

ORIGINAL PAPER

Ofatumumab with iphosphamide, etoposide and cytarabine for patients with transplantation-ineligible relapsed and refractory diffuse large B-cell lymphoma

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Summary

The efficacy of salvage treatment of diffuse large B-cell lymphoma (DLBCL) patients who relapse or progress (rrDLBCL) after initial therapy is limited. Efficacy and safety of ofatumumab with iphosphamide, etoposide and cytarabine (O-IVAC) was evaluated in a single-arm study. Dosing was modified for elderly patients. Patients received up to six cycles of treatment. The primary end-point was the overall response rate (ORR). Patients were evaluated every two cycles and then six and 12 months after treatment. Other end-points included progression-free survival (PFS), event-free survival (EFS), overall survival (OS) and safety. Seventy-seven patients received salvage treatment with O-IVAC. The average age was 56.8 years; 39% had an Eastern Cooperative Oncology Group (ECOG) performance status of at least 3; 78% had disease of Ann Arbor stage 3 or 4; 58% received one or more prior salvage therapies. The ORR for O-IVAC was 54.5%. The median duration of study follow-up was 70 months. The median PFS and EFS were 16.3 months each. The median OS was 22.7 months. Age, ECOG performance status and the number of prior therapy lines were independent predictors of survival. Treatment-related mortality was 15.5%. O-IVAC showed a high response rate in a difficult-to-treat population and is an attractive treatment to bridge to potentially curative therapies.

KEYWORDS

IVAC protocol, ofatumumab, refractory and relapsed diffuse large B-cell lymphoma, salvage treatment

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) represents 25% of non-Hodgkin B-cell lymphomas in adults.¹ Around 70% of patients achieve long-term survival treated with anthracycline-containing immunochemotherapy regimens, such as R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone).^{2–4} Salvage therapy followed by autologous stem cell transplant (ASCT) still remains the standard of care for patients with relapsed and refractory DLBCL (rrDLBCL), providing durable benefits for around 40% of patients.^{5–7} A few years ago, treatment options for patients not eligible for ASCT included conventional chemotherapy, radiotherapy, rituximab-based regimens and optimal supportive care.^{8,9} However, poor outcomes for patients not eligible for ASCT or after transplant failure^{10–12} accelerated research efforts to discover new treatments for rrDLBCL. The SCHOLAR-1 study¹¹ created a historical benchmark for future studies in rrDLBCL.

Recently, chimaeric antigen receptor T (CAR T)-cell therapies were approved^{13–15} for patients with rrDLBCL after two or more lines of systemic treatment. The therapies demonstrated superior response and overall survival (OS) compared to conventional chemotherapies. CAR T-cells had a cellular therapy-specific treatment profile, including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. The use of CAR T-cells was restricted by the ineffectiveness and/or toxicity of bridging therapies.¹⁶

Other recently approved treatment options for patients not eligible for ASCT after the first relapse include polatuzumab vedotin^{17,18} and tafasitamab with lenalidomide.¹⁹ Treatments evaluated in the third line include anti-CD19 antibody loncastuximab tesirine²⁰ and selinexor.²¹

Ofatumumab is a fully human monoclonal IgG1κ-antibody targeting a small-loop CD20 epitope. Preclinical data showed that ofatumumab is more effective in inducing complement-dependent cytotoxicity (CDC) in the DLBCL tumour samples than rituximab.²² Efficacy and safety of ofatumumab were studied in chronic lymphocytic lymphoma,^{23,24} DLBCL^{25–29} and follicular lymphoma.³⁰ Ofatumumab used alone or in combinations was well tolerated and active also in physically frail patients.^{25,29}

The IVAC protocol (iphosphamide, etoposide, cytarabine) in combination with CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate) proved to be effective in Burkitt lymphoma³¹ and high-risk DLBCL.³² CODOX-M/IVAC did not result in better response rates than standard salvage chemotherapies in patients with primary refractory or relapsed high-grade B-cell lymphoma.³³ This regimen led to survival benefits for untreated patients with DLBCL³²; however, the toxicity of CODOX-M/IVAC was excessive^{32,33} for patients with rrDLBCL unable to tolerate ASCT. To improve the safety profile, dose reductions were recommended.³⁴ IVAC regimen combined with rituximab (R-IVAC) was previously used to treat rrDLBCL. The combination was effective, with an overall response rate (ORR) of

54%, but all patients suffered from high-grade haematologic toxicity³⁵ that significantly limited treatment compliance in this vulnerable population of patients. Adjustment of drug doses in the IVAC regimen based on the patient's age and switching monoclonal antibody into ofatumumab would improve the efficacy and safety of the regimen.

This Polish Lymphoma Research Group trial, PLRG8, aimed to evaluate the efficacy and safety of O-IVAC (ofatumumab combined with the IVAC regimen) in the salvage treatment of patients with rrDLBCL who failed R-CHOP and were ineligible for high-dose therapy followed by ASCT.

METHODS

Patients

Key inclusion criteria included: patients with histologically confirmed CD20-positive DLBCL; aged 18 years or older; with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3; and relapsing following prior R-CHOP treatment. All patients were considered ineligible for ASCT by their treating physician or relapsed or progressed after ASCT in the past. Patients who had previously received anti-CD20 treatment other than rituximab were not eligible.

The diagnosis of CD20⁽⁺⁾ DLBCL had to be made according to 2008 WHO criteria.³⁶ At the discretion of the treating physician, the primary diagnostic material (paraffin block and stained slides) was sent to the Pathology Department of Maria Skłodowska-Curie National Research Institute of Oncology in Warsaw for central review. Complete eligibility and exclusion criteria are available in Table S1. All patients were required to give written informed consent.

Study design and procedures

The PLRG8 study was a phase II, multicentre, open-label, prospective clinical trial conducted at eight sites in Poland (Table S2) to evaluate the efficacy and safety of O-IVAC salvage treatment in patients with rrDLBCL. Depending on age, patients started treatment with O-IVAC or modified O-IVAC regimens.

Patients aged less than 60 years old received O-IVAC regimen including ofatumumab 1000 mg iv on day 1, etoposide 60 mg/m² iv on days 1–5, iphosphamide 1500 mg/m² iv on days 1–5 with mesna (depending on local practice), cytarabine 2 g/m² iv every 12 h (total of four doses) 1–2 days, methotrexate 12 mg it, on day 5, granulocyte colony-stimulating factor (G-CSF) on day 6, 5 µg/kg sc daily until absolute neutrophil count (ANC) above 1.0 × 10⁹/l.

Patients aged 60 years or older received modified O-IVAC regimen including ofatumumab 1000 mg iv on day 1, etoposide 60 mg/m² iv on days 1–5, iphosphamide 1000 mg/m² iv on days 1–5 with mesna (depending on local practice), cytarabine 0.5–1.0 g/m² iv based on the investigator's decision, every 12 h (total of four doses) 1–2 days, methotrexate 12 mg

it or by local practice on day 5, GCSF on day 6, 5 µg/kg sc daily until ANC above $1.0 \times 10^9/l$.

The above regimens were administered in 21-day treatment cycles, or as soon as ANC was higher than $1.5 \times 10^9/l$ and thrombocyte count (PLT) was higher than $75 \times 10^9/l$ but not later than 42 days after the first day of the previous cycle. Patients achieving response after two cycles of the treatment continued treatment to achieve the best response. The maximum number of treatment cycles allowed per protocol was six. Patients were followed for 12 months after completing treatment at regular three-month intervals. After completion of participation in the study, patients were followed up by investigators for survival.

Assessments and outcomes

The primary end-point of the study was the ORR, defined as the proportion of patients achieving complete (CR) or partial response (PR) after treatment. Patients were evaluated for response after every two treatment cycles and then six and twelve months after the last treatment cycle. Response to treatment was evaluated with computed tomography (CT) or positron emission tomography/computed tomography (PET/CT), if available. The 2007 Revised International Working Group criteria were used to assess response.^{37,38} Additional tests were performed if clinically indicated.

Secondary end-points included event-free survival (EFS), progression-free survival (PFS) and OS, and treatment safety. EFS was defined as the time from the beginning of the treatment and one of the following: disease progression, relapse, death, starting new anticancer therapy, patient's refusal to continue study treatment or treatment discontinuation for any reason. PFS was defined as the time between the start of treatment and disease progression or death. OS was defined as the time from the start of treatment to death from any cause.

Adverse events, vital signs, physical status and results of laboratory tests were assessed at the time of patient visits during the study. All observed adverse events were described in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03.³⁹

Data analysis

A Simon's two-stage optimal design was used to calculate the sample size.⁴⁰ The design was based on testing the null hypothesis that the ORR was 45% or less, against the alternative hypothesis that the ORR achieved under the planned treatment was at least 60%. With a one-sided alpha of 0.05 and a power of 80%, a total of 77 patients (both stages) were required to enrol in the study. Stage 1 required enrolment of 26 patients and less than 13 patients with ORR indicated for early discontinuation of the trial for futility. If this criterion was not met, stage 2 followed and a subsequent 51 patients

were enrolled. To reject the null hypothesis at least 42/77 patients were required to achieve an objective response.

Chi-squared or Fisher's exact tests and Student's *t*-test were used to compare categorical and continuous variables, respectively. Efficacy analyses were done in the intention-to-treat (ITT) population. The ITT population included all patients enrolled in the study. ORR was reported with two-sided 95% exact confidence intervals (CIs), and the number and percentage of patients in each response category were descriptively tabulated. For time-to-event end-points (PFS, EFS and OS) Kaplan–Meier estimates were presented, along with medians and 95% CIs. Odds ratios (OR) and 95% CIs were calculated using multiple logistic regression analyses in which ORR was the dependent variable and age, number of comorbidities, number of treatment lines, time from the last treatment, ECOG performance status, Ann Arbor status, and presence of systemic symptoms of the disease were the independent variables. We used Cox regression models to estimate hazard ratios (HRs) and 95% CIs. A reverse Kaplan–Meier method was used for follow-up calculation of the association between PFS, EFS and OS and the above-listed baseline factors. All regression models used a stepwise backward selection method. The results were considered statistically significant at $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics version 23.0 (Predictive Solution Ltd., Krakow, Poland).

Ethics

The study was approved by the Ethics Committee at the Maria Skłodowska-Curie National Institute of Oncology (approval note 58/2011) and conducted in accordance with ethical principles defined by the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent before participation. The PLRG8 study is registered with ClinicalTrials.gov, NCT01481272 and EudraCT, 2010–023568-42.

RESULTS

Patients

After the first stage of enrolment, 15 of 26 patients achieved a response of PR or better, the futility criterion was not met and finally, a total of 77 patients with CD20-positive rrDLBCL were enrolled between 15 November 2011 and 11 May 2016. Every patient received at least one cycle of O-IVAC and all were part of the ITT population. The baseline patient characteristics are summarised in [Table 1](#) and are typical for transplant-ineligible patients with rrDLBCL. Most frequent reasons for ASCT non-eligibility included resistance to chemotherapy ($n = 46, 59.7\%$), advanced age and ECOG 3 ($n = 30, 39.0\%$) with more than one factor existing in some patients. Seven patients (9.1%) had a history

TABLE 1 Patient characteristics

Patient characteristics	All patients N = 77	Patients aged <60 years old N = 39	Patients aged ≥60 years old N = 38	p-Value
Female sex, n (%)	33 (42.9%)	19 (50.0%)	14 (35.9%)	0.21
Age, mean (SD), years	56.8 (13.6)	46.5 (11.3)	70.0 (5.5)	<0.0001
ECOG performance status, n (%)				0.13
1	13 (16.8%)	9 (23.7%)	4 (10.3%)	
2	34 (44.2%)	18 (47.4%)	16 (41.0%)	
3	30 (39.0%)	11 (28.9%)	19 (48.7%)	
Presence of systemic symptoms of the disease, n (%)	37 (48.1%)	17 (44.7%)	20 (51.3%)	0.56
Presence of ≥1 comorbidity, n (%)	50 (64.9%)	20 (52.6%)	30 (76.9%)	0.03
Ann Arbor clinical stage, n (%)				0.83
1–2	17 (22.1%)	8 (21.1%)	9 (23.1%)	
3	18 (23.4%)	8 (21.1%)	10 (25.6%)	
4	42 (54.5%)	22 (57.9%)	20 (51.3%)	
Time from diagnosis to study enrolment, median (IQR), months	13 (8–34)	16 (9–34)	11 (8–25)	0.31
Number of salvage therapies				0.10
0	32 (41.5%)	9 (23.7%)	23 (59.0%)	
1	17 (22.1%)	9 (23.7%)	8 (20.5%)	
2	17 (22.1%)	12 (31.6%)	5 (12.8%)	
≥3	11 (14.3%)	8 (21.1%)	3 (7.7%)	
Refractory to R-CHOP*, n (%)	46 (59.7%)	18 (46.1%)	28 (73.6%)	0.01
ASCT in the past, n (%)	7 (9.1%)	7 (18.4%)	0 (0.0%)	<0.006
Time since the last therapy, days				0.62
<66	25 (32.4%)	14 (36.8%)	11 (28.2%)	
66–196	26 (33.8%)	13 (34.2%)	23 (33.3%)	
>196	26 (33.8%)	11 (28.9%)	15 (38.5%)	

*- response for <6 months.

Abbreviations: ASCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone.

of a prior transplantation. Older patients were more frequently refractory to R-CHOP and less frequently treated with ASCT in the past. Other characteristics of patients receiving full-dose and age-adjusted treatment were well balanced (Table 1).

Half of the patients ($n = 38$, 49.4%) received full-dose O-IVAC therapy. Patients received a median of three cycles of the treatment (range, 1–6). Sixty patients received two or more cycles (77.9%), at least 34 patients received four cycles (44.1%) and 12 patients received the planned number of six cycles of O-IVAC. During the treatment phase, 11 patients died and three withdrew their consent to participate in the study. In the 12-month post-treatment phase, 28 patients died (including patients who withdrew in the treatment phase), 20 patients were lost to follow-up after progression of the disease, and 18 patients were alive on the last study visit. After the study, eight and four patients proceeded to ASCT and allogeneic stem cell transplantation, respectively. At the end of follow-up, six patients after ASCT and one after allogeneic stem cell transplantation were alive.

Efficacy

The best ORR (if the response improved after the end of treatment evaluation) was 54.5% (42/77), and the CR rate was 28.6% (Table 2). Overall, 51.9% of patients achieved CR ($n = 8$) or PR ($n = 32$) after two cycles of treatment and subsequent cycles improved response. The response was similar in younger and older patients (Table 2). Using a multivariate logistic regression analysis (Table S3), the independent clinical predictor of response was the presence of systemic symptoms of the disease (Table 3). ORR in patients with and without systemic symptoms was 64.9% and 40.0% respectively (OR = 0.36; 95% CI: 0.14–0.91; $p = 0.031$).

The median follow-up was 70 months (95% CI: 63–76 months). Overall, 66 patients experienced disease progression or died during the study. The median PFS and EFS were 16.3 months (95% CI: 13.0–19.5 months) and 16.2 months (95% CI: 13.7–18.8 months) respectively (Figure 1A,B). In the multivariate analysis, ECOG performance status, number of prior salvage therapies and time from the last therapy were

TABLE 2 Best response to treatment

	All patients N = 77	Patients aged <60 years old N = 39	Patients aged ≥60 years old N = 38	p-Value
Best response, n (%)				0.82
CR	22 (28.6%)	10 (26.3%)	12 (30.8%)	
PR	20 (26.0%)	11 (28.9%)	9 (23.1%)	
SD	8 (10.4%)	3 (7.9%)	5 (12.8%)	
PD	27 (35.1%)	14 (36.8%)	13 (33.3%)	
ORR (CR + PR)	42 (54.5%)	21 (55.2%)	21 (53.9%)	0.91
Disease control (CR + PR + SD)	50 (65.9%)	24 (63.1%)	26 (66.7%)	0.74

Abbreviations: CR, complete response; ORR, overall response rate; PD, disease progression; PR, partial response; SD, stable disease.

statistically highly significant factors predictive of PFS and EFS (Table S4). Prognostic factors associated with PFS are presented in Table 3 and Figure S1. One-year PFS and EFS were 61% each (95% CI: 49.8%, 72.2%). PFS after three and five years of observations was 33.8% (95% CI: 23.0%–44.6%) and 24.5% (95% CI: 14.3%–34.7%) respectively.

The median OS was 22.7 months (95% CI: 15.9–29.5 months) (Figure 1C). In the multivariate analysis, age less than 60 years old, ECOG performance status, and time from the last therapy were independent predictive factors for OS (Table 4, Table S4 and Figure S2). OS at one, three and five years was 84.4% (95% CI: 76.1%–92.5%), 38.3% (95% CI: 27.1%–49.5%) and 30.6% (95% CI: 20.0%–41.2%).

Safety

A total of 885 adverse events were reported; the majority were grades 3 and 4 (78.9%). The most common events were 587 haematologic adverse events (66.4%) that affected every patient. Neutropenia and thrombocytopenia were the most common haematologic adverse events; 25 patients experienced febrile neutropenia (Table S5). The most common groups of adverse events are summarised in Table 5. There were no unexpected adverse events.

During the study, 39 patients died; 28 deaths were related to disease progression and 12 patients died of treatment-related toxicity (Table 5).

DISCUSSION

In 2011, when this study was initiated, there was no standard of care for patients with rrDLBCL ineligible for ASCT; however, several therapeutic options were available despite limited proof of their therapeutic value.¹² More than 13 regimens are currently recommended by NCCN guidelines.⁹ In the PLRG8 study, ORR to age-adjusted dose level of O-IVAC was 54.5%, with over half of responders achieving CR and a median OS of 22.7 months. These results compare favourably with the benchmark from the SCHOLAR-1 study,¹¹ where pooled ORR was 26% with a CR rate of 7% and a median OS

TABLE 3 Independent predictors of progression-free survival

	Median PFS (95% CI), months	HR (95% CI)	p-Value
ECOG performance status			
1	Not reached	1	0.038
2		3.0 (1.2–7.4)	0.019
3	12.0 (2.6–21.5)	3.3 (1.3–8.6)	0.012
Number of treatment lines after R-CHOP			0.017
0	12.0 (5.6–18.5)	1	
1	14.7 (10.7–18.7)	0.5 (0.2–1.0)	0.047
2	23.4 (7.0–39.9)	0.3 (0.1–0.8)	0.017
≥3	26.7 (1.1–52.3)	0.3 (0.1–0.6)	0.004
Time since the last therapy, days			<0.001
<66	7.6 (3.7–11.4)	1	
66–196	12.0 (7.8–16.2)	0.4 (0.2–0.7)	0.005
>196	66.4 (45.01–87.7)	0.1 (0.0–0.2)	<0.001

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS, progression-free survival.

of 6.3 months. O-IVAC resulted in encouraging outcomes in a difficult-to-treat population with almost 40% of patients with ECOG performance status 3. For comparison, in the SCHOLAR-1 study¹¹ only 14% of patients had ECOG performance status 2–4. In addition, fewer patients were primary refractory in the SCHOLAR-1 than in our study. Predictors of survival after relapse are already known^{41,42}; unfortunately, serum lactate dehydrogenase (LDH) activity was not consistently recorded, and International Prognostic Index score could not be determined for all patients.

Rituximab-based regimens are routinely used to treat newly diagnosed DCBCL and are commonly used in the second-line treatment.^{5,43,44} In our study, we sought to improve efficacy by

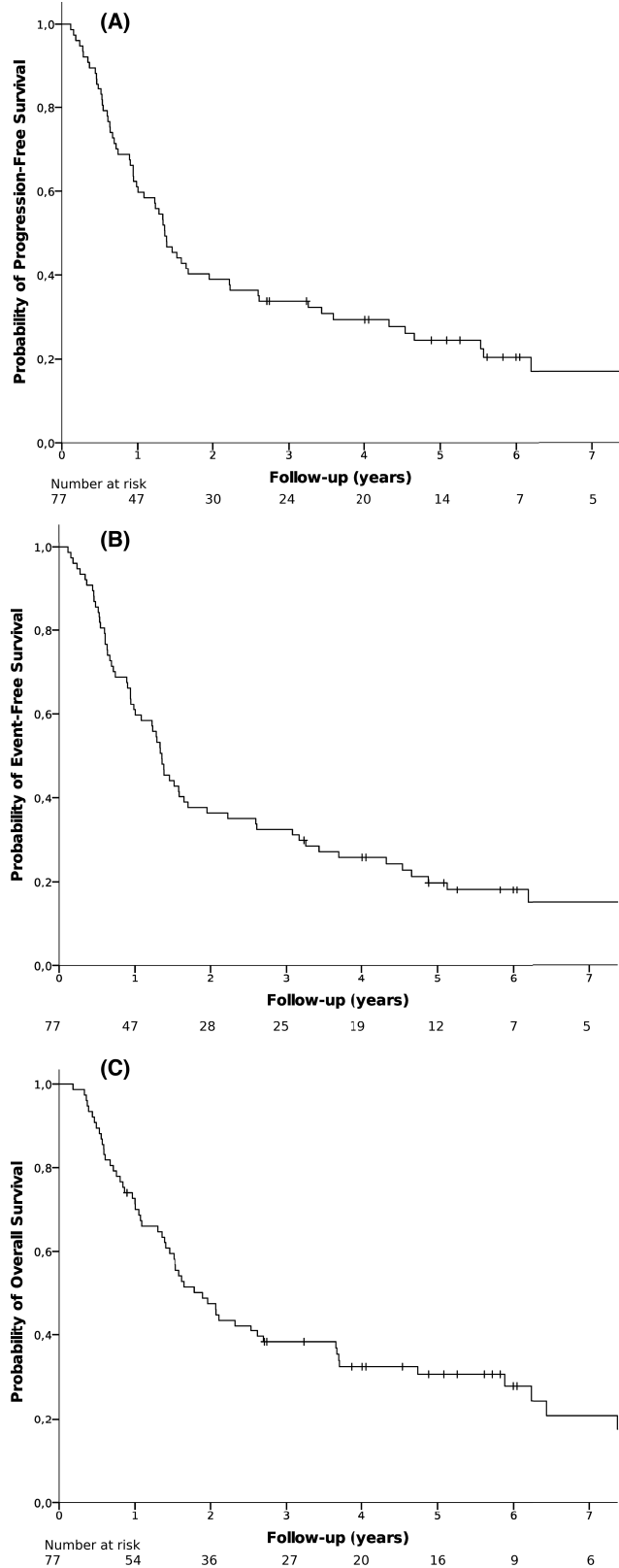


FIGURE 1 Progression-free survival (A), event-free survival (B) and overall survival (C) in transplantation-ineligible refractory and relapsed diffuse large B-cell lymphoma treated with ofatumumab with etoposide, iphosphamide and cytarabine

substituting rituximab with an alternative anti-CD20 antibody with an expectedly enhanced mechanism of anti-lymphoma activity. O-IVAC treatment resulted in ORR similar to that observed in other rituximab-containing regimens,^{44–48} including R-IVAC.³⁵ It should be noted that patients participating in studies with other salvage therapies typically had better performance status, were less frequently primary refractory and had fewer previous lines of therapy than patients in the PLRG8 study, e.g. in the study evaluating R-IVAC, 77.7% of patients had ECOG 0–1.³⁵ Nonetheless, O-IVAC is a treatment of modest efficacy compared to available options for rrDCBCL patients.⁴⁹ Given that the ORCHARRD study showed no difference in efficacy between ofatumumab and rituximab in combinations with cisplatin, cytarabine and dexamethasone followed by ASCT in patients with rrDCBCL,²⁶ it seems unlikely that the addition of ofatumumab to the IVAC regimen might have contributed substantially to activity of our regimen. These results were not known at the time of initiation of the PLRG8 trial.

Like with R-IVAC,³⁵ high-grade treatment-related adverse events, mainly haematologic, were observed in all patients. Both disease- and treatment-related mortality was substantial, not unusual in heavily pre-treated patients with advanced disease.⁵⁰ The toxicity of O-IVAC was consistent with what can be expected from the component cytotoxic agents in that regimen.

Therapies that were recently approved changed the landscape of treatment for rrDCBCL. Outcomes of the ZUMA-1, JULIET and TRANSCEND trials with CAR T-cell products had efficacy outcomes higher than results of historical conventional salvage treatments.^{13,16,51,52} Studies GO29365 and L-MIND directly addressed the unmet need for effective and tolerable regimens for patients with rrDCBCL who are ineligible for or failed to prior ASCT. Polatuzumab vedotin with bendamustine and obinutuzumab resulted in a significantly higher CR rate (40% vs 17%) and reduced the risk of death by 58% compared to rituximab and bendamustine.¹⁷ Combination of tafasitamab with lenalidomide resulted in 61% ORR and was well tolerated.¹⁹ The high CR rates and prolonged disease control suggest that these new treatments may bridge to consolidative therapies. New medical technologies meet patient needs, which were vital at the time of the initiation of the PLRG8 study; however, economic barriers to improve access to these treatments remain.

Overall, O-IVAC showed a rapid response in a difficult-to-treat population, with a median PFS of 16.3 months, making it an attractive option as a treatment regimen that may bridge to consolidative and curative therapies. A parallel course of the EFS and PFS may indicate that progression was the main event resulting in treatment cessation. Age adjustment of dosage used in our protocol likely contributed to attenuation of the early toxicity without affecting the outcome. Several patients proceeded to consolidative therapies despite initial ineligibility. The efficacy of O-IVAC in the context of bridging treatment needs further study and comparison to other modern therapies, including anti-CD19 antibodies or antibody–drug conjugates.²⁰

TABLE 4 Independent predictors of overall survival

	Median OS (95% CI), months	HR (95% CI)	p-Value
Age, years			
< 60	27.8 (16.0–39.6)	1	
≥ 60	18.4 (13.3–23.6)	1.8 (1.0–3.2)	0.034
ECOG performance status			
1	Not reached	1	0.017
2	24.8 (13.6–36.0)	3.3 (1.2–9.0)	0.018
3	22.7 (15.9–29.5)	4.5 (1.6–12.4)	0.004
Time since the last therapy, days			
< 66	10.1 (0.0–21.2)	1	0.017
66–196	16.8 (10.0–23.7)	0.5 (0.2–0.9)	0.017
> 196	77.8 (50.0–99.6)	0.2 (0.1–0.3)	<0.001

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival.

TABLE 5 Number of adverse events with grades 1–5 in system organ classes, as assessed by Common Terminology Criteria of Adverse Events (CTCAE) v. 4.0

System organ class	Adverse events				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Haematopoietic system disorders	7	44	175	412	2
Respiratory system disorders	11	14	16	4	2
Circulatory system disorders	–	5	4	2	3
Urogenital system disorders	2	4	8	2	1
Alimentary system disorders	6	15	17	–	–
Nervous system disorders	3	4	4	2	–
Musculoskeletal and connective tissue disorders	5	1	–	–	–
Skin and subcutaneous tissue disorders	–	19	2	4	–
Infections	2	13	21	7	4
General disorders	11	18	10	4	–
Eye/ear/nose disorders	2	–	3	–	–

CONCLUSIONS

The dose-adjusted O-IVAC regimen produced rapid and durable responses in heavily pre-treated patients with transplantation-ineligible rrDLBCL. Treatment-related toxicity, mostly haematologic, was substantial but manageable in most patients. The IVAC regimen, with or without ofatumumab, may be considered an alternative bridge option to novel consolidation treatments.

CONFLICT OF INTERESTS

Anna Borawska, Andrzej Lange, Agata Malenda, Beata Kumiega, Beata Ostrowska, Grzegorz Rymkiewicz, Jacek Najda, Katarzyna Domańska-Czyż, Lidia Popławska, Łukasz Targoński, Monika Chelstowska, Michał Osowiecki, Monika Mordak-Domagala, Monika Świerkowska, Marcin Szymański, Robert Konecki, Tomasz Szpila, Wanda Knopińska-Posłuszny and Wojciech Michalski have no

conflict of interests to declare. Agnieszka Druzd-Sitek received lecture honoraria from Amgen, Takeda and Celgene-BMS. Sebastian Giebel received lecture and consulting fees from Gilead, Novartis, Roche and Servier. Andrzej Pluta received consulting fees from Kedrion Pharma. Ewa Paszkiewicz-Kozik received lecture fees from Roche, Takeda, Abbvie and travel grants from Roche. Jan Maciej Zaucha received consulting fees from Abbvie, Takeda, Roche, Amgen, BMS, Gilead, speaker fees from Novartis, Takeda, Abbvie, Janssen and travel grants from Roche and Gilead. Joanna Romejko-Jarosińska received lecture honoraria from Roche, Takeda, Abbvie, Gilead and Servier. Jan Walewski received consulting fees from Roche, Takeda, Abbvie, Novartis and Gilead, research funding from Roche and GSK/Novartis and lecture honoraria from Roche, Takeda, Janssen-Cilag, Servier, Abbvie, Amgen, Novartis and Gilead. Michał Taszner received lecture honoraria from Takeda, Roche and Celgene and travel grants from Novartis.

AUTHOR CONTRIBUTIONS


Ewa Paszkiewicz-Kozik, Jan Walewski, Michał Taszner, Monika Mordak-Domagala, Joanna Romejko-Jarosińska, Wanda Knopińska-Posłuszny, Jacek Najda, Anna Borawska, Monika Chelstowska, Monika Świerkowska, Anna Dąbrowska-Iwanicka, Agata Malenda, Agnieszka Druzd-Sitek, Robert Konecki, Beata Kumiega, Michał Osowiecki, Beata Ostrowska, Tomasz Szpila, Marcin Szymański, Łukasz Targoński, WK, Katarzyna Domańska-Czyż, Lidia Popławska, Sebastian Giebel, Andrzej Lange, Andrzej Pluta, Jan Maciej Zaucha performed the research; Jan Walewski, Ewa Paszkiewicz-Kozik designed the research study; Grzegorz Rymkiewicz centrally reviewed primary biopsy material; Wojciech Michalski analysed the data; Ewa Paszkiewicz-Kozik, Jan Walewski wrote the paper. All authors reviewed and approved the manuscript. The authors acknowledge the other investigators participating in this study. Marcin Balcerzak of Medink provided medical writing support.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the Supporting information of this article or are available on request from the corresponding author.

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SUPPORTING INFORMATION

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