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Comparison of zuberitamab plus CHOP versus rituximab plus CHOP for the treatment of drug-naïve patients diagnosed with CD20-positive diffuse large B-cell lymphoma: a phase 3 trial

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ABSTRACT

Background In patients with untreated CD20-positive diffuse large B-cell lymphoma (DLBCL), a phase 3 trial was carried out to evaluate the efficacy and safety of zuberitamab plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone; Hi-CHOP) versus rituximab plus CHOP (R-CHOP) treatment regimens.

Methods In a 2:1 ratio, eligible patients were assigned randomly to receive treatment of six cycles of either 375 mg/m^2 zuberitamab or rituximab together with conventional CHOP chemotherapy. The objective response rate (ORR) at C6D50 served as the primary endpoint, and a non-inferiority margin of 10% was established. The secondary endpoints included the complete response (CR) rate at C6D50, duration of response (DOR), progression-free survival (PFS) and event-free survival (EFS) judged by blinded-independent review committee (BIRC), overall survival (OS) and safety outcomes.

Results Of the 487 randomized patients, 423 patients including 287 in the Hi-CHOP and 136 in the R-CHOP groups completed the C6D50 assessment. For the full analysis set (FAS) and per-protocol set (PPS), BIRC-assessed ORR at C6D50 for the Hi-CHOP and R-CHOP groups were 83.5% versus 81.4% and 95.3% versus 93.7%, respectively. The non-inferiority was confirmed as the lower limit of the two-sided 95% CI for the intergroup differences of −5.2% and −3.3%; both were >−10% in the FAS and PPS. The BIRC-assessed CR rate of Hi-CHOP was significantly higher in PPS (85.7% vs 77.3%, p=0.038), but comparable in FAS (75.2% vs 67.9%, p=0.092). After a median follow-up of 29.6 months, patients in the Hi-CHOP group had a slight advantage with regard to the DOR (HR 0.74, p=0.173), PFS (HR 0.67, p=0.057), EFS (HR 0.90, p=0.517) and OS (HR 0.60, p=0.059). Patients with the germinal-center B

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ As a "me-too" antibody related to rituximab, the recombinant human-mouse chimeric anti-CD20 monoclonal antibody-zuberitamab (HS006, $C_{6458}H_{9946}N_{1696}O_{2019}S_{46}$) differs from rituximab by 26 amino acids in the heavy chains and light chains. In a previous phase 1 dose-escalating trial, zuberitamab was well tolerated up to a dose of 625 mg/m^2, and after the first dose the number of CD19+B cells rapidly decreased, an effect that persisted for up to 24 weeks after additional doses.

WHAT THIS STUDY ADDS

⇒ In this trial, zuberitamab (375 mg/m^2) plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone; Hi-CHOP) regimen was non-inferior to rituximab plus CHOP regarding the tumor response but with superiority in the CR rates. Moreover, patients appeared to have a slight survival benefit from the Hi-CHOP regimen, especially in patients with the germinal center B cell-like subtype. The zuberitamab plus CHOP regimen was well tolerated in patients with untreated diffuse large B-cell lymphoma (DLBCL), with no new significant safety issues detected.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results provide a rationale for further development of Hi-CHOP as initial therapy for DLBCL, that is, CD20-positive patients. Future studies will explore the clinical development of zuberitamab in other disease-like autoimmune conditions.

cell-like subtype who received Hi-CHOP exhibited statistically significant improvements in ORR (p=0.034) and CR rate (p=0.038) at C6D50, EFS (p=0.046) and OS (p=0.014). Treatment-emergent adverse event occurrence rates were comparable across groups (all p>0.05). Infusion-related responses occurred more often in the Hi-CHOP group (32.1% vs 19.9%, p=0.006), all of grade 1–3 severity.

Conclusions Zuberitamab (375 mg/m^2) plus CHOP was non-inferior to R-CHOP regarding ORR but exhibited a higher CR rate and was well tolerated in CD20-positive, previously untreated Chinese patients with DLBCL.

Trial registration number Chinese Clinical Trial Registry, ChiCTR2000040602, retrospectively registered.

BACKGROUND

The most prevalent non-Hodgkin's lymphoma (NHL) in adults is diffuse large B-cell lymphoma (DLBCL), which is heterogeneous and has diverse clinical characteristics and prognoses. The current first-line treatment for DLBCL is still rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone; rituximab plus CHOP (R-CHOP)). For patients with DLBCL treated with R-CHOP,[1] compared with the conventional CHOP regimen, the 10-year progression-free survival (PFS) rate increased from 20.0% to 36.5% and the 10-year overall survival (OS) rate increased from 27.6% to 43.5%. However, 30–40% of patients with DLBCL still experienced recurrence after R-CHOP treatment, and 10% of these patients were challenging to treat because of primary or secondary medication resistance.[2 3] In earlier trials conducted over the past two decades, attempts have been made to substitute anti-CD20 monoclonal antibody (mAb) regimens with more intensive chemotherapy regimens or otherwise increase the efficacy of R-CHOP regimens; however, an enhanced survival benefit has not materialized.[4–7] In addition, traditional rituximab regimens require substantial costs that limit their widespread utilization, especially for elderly patients with DLBCL or patients in developing countries.[8] Thus, in order to meet the as yet unmet clinical needs of patients with DLBCL, further therapeutic approaches to increase their survival benefit or decrease the cost burden are being investigated.

As a me-too antibody related to rituximab, the innovative recombinant human-mouse chimeric anti-CD20 mAb-zuberitamab (HS006, $C_{6458}H_{9946}N_{1696}O_{2019}S_{46}$; Zhejiang BioRay Biopharmaceutical, China) differs from rituximab by 26 amino acids in the heavy chains (16 amino acids in the variable region, 1 amino acid in the constant region) and light chains (9 amino acids in the variable region).[9] The term me-too drug is more value-neutral than biosimilar, defined as a new drug entity with independent intellectual property rights that has a similar but not identical chemical structure or the same action mechanism with breakthrough drugs (first-in-class drug) already on the market.[10] Additionally, when compared with rituximab, zuberitamab has a weaker complement-dependent cytotoxicity impact but a more intense antibody-dependent cellular cytotoxicity (ADCC) effect, with relative affinity constants (Ka) for CD20 of 2.25×10^8 nM and 2.03×10^8 nM, respectively. In preclinical investigations, zuberitamab was found to have similar pharmacodynamics, safety and pharmacokinetics properties to rituximab at the same dosages.[11] In a phase 1 dose-escalating trial, zuberitamab was well tolerated up to a dose of 625 mg/m^2, and after the first dose the number of CD19+B cells rapidly decreased, an effect that persisted for up to 24 weeks after additional doses.[11] For first-line treatment of DLBCL, we carried out a multicenter, phase 2 randomized controlled trial (NCT03485118) that compared the actions of zuberitamab (375 mg/m^2 and 500 mg/m^2) plus CHOP versus R-CHOP (control group). Regarding the objective response rate (ORR, both >90%), the frequency of adverse events (AEs), and infusion-related reactions (IRR), zuberitamab (375 mg/m^2) plus CHOP and zuberitamab (500 mg/m^2) plus CHOP did not substantially differ from R-CHOP.

Here we report the results of a multicenter, randomized, double-blind, phase 3 trial with CD20-positive, patients with previously untreated DLBCL across 42 centers in China using a non-inferiority design based on prior research. The efficacy and safety of zuberitamab (375 mg/m^2) plus CHOP (Hi-CHOP) were assessed and compared with the conventional R-CHOP regimen in the current trial.

METHODS

Trial design and patients

This was a multicenter, double-blind, randomized phase 3 clinical trial, in which eligible patients were assigned randomly in a 2:1 ratio to either the Hi-CHOP group or the R-CHOP group to receive six cycles of either zuberitamab or rituximab plus conventional CHOP treatment. Patients ranged in age from 18 to 75 years, and a survival time of >6 months was anticipated. All of the enrolled patients had recently been diagnosed with CD20-positive DLBCL, which was confirmed by histopathological analysis. Patients were eligible for inclusion if they had an Eastern Cooperative Oncology Group performance status of 0–2, a baseline International Prognostic Index (IPI) of 0–3 and at least 1 two-dimensional measurable lesion that met the following criteria: had a long-axis diameter >1.5 cm and a short-axis diameter >1.0 cm for nodal lesions; and a long-axis diameter ≥1.0 cm for extranodal lesions. The main exclusion criteria were: patients with contraindications to any drugs included in CHOP; high-grade B-cell lymphomas (including not otherwise specified and high-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements); transformed DLBCL (eg, transformed from follicular lymphoma; chronic lymphocytic leukemia, or small B-cell lymphoma); DLBCL with secondary central nervous system involvement; or other subtypes of DLBCL as indicated in the online supplemental appendix 1 and study protocol (online supplemental file 2).

Masking and randomization

Eligible patients were randomly assigned to receive either Hi-CHOP or R-CHOP in a 2:1 ratio using a

central randomization approach without stratification criteria. Through an Interactive Web Response System, the pharmaceutical code and randomization number for each patient was obtained. The RAVE-RTSM system automatically assigned the randomization numbers and dose groups during the enrollment process to keep the investigators, sponsor and patients blind to the group assignments. Enrollment was conducted in a double-blind, randomized block fashion. A planned unblinding procedure was carried out 2 years after the final patient received their initial dosages.

Treatment

For six rounds, eligible patients were scheduled to receive zuberitamab or rituximab plus conventional CHOP chemotherapy every 3 weeks. On day 0 of each cycle, zuberitamab or rituximab (375 mg/m^2) was administered intravenously; on day 1, cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2) and vincristine (1.4 mg/m^2, no more than 2 mg) was administered intravenously; and prednisone (100 mg) was given orally once daily on day 1 through day 5 of each cycle. Within 60 min of the administration of zuberitamab or rituximab, patients received an antihistamine medication such as diphenhydramine hydrochloride (40 mg, intramuscular), prednisone (100 mg, orally), or equivalent doses of methylprednisolone and dexamethasone. Acetaminophen (1,000 mg) was administered at the discretion of the researcher. Since only patients with neutrophil counts ≥1.5×10^9/L were included and dose-intensive R-CHOP regimen was not used in this trial, no special treatment was indicated for primary prophylaxis of neutropenia. Additionally, prophylactic usage of granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor was administered in accordance with the American Society of Clinical Oncology recommendations if severe neutropenia or febrile neutropenia/infection was detected.

Imaging was obtained during the first 3 years for each patient and a blinded independent review committee (BIRC) evaluated the effectiveness of treatment using the Cheson 2007 and Lugano 2014 criteria based on imaging examinations performed at baseline, C3D20 (enhanced positron-emission tomography and CT (PET-CT)), C6D20 (enhanced CT), and C6D50 (enhanced PET-CT) up to 3 years after the initial administration or the occurrence of endpoint events. Following the first administration of the study drugs, the follow-up visits took place once every 2 months in the first year (a total of three times), once every 3 months in the second year, and once every 6 months in the third year.

Outcomes and assessments

The primary outcome was the ORR which was the complete response (CR) plus the partial response (PR) rates at C6D50, as determined by the BIRC and calculated in the full analysis set (FAS) and per-protocol set (PPS).

The secondary endpoints were the BIRC-assessed CR rate at C6D50, the duration of response (DOR) rates at 1, 2 and 3 years after the initial responses, the PFS rates at 1, 2 and 3 years after randomization, the estimated event-free survival (EFS) rates at 1, 2 and 3 years after randomization, and the estimated OS rates at 1, 2 and 3 years after randomization. The BIRC assessed ORR and CR rate at C6D50 were subjected to subgroup analysis based on the baseline variables of age (≤60 vs >60 years old), gender (male vs female), IPI score (0–1 vs 2 vs 3–4), anti-drug antibody (ADA) status (positive vs negative), cell of origin (germinal center B cell-like (GCB) vs non-GCB), extralymphatic involvement (yes vs no), B symptoms (yes vs no) and lactate dehydrogenase (normal vs elevated). For patients with GCB subtypes and non-GCB subtypes, Kaplan-Meier survival analysis of DOR, PFS, EFS and OS were also evaluated.

Treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and IRRs, were recorded, following the guidelines of the Medical Dictionary for Regulatory Activities (V.23.0), during the six-cycle treatment period, and all of them were included in the safety assessments. The Common Terminology Criteria for Adverse Events (V.4.03) were used to rate the severity of TEAEs. Additionally, evaluated parameters were various laboratory indicators, the ECG, vital signs and immunogenicity. In online supplemental appendix 2, the definitions and methods for determining the results are listed in detail.

Sample size

This trial had a non-inferiority design and the primary endpoint was BIRC-assessed ORR at C6D50. The non-inferiority margin was <12% in previous rituximab-related studies,[12 13] and the non-inferior margin was conservatively set at 10% in the present trial, based on clinical judgments and prior research. Assuming that the ORR in the R-CHOP group (control group) was 88% on basis of the rituximab-related studies[14–16] and previous phase 2 clinical trial of zuberitamab (both arms ORR ≥90%). Finally, a total of 480 patients would provide 80% power to conclude non-inferiority with a two-sided α level of 0.05, considering a 20% dropout rate, and a ratio of 2:1 in the two treatment groups, with 320 in the Hi-CHOP group and 160 in the R-CHOP group, respectively.

Statistical analysis

SAS V.9.4 was used to conduct all statistical analyses. A difference was deemed to be statistically significant if the p value was <0.05. Non-inferiority tests were used to compare the ORR at C6D50 (α=0.025, one-sided) and two-sided testing (α=0.05) were used to examine the other hypotheses. In online supplemental appendix 3, the analysis set's definition is listed.

The primary outcome was the ORR at C6D50 as measured by the BIRC and the 95% CI of ORR for each group was calculated using the Clopper-Pearson method. The Wald method was used to compute the difference in ORR between the two groups (Hi-CHOP-R-CHOP)

and its 95% two-sided CI for an approximately normal distribution. Patients without C6D50 response evaluation were treated as non-responders in both groups in accordance to the intention-to-treat principle. The non-inferiority margin was determined at 10%, and non-inferiority was deemed to have been achieved, if the lower limit of the two-sided 95% CI for the intergroup difference in ORR was >−10%. A sensitivity analyses (ie, per-protocol analyses) was performed for primary and secondary endpoints to confirm the consistency of the efficacy outcomes and patients in the Hi-CHOP and R-CHOP groups who were excluded from the PPS were identified prior to unblinding, further reducing bias. The two groups' ORR and CR rates were compared using Fisher's exact or Pearson's χ^2 tests. The median DOR, PFS, EFS, OS and 95% CIs were determined using the Kaplan-Meier method, and the log-rank test was used to look for potential differences between groups. A Cox proportional hazards model was used to calculate the HR and the 95% CI between two groups under the proportional hazard's assumption. The Kaplan-Meier method was employed to estimate the 1-year, 2-year and 3-year DOR, PFS, EFS and OS rates, as well as their 95% CIs, and the Wald-type test was then used to compare rates between groups. Multivariable analyses were done by use of logistic regression model to estimate the OR for ORR at C6D50, while Cox proportional-hazard models were used to estimate HR for PFS, EFS and OS. Other indicators were evaluated using Fisher's exact test for categorical data and the Wilcoxon non-parametric test to compare variables that were continuous.

RESULTS

Patients and treatment exposure

Between October 2018 and September 2020, 762 patients were screened in 42 centers across China, of whom 275 failed to meet the enrollment criteria. Finally, 487 patients were randomly allocated to Hi-CHOP (n=329) or R-CHOP (n=158) groups and 483 patients received the Hi-CHOP (n=327) or R-CHOP (n=156) treatment (figure 1). Of these 483 patients, 423 completed the C6D50 assessment, with 287 in the Hi-CHOP group and 136 in the R-CHOP group. As a result, a total of 60 patients discontinued the treatment without completing the C6D50 assessment due to AEs (n=26), withdrawal of informed consent (n=15), a shift to new anti-lymphoma treatment (n=8), disease progression (n=5), protocol deviation (n=2), loss of follow-up (n=1), death (n=1) or other reasons (n=2) (figure 1). Finally, 483 patients were allocated to the FAS and safety set and 407 to the PPS.

The demographic and baseline characteristics were virtually identical in the two groups (all p>0.05) (table 1). There were 3 (0.9%) patients with double hit lymphoma initially randomized to receive the Hi-CHOP regimen caused by a major protocol deviation. Of 483 patients, most patients completed six cycles of treatments, including 291 (89.0%) in the Hi-CHOP group and 138 (88.5%) in the R-CHOP group (p=0.497). No significant differences were found between groups with regard to adherence to cyclophosphamide, doxorubicin, vincristine or prednisone (all p>0.05), with medication adherence being 80–120% for the majority of patients (482, 99.8%).

Efficacy

In the FAS, the primary endpoint-BIRC-assessed ORR at C6D50 was 83.5% (95% CI: 79.0% to 87.3%) for the Hi-CHOP group and 81.4% (95% CI: 74.4% to 87.2%) for the R-CHOP group, with an intergroup difference of 2.1% (95% CI: −5.2% to 9.4%) (table 2). The BIRC-assessed ORR at C6D50 was 95.3% (95% CI: 92.2% to 97.5%) and 93.7% (95% CI: 88.1% to 97.3%) in the PPS, with an intergroup difference of 1.6% (95% CI: −3.3% to 6.5%). Non-inferiority was confirmed when the lower limit of the two-sided 95% CIs for the intergroup differences were both >−10% in the FAS and PPS. With regard to the secondary endpoints, the CR rate appeared to be slightly higher in the Hi-CHOP patients compared with those in the R-CHOP group in the FAS (75.2% vs 67.9%), but statistical significance was not reached (p=0.092), while PPS analysis revealed a statistically significant difference (85.7% vs 77.3%, p=0.038).

At the data cut-off date (August 31, 2022), the median follow-up time was 29.6 months (range, 0.07–39.1). As shown in figure 2, DOR (HR 0.74, 95% CI: 0.48 to 1.14; p=0.173), PFS (HR 0.67, 95% CI: 0.44 to 1.01; p=0.057), EFS (HR 0.90, 95% CI: 0.65 to 1.24; p=0.517) and OS (HR 0.60, 95% CI: 0.36 to 1.03; p=0.059) were marginally better in patients treated with Hi-CHOP, but statistical significance was not reached between groups. The 1-year, 2-year and 3-year DOR (87.4% vs 82.4%; 81.9% vs 74.4%; 70.7% vs 68.7%), PFS (88.1% vs 80.9%; 82.5% vs 73.5%; 78.0% vs 70.9%), EFS (74.7 vs 71.3; 67.9% vs 62.8%; 61.6% vs 60.6%) and OS (96.3% vs 94.2%; 92.2% vs 85.4%; 87.7% vs 83.1%) rates were marginally higher in Hi-CHOP treated patients compared with R-CHOP treated patients (table 2).

Multivariate analysis also showed that the treatment option (Hi-CHOP vs R-CHOP) was not an independent prognosis factor for ORR, PFS, EFS and OS (online supplemental tables 1 and 2). Regardless of the treatment regimen, multivariate analysis found that GCB subset appeared to be associated with a better PFS (HR 0.52, 95% CI: 0.30 to 0.90; p=0.020) and EFS (HR 0.59, 95% CI: 0.40 to 0.86; p=0.006), while IPI 2 was associated with a worse PFS (HR 2.40, 95% CI: 1.41 to 4.09; p=0.001) and EFS (HR 1.90, 95% CI: 1.31 to 2.75; p<0.001), and IPI 3–4 was associated with a worse PFS (HR 2.67, 95% CI: 1.56 to 4.58; p<0.001), EFS (HR 1.60, 95% CI: 1.07 to 2.39; p=0.021) and OS (HR 4.22, 95% CI: 2.25 to 7.89; p<0.001). In addition, patients with bulky disease had a lower risk for ORR (OR 0.44, 95% CI: 0.23 to 0.81; p=0.008), but had a higher risk for EFS (HR 2.06, 95% CI: 1.42 to 3.00; p<0.001).

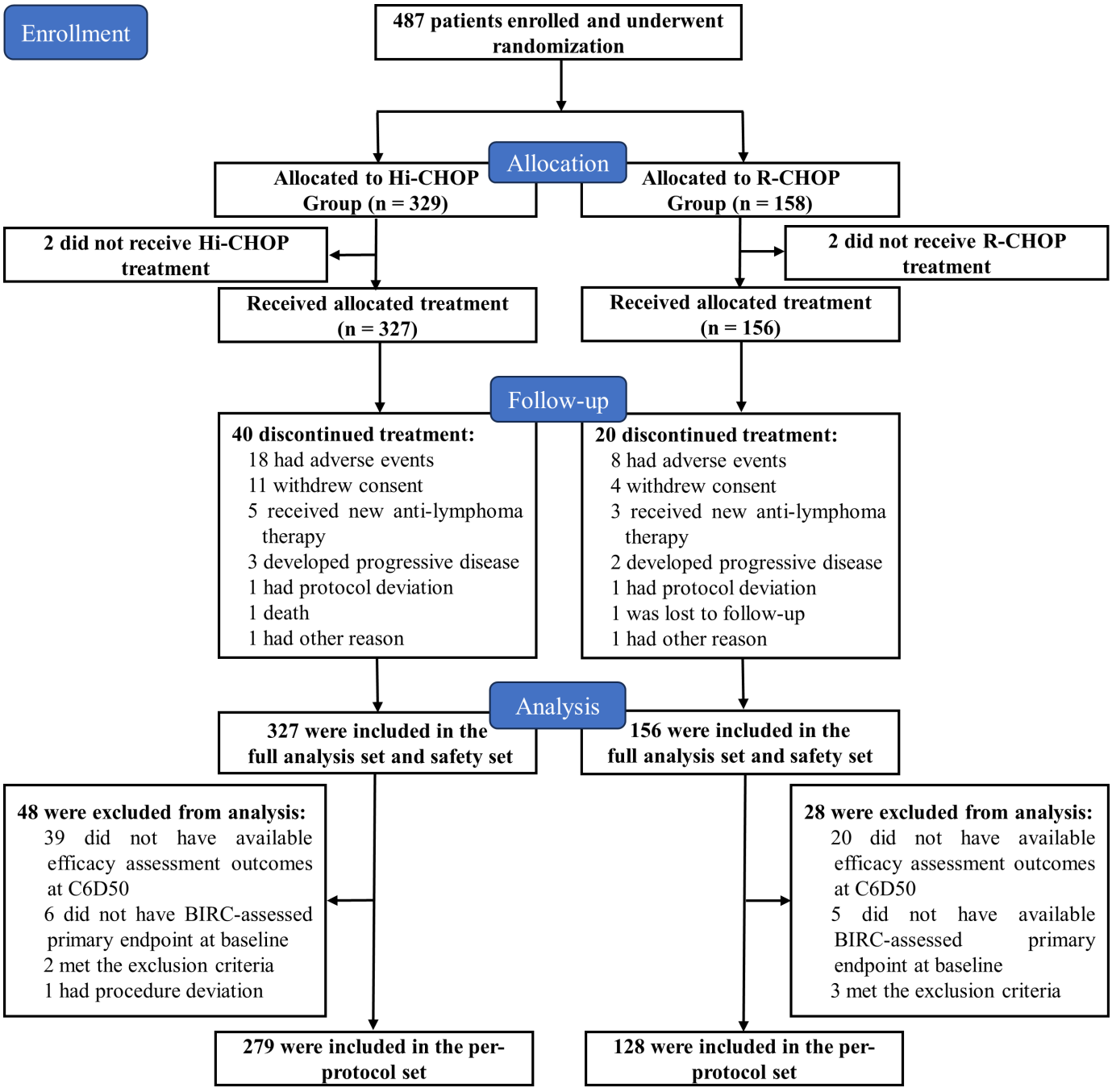

Figure 1 Flowchart of the patients' disposition. BIRC, blinded independent review committee; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; FAS, full analysis set; Hi-CHOP, zuberitamab plus CHOP; PPS, per-protocol set; SS, safety set; R-CHOP, rituximab plus CHOP.

A subgroup analysis was conducted and the results revealed that the BIRC-assessed ORR and CR rates at C6D50 for GCB subtype patients in the Hi-CHOP group were significantly higher than that in the R-CHOP group (p=0.034and p=0.038; online supplemental figure 1). Further analysis of DOR, PFS, EFS and OS for patients with the GCB subtype revealed that the Hi-CHOP regimen had significant benefits in terms of EFS (HR 0.51, 95% CI: 0.27 to 1.00; p=0.046) and OS (HR 0.25, 95% CI: 0.07 to 0.83; p=0.014), whereas DOR (HR 0.47, 95% CI: 0.18 to 1.26; p=0.126) and PFS (HR 0.41, 95% CI: 0.16 to 1.07; p=0.060) were marginally higher in the Hi-CHOP treated patients (figure 3). In addition, the efficacy in non-GCB patients treated with Hi-CHOP was equivalent to that of the R-CHOP group (all p>0.05; online supplemental figure 2).

Safety

The occurrence rates of TEAEs (99.7% vs 100.0%, p=1.000), drug-related TEAEs (87.8% vs 82.1%, p=0.095), SAEs (44.3% vs 50.0%, p=0.283) and drug-related SAEs (25.1% vs 27.6%, p=0.579) were remarkably similar in

Table 1 Baseline characteristics (FAS)

Variables	Hi-CHOP (N=327)	R-CHOP (N=156)
Age (years), median (range)	56.0 (20–75)	55.0 (18–73)
Age category, n (%)		
≤60 years	207 (63.3)	101 (64.7)
>60 years	120 (36.7)	55 (35.3)
Gender, n (%)		
Female	176 (53.8)	86 (55.1)
Male	151 (46.2)	70 (44.9)
Body surface area (m^2), median (range)	1.7 (1.2–2.3)	1.7 (1.3–2.2)
DLBCL, n (%)	324 (99.1)	154 (98.7)
NOS	322/324 (99.4)	154 (100.0)
Non-NOS	1/324 (0.3)	0
Unclassifiable	1/324 (0.3)	0
SPD (mm^2), median (range)	1918.7 (80.0–38 529.0)	2133.0 (165.4–20 741.0)
Greatest tumor diameters (mm), median (range)	40.5 (15–190)	41.3 (15.2–160)
Bulky disease, n (%)*	46 (14.1)	26 (16.7)
Extralymphatic involvement, n (%)	70 (21.4)	40 (25.6)
Ann/Arbor stage, n (%)		
I	47 (14.4)	14 (9.0)
II	120 (36.7)	56 (35.9)
III	81 (24.8)	40 (25.6)
IV	79 (24.2)	46 (29.5)
B symptoms, n (%)	31 (9.5)	23 (14.7)
Cell of origin, n (%)		
GCB	92 (28.1)	52 (33.3)
Non-GCB	228 (69.7)	99 (63.5)
Unclassified	7 (2.1)	5 (3.2)
ECOG PS, n (%)		
0	121 (37.0)	51 (32.7)
1	202 (61.8)	101 (64.7)
2	4 (1.2)	4 (2.6)
IPI score, n (%)		
0	80 (24.5)	38 (24.4)
1	92 (28.1)	35 (22.4)
2	84 (25.7)	38 (24.4)
3	70 (21.4)	44 (28.2)
4	1 (0.3)	1 (0.6)
Elevated LDH, n (%)	130 (39.8)	60 (38.5)
HBsAg positive, n (%)	47 (14.4)	29 (18.7)
HBcAb positive, n (%)	181 (55.5)	90 (58.1)

*A maximum diameter ≥7.5 cm.
CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; GCB, germinal center B-cell-like; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; Hi-CHOP, zuberitamab plus CHOP; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NOS, not otherwise specified; PS, performance status; R-CHOP, rituximab plus CHOP; SPD, sum of the product of the diameters.

Table 2 Efficacy outcomes assessed by a blinded independent review committee (FAS)

Variables	Hi-CHOP (N=327)	R-CHOP (N=156)	P value
ORR at C6D50, n (%)	273 (83.5)	127 (81.4)	0.572
Difference (95% CI), %	2.1 (–5.2, 9.4)		
Overall response at C6D50, n (%)			
CR	246 (75.2)	106 (67.9)	0.092
Difference (95% CI), %	7.3 (–1.4, 16.0)		
PR	27 (8.3)	21 (13.5)	
SD	3 (0.9)	0	
Relapsed disease/PD	10 (3.1)	9 (5.8)	
Not evaluated	41 (12.5)	20 (12.8)	
DOR			
Events, n (%)	52 (16.6)	33 (22.0)	
Death	4 (1.3)	6 (4.0)	
Progressive or relapsed	48 (15.3)	27 (18.0)	
12-month DOR rate estimate (95% CI), %	87.4 (82.8, 90.8)	82.4 (74.7, 88.0)	
24-month DOR rate estimate (95% CI), %	81.9 (76.5, 86.2)	74.4 (65.4, 81.4)	
36-month DOR rate estimate (95% CI), %	70.7 (53.8, 82.4)	68.7 (55.9, 78.5)	
PFS			
Events, n (%)	53 (16.2)	37 (23.7)	
Death	4 (1.2)	6 (3.8)	
Progressive or relapsed	49 (15.0)	31 (19.9)	
12-month PFS rate estimate (95% CI), %	88.1 (83.6, 91.4)	80.9 (73.1, 86.6)	
24-month PFS rate estimate (95% CI), %	82.5 (77.3, 86.6)	73.5 (64.8, 80.4)	
36-month PFS rate estimate (95% CI), %	78.0 (71.7, 83.1)	70.9 (61.6, 78.3)	
EFS			
Events, n (%)	109 (33.3)	57 (36.5)	
Death	5 (1.5)	6 (3.8)	
Progressive or relapsed	49 (15.0)	31 (19.9)	
Received new anti-lymphoma therapy	55 (16.8)	20 (12.8)	
12-month EFS rate estimate (95% CI), %	74.7 (69.5, 79.2)	71.3 (63.3, 77.9)	
24-month EFS rate estimate (95% CI), %	67.9 (62.3, 72.9)	62.8 (54.3, 70.2)	
36-month EFS rate estimate (95% CI), %	61.6 (55.2, 67.4)	60.6 (51.8, 68.3)	
OS			
Patients who died, n (%)	32 (9.8)	24 (15.4)	
12-month OS rate estimate (95% CI), %	96.3 (93.5, 97.9)	94.2 (89.1, 96.9)	
24-month OS rate estimate (95% CI), %	92.2 (88.7, 94.7)	85.4 (78.7, 90.2)	
36-month OS rate estimate (95% CI), %	87.7 (82.3, 91.5)	83.1 (75.7, 88.5)	

Note. The cut-off date for the analysis was August 31, 2022, with a median follow-up period of 29.6 months.
.CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; DOR, duration of response; EFS, events-free survival; FAS, full analysis set; Hi-CHOP, zuberitamab plus CHOP; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R-CHOP, rituximab plus CHOP; SD, stable disease.

both groups. The rate of occurrence of grade ≥ 3 TEAEs was 92.0% in the Hi-CHOP group and 92.3% in the R-CHOP group, among which the most frequent TEAEs were decreased neutrophil (75.5% vs 75.0%), white blood cell (WBC) (67.9% vs 62.8%), lymphocyte (29.7% vs 26.9%) counts and anemia (12.8% vs 9.0%) (table 3), findings also reported for drug-related TEAEs, listed in online supplemental table 3. The most commonly reported SAEs were pulmonary inflammation (7.6% vs 7.1%), a decreased WBC count (7.3% vs 6.4%), infectious

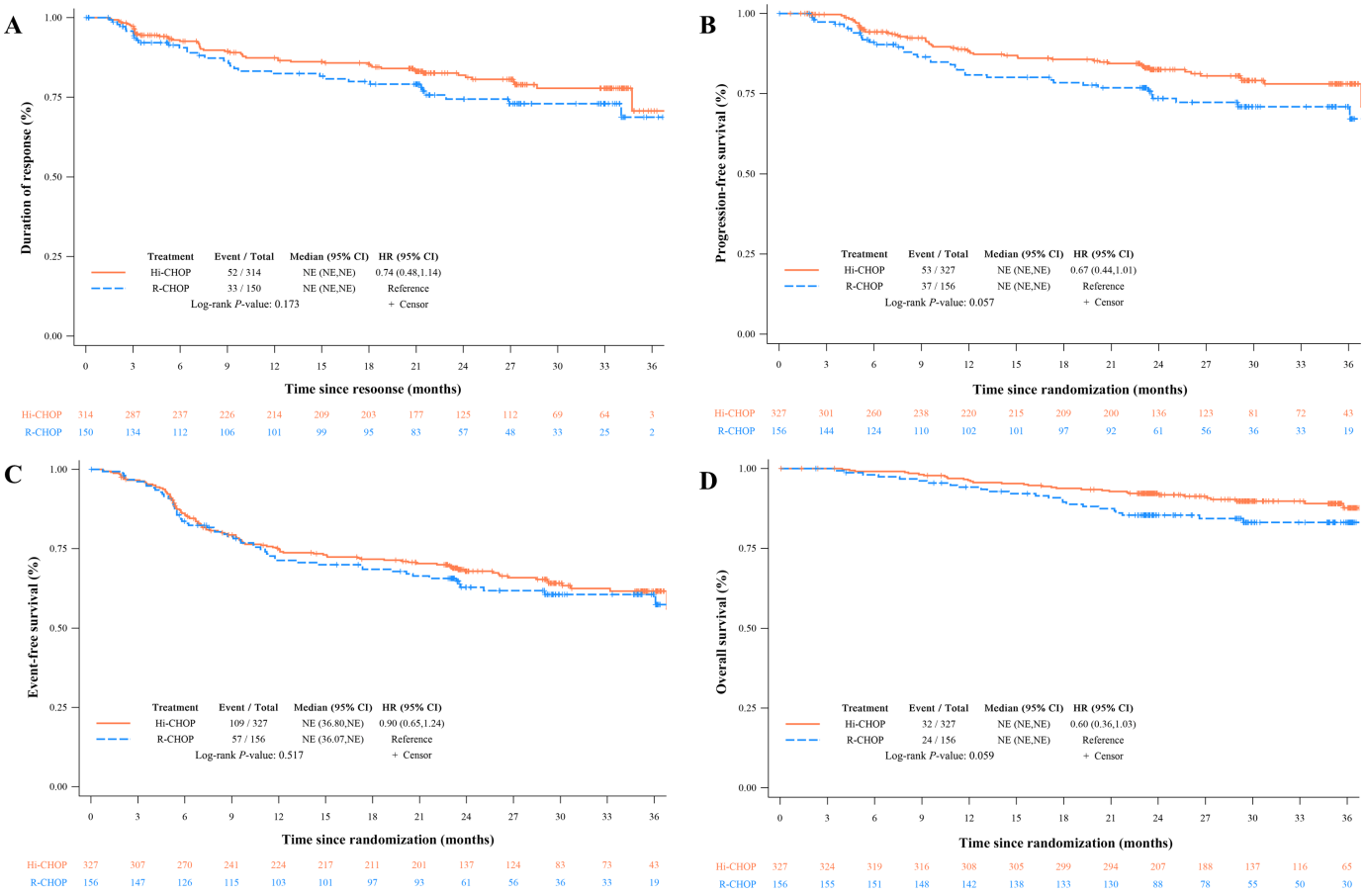

Figure 2 Kaplan-Meier curves of BIRC-assessed efficacy outcomes for patients in the Hi-CHOP and R-CHOP groups (FAS). (A) Duration of response, (B) progression-free survival, (C) events-free survival, (D) overall survival. Note: The cut-off date for the analysis was August 31, 2022, with a median follow-up period of 29.6 months. BIRC, blinded independent review committee; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; FAS, full analysis set; Hi-CHOP, zuberitamab plus CHOP; NE, not evaluable; R-CHOP, rituximab plus CHOP.

pneumonia (6.7% vs 9.0%) and febrile neutropenia (5.2% vs 3.8%) in the two groups. 55 patients died, 32 (9.8%) in the Hi-CHOP group and 23 (14.7%) in the R-CHOP group, mainly attributed to disease progression (4.6% vs 9.0%). A few cases (0.9% vs 1.3%) were associated with the experimental drugs, including infectious pneumonia, septic shock and disease progression.

The rate of occurrence of IRR was significantly greater in the Hi-CHOP group (32.1% vs 19.9%, p=0.005), mainly manifesting as chills (20.8% vs 7.7%), fever (16.5% vs 8.3%) and elevated blood pressure (5.2% vs 0.6%). The severity of IRR was primarily grade 1 or grade 2, and only 5 (1.5%) patients in the Hi-CHOP group developed grade 3 IRR, but none in the R-CHOP group. Of the five patients with grade 3 IRRs, four patients (1.22%) experienced drug-related IRR, including two patients with elevated blood pressure and two with hypertension. IRR mainly occurred 1–2 hours after the first dose and most of them were self-limiting. Only one patient in each group had drug-related IRR and did not recover, while one patient in the Hi-CHOP group withdrew from the trial due to the drug-related IRR, but nevertheless recovered. When patients had drug-related IRR, the main measures were to reduce the infusion speed or discontinue the drug administration. Therefore, Hi-CHOP patients had a higher incidence of drug-related TEAEs leading to discontinuation or delayed infusion during the trial (33.9% vs 24.4%, p=0.035), which were mainly chills and fever. A total of 9 patients experienced hepatitis B virus (HBV) reactivation, with 7 (2.1%) in the Hi-CHOP group and 2 (1.3%) in the R-CHOP group. Overall, 44 (13.5%) patients treated with the Hi-CHOP regimen and 28 (17.9%) the R-CHOP regimen had TEAEs that led to their withdrawal from the trial. Of these, 13 (4.0%) patients and 8 (5.1%) patients experienced drug-related TEAEs. No significant changes were detected with regard to laboratory tests, vital signs, physical examinations or other safety-related indicators in the Hi-CHOP and R-CHOP groups.

Immunogenicity

Only one patient in the Hi-CHOP group was positive for the ADA test at baseline, but the test result was negative at follow-up. The cumulative rate of positive-ADA was 2.1% (7/327) in the Hi-CHOP group and 0.6% (1/156) in the R-CHOP group (p=0.446). It is noteworthy that the neutralizing antibody tests were all negative in patients with positive ADA test results.

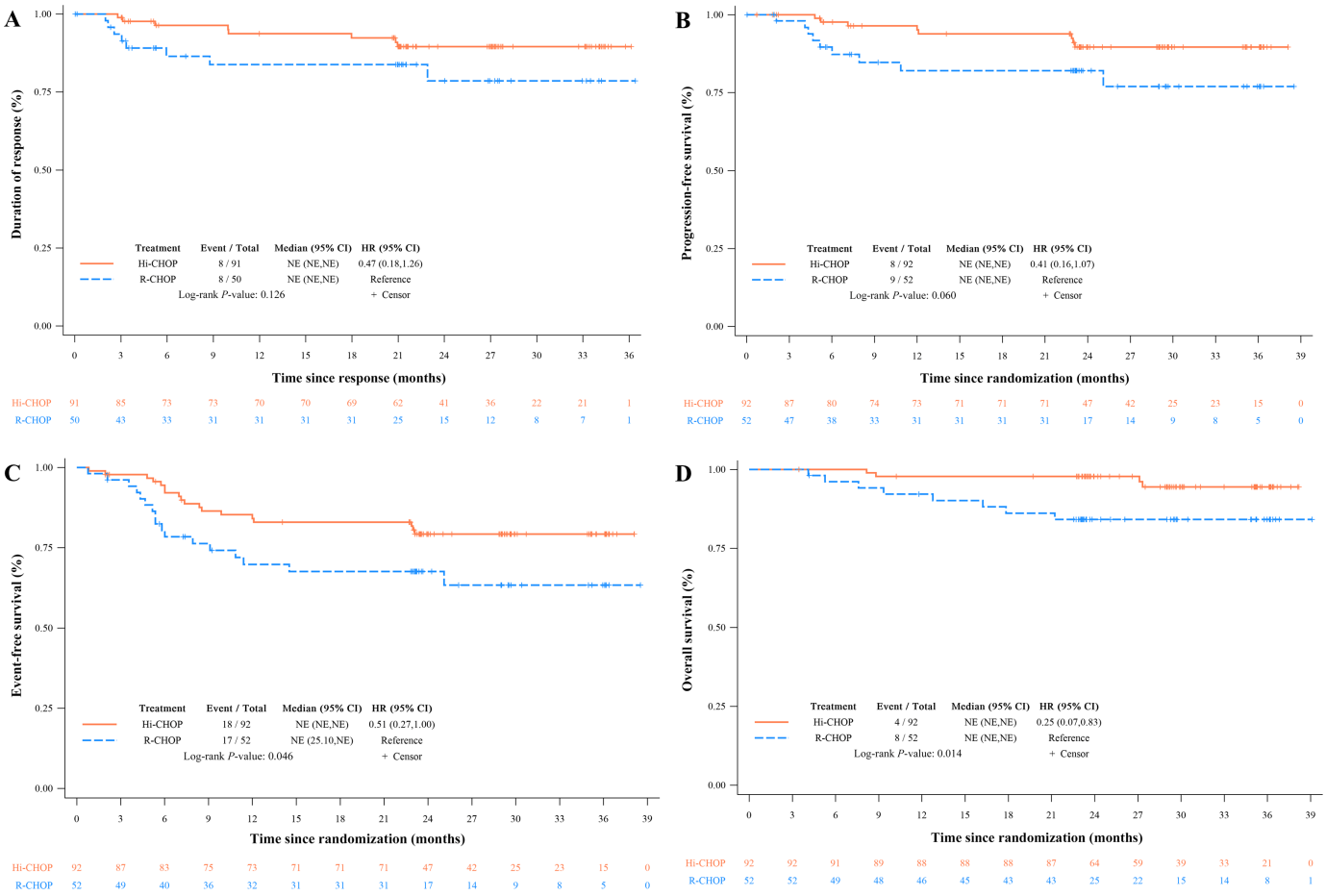

Figure 3 Kaplan-Meier curves of the BIRC-assessed efficacy outcomes for GCB patients in the Hi-CHOP and R-CHOP groups (FAS). (A) Duration of response, (B) progression-free survival, (C) events-free survival and (D) overall survival note. The cut-off date for the analysis was August 31, 2022, with a median follow-up period of 29.6 months. BIRC, blinded independent review committee; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; FAS, full analysis set; GCB, germinal center B-cell-like; Hi-CHOP, zuberitamab plus CHOP; NE, not evaluable; R-CHOP, rituximab plus CHOP.

DISCUSSION

The current phase 3 trial conducted in Chinese patients with previously untreated CD20-positive DLBCL demonstrated that Hi-CHOP was non-inferior to R-CHOP in lymphoma response as the lower limit of the two-sided 95% CI for the intergroup differences for ORR at C6D50 assessed by the BIRC were −5.2% and −3.3%, which were both >−10% based on FAS and PPS analysis. After a median follow-up period of 29.6 months (range, 0.07–39.1), DOR, PFS, EFS and OS were not significantly different between the two groups, but Hi-CHOP regimen reduced the risk of recurrence (HR 0.67) and death (HR 0.60) in patients with previously untreated DLBCL. Multivariate analysis also showed that the treatment option (Hi-CHOP vs R-CHOP) was not an independent prognosis factor for ORR, PFS, EFS and OS, also indicating that Hi-CHOP was non-inferior to the R-CHOP regimen with regard to the efficacy outcomes in patients with previously untreated CD20-positive DLBCL.

Previous studies have demonstrated that PFS was strongly correlated with OS, thus PFS was more often used as a surrogate endpoint for OS in patients with untreated DLBCL.[17 18] In addition, the EFS and CR rates also can be used as surrogate endpoints in patients with newly diagnosed DLBCL.[19 20] The CR rate and ORR also can serve as potential surrogate endpoints to make timely drug development decisions and accelerate drug approval. However, because very limited trials have reported these two endpoints in DLBCL, there is no clear relationship between ORR and PFS/OS. A meta-analysis that included 73 trials involving 6071 patients with NHL indicated that ORR was as good as CR rate when used as a potential alternative endpoint for PFS. As the proportion of newly treated patients increased, the correlation with PFS (R^2) increased, and the median PFS also lengthened ($p<0.005$), irrespective of the treatment options.[21] In addition, studies related to rituximab biosimilars also used ORR as the primary endpoint in patients with untreated DLBCL, and the final results both met the preset endpoint.[12 13 22] Therefore, ORR served as a primary endpoint in the present trial. We also indicated CR rate, DOR PFS, EFS OS as secondary endpoints together with ORR (concomitantly) for a comprehensive assessment of clinical benefit in patients with DLBLC primarily treated with Hi-CHOP and R-CHOP.

Table 3 The most common TEAEs (incidence ≥10%) occurred during the treatment period (SS)

	Hi-CHOP (N=327)		R-CHOP (N=156)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hematological toxic events, n (%)				
Decreased white blood cell count	293 (89.6)	222 (67.9)	139 (89.1)	98 (62.8)
Decreased neutrophil count	292 (89.3)	247 (75.5)	139 (89.1)	117 (75.0)
Anemia	185 (56.6)	42 (12.8)	81 (51.9)	14 (9.0)
Decreased lymphocyte count	128 (39.1)	97 (29.7)	61 (39.1)	42 (26.9)
Decreased platelet count	108 (33.0)	21 (6.4)	48 (30.8)	9 (5.8)
Non-hematological toxic events, n (%)				
Alopecia	142 (43.4)	0	63 (40.4)	0
Fever	98 (30.0)	4 (1.2)	30 (19.2)	0
Elevated ALT	92 (28.1)	1 (0.3)	42 (26.9)	1 (0.6)
Elevated AST	84 (25.7)	2 (0.6)	36 (23.1)	1 (0.6)
Chill	70 (21.4)	0	12 (7.7)	0
Constipation	67 (20.5)	1 (0.3)	32 (20.5)	2 (1.3)
Nausea	61 (18.7)	0	26 (16.7)	0
Asthenia	58 (17.7)	0	25 (16.0)	0
Hypokalemia	52 (15.9)	4 (1.2)	25 (16.0)	7 (4.5)
Vomiting	48 (14.7)	1 (0.3)	23 (14.7)	0
Pulmonary inflammation	46 (14.1)	13 (4.0)	21 (13.5)	5 (3.2)
Hypoesthesia	46 (14.1)	0	25 (16.0)	0
Cough	45 (13.8)	0	19 (12.2)	0
Infectious pneumonia	45 (13.8)	20 (6.1)	18 (11.5)	16 (10.3)
Hypoalbuminemia	44 (13.5)	0	19 (12.2)	0
Weight loss	43 (13.1)	0	21 (13.5)	1 (0.6)
Decreased appetite	40 (12.2)	1 (0.3)	20 (12.8)	0
Weight gain	36 (11.0)	2 (0.6)	21 (13.5)	2 (1.3)
Insomnia	35 (10.7)	0	12 (7.7)	0
Upper respiratory infection	33 (10.1)	4 (1.2)	20 (12.8)	5 (3.2)
Elevated LDH	33 (10.1)	0	9 (5.8)	0
Elevated γ-GGT	31 (9.5)	2 (0.6)	19 (12.2)	2 (1.3)
Urinary tract infection	30 (9.2)	1 (0.3)	22 (14.1)	2 (1.3)
Hyperglycemia	29 (8.9)	4 (1.2)	17 (10.9)	2 (1.3)
Diarrhea	28 (8.6)	2 (0.6)	17 (10.9)	1 (0.6)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; GGT, glutamyl transferase; Hi-CHOP, zuberitamab plus CHOP; LDH, lactate dehydrogenase; R-CHOP, rituximab plus CHOP; SS, safety set; TEAE, treatment-emergent adverse event.

Alizadeh *et al*[23] conducted gene expression profiling of DLBCL samples, and classified DLBCL into at least two subtypes according to the cell origin, namely (1) GCB and (2) activated B-cell-like (ABC). Several studies have reported that patients with the GCB subtype appeared to have a favorable prognosis in comparison to non-GCB subtype patients,[7 24] and similar trends were also observed regarding PFS and EFS in the present trial. One possible explanation is that ABC-DLBCL is characterized by constitutive activation of the nuclear factor kappa-B (NF-κB) signaling pathway, which may block chemotherapy-induced apoptosis and lead to poor prognosis, while GCB-DLBCL is derived from normal germinal B cells with a lower expression of NF-κB target gene.[25] Another explanation is that GCB-DLBCL had a significantly higher expression of major histocompatibility complex class II and CD20 antigen than ABC-DLBCL, which also results in a better prognosis.[26–28] In addition, an exploratory subgroup analysis also found that patients with the GCB subtype seemed to benefit more from the Hi-CHOP

regimen, with a significant improvement in BIRC-assessed ORR (p=0.034) and CR rate (p=0.038) at C6D50, EFS (HR 0.51, p=0.046) and OS (HR 0.25, p=0.014). Changes in the amino acid sequence of zuberitamab improved the stability of binding to CD20, as demonstrated in preclinical stability studies where about 45% of zuberitamab remained on the surface of Daudi cells after 24 hours of reaction, while only 30% of rituximab remained. In addition, the Fc segment was modified by defucosylation of glycosylation which improved the ADCC effects of zuberitamab.[29] Similar to obinutuzumab,[30] these changes in the amino acid sequence and stronger ADCC effects may have explained the potential benefits in patients with GCB-DLBCL who were treated with Hi-CHOP, findings that clearly warrant further investigation.

The occurrence rates of TEAEs, drug-related TEAEs and SAEs were not significantly different between the two groups. The most commonly occurring hematological toxic events were decreased neutrophil, WBC and lymphocyte counts in the two groups, results consistent with the findings of similar studies.[12 31 32] As one of the most commonly encountered TEAEs induced by rituximab, IRR is worthy of further attention in clinical practice. The incidence of IRR was higher in Hi-CHOP patients (32.1% vs 19.9%, p=0.005), mainly presenting as chills and fever, and the majority of severities were grade 1 or grade 2, with only 5 (1.5%) cases in the Hi-CHOP group developed grade 3 IRR. The mechanism of IRR is unknown, but it is believed to be related to the activation of lymphocytes and the release of cytokines.[33] One possible explanation for the higher incidence of IRR is stronger activation on binding to CD20 cells.[34] Hong *et al* found that patients with DLBCL with grade ≥2 IRR seemed to have a shorter EFS and OS; bone marrow involvement may be the best predictive indicator of IRR.[35] However, Cho *et al* reported that IRR was not related to OS or PFS in patients with DLBCL treated with R-CHOP.[36] Thus, the relationship between IRR and efficacy outcomes remains equivocal. In the present trial, IRR mainly occurred 1–2 hours after the first dose, and were mainly self-limiting. Another concern was HBV reactivation, with the HBV carrier rate being high in patients with DLBCL in China. The use of chemotherapy drugs or rituximab may cause HBV reactivation, leading to fulminant hepatitis and other severe consequences.[37] Moreover, being hepatitis B surface antigen (HBsAg) positive was related to the lower CR rate in Chinese patients with DLBCL.[38] In the present trial, oral entecavir was started before enrollment and continued for at least 1 year after the last dose in patients who were HBsAg or hepatitis B core antibody positive, and had HBV-DNA<1×10^3 IU/mL, following the guidelines for HBV reactivation management. Overall, the incidence of HBV activation was lower in both groups (2.1% vs 1.3%). Furthermore, the Hi-CHOP regimen was well tolerated by previously untreated Chinese patients with CD20-positive DLBCL.

R-CHOP is being considered a cost-effective alternative to CHOP in young patients with DLBCL with good prognosis, as the higher costs associated with rituximab are offset by significantly reduced salvage treatment costs.[39] However, the cost-effective of R-CHOP for elderly patients with DLBCL was controversial in real-world studies.[8 40] It is important to note that the economic aspects of treatment remain a key issue, as the price of rituximab remains high for Chinese patients who do not have strong financial support. In recent years, the Chinese government has stepped up its support for the development of local me-too drugs with the same target and has implemented a reimbursement-linked drug price negotiation annually since 2017 in order to reduce the prices of expensive medicines. From the phase 2 trial of zuberitamab for the treatment of primary immune thrombocytopenia, zuberitamab was estimated to cost about US$781 per treatment cycle, significantly less than the US$4,361 per cycle of rituximab.[41] Moreover, zuberitamab has been covered by Chinese medical insurance since December 2023, which has reduced the burden of treatment costs and provided a convenient pathway for the utilization of zuberitamab for patients with untreated CD20-positive DLBLC in China.

There were a number of limitations to the present clinical trial. The non-inferiority design was employed for the primary endpoint; thus, the efficacy outcomes and subgroup analysis should be interpreted cautiously due to the small sample size. The correlation between a higher incidence of IRR and the Hi-CHOP regimen was not clear, a finding that warrants further research and analysis. In addition, we did not set the stratification factors prior to the randomization, since the phase 3 trial was conducted in China without racial heterogeneity, and patients with IPI 0–3 were enrolled, and was relatively limited to low/low-intermediate risk population. Moreover, another possible stratification factor, bulky disease, has prognostic significance in young patients with good-prognosis DLBCL who were treated with R-CHOP, but the prognostic significance in the wider population is unverified and cut-off values are also uncertain.[42 43] The final results showed that the baseline characteristics of enrolled patients in the two groups were generally well balanced (all p>0.05), also indicating that the homogeneity of the enrolled population in the present trial was relatively high as prespecified.

CONCLUSION

The zuberitamab (375 mg/m^2) plus CHOP regimen was non-inferior to rituximab plus CHOP regarding the tumor response but with superiority in the CR rate by the BIRC in PPS. With a median follow-up time of 29.6 months (range, 0.07–39.1), patients treated with the Hi-CHOP regimen showed marginally higher survival. Moreover, patients with the GCB subtype appeared to have benefited more from the Hi-CHOP regimen compared with those with the non-GCB subtype. The Hi-CHOP regimen was well tolerated by patients with previously untreated CD20-positive DLBCL, with no new significant safety

issues detected. Based on the efficacy and safety data of the current trial, the National Medical Products Administration in China approved the use of zuberitamab as the initial therapy for DLBCL, that is, CD20-positive patients on May 17, 2023. The clinical development of zuberitamab in other disease-like autoimmune conditions will be explored in future studies.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The Sun Yat-sen University Cancer Center (approval number: A2018-031-01), Beijing Cancer Hospital (approval number: 2018YW29), Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (approval number: 2018-50), and all other participating centers' ethical committees authorized the study. The Declaration of Helsinki and Good Clinical Practice were strictly followed during the execution of the trial. All participants' written informed consent or the equivalent was obtained from their legal representatives.

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