Annals of Hematology (2025) 104:2823–2830
https://doi.org/10.1007/s00277-025-06412-z

RESEARCH

Polatuzumab Vedotin, zanubrutinib and rituximab (Pola-ZR) achieved rapid and deep response in untreated frail and elderly DLBCL

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Received: 18 August 2024 / Accepted: 12 May 2025 / Published online: 16 May 2025

Abstract

First-line treatment balancing efficacy and safety is urgently needed for frail and elderly diffuse large B-cell lymphoma (DLBCL) patients. We designed a triplet chemo-light regimen, Pola-ZR, in previously untreated frail and elderly DLBCL patients to assess the efficacy and safety in a prospective DLBCL cohort (NCT06203652). Polatuzumab vedotin was given 1.8 mg/KG intravenously on day 1, zanubrutinib 160 mg twice a day orally from day 1 to day 21, and rituximab 375 mg/m^2 intravenously on day 1. Twenty-one days were a cycle. If assessed complete response (CR) after 6 cycles, patients would receive zanubrutinib alone for another 6 cycles. PET/CT or contrast-enhanced CT scan was scheduled every 3 cycles. The primary end point was overall response rate (ORR) after 6 cycles. Twenty-four patients were enrolled from 01 Apr 2023 to 20 Dec 2023. Median age was 73. Sixteen (66.7%) patients had an international prognostic index score of 3 to 5. After a median follow-up of 10.2 months, the CR rate and ORR after 6 cycles was 83% and 83%. Non-responders had high total metabolic tumour volume. Lung infection was the major safety concern. PJP prophylaxis was recommended. Pola-ZR regimen showed rapid and deep response with manageable safety profiles in both GCB and non-GCB subtypes.

Key points

- Polatuzumab vedotin, zanubrutinib and rituximab (Pola-ZR) achieved a CR rate of 83% in untreated frail and elderly DLBCL patients.
- Lung infection was the major concern during Pola-ZR treatment. Pneumocystis Jirovecii Pneumonia (PJP) prophylaxis was recommended.

Keywords Diffuse large B-cell lymphoma · Elderly · Polatuzumab vedotin · Zanubrutinib · Response

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of B-cell lymphoma worldwide with an increased incidence of 55.6% in patients over 65 years old [1, 2]. The 5-year overall survival (OS) for DLBCL patients older than 65 years old were 54% [3].

First-line treatment balancing efficacy with safety is urgently needed for frail and elderly DLBCL patients. Currently, the attenuated combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-miniCHOP), is the standard of care for this population, with a 2-year progression-free survival (PFS) of 47% and a 2-year OS of 59% in previous study. But 8% of patients died of treatment-related toxicities [4]. Novel agents like Bruton Tyrosine Kinase (BTK) inhibitors and immunomodulatory

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*Presented in abstract form at the 65th annual meeting of the American Society of Hematology, San Diego, CA, 9 December 2023.[12]

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agents were implemented in multiple studies showing that chemo-free regimens were well tolerated in first-line elderly DLBCL patients, yet with limited efficacy [5]. ORR was 77% when R2 was incorporated with zanubrutinib in our previous report [6].

Polatuzumab vedotin is an anti-CD79b antibody-drug conjugate proved to have synergistic effect with rituximab in cell-line research and with immunochemotherapy in previously untreated DLBCL patients [7]. In POLARIX study, Pola-R-CHP significantly improved PFS compared to standard R-CHOP in first-line treatment of DLBCL aged from 18 to 80. Major adverse events were comparable in two arms [8, 9]. Likewise, polatuzumab vedotin was designed to substitute vincristine in R-miniCHOP in first-line treatment of patients over 80 years old, but the final results are still awaiting [10].

We explored a combination of polatuzumab vedotin-based chemo-light regimen in a prospective DLBCL cohort. Preliminary results were reported at the 65th American Society of Hematology Annual Meeting [11]. This manuscript reports the updated follow-up of the efficacy and safety of polatuzumab vedotin, zanubrutinib and rituximab (Pola-ZR) in first-line treatment of frail and elderly DLBCL patients.

Methods

Patients

This study was approved by Ethic Committee of Zhongshan Hospital, Fudan University in accordance with Declaration of Helsinki (Approval No. B2023-184). All patients agreed to the informed consents. Patients aged over 70 years old or between 60 and 69 years old, but with an ECOG performance status score of 2 to 4 were enrolled in this study. All patients were newly-diagnosed CD20-positive DLBCL per 2016 World Health Organization classification of lymphoid neoplasms including DLBCL transformed from indolent B-cell lymphomas [12]. Richter's syndrome was excluded. None of the patients received any anti-DLBCL treatment during the period between diagnosis and enrollment. Patients with positive total antibodies to hepatitis B surface antigen were permitted if hepatitis B virus DNA was below 50 IU by polymerase chain reaction at baseline. Exclusion criteria included central nervous system involvement and contradictions to polatuzumab vedotin, zanubrutinib or rituximab.

Treatment and assessment

All patients received at least one cycle of Pola-ZR. Polatuzumab vedotin was given at a dosage of 1.8 mg/KG intravenously on day 1, zanubrutinib 160 mg twice a day orally from day 1 to day 21, and rituximab 375 mg/m^2 intravenously on day 1 from cycle 1 to cycle 6. Twenty-one days were a cycle. 18 F-Fluorodeoxyglucose Positron Emission Tomography (PET/CT) or Computed Tomography (CT) of contrast of cervical, thoracic, abdominal and pelvic parts was scheduled every 3 cycles. Treatment response was assessed by 2014 Lugano response criteria [13]. If assessed CR or partial response (PR) after the first three cycles of Pola-ZR, the patient would continue to another three cycles of Pola-ZR. If assessed CR after 6 cycles of Pola-ZR, the patient would receive zanubrutinib monotherapy 160 mg twice a day orally for another 6 cycles (Supplemental Figure S1).

Granulocyte colony-stimulating factor (G-CSF) prophylaxis was determined by physicians. Patients with positive anti-hepatitis B core antibody received entecavir to prevent hepatitis B from reactivation. Prophylaxis of PJP or cytomegalovirus (CMV) were implemented per physician's preference.

Adverse events were graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Dose modifications, interruption and discontinuation of any one of the three agents were permitted and documented.

End points and follow-up procedure

The primary end point was ORR after the first 6 cycles of Pola-ZR, defined as the portion of CR and PR by the investigator's assessment. Secondary end points included CR rate after 6 cycles of Pola-ZR, PFS, OS and safety. Patients were scheduled for follow-up every 21 days during the treatment. Adverse events would be recorded and graded throughout the whole procedure. Subsequent anti-lymphoma treatment after disease progression or relapse would be recorded.

PET/CT metabolic parameters

Exploratory end points included metabolic tumour volume (MTV), and total lesion glycolysis (TLG) for all lesions. Enrolled patients all received a PET/CT scan at baseline. A vendor-provided workstation (uWS-MI, United Imaging Healthcare) was used to process the data. Volumes of interest (VOIs) around the lesion was auto-contoured and segmented by adaptive threshold segmentation algorithm. MTV was obtained by summing the metabolic volumes of all individual lesions. TLG was calculated by multiplying the average value of different measurements of standardized

uptake values (SUVs) within the VOI (SUV_{mean}) by MTV for each individual lesion and then summed together. Avoiding intrahepatic lesions and large blood vessels, VOIs within a VOIs with diameter of 20 mm were placed in the right lobe of the liver, which the average standardized uptake value of lean body weight (SUL_{mean}), the average SUL of a region of interest centred on the highest uptake region within the contoured area (SUL_{peak}) and the maximum value for SUL in a VOI (SUL_{max}) were obtained.

Statistical analysis

Kaplan-Meier survival curves were used to calculate the median follow-up time, estimated PFS and OS. Estimates of the treatment effect were expressed as hazard ratios and corresponding 95% confidence intervals and were derived with the use of a stratified Cox proportional-hazards analysis. In patients who were progression-free at the time of data cutoff, PFS data were censored at the date of the last disease assessment. For patients who had no tumour assessment after the baseline assessment, PFS data were censored at the date of enrollment. Baseline TMTV and TLG were dichotomized based on receiver operating characteristic (ROC) curves. Associations between baseline TMTV, TLG, and PFS, OS, were assessed using the Kaplan–Meier (log rank) survival curves. Statistical analyses were performed using solutions statistical package for the social sciences, SPSS 27.0 (IBM, Inc.). P values < 0.05 were considered significant.

Table 1 Clinical characteristics at baseline

	N = 24
Median age, years (range)	73 (65–87)
Female, n (%)	13 (54.2)
Age category, n (%)	
60–69	3 (12.5)
≥ 70	21 (87.5)
Ann Arbor stage, n (%)	
I-II	5 (20.8)
III-IV	19 (79.2)
Number of extranodal sites, n (%)	
0–1	12 (50.0)
≥ 2	12 (50.0)
ECOG performance status score, n (%)	
0–1	11 (45.8)
2–4	13 (54.2)
IPI score, n (%)	
0–2	8 (33.3)
3–5	16 (66.7)
High LDH (> 245 U/L), n (%)	11 (45.8)
Bone marrow involved, n (%)	7 (29.2)
Cell of origin by Hans Algorithm, n (%)	
GCB	4 (16.7)
non-GCB	20 (83.3)
Double-expressor, n (%)	
Positive	1 (4.2)
Negative	21 (87.5)
Unknown	2 (8.3)
Double-hit or triple-hit, n (%)	
Positive	1 (4.2)
Negative	17 (70.8)
Unknown	6 (25.0)

Results

Patients

Twenty-four patients were enrolled in this study from April 1st 2023 to December 20th 2023 in a prospective DLBCL cohort in Zhongshan Hospital affiliated to Fudan University. All patients were newly-diagnosed CD20-positive DLBCL by tissue pathological immunohistostaining. Twenty-three patients were classified as DLBCL, NOS, including one patient with a history of cured DLBCL 18 years ago. One patient was transformed from gastric marginal zone lymphoma.

Most patients were aged over 70 years old, accounting for 87.5%. Thirteen patients (54.2%) had an ECOG performance status score of 2 to 4. Nineteen patients (79.2%) were staged III-IV by Ann Arbor staging system. Sixteen patients (66.7%) had an International Prognostic Index (IPI) score of 3 to 5. Both GCB and non-GCB type were enrolled in this study, accounting for 16.7% and 83.3%, respectively. (Table 1).

Among all 24 patients, sixteen of them had multiple comorbidities at baseline including common diseases like diabetes or hypertension, and critical illnesses. One patient was complicated with colon cancer and completed planned anti-colon cancer chemotherapy one month prior to enrollment. One patient was on maintenance hemodialysis, one had a newly-onset pulmonary embolism before enrollment, and one had a history of severe pulmonary hypertension, asthma, and chronic obstructive pulmonary disease.

Treatment exposure

All 24 patients received at least one cycle of Pola-ZR. At cut-off date 31 May 2024, the median follow-up was 10.2 months. The median cycle of treatment was 8 (range: 1–12). Twenty-three patients were evaluable for efficacy analysis. The one unevaluable patient did not have assessable lesions at baseline, because DLBCL was a finding of the colon cancer surgery. All involved lesions were resected. Among the 23 patients, eighteen patients completed the 6 cycles of Pola-ZR as planned. The other 5 patients discontinued due to adverse events, death or patients' refusal for personal reasons. Altogether 19 patients reached the primary end point,

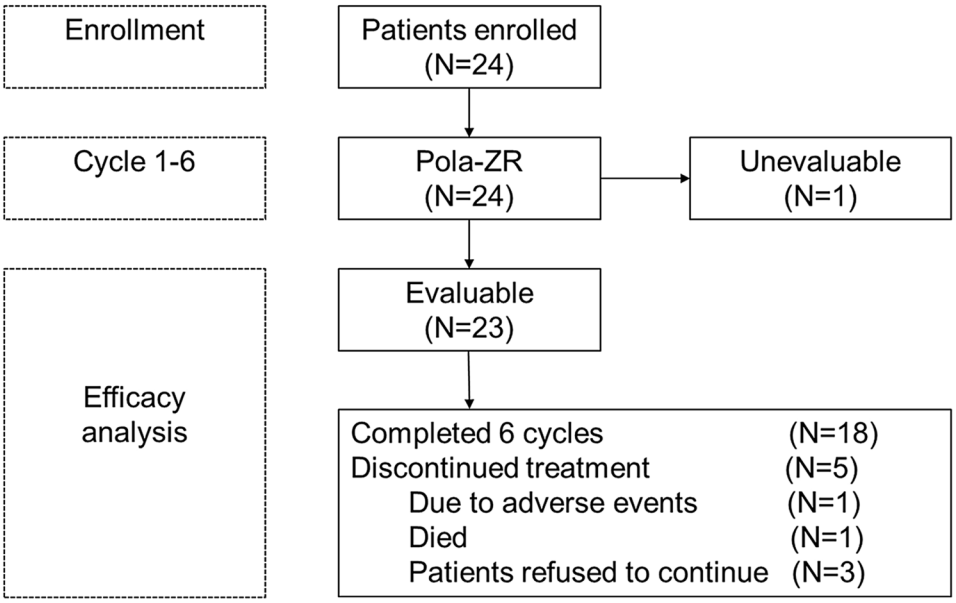

Fig. 1 CONSORT diagram

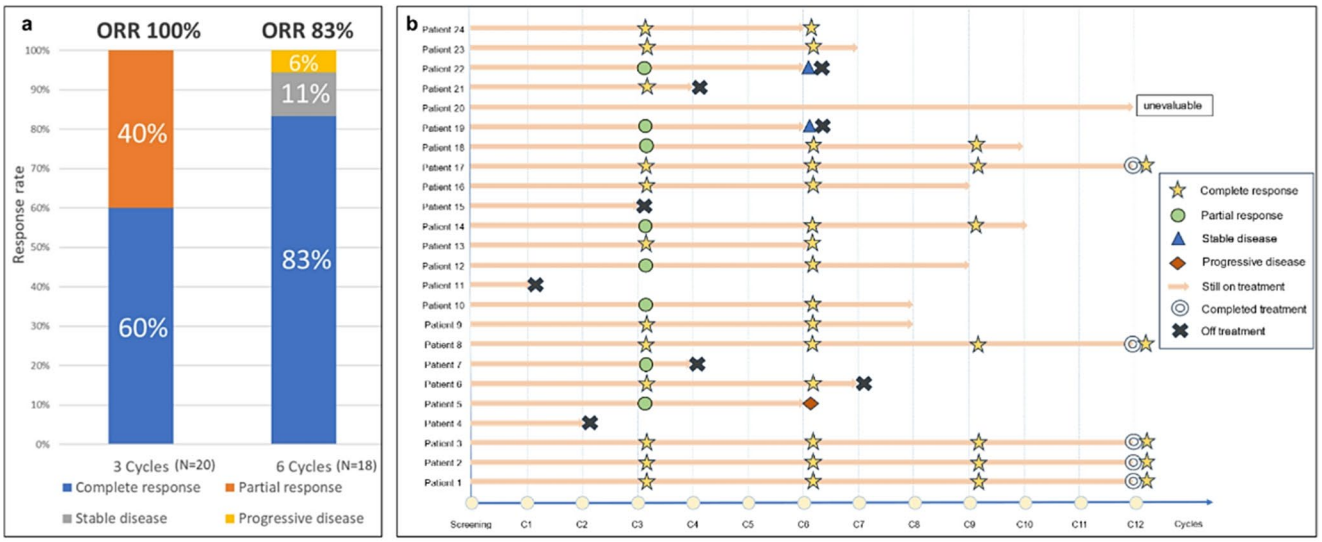

Fig. 2 Efficacy of Pola-ZR regimen. **a**: Assessment results after 3 cycles and 6 cycles of Pola-ZR. **b**: Swimming plot of Pola-ZR treatment

accounting for 79.2%, including the forementioned patient without assessable lesions (Fig. 1).

Efficacy

Eighteen assessable patients reached the primary end point and had an ORR of 83% after 6 cycles of Pola-ZR treatment. Fifteen (83%) patients (2 GCB, 13 non-GCB) were assessed CR, two (11%) patients (2 non-GCB) were stable disease (SD), and one (6%) patient (non-GCB) was progressive disease (PD). Altogether 20 patients had the assessment results after 3 cycles of Pola-ZR. Eight patients were PR, and twelve patients were CR. The ORR after 3 cycles of Pola-ZR was 100% (Fig. 2). All patients with CR results after 6 cycles of Pola-ZR continued to zanubrutinib monotherapy. We provided successive PET/CT images of a typical patient in Fig. 3. She was classified GCB type of DLBCL at baseline, and achieved CR after 3 cycles of Pola-ZR. Response continued as she went on treatment. Patients assessed SD or PD after 6 cycles of Pola-ZR were switched to second-line treatment. As for the one PD patient, the peripheral lesions all regressed, but she developed central nervous system infiltration confirmed by magnetic resonance imaging. For patients with progressive disease, subsequent anti-lymphoma therapy constituted of multi-agent immunochemotherapy.

After a median follow-up of 10.2 months (95% CI: 8.245–12.288), the estimated 1-year PFS was 86.5%. After a

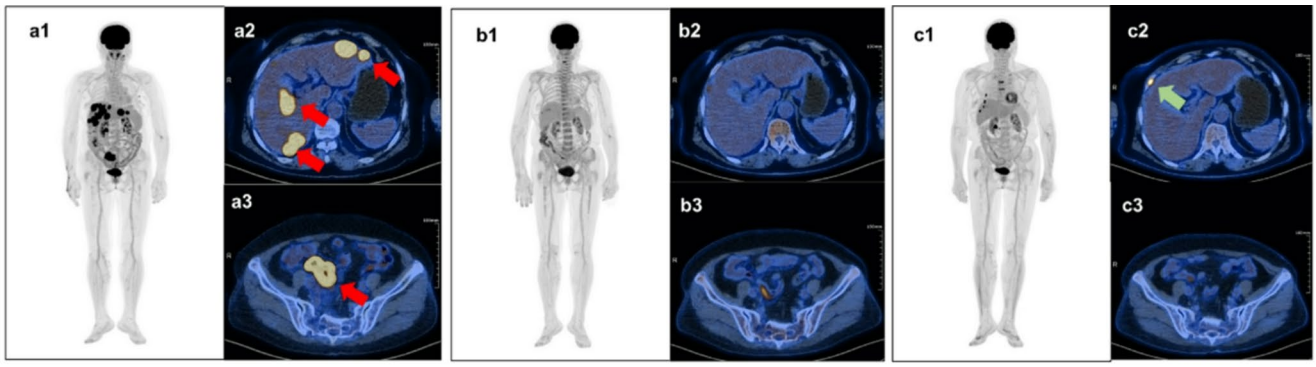

Fig. 3 Successive assessment results of a typical patient based on PET/CT imaging. **a1**, **a2**, and **a3**: PET/CT at baseline. The red arrows pointed to the lymphoma sites. **b1**, **b2**, and **b3**: PET/CT after 3 cycles of Pola-ZR (Deauville score 2). **c1**, **c2**, and **c3**: PET/CT after 6 cycles of Pola-ZR (Deauville score 1). The green arrow pointed to the rib fracture site after a car accident

Table 2 Adverse events

Adverse events, *n* (%)	*N*=24	
	Grade 1–2	Grade 3–5
Hematological adverse events		
White blood cell count decreased	9 (37.5)	1 (4.2)
Neutrophil count decreased	6 (25.0)	2 (8.3)
Platelet count decreased	2 (8.3)	0 (0)
Anemia	1 (4.2)	0 (0)
Non-hematological adverse events		
Lung infection	4 (16.7)	10 (41.7)
Peripheral neuropathy	5 (20.8)	0 (0)
Arrhythmia	3 (12.5)	1 (4.2)
Small intestinal obstruction	3 (12.5)	0 (0)
Alanine aminotransferase increased	1 (4.2)	2 (8.3)
Aspartate aminotransferase increased	1 (4.2)	2 (8.3)
Upper respiratory infection	2 (8.4)	0 (0)
Hypertension	2 (8.4)	0 (0)
Urinary tract infection	1 (4.2)	1 (4.2)
Dizziness	1 (4.2)	1 (4.2)
Diarrhea	1 (4.2)	0 (0)
Hypokalemia	1 (4.2)	0 (0)
Creatinine increased	1 (4.2)	0 (0)
Hyperuricemia	1 (4.2)	0 (0)
Fatigue	1 (4.2)	0 (0)
Epistaxis	1 (4.2)	0 (0)
Petechiae	1 (4.2)	0 (0)

median follow-up of 10.2 months (95% CI: 8.128–12.406), the estimated 1-year OS was 95.8%. The median PFS and OS were not reached.

Safety

An overview of major adverse events was shown in Table 2. White blood cell count decrease and neutropenia were the most common hematological adverse events, accounting for 41.7% and 33.3% of any grade, respectively, mainly at grade 1 to 2. Grade 3 to 5 neutropenia was 8.3%. Grade 3 to 5 anemia or platelet count decrease was not observed.

Lung infection was the major non-hematological adverse event, accounting for 16.7% in grade 1 to 2, and 41.7% in grade 3 to 5. Altogether 10 patients went through grade 3 to 5 lung infection. Nine of them recovered under best supportive care, while one patient died after 3 cycles of Pola-ZR of respiratory failure. This patient had asthma, severe pulmonary hypertension and chronic obstructive pulmonary disease at baseline, and was not eligible for standard immunochemotherapy like R-miniCHOP in the first place. Tumour regression could be observed on chest CT scan without contrast when reviewing pneumonia. Among the 14 patients with lung infection of any grade, we explored the etiological examination and found that 2 patients were infected with COVID-19, two with PJP, one with CMV, and nine with other assumed bacterial infection without specific pathogen findings and recovered under empirical antibiotics. Two patients underwent grade 3 to 5 liver enzymes elevation. Zanubrutinib was discontinued for this reason, and they all recovered from liver function impairment. In one patient with major bulky involvement around the nasal parts, he went through grade 2 epistaxis when the bulk quickly regressed after the first cycle of Pola-ZR. After supportive treatment with the help of ENT department, he recovered from epistaxis and received the next cycle of treatment as planned. Grade 3 to 5 major off-target side effect of BTK inhibitors were not observed. We did not see any reactivation of HBV in our cohort. Peripheral neuropathy occurred as grade 1 to 2, accounting for 20.8%. Numbness was relieved under supportive care.

Dose adjustment was performed per drug leaflets. Zanubrutinib was reduced to 80 mg twice a day in one patient with grade 3 liver enzymes elevation, and was discontinued in one patient with psoriasis at baseline due to repeated episodes of skin lesions. Discontinuation of polatuzumab vedotin due to drug-related adverse events was not observed.

PET/CT metabolic parameters

All patients received a PET/CT scan at baseline. We collected and calculated the TMTV, and TLG of 21 patients with PET/CT data at our center. The cut-off values for TMTV and TLG were 175.29 cm^3 and 2,317 ml by ROC analysis, respectively. Patients were then dichotomized into high TMTV, low TMTV, and high TLG, low TLG accordingly. Among the 21 patients, 16 patients had assessment results (13 CR, 2 SD, 1 PD) after 6 cycles of Pola-ZR. All SD or PD patients were categorized into high TMTV group. The only PD patient had the highest TMTV count 1,352.83 cm^3, and the highest TLG count 8,221 ml among all 21 patients. Kaplan-Meier curves showed no significant difference of 1-year PFS or 1-year OS in high TMTV vs. low TMTV groups (1-year PFS rate: 75.0% vs. not reached, $P=0.148$; 1-year OS rate: 92.3% vs. not reached, $P=0.433$). There was also no significant difference of 1-year PFS or 1-year OS in high TLG vs. low TLG groups (1-year PFS rate: 66.7% vs. 92.9%, $P=0.144$; 1-year OS rate: not reached vs. 93.3%, $P=0.527$) (Supplemental S3). Univariate followed by multivariate Cox regression analysis showed no statistical association between high/low TMTV or high/low TLG with PFS or OS. But PFS or OS were not associated with other characteristics in the multivariate model including IPI score, age and cell-of-origin (COO) subtypes either in this cohort.

Discussion

We first reported the combination of polatuzumab vedotin with zanubrutinib and rituximab (Pola-ZR) in frontline therapy for frail and elderly DLBCL in the 65th ASH meeting and then updated follow-up in the 29th EHA conference [11, 14]. At the cut-off date 31 May, 2024, there were altogether 24 patients enrolled in this study, and here we updated the latest follow-up as all assessable intention-to-treat patients reached the primary end point. In the past two decades, R-miniCHOP is the standard of care for patients aged over 75 years old, with a 2-year PFS 47% in clinical trial and 51% in real-world studies [4, 15]. However, 8% of patients died of treatment-related toxicities in R-miniCHOP arm [4]. Chemo-free regimens incorporating BTK inhibitors with R2 have been frequently reported, yielding an ORR up to 70% in previously untreated elderly DLBCL patients [5, 6]. Hematological toxicities were the major adverse events. Till now, a first-line therapy incorporating both efficacy and safety is still an unmet need in elderly and frail DLBCL patients. Both polatuzumab vedotin and BTK inhibitors were reported to have synergistic effect with rituximab [16, 17–18]. Compared with ibrutinib, zanubrutinib showed less interference with ADCC effect of anti-CD20 antibody and could promote anti-CD20 antibody's effect instead [19, 20–21]. Therefore, we brought up with Pola-ZR after the approval of polatuzumab vedotin in China, in exploration to improve the response rate with tolerable toxicities for this population.

All DLBCL patients were enrolled in this study regardless of COO subtypes and comorbidities. For these patients who would not be eligible for any clinical trial, they were still benefited from Pola-ZR with moderate tolerance. We explored Pola-ZR in a prospective DLBCL cohort, in that case we could observe the safety and tolerance of this triplet regimen in a real-world setting, but not just in patients with sufficient function reserves and better ECOG PS score.

Efficacy

Eighteen patients were assessable in our cohort. ORR and CR rate after 6 cycles of Pola-ZR were 83% and 83%, respectively. The expected 1-year PFS and 1-year OS were 86.5% and 95.8% after a median follow-up of 10.2 months and 10.2 months. Response was seen after 3 cycles of treatment for all patients. Both non-GCB and GCB type were benefited. In our study, Pola-ZR achieved rapid response in elderly and frail DLBCL patients, and was COO-agnostic. To further clarify the molecular differences and responses to the combination of Pola-ZR in DLBCL, we initiated a prospective trial of Pola-ZR in previously untreated elderly and frail DLBCL patients (NCT05940064) in December, 2023. Until 17 October, 2024, we have enrolled more than 20 patients in this prospective trial. Molecular sequencing was performed simultaneously in this prospective cohort within the coverage of ethical rules. Further data concerning molecular typing will be disclosed in the future.

Safety

Hematological toxicities were lower than that in Pola-R-CHP combination. Besides, GCSF prophylaxis was not mandatory in our study. Peripheral neuropathy was modest and was not a cause for discontinuation. Lung infection remained to be the major concern. But nine out of ten patients who underwent grade 3 to 5 lung infection recovered under best supportive care. PJP was the most common cause for lung infection, and COVID-19 was second to it. We recommend PJP prophylaxis for all patients receiving Pola-ZR and are revising our protocol for prospective Pola-ZR trial for PJP prophylaxis. Arrhythmia was the sole

adverse events observed during the follow-up. As shown in Table 2., one patient (4.2%) with repeated atrial and ventricular premature beats was graded 3 to 4, and three patients (12.5%) with accidental atrial premature beats, ventricular premature beats, and low-grade atrioventricular block, respectively, were graded 1 to 2. All patients recovered to normal or low-grade arrhythmia under supportive care. No other severe cardiovascular events were observed. Cardiovascular safety was well-managed when zanubrutinib was combined with polatuzumab vedotin and rituximab or applied solely.

Metabolic parameters

In previous studies, TMTV was associated with shorter PFS and OS in DLBCL patients [22, 23]. There were multiple methods to calculate TMTV and the values differed [24]. Common PET image segmentation techniques included manual, fixed, percentage, adaptive, gradient, and advanced algorithm. The optimal segmentation algorithm has not been universally established at present. In our study, we used an adaptive method to segment the lesions and calculate TMTV and TLG at baseline. ΔTMTV was not included in this study, as lesions were barely segmented after 3 cycles of Pola-ZR due to rapid tumor regression. All non-responders in our cohort were categorized into high TMTV group ($\geq$175.29 cm^3) determined by ROC curves. High TMTV and high TLG ($\geq$2,317 ml) were not statistically associated with shorter PFS or OS in Kaplan-Meier analysis, but we could see the difference by numbers and a trend in two groups that high TMTV and high TLG might be predictors for shorter PFS and OS with longer follow-up. As few patients in our study underwent progression or death, longer follow-up will be documented to further clarify the statistical association between metabolic parameters and survival. Notably, the previous TMTV and TLG results in literature were documented under the treatment of R-CHOP or R-CHOP-like regimens. The predictive significance of TMTV and TLG in the era of polatuzumab vedotin was not well established. We hoped that our data could provide evidence supporting the predictive significance of TMTV and TLG for DLBCL patients under the treatment of Polatuzumab vedotin-based therapies. TMTV was also recorded in our forementioned prospective trial of Pola-ZR to help elucidate the prognostic value. Up till now Pola-ZR was still a possible option for elderly and frail DLBCL patients with high TMTV burden.

In conclusion, Pola-ZR achieved rapid and deep response in previously untreated frail and elderly DLBCL patients with tolerable toxicities. We initiated a prospective phase 2b study (NCT05940064) to further eliminate the efficacy of this combination. Ongoing treatment and follow-up of these 24 patients will also be further updated.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-025-06412-z.

Acknowledgements The authors thank all the patients and their family, and study nurses.

Author contributions Y.R. performed the study, collected data, analyzed results, made the figures and wrote the manuscript; H.T. analyzed the metabolic parameters and wrote part of the manuscript; J.Z. performed the study and follow-up, collected data, and reviewed the manuscript; L.C., L.Y., L.J., Y.K., X.Z., Z.C., and J.L. performed the study and follow-up; P.L. designed and led the study, and reviewed the manuscript. Y.R., H.T., and J.Z. contributed equally to this study as co-first authors.

Funding No funding was received for conducting this study.

Data availability Deidentified individual participant data that underlie the reported results will be made available 3 months after publication for a period of 5 years upon e-mail request to corresponding author liu.peng@zs-hospital.sh.cn. Proposals for access of protocols should be sent to liu.peng@zs-hospital.sh.cn.

Declarations

Competing interests The authors declare no competing interests.

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