.401
Yes	33 (22.9%)	27 (18.9%)	
No	111 (77.1%)	116 (81.1%)	
MYC rearrangement			0.475
Yes	0 (0%)	2 (1.4%)	
No	144 (100%)	141 (98.6%)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; LDH, lactate dehydrogenase; IPI, international prognostic index; IQR, interquartile range; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; ULN, upper limit of normal.

contralateral testis was applied in patients with testicular involvement.

In the intent-to-treat analysis, the 2-year PFS rate was 95% (95% CI, 92% to 99%) of the 4R-CHOP+4R arm versus 94% (95% CI, 91% to 98%) of the 6R-CHOP+2R arm (Figure 2A). The absolute difference of the 2-year PFS rate between the two arms was 1% (95% CI, -5% to 7%), thus meeting the criterion for non-inferiority (the prespecified non-inferiority margin was -8%, $P < 0.001$), demonstrating the non-inferior efficacy of four cycles of R-CHOP plus four cycles of rituximab compared to six cycles of R-CHOP plus two cycles of rituximab. The 2-year OS rate

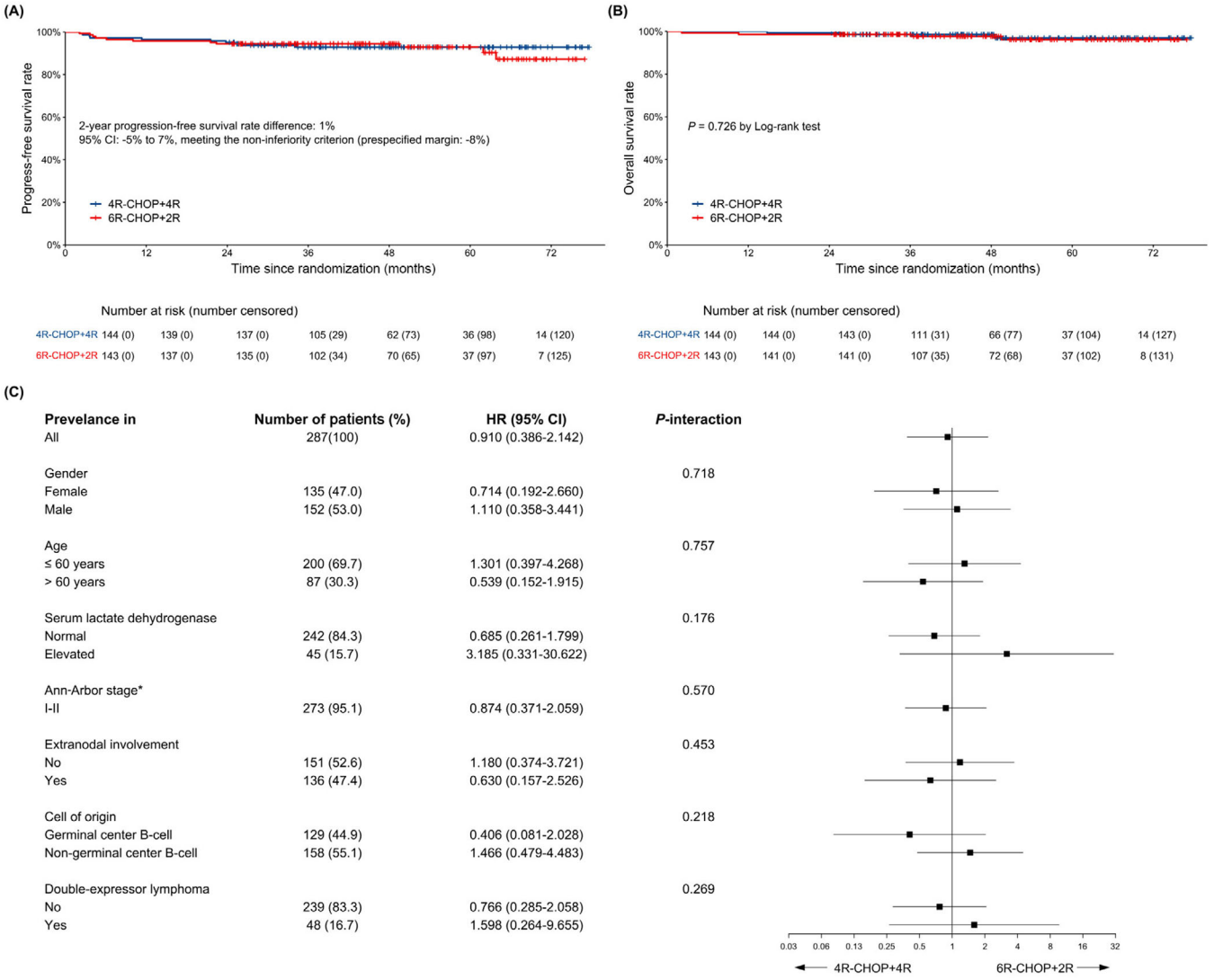

FIGURE 2 Survival in all and subgroups of patients. (A) Kaplan-Meier survival curve of PFS in the intent-to-treat analysis set. The 2-year PFS rate was 95% and 94% in the 4R-CHOP+4R and 6R-CHOP+2R arms, respectively. The absolute difference of the 2-year PFS rate between the two arms was 1% (95% CI, -5% to 7%), meeting the criterion for non-inferiority (the prespecified non-inferiority margin was -8%, $P < 0.001$). (B) Kaplan-Meier survival curve of OS in the intent-to-treat analysis set. The 2-year OS rate was 99% in both arms, respectively. (C) Forest plot for PFS in subgroups of patients, showing no significant difference was observed between the two treatment arms across subgroups. *No event was observed in patients with Ann Arbor stage III-IV, hence not shown in the Figure.
Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; R, rituximab; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone.

was 99%, and the 2-year EFS rate was 94% in both arms, respectively (2-year OS rate: 95% CI, 98% to 100% [4R-CHOP+4R arm] vs. 95% CI, 97% to 100% [6R-CHOP+2R arm], Figure 2B; 2-year EFS rate: 95% CI, 90% to 98% [both arms]). At the end of treatment, 140 (97.2%) of 144 patients in the 4R-CHOP+4R arm versus 138 (96.5%) of 143 patients in the 6R-CHOP+2R arm had a complete response (Table 2). Four (2.8%) patients progressed while on therapy or at end-of-treatment evaluation in each group, and a total of 11 (4.0%) patients relapsed after therapy. The relapse rates were similar (4.3% for the 4R-CHOP+4R group and 3.6% for the 6R-CHOP+2R group, Table 2). Three patients suffered from CNS relapse. Two (18.2%, one in each group) of 11 patients relapsed after a complete response within 12 months after the end of treatment. Six patients (54.5%, four in the 4R-CHOP+4R group and two in the 6R-CHOP+2R group) occurred within 24 months, and 3 (27.3%, one in the 4R-CHOP+4R group and two in the 6R-CHOP+2R group) after 24 months. The median time from enrollment to relapse was 23.8 months (range, 10.0-63.8 months) for the entire group, without difference between the two treatment arms (Supplementary Figure S1). There

TABLE 2 Response and relapse rates (intention-to-treat population).

Response	Four cycles of R-CHOP plus four cycles of rituximab group ($n = 144$)	Six cycles of R-CHOP plus two cycles of rituximab group ($n = 143$)
Complete response, n (%; 95% CI)	140 (97.2%; 93.0% to 99.2%)	138 (96.5%; 92.0% to 98.9%)
Partial response	0	0
Stable disease	0	0
Progressive disease, n (%)	4 (2.8%)	4 (2.8%)
Not evaluated or missing data[a]	0	1
Relapse after complete response, n/N (%; 95% CI)	6/140 (4.3%; 1.6% to 9.1%)	5/138 (3.6%; 1.2% to 8.3%)

[a]One patient in the 6R-CHOP+2R group discontinued chemotherapy because of therapy-associated death without having a response assessment.
Abbreviations: 95% CI, 95% confidence interval; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone.

TABLE 3 Adverse events in the last four cycles of treatment.

Events	Four cycles of R-CHOP plus four cycles of rituximab group ($n = 144$)		Six cycles of R-CHOP plus two cycles of rituximab group ($n = 143$)		*P* value
	Grade 3	Grade 4	Grade 3	Grade 4	
Hematological events					
Neutropenia	23 (16.0%)	1 (0.7%)	45 (31.5%)	65 (45.5%)	< 0.001
Anaemia	0	0	0	1 (0.7%)	0.498
Thrombocytopenia	0	0	5 (3.5%)	1 (0.7%)	0.038
Febrile neutropenia	0	0	12 (8.4%)	0	< 0.001
Non-hematological events					
Infection	3 (2.1%)	0	19 (13.3%)	1 (0.7%)	< 0.001
Increase in liver enzymes	1 (0.7%)	0	1 (0.7%)	0	1.000
Mucositis	0	0	1 (0.7%)	0	0.498
Nausea or vomiting	0	0	1 (0.7%)	0	0.498
Neurological toxicity	0	0	1 (0.7%)	0	0.498

Abbreviations: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone.

were 7 deaths, 3 in the 4R-CHOP+4R arm and 4 in the 6R-CHOP+2R arm. Five patients died of progressive disease (2 patients died [1 patient in each group] within 12 months after enrollment, and 3 patients [2 patients in the 4R-CHOP+4R group and 1 patient in the 6R-CHOP+2R group] died after relapsed disease more than 24 months after enrollments), 1 died of infection during treatment, and 1 died of chronic obstructive pulmonary disease 4 years after treatment.

Hematological and non-hematological adverse events in the last four cycles are listed in Table 3. The most common grade 3-4 adverse event was neutropenia. Grade 3-4 neutropenia occurred less frequently in the last four cycles of rituximab alone in the 4R-CHOP+4R arm (24 [16.7%], including 23 [16.0%] of grade 3 and 1 [0.7%] of grade 4) than in the last four cycles (two cycles of R-CHOP plus two cycles of rituximab) in the 6R-CHOP+2R arm (110 [76.9%], including 45 [31.5%] of grade 3 and 65 [45.5%] of grade 4) ($P < 0.001$), as well as febrile neutropenia (0 [0%] versus 12 [8.4%], $P < 0.001$) and infection (3 [2.1%] versus 20 [14.0%], the latter including 19[13.3%] of grade 3 and 1 [0.7%] of grade 4, $P < 0.001$). One patient in the 6R-CHOP+2R arm died during treatment after five cycles of R-CHOP because of pulmonary infection.

In the post-hoc per-protocol analysis of 285 patients, the 2-year PFS rate was 95% (95% CI, 92% to 99%) in the 4R-CHOP+4R arm versus 94% (95% CI, 91% to 98%) in the 6R-CHOP+2R arm. The 2-year OS rate was 99% in both arms (95% CI, 98% to 100% in the 4R-CHOP+4R arm and 95% CI, 97% to 100% in the 6R-CHOP+2R arm). Long-term outcomes were also estimated in post-hoc analyses. The estimated 4-year PFS rate was 93% (95% CI, 89% to 97%) in the 4R-CHOP+4R arm versus 94% (95% CI, 91% to 98%) in the 6R-CHOP+2R arm. The estimated 4-year OS rate was 99% (95% CI, 97% to 100%) in the 4R-CHOP+4R arm versus 98% (95% CI, 95% to 100%) in the 6R-CHOP+2R arm.

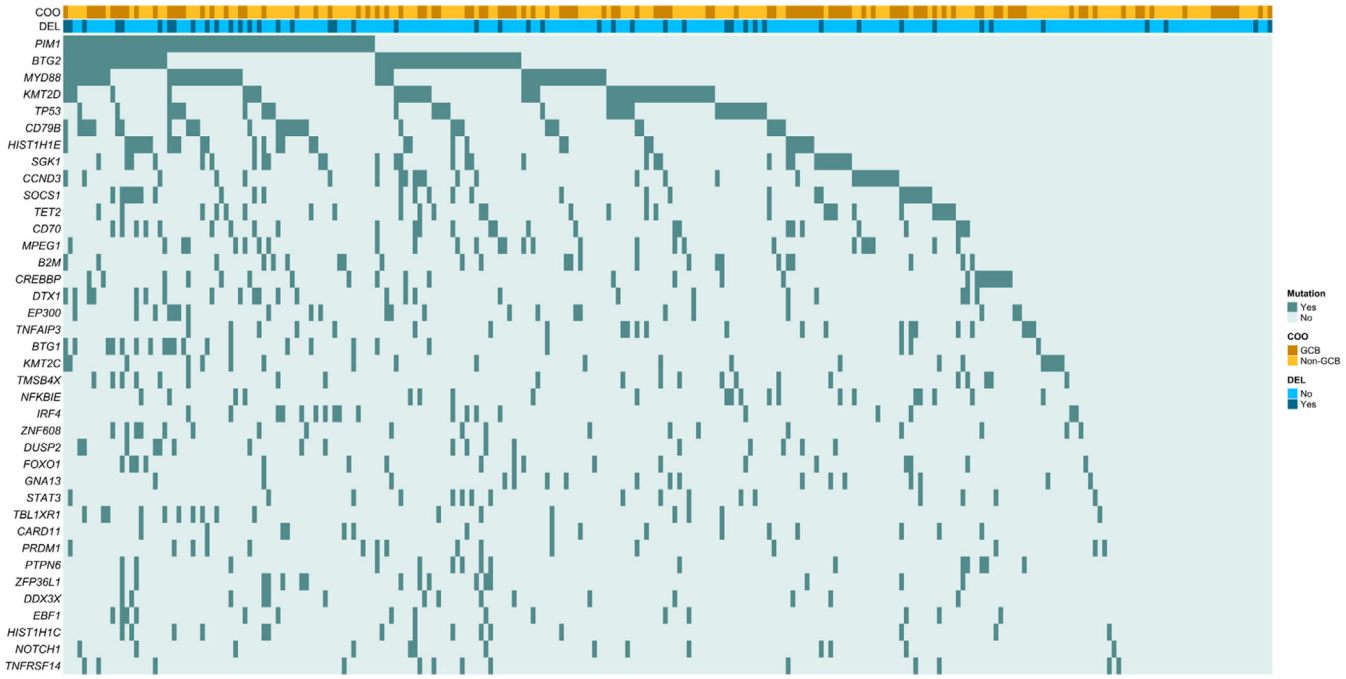

FIGURE 3 Genetic aberrations of patients ($n = 256$). Gene mutations identified by next-generation sequencing. Genes with a mutation rate greater than 5% were shown. The most frequently mutated genes included *PIM1* (25.8%), *BTG2* (20.7%), *MYD88* (19.1%), *KMT2D* (17.2%), *TP53* (12.9%), *CD79B* (12.5%), *HIST1H1E* (12.5%), and *SGK1* (12.5%).
Abbreviations: COO, Cell of origin according to Hans classification; DEL, double-expressor lymphoma; GCB, germinal center B-cell.

In post-hoc subgroup analysis, no significant difference was observed between the two treatment arms (Figure 2C). All 287 patients had a COO profile, 129 (44.9%) patients were classified as GCB and 158 (55.1%) as non-GCB (Supplementary Table S1). All the patients have BCL2 and MYC expression data, and 48 (16.7%) patients presented with DEL while 239 (83.3%) did not. No PFS superiority was found in either arm according to IPI risk factors, COO profile or DEL status. All the patients had Ki67 expression data, and 41 (14.3%) patients were with high Ki67 expression (> 90%). Deauville scores of interim PET were evaluated in all 287 patients, with 9 (3.1%) patients having a Deauville score of 3 and the other 278 (96.9%) patients having a Deauville score of 1-2. Genetic aberrations of low-risk DLBCL patients were also explored. Targeted sequencing, WES and WGS were performed on 203, 44, and 9 patients, respectively, in 128 patients for each treatment arm. Fifty-five genes related to the tumorigenesis of DLBCL were analyzed (Figure 3). The most frequently mutated genes (> 10%) included *PIM1* (66/256, 25.8%), *BTG2* (53/256, 20.7%), *MYD88* (49/256, 19.1%), *KMT2D* (44/256, 17.2%), *TP53* (33/256, 12.9%), *CD79B* (32/256, 12.5%), *HIST1H1E* (32/256, 12.5%), *SGK1* (32/256, 12.5%), *CCND3* (28/256, 10.9%), *SOCS1* (28/256, 10.9%), *TET2* (28/256, 10.9%), *CD70* (27/256, 10.5%), and *MPEG1* (27/256, 10.5%).

In the univariate analysis for PFS, clinical or pathological factors, including age, serum LDH, performance status (ECOG 0 or 1), Ann Arbor stage, extranodal involvement (yes or no), COO profile, DEL status, Ki67 index, and Deauville score at interim PET, had no obvious effect on PFS. Besides, no oncogenic mutations were found predictive for PFS (Supplementary Table S2). Through comparison of characteristics of patients who achieved PFS24 and those who did not (PFS12 was analyzed in the same way), a significant difference was found for the Deauville score, revealing an increase in the risk of failing to achieve PFS24 and PFS12 among patients with Deauville 3 at interim PET (Supplementary Table S1). Univariate analysis for OS was not obtained since only seven deaths occurred in the 287 analyzed patients.

In the post-hoc analysis, 21 patients with positive interim PET were also analyzed. A significantly worse prognosis was noted in patients with positive interim PET (not achieving interim CR) than those with negative interim PET (achieving interim CR), whose demographic and clinical characteristics were generally similar to those with negative interim PET. As for oncogenic mutations, significantly increased *TP53* mutations (47.4% versus 12.9%, $P < 0.001$) were observed in patients with positive interim PET (Supplementary Table S3). Besides, *TP53* mutations

TABLE 4 Summary of key phase III studies in low-risk DLBCL/limited-stage DLBCL.

Study	Treatment arms (*n*)	Inclusion criteria	iPET involved	Histology	Stage[a]	Age[a]	ECOG PS[a]	LDH >ULN[a]	EI[a]	IPI[a]	Median follow up	Response rate	PFS	OS
Pfreundschuh et al. 2006 [5], Phase III, RCT, MInT	R-CHOP-like × 6 (n = 413) vs CHOP-like × 6 (n = 410)	Age 18-60 years, aaIPI 0-1, stage II-IV or stage I with bulk, DLBCL	No	87% DLBCL	Stage I/II (73%)	100% under 60 years	0-1 (99%)	29%	34%	aaIPI = 0 (43%), aaIPI = 1 (57%)	72 months (range 0.03-119 months)	CR: 86% vs. 68%; PD: 4% vs 11%	3y-PFS: 85% vs. 68%; 6y-PFS: 80.2% vs. 63.9%	3y-OS: 93% vs 84%; 6y-OS: 80.2% vs 63.9%
Poeschel et al. 2019 [6], Phase III, open-label, non-inferiority RCT, FLYER	R-CHOP × 4 + R × 2 (n = 293) vs R-CHOP × 6 (n = 295); Non-inferiority margin -5.5%	Age 18-60 years, aaIPI 0, no bulk (< 7.5cm), aggressive B-NHL	No	85% DLBCL	Stage I/II (99%)	100% under 60 years	0-1 (100%)	0%	32%	aaIPI = 0 (99%)	66 months (IQR 42-100 months)	CR/Cru: 91% vs 92%; PR: 3% vs. 4%; SD: 0% vs <1%	3y-PFS: 96% vs 94%; 5y-PFS: 94% vs 94%	3y-OS: 99% vs 98%; 5y-OS: 97% vs 98%
Lamy et al. 2018 [25], Phase III, RCT, LYSA/ GOELAMS	R-CHOP × 4 + IFRT vs R-CHOP × 4 if smIPI = 0 (age ≤ 60 years, normal LDH, ECOG PS = 0, and stage I, n = 158), R-CHOP × 6 + IFRT vs R-CHOP × 6 if smIPI ≥ 1 (n = 123)	Age 18-75 years, stage I/II, no bulk (< 7 cm), DLBCL	Yes; Treatment according to random assignment if CR after 4 cycles. 2 additional cycles followed by IFRT if PR	100% DLBCL	Stage I/II	36% above 60 years	0-1 (97%)	18%	39%	smIPI = 0 (56%), smIPI = 1 (38%), smIPI = 2-3 (6%)	64 months (range 24-132 months)	CR: 94% (no IFRT) vs. 98% (with IFRT); PR: 5% vs 1%; PD: 0% vs <1%	NA	5y-OS: 92% vs 96%
Pfreundschuh et al. 2017 [27], Phase III, RCT OPTIMAL > 60	CHOP-14 × 4 + R × 8 vs CHLIP-14 × 4 + R × 8, additional 2 × CHOP/CHLIP + ISRT if PET-positive	Age 61-80 years, IPI = 1 (age > 60 years), no bulk (<7.5 cm)	Yes	NA	NA	100% above 60 years	NA	NA	NA	NA	NA	NA	2y-PFS: 94%	2y-OS: 98%
Bologna et al. 2021 [29], Phase III, RCT, LYSA LNH 09-1B	R-CHOP × 2 then R-CHOP × 2 if PET-negative and R-CHOP × 4 if PET-positive (n = 319) vs R-CHOP × 6 (n = 331)	Age 18-80 years, aaIPI 0, bulk > 10cm permitted, DLBCL/FL3B	Yes	NA	Stage I/II	44% above 59 years	NA	NA	53%	NA	61 months (IQR 42-78 months)	NA	3y-PFS: 92% vs 89%	NA
Our Study	R-CHOP × 4 + R × 4 (n = 144) vs R-CHOP × 6 + R × 2 (n = 143); Non-inferiority margin -8%	Age 14-75 years, ECOG 0-1, IPI 0-1, no bulk (< 7.5 cm), DLBCL, CR after R-CHOP × 4	Yes; Patients achieving CR after 4 cycles were included in the randomization	100% DLBCL	Stage I/II (95%)	30% above 60 years	0-1 (100%)	16%	47%	IPI = 0 (49%), IPI = 1 (51%)	47 months (IQR 37-62 months)	CR: 97% vs 97%; PD: 3% vs 3%	2y-PFS: 95% vs 94%; 4y-PFS: 93% vs 94%	2y-OS: 99% vs 99%; 4y-OS: 99% vs 98%

[a]These data represent the percentage of patients with specific clinical characteristics.

Abbreviations: 2y, 2 years (the same for 3y and 4y); aaIPI, age-adjusted IPI; B-NHL, B-cell non-Hodgkin lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CHLIP, cyclophosphamide, doxorubicin, liposomal vincristine, prednisolone; CR, complete response; Cru, complete response unconfirmed; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL3B, follicular lymphoma grade 3B; EI, Extranodal involvement; IFRT, involved-field radiotherapy; iPET, interm positron emission tomography with computed tomography; IPI, international prognostic index; IQR, inter-quartile range; ISRT, involved-site radiotherapy; LDH, lactate dehydrogenase; NA, not applicable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, rituximab; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone; RCT, randomized controlled trial; SD, stable disease; smIPI, stage-modified IPI; ULN, upper limit norm.

conferred inferior survival in low-risk DLBCL patients ($P = 0.015$) when patients of positive interim PET were also included (Supplementary Table S4).

4 | DISCUSSION

Several large studies have focused on patients with low-risk or limited-stage DLBCL (Table 4). We conducted a phase III randomized controlled trial in low-risk DLBCL patients, irrespective of age and other IPI risk factors. We found that 4 cycles of R-CHOP plus 4 cycles of rituximab was not inferior to 6 cycles of R-CHOP plus 2 cycles of rituximab in DLBCL without IPI risk factors or with any of the five risk factors, including age, serum LDH, performance status (ECOG 0 or 1), Ann Arbor stage, and extranodal involvement (yes or no). As expected, fewer hematological and non-hematological toxicities occurred as the cycles of chemotherapy were reduced, which was consistent with the FLYER study, which comprised young patients with IPI = 0 and non-bulky disease [6] and with the LYSA/GOELAMS 02-03 study, which included patients with limited and non-bulky disease undergoing 4 cycles of R-CHOP in subgroups with ECOG 0, stage I and IPI = 0 [25]. Our study extended the strategy of interim-PET-adapted shortening of chemotherapy not only to young patients without risk factors (consistent with the FLYER study and the LYSA/GOELAMS 02-03 study), but also to low-risk patients over 60 years and young patients with one risk factor according to IPI.

As a widely proven independent prognostic tool in DLBCL [7, 8, 10], interim-PET-guided treatment decisions are of much value, especially in low-risk or limited-stage DLBCL. The phase II S1001 study also used a PET-adapted strategy in localized DLBCL, where patients with non-bulky stage I/II DLBCL achieving negative interim PET after three cycles of R-CHOP proceeded with one additional cycle of R-CHOP and obtained 5-year PFS rate of 89% and 5-year OS rate of 91% [26]. Another phase III ongoing OPTIMAL > 60 study focuses on elderly patients (> 60 years, IPI = 1) under the PET-adapted strategy, where patients without bulky disease and achieving negative interim PET after 4 cycles of R-CHOP, proceeded with 4 additional cycles of rituximab and showed 2-year PFS rate of 94% and 2-year OS rate of 98% [27]. We demonstrated that for all low-risk IPI DLBCL patients with negative interim PET after 4 cycles of R-CHOP, in any of the subgroups, reduction of 2 cycles of chemotherapy proved equally effective as 6 cycles of R-CHOP. Besides, our study provides data for further research on the optimal timing of interim PET in low-risk DLBCL patients.

The prognosis for patients who fail to achieve PFS12 remains poor [4, 28]. Novel targeted approaches may be promising for these patients failing to achieve PFS12, such as preemptive CAR-T cell therapy, antibody-drug conjugates, and bispecific antibodies [11]. On the contrary, achieving PFS24 is closely related to excellent long-term remission in DLBCL. Our study indicated that Deauville 3 at interim PET was an adverse prognostic factor for PFS12 and PFS24. Given the relatively small number of patients with Deauville 3 at interim PET, the results of the other two large-cohort prospective trials in DLBCL (OPTIMAL > 60 [27] and LNH 09-1B [29]), as well as our ongoing phase III GLORIA trial [NCT05018520], could provide more evidence on the interpretation of Deauville 3 at interim PET. Nevertheless, there is no doubt that PET-guided treatment strategies pave the way for future studies.

In our study, none of the clinical or biological factors was found with independent prognostic significance in patients of negative interim PET after four cycles of R-CHOP. As an additional finding of our study, patients with positive interim PET showed significantly increased *TP53* mutations. Upon further analyses, we found that when patients of positive interim PET were also included, *TP53* mutations indicated shorter OS than wild-type *TP53*, which were confirmed as unfavorable prognostic factors in all patients with DLBCL [16–18]. This indicated that even in low-risk DLBCL with a generally favorable prognosis, patients with *TP53* mutations might need treatment beyond R-CHOP. Moreover, patients with positive interim PET are likely to harbor high-risk biological features, accounting for the inferior prognosis. Therefore, positive interim PET and molecular characteristics may be major considerations in the subsequent therapeutic options in low-risk DLBCL patients.

The limitation of our study is that this prospective trial is conducted in a single center, and a large-scale randomized multicenter clinical trial (NCT05018520) is ongoing to provide more evidence of 4 cycles of R-CHOP in low-risk (IPI 0-1) DLBCL patients.

5 | CONCLUSIONS

Four cycles of R-CHOP plus 4 cycles of rituximab demonstrated comparable clinical efficacy to 6 cycles of R-CHOP plus 2 cycles of rituximab but demonstrated fewer adverse events in DLBCL patients with low-risk, non-bulky disease achieving negative interim PET. This interim PET-adapted strategy ensures durable remission in low-risk DLBCL and identifies patients with positive interim PET who may bear potential high-risk biological features as candidates for novel mechanism-based targeted approaches or future clinical trials.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Qing Shi collected and analyzed clinical data, prepared biological samples, and wrote the article. Yang He gathered detailed clinical information and prepared biological samples. Hong-Mei Yi reviewed the histological diagnoses and collected detailed pathological information. Rong-Ji Mu was responsible for statistical review. Xu-Feng Jiang reviewed the PET-CT scans and collected clinical data. Di Fu, and Lei Dong collected genetic information and analyzed the sequencing data. Wei Qin collected and analyzed clinical data. Peng-Peng Xu designed the study, wrote the protocol, and recruited patients. Shu Cheng recruited patients and collected clinical data. Qi Song reviewed the CT scans. Sai-Juan Chen gave advice on the study. Li Wang and Wei-Li Zhao designed and conceived the study, directed and supervised the research, and wrote the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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CONFLICT OF INTEREST STATEMENT

We declare no competing interests.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of Shanghai Ruijin Hospital (2016-14), with informed consent obtained from all patients in accordance with the Declaration of Helsinki. This trial was registered at ClinicalTrials.gov, number NCT02752815. https://clinicaltrials.gov/ct2/show/NCT02752815.

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Swerdlow SA-O, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–90.
2. Ruppert AS, Dixon JG, Salles G, Wall A, Cunningham D, Poeschel V, et al. International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI. Blood. 2020;135(23):2041–8.
3. Maurer MJ, Habermann TM, Shi Q, Schmitz N, Cunningham D, Pfreundschuh M, et al. Progression-free survival at 24 months (PFS24) and subsequent outcome for patients with diffuse large B-cell lymphoma (DLBCL) enrolled on randomized clinical trials. Ann Oncol. 2018;29(8):1822–7.
4. Shah NN, Ahn KW, Litovich C, He Y, Sauter C, Fenske TS, et al. Is autologous transplant in relapsed DLBCL patients achieving only a PET+ PR appropriate in the CAR T-cell era? Blood. 2021;137(10):1416–23.
5. Pfreundschuh M, Trümper L, Osterborg A, Pettengell R, Trneny M, Imrie K, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol. 2006;7(5):379–91.
6. Poeschel V, Held G, Ziepert M, Witzens-Harig M, Holte H, Thurner L, et al. Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial. Lancet. 2019;394(10216):2271–81.
7. Burggraaff CN, de Jong A, Hoekstra OS, Hoetjes NJ, Nievelstein RAJ, Jansma EP, et al. Predictive value of interim positron emission tomography in diffuse large B-cell lymphoma: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2019;46(1):65–79.

8. Burggraaff CN, Eertink JJ, Lugtenburg PJ, Hoekstra OS, Arens AIJ, de Keizer B, et al. (18)F-FDG PET Improves Baseline Clinical Predictors of Response in Diffuse Large B-Cell Lymphoma: The HOVON-84 Study. J Nucl Med. 2022;63(7):1001–7.
9. Yim SK, Yhim HY, Han YH, Jeon SY, Lee NR, Song EK, et al. Early risk stratification for diffuse large B-cell lymphoma integrating interim Deauville score and International Prognostic Index. Ann Hematol. 2019;98(12):2739–48.
10. Dührsen U, Müller S, Hertenstein B, Thomssen H, Kotzerke J, Mesters R, et al. Positron Emission Tomography-Guided Therapy of Aggressive Non-Hodgkin Lymphomas (PETAL): A Multicenter, Randomized Phase III Trial. J Clin Oncol. 2018;36(20):2024–34.
11. Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. N Engl J Med. 2021;384(9):842–58.
12. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000;403(6769):503–11.
13. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004;103(1):275–82.
14. Johnson NA, Slack GW, Savage KJ, Connors JM, Ben-Neriah S, Rogic S, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012;30(28):3452–9.
15. Han Y, Yang J, Liu P, He X, Zhang C, Zhou S, et al. Prognostic Nomogram for Overall Survival in Patients with Diffuse Large B-Cell Lymphoma. Oncologist. 2019;24(11):e1251–e61.
16. Xu-Monette ZY, Wu L, Visco C, Tai YC, Tzankov A, Liu WM, et al. Mutational profile and prognostic significance of TP53 in diffuse large B-cell lymphoma patients treated with R-CHOP: report from an International DLBCL Rituximab-CHOP Consortium Program Study. Blood. 2012;120(19):3986–96.
17. Chiappella A, Diop F, Agostinelli C, Novo M, Nassi L, Evangelista A, et al. Prognostic impact of TP53 mutation in newly diagnosed diffuse large B-cell lymphoma patients treated in the FIL-DLCL04 trial. Br J Haematol. 2022;196(5):1184–93.
18. Shouval R, Alarcon Tomas A, Fein JA, Flynn JR, Markovits E, Mayer S, et al. Impact of TP53 Genomic Alterations in Large B-Cell Lymphoma Treated With CD19-Chimeric Antigen Receptor T-Cell Therapy. J Clin Oncol. 2022;40(4):369–81.
19. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059–68.
20. Shen R, Xu PP, Wang N, Yi HM, Dong L, Fu D, et al. Influence of oncogenic mutations and tumor microenvironment alterations on extranodal invasion in diffuse large B-cell lymphoma. Clin Transl Med. 2020;10(7):e221.
21. Engert A, Haverkamp H, Kobe C, Markova J, Renner C, Ho A, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. Lancet. 2012;379(9828):1791–9.
22. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203–10.
23. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857–72.
24. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579–86.
25. Lamy T, Damaj G, Soubeyran P, Gyan E, Cartron G, Bouabdallah K, et al. R-CHOP 14 with or without radiotherapy in non-bulky limited-stage diffuse large B-cell lymphoma. Blood. 2018;131(2):174–81.
26. Persky DO, Li H, Stephens DM, Park SI, Bartlett NL, Swinnen LJ, et al. Positron Emission Tomography-Directed Therapy for Patients With Limited-Stage Diffuse Large B-Cell Lymphoma: Results of Intergroup National Clinical Trials Network Study S1001. J Clin Oncol. 2020;38(26):3003–11.
27. Pfreundschuh M, Murawski N, Christofyllakis K, Altmann B, Ziepert M, Haenel M, et al. Excellent Outcome of Elderly Patients with Favourable-Prognosis DLBCL Treated with 4 Cycles CHOP/Chlip-14 Plus 8 Applications of Rituximab and a PET-Based Intensification Strategy That Includes Involved-Site Radiotherapy (IS-RT): Results of the First 120 Patients of the OPTIMAL>60 Trial of the Dshnhl. Blood. 2017;130(Supplement 1):1549.
28. Wang S, Wang L, Hu J, Qian W, Zhang X, Hu Y, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from a multicenter real-world study in China. Cancer Commun (Lond). 2021;41(3):229–39.
29. Bologna S, Vander Borght T, Briere J, Ribrag V, Damaj GL, Thieblemont C, et al. Early positron emission tomography response-adapated treatment in localised diffuse large B-cell lymphoma (aaIPI = 0): results of the phase 3 LYSA LNH 09-1B trial. Hematol Oncol. 2021;39(S2).

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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