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ORIGINAL PAPER

A phase II trial to evaluate the combination of pixantrone and obinutuzumab for patients with relapsed aggressive lymphoma: Final results of the prospective, multicentre GOAL trial

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Summary

The prognosis of patients with relapsed diffuse large B-cell lymphoma (DLBCL) remains poor with current options. Here we prospectively evaluated the combination of pixantrone with obinutuzumab for up to six cycles for patients with relapsed or refractory DLBCL. Overall response rate (ORR) was the primary end-point. Sixty-eight patients were evaluated, median age was 75 years, median number of prior lines was three (range 1–10), 52 patients (76.5%) were diagnosed with DLBCL and 16 (23.5%) patients had transformed indolent lymphoma or follicular lymphoma (FL) IIIB. ORR was 35.3% for all and 40% for evaluable patients (16.6% complete response), median progression-free survival (PFS) and overall survival (OS) were 2.8 months and 8 months, respectively. Analysis of the cell of origin revealed a superior course for patients with non-GCB (germinal centre B-cell-like) phenotype [median OS not reached (n.r.) vs 5.2 months]. Patients with one prior line had an improved

Trial registration: ClinicalTrials.gov *identifier:* NCT02499003'

outcome over patients treated in later lines (PFS n.r. vs 2.5 months). Disease progression was the main reason for premature termination. Adverse events were mainly haematologic. The combination treatment revealed no unexpected adverse events. Most relevant non-haematologic toxicity was infection in 28% of patients. In summary, pixantrone–obinutuzumab showed clinical activity with sometimes long-term remission; however, the trial failed to meet its primary end-point.

KEYWORDS
diffuse large B-cell lymphoma, obinutuzumab, pixantrone, relapse treatment

INTRODUCTION

Prognosis of patients with diffuse large B-cell lymphoma (DLBCL) and other aggressive lymphoma entities has improved with the addition of rituximab. R-CHOP-21 (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone) and its variants are accepted as standard of care worldwide.[1] Nevertheless, a substantial proportion of patients fail first-line treatment. Although transplantation strategies or nowadays CAR-T-cell therapies can induce long-lasting remissions in approximately 40% of relapsed or refractory aggressive non-Hodgkin lymphoma (RR aNHL),[2,3] patients with disease progression after transplantation or patients not eligible for these strategies face an invariably dismal prognosis.[4] Current data show that even in patients undergoing high-dose consolidation, not more than one third of patients in first relapse achieve a long-term remission.[5] In the event of failure of high-dose therapy or intolerance to this treatment modality, regimens like gemcitabine/oxaliplatin or others are applied.[5–7] Recently, treatments like polatuzumab with bendamustin–rituximab (BR) have been added to the therapeutic armamentarium, showing benefits if compared to BR alone,[8] while pathway inhibitors have failed to make a change to standard treatment concepts for DLBCL.[9] However, despite these improvements after a follow-up of 12 months only half of the patients with RR aNHL are alive, and results are even more disappointing in later relapse lines.

Obinutuzumab is a glyco-engineered type II anti-CD20 antibody. Preclinically, improved antibody-dependent cellular cytotoxicity and induction of direct cell death and ability to overcome rituximab resistance were observed.[10,11] In clinical use, efficacy was proven as a single agent in a variety of lymphoma entities including patients failing rituximab (R)-containing first-line therapy.[12] However, obinutuzumab failed to improve results if combined with CHOP as compared to R-CHOP in first-line treatment of naïve DLBCL. Interestingly, data from a subgroup analysis demonstrated benefit in patients with a strong GCB (germinal centre B-cell-like)-phenotype,[13,14] although this has not been confirmed in other series. Furthermore, recent data suggest that switching from the anti-CD20 monoclonal antibody may be useful in patients with relapsed lymphoma.[15]

Anthracyclines have been a mainstay for the treatment of aggressive lymphomas and are considered fundamental for curative approaches in first line. However, cumulative dose-related cardiotoxicity eliminates this class of agents from higher treatment lines.[16] Using pixantrone dimaleate as re-exposition against this drug class has become possible and has been shown to be feasible. Pixantrone is a drug structurally related to anthracyclines and especially anthracenediones, and was initially developed to reduce anthracycline-induced cardiotoxicity. Pixantrone has shown promising activity in haematologic tumours in early trials[17] and results demonstrating superiority of pixantrone as single agent versus other single-agent chemotherapeutic options in patients with RR aNHL paved the way for the current EMA approval.[18] Experiences from further antibody–drug combinations lead to the assumption that the effects of pixantrone will be augmented by a monoclonal antibody without increasing toxicity. A recent phase III trial failed to prove superiority of pixantrone if combined with rituximab over gemcitabine and rituximab,[19] but data of the combination with obinutuzumab were not available. Therefore, this trial aimed to test prospectively the combination of pixantrone and obinutuzumab to evaluate its therapeutic potency and its suitability to overcome resistance to preceding therapies and to serve as future backbone treatment in DLBCL patients not being candidates for intensive treatment.

METHODS

Study design

This was a prospective, non-randomized, multicentre phase II, open-label-study approved by the competent authorities and the appropriate Ethics Committees. It was conducted in accordance with the German Medicines Act (AMG) and Good Clinical Practice guidelines.

Patients — eligibility

Adult patients (≥18 years) with relapsed or refractory aggressive lymphoma (DLBCL, follicular lymphoma (FL) IIIB or

transformed indolent lymphoma) were eligible. Patients with transformed lymphoma were limited to a quorum of 25%.

Patients had to have had at least one prior line of treatment. Further criteria were: Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, at least one measurable tumour lesion (>1.5 cm × >1.0 cm), adequate haematopoietic reserve as well as an appropriate liver and renal function. Pregnant or lactating women were excluded. A detailed description can be found in Appendix S1.

Central pathology and determination of cell of origin

A central histological review was mandatory, and gene expression profiling was performed to determine the cell of origin (COO), if possible. The COO was determined using the NanoString platform as previously described[20]; for details see Appendix S1.

Treatment regimen

Patients received 1000 mg of obinutuzumab on days 1, 8 and 15 (first cycle) or day 1 of any following cycle in combination with 50 mg/m^2 pixantrone on days 1, 8 and 15 of a 28-day cycle for up to six cycles. In the event of haematologic toxicities stepwise dose reductions were allowed for pixantrone only. Granulocyte colony-stimulating factor (G-CSF) use and consolidating 3D radiation were allowed based on the investigators' discretion.

Evaluations

Response was defined according to the International Response Criteria.[21] Initial staging included computed tomographic (CT) scans. Restaging was scheduled after three cycles and at the end of treatment, approximately 4–6 weeks after the last application and every six months for 24 months thereafter. Later patients were followed according to clinical standards.

Objectives

The primary end-point was the objective overall response rate (ORR) after six treatment cycles or at the individual end of treatment. Secondary end-points were the safety profile, progression-free survival (PFS), duration of remission, overall survival (OS) in the entire group or prognostic or biological subgroup.

Statistical considerations

Based on prior single-agent activity of pixantrone and obinutuzumab and with respect to other treatment options an ORR of 40% (or 31 patients with an ORR) would be a reasonable basis for subsequent investigations of this combination. Based on this estimation and a power of 80%, this trial aims for an objective response in 55% of patients, resulting in a number of at least 64 evaluable patients. For overall response assessments the last observation carried forward (LOCF) method was applied in case of missing values.

Proogressin-free survival was defined as time from first intake/dose of trial medication to first documentation of objective progression or to death due to any cause, or censored at the last evaluation date. OS was measured as time from first dose to date of death or was censored at the last date of patient contact. Results for time-to-event end-points were calculated according to the Kaplan–Meier estimator. SAS Version 9.4 (SAS Institute, Cary, NJ, USA) was used for all calculations.

RESULTS

Patients

A total of 70 patients were enrolled, and 68 patients received at least one dose of study medication, defining the intention to treat (ITT) population. Two patients did not receive any treatment due to their deviating from the inclusion criteria (extensive thrombopenia, indolent histology in reference pathology). Patient characteristics are summarized in Table 1. In brief, 37 females and 31 males were treated and the median age was 75 years old (range 35–86). The median number of prior regimens was three and all patients were pretreated with rituximab; 62 (91.2%) patients had received a CHOP-like therapy as primary treatment. Remaining patients had been treated for indolent lymphoma initially. Ten patients (14.7%) had previously received a high-dose therapy and an autologous stem cell transplantation during the course of the disease. Median time since last treatment was 3.4 months, underlying the poor risk characteristics of this patient group. Best response to the individual last line of treatment prior to the GOAL treatment was partial response or better in 43% and 46% had progressive disease. The first patient was enrolled in August 2015 and the last patient three years later in July 2018. The last treatment of the last patient was in January 2019 and last follow-up took place in 2021.

Overall response rate

Responses were evaluable in 60/68 patients enrolled (Table 2A). Patients with no restaging had either progressed and died early due to disease progression or had stopped treatment due to an adverse event (AE) prior to any restaging. The ORR of all evaluable patients was 40% [16.6% complete response (CR), 23.3% partial response (PR)]. Among all additional patients, 8.3% had stable disease as best response, resulting in a disease control rate of 48.2%. For all patients the ORR was 35.3%. Thus, the trial did not meet its primary efficiency end-point.

TABLE 1 Patient characteristics at inclusion

Characteristics	Total
Overall evaluable patients	*n* = 68
Age (years), median (range)	75 (35–86)
Age > 60 years, *n* (%)	54 (79.4%)
Sex, n (%)	
Female	37 (54.4%)
Male	31 (45.6%)
Lymphoma diagnosis at screening	
DLBCL	52 (76.5%)
Follicular lymphoma IIIB	2 (2.9%)
Transformed DLBCL	8 (11.8%)
Transformed to FL IIIB	1 (1.5%)
Transformed to Burkitt-like Lymphoma	1 (1.5%)
Other	4 (5.9%)
Stage at first diagnosis, *n* (%)	
I	12 (17.6%)
II	17 (25%)
III	12 (17.6%)
IV	25 (36.8%)
B-symptoms	
Yes	10 (14.7%)
No	58 (85.3%)
Elevated ldh	53 (77.9%)
Prior number of regimens (median 3; range: 1–10)	
1	14 (20.6%)
2	16 (23.5%)
≥3	38 (55.9%)
Prior rituximab	68 (100%)
Prior CHOP-like treatment	62 (91.2%)
Prior autologous stem cell transplantation, *n* (%)	10 (14.7%)
Prior allogeneic stem cell transplantation, *n* (%)	2 (2.9%)
ECOG performance status at screening, *n* (%)	
0	21 (30.9%)
1	39 (57.4%)
2	8 (11.8%)
Baseline IPI score, *n* (%)	
IPI 1	6 (8.8%)
IPI 2	23 (33.8%)
IPI 3	26 (38.2%)
IPI 4	12 (17.6%)
IPI 5	1 (1.5%)
Response to *first-line therapy*	
Complete response (CR/CRu)	20 (29.4%)
Partial response (PR)	19 (27.9%)
Stable disease (SD)	2 (2.9%)
Progressive disease (PD)	11 (16.2%)
n.a.	16 (23.5%)
Response to *most recent prior therapy*	
Complete response (CR/CRu)	15 (22%)
Partial response (PR)	14 (20.6%)
Stable disease (SD)	3 (4.4%)
Progressive disease (PD)	31 (45.6%)
n.a.	5 (7.4%)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; n.a., not available.

Analysing different subgroups, no significant differences of ORR were detectable in DLBCL versus transformed lymphoma: 40.4% (21/52) vs 18.8% (3/16) and International Prognostic Index (IPI) ≤2 vs >2: 41.4% (12/29) vs 30.8% (12/39), whereas significant differences were found between first versus higher relapse: 64.3% (9/14) vs 27.8% (15/54) (p = 0.0109) and lactate dehydrogenase (LDH) less than upper limit of normal (ULN) versus more than ULN: 60% (9/15) vs 28.3% (15/53) (p = 0.0233).

In patients with available diagnostic material, COO analysis was performed as described above. Analysing all materials available, overall response rates differed significantly between GCB and non-GCB: 22.7% (5/22) vs 55% (11/20) (p = 0.0315). Excluding patients with transformed lymphoma resulted in a non-significant difference of ORR for GCB versus non-GCB: 30.8% (4/13) vs 50% (9/18).

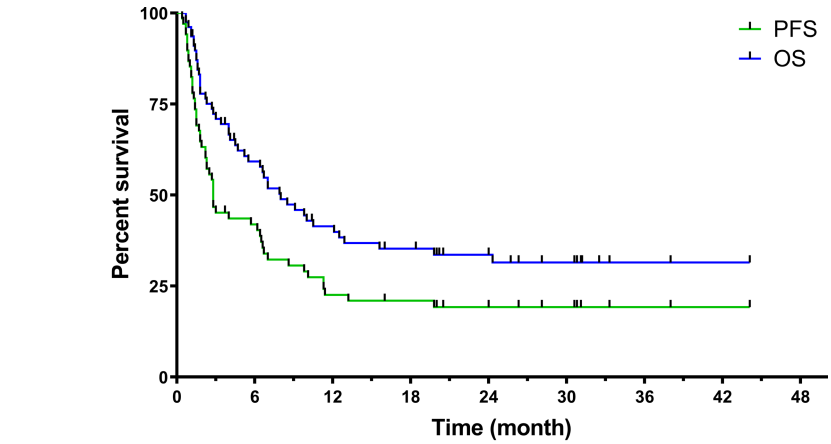
Progression-free survival and overall survival

The median overall PFS and OS for the entire population were 2.8 and 8 months, with a median follow up of 1.16 years (Figure 1). There was no significant difference between patients with either DLBCL or transformed non-Hodgkin lymphoma (PFS/OS: 2.9 and 9.2 months vs 2.6 and 6.7 months). However, the number of prior treatment lines did significantly affect outcome, with median PFS and OS not reached for patients with only one prior line compared to 2.5 and 6.4 months for patients with a higher number of prior treatment lines (Figure 2). Wheras LDH was able to significantly discriminate risk, IPI failed to do so in our cohort. Interestingly, non-GCB patients seem to benefit more from a combination of pixantrone and obinutuzumab. PFS and OS were 6.5 and not reached for non-GCB patients compared to 1.8 and 5.2 months for GCB patients (p = 0.029 and 0.0043) (Figure 3). When patients were separated into ABC and unclassifiable DLBCL, PFS for ABC DLBCL patients was 10.1 months and OS 15.6 months respectively, whereas in unclassifiable DLBCLs the corresponding figures were 4.2 months and not reached. As patients with transformed NHL may have a different prognosis, we performed

TABLE 2A Overall response

	CR	PR	ORR	SD	PD	n.a.	*p*
All patients (*n* = 68)	10 (14.7%)	14 (20.6%)	24 (35.3%)	5 (7.4%)	31 (45.6%)	8 (11.8%)	
All evaluable (*n* = 60)	10 (16.6%)	14 (23.3%)	24 (40%)	5 (8.3%)	31 (51.7%)		
DLBCL (*n* = 52)			21 (40.4%)				0.1133
Transformed (*n* = 16)			3 (18.8%)				
One relapse (*n* = 14)			9 (64.3%)				**0.0109**
>1 relapse (*n* = 54)			15 (27.8%)				
IPI (0–2) *n* = 29			12 (41.4%)				0.3652
IPI (>2) *n* = 39			12 (30.8%)				
LDH < ULN (*n* = 15)			9 (60%)				**0.0233**
LDH > ULN (*n* = 53)			15 (28.3%)				
GCB (*n* = 22)			5 (22.7%)				**0.0315**
Non-GCB (*n* = 20)			11 (55.0%)				
GCB, DLBCL only (*n* = 13)			4 (30.8%)				0.2843
Non-GCB, DLBCL only (*n* = 18)			9 (50.0%)				

For eight patients no response assessment was available. For subgroups only ORR is given due to particularly small numbers for the other response categories.



Numbers at risk							
PFS	68	27	15	13	9	7	3
OS	78	41	28	23	17	12	6

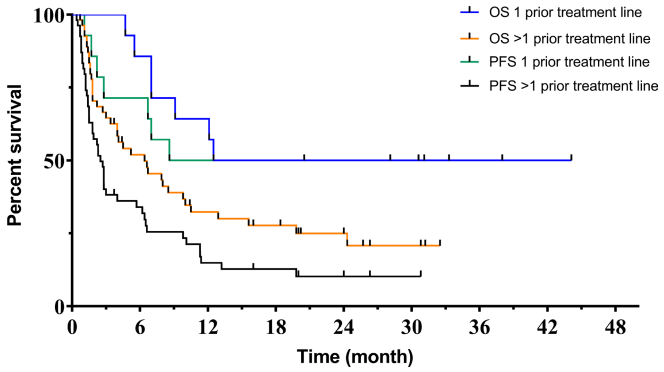
FIGURE 1 Kaplan–Meier curves of overall survival (OS) and progression-free survival (PFS) for the entire cohort of patients. Results for time-to-event end-points were analysed according to the Kaplan–Meier estimator. Median PFS and OS for the entire cohort were 2.8 months and 8 months respectively [Colour figure can be viewed at wileyonlinelibrary.com]

an additional analysis excluding these patients. However, the results still remained significant for OS (2.7 vs 15.6 months, $p = 0.048$) (all Table 2B). If patients were grouped according to their initial response duration after first-line treatment (less than versus more than12 months), a PFS difference was detected of (see Figure S1) 2.3 months vs 8.7 months ($p = 0.0001$), and OS was 4.8 months and not reached, $p = 0.0028$, respectively.

After one year, 23 patients (37%) remained alive. Of the responding patients, 11 patients remained in remission after more than one year and up to four years. Three patients received an allogeneic transplantation during the further disease course, but due to the low number no specific analysis of these patients was performed.

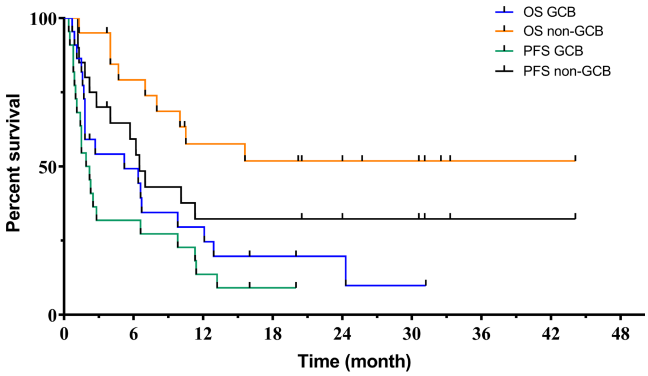
Completion of treatment

In total, 20 (29.4%) out of 68 patients patients completed the entire study treatment. Median treatment duration was 76 days (obinutuzumab) and 81 days (pixantrone). Reasons for premature treatment discontinuation were (more than one may apply): progression of lymphoma (31 events), AE (10 events), death (three events) or other reasons (eight events).



	Numbers at risk							
1 line	PFS	14	11	8	8	7	6	3
	OS	14	13	10	8	7	6	3
> 1 line	PFS	54	17	8	6	3	2	1
	OS	54	25	15	11	7	4	1

FIGURE 2 Kaplan–Meier curves of overall survival (OS) and progression-free survival (PFS) depending on prior lines of treatment. Results for time-to-event end-points were analysed according to the Kaplan–Meier estimator. Median OS and PFS for patients with one prior treatment line were not reached. Median OS and PFS for patients with more than one prior treatment line were 6.4 months and 2.5 months respectively [Colour figure can be viewed at wileyonlinelibrary.com]



	Numbers at risk							
GCB	PFS	22	8	4	2	1	1	1
	OS	22	11	7	4	3	2	1
non-GCB	PFS	20	12	7	7	5	5	2
	OS	20	16	11	10	7	6	2

FIGURE 3 Kaplan–Meier curves of overall survival (OS) and progression-free survival (PFS) depending on the COO profile. Results for time-to-event end-points were analysed according to the Kaplan–Meier estimator. Median OS and PFS for non-GCB patients were not reached and 6.5 months. Median OS and PFS for GCB patients were 5.2 months and 1.9 months respectively. COO, cell of origin; GCB, germinal centre B-cell-like [Colour figure can be viewed at wileyonlinelibrary.com]

The median number of cycles initiated was three, wheras the median number of completed cycles was two (range: 0–6).

Safety

Overall, a total number of 913 AEs were reported (13.4 per patient), among which 377 AEs (41%) were graded as severe. Table 3 summarizes related severe AEs or AEs with a frequency above 10% or events of special interest allocated to the MedDRA system organ classes. Most frequent haematologic AEs (any grade) were [number of patients (percentage)]: leukopenia in 46 (68%), neutropenia in 46 (68%), thrombocytopenia in 15 (22%) and anaemia in 17 patients (25%). Grade 3/4 haematologic adverse events in all treatment levels and comprising all cycles occurred as follows: leukopenia in 44 (65%), neutropenia in 46 (68%), thrombocytopenia in 14 (21%) and anaemia in nine patients (13%). Haematologic toxicities were the main reason for dose reduction or omitting pixantrone applications. 12 (18%) patients required either red blood cell or platelet transfusions and in 41 patients (60%) G-CSF was used.

The most frequent non-haematologic treatment-emergent adverse events of any grade were fatigue in 19 (28%), diarrhoea and nausea in 15 (22%), constipation and dyspnoea in 12 (18%) and cough in 10 (15%) patients. Grade 3/4 non-haematologic adverse events were rare and included pneumonia in six (9%), increased gamma-glutamyl transferase (γ-GT) and hypertension in four (6%) and acute kidney injury and hypokalaemia in three

TABLE 2B Progression-free and overall survival

	Median PFS (months)	*p*	Median OS (months)	*p*
All evaluable (*n* = 68)	2.8		8	
DLBCL (*n* = 52)	2.9	0.5660	9.2	0.4573
Transformed (*n* = 16)	2.6		6.7	
HR (transformed vs DLBCL)	1.201 (0.641–2.247)	0.5678	1.295 (0.653–2.570)	0.4592
1. Relapse (*n* = 14)	n.r.	**0.0044**	n.r.	**0.0271**
>1. Relapse (*n* = 54)	2.5		6.4	
HR (1 vs >1)	0.203 (0.100–0.413)	<0.0001	0.295 (0.143–0.607)	0.0009
IPI (0–2) (*n* = 29)	2.8	0.6207	10.6	0.2022
IPI (>2) (*n* = 39)	2.5		6.7	
HR (0–2 vs >2)	0.872 (0.505–1.504)	0.6221	0.679 (0.373–1.237)	0.2057
LDH < ULN (*n* = 15)	n.r.	**0.0047**	n.r.	**0.0064**
LDH > ULN (*n* = 53)	2.3		5.5	
HR (<ULN vs >ULN)	0.348 (0.162–0.748)	0.0068	0.319 (0.134–0.759)	0.0098
GCB (*n* = 22)	1.8	**0.0299**	5.2	**0.0043**
Non-GCB (*n* = 20)	6.5		n.r.	
HR (GCB vs Non-GCB)	2.131 (1.056–4.289)	0.0346	3.060 (1.363–6.870)	0.0067
GCB, DLBCL only (*n* = 13)	1.5	0.2066	2.7	**0.0486**
Non-GCB, DLBCL only (*n* = 18)	6.2		15.6	
HR (GCB vs Non-GCB)	1.676 (0.744–3.776)	0.2129	2.425 (0.974–6.036)	0.0570

Abbreviations: CR, Complete response; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell-like; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase; n.a., not available; n.r., not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; ULN, upper limit of normal.

patients (4%). Infectious complications occurred in 38 patients (56%) including urinary tract infection, pneumonia and nasopharygitis. No grade 5 events due to an AE were observed.

DISCUSSION

Despite recent developments, results of treatment of patients with relapsed and refractory aggressive lymphoma frequently remain disappointing. Therefore, novel therapeutic options are urgently warranted for salvage, bridging or palliative treatment. Pixantrone and obinutuzumab have demonstrated clinical benefit in RR aggressive lymphoma (AL) as single agents. To this end, we have addressed the efficacy of combining both agents. We enrolled a patient population in which the majority of patients had received multiple prior treatments. Median time since last treatment was 0.28 years. Overall, treatment was well tolerated with a favourable toxicity profile underlining feasibility; accordingly the main reason for premature termination was disease progression. Major toxicities were either haematologic or infections; however, no patient died due to infection. Importantly, re-exposing patients to pixantrone after prior doxorubicin use did not result in relevant cardiac toxicity.

Overall response rate was 35.3% for the entire cohort of patients and 40% for the evaluable population. Therefore, the trial failed to reach its primary end-point. Interestingly, response rates observed are comparable to the response rate obtained with the preceding therapy of our patient cohort, whereas a reduction of response rates is generally noticed with more advanced treatment lines. However, focussing on specific subgroups, e.g. 64.3% of patients with only one prior line and 60% of patients with normal LDH achieved an objective response. In contrast, results for high-risk populations, with elevated LDH or multiple prior treatments, were inferior.

In line with this finding, PFS and OS were better for patients with good risk features, e.g. for patients with one prior line median PFS and OS were not reached, whereas for the entire cohort PFS and OS were 2.8 and 8 months, respectively. We also investigated the prognostic role of gene expression profiling.[22] Interestingly, in contrast to other trials,[23] non-GCB-phenotype was associated with a prolonged PFS and OS and this holds also true for OS after excluding patients with transformed lymphoma. The molecular mechanisms for this differential response are unclear. In addition, for the GCB cohort, median OS was not reached. However, due to the limited number of patients, calculation of confounding factors was not possible with sufficient power.

Treatment selection for patients with relapsed AL is highly variable, based on lack of clear superiority of currently used combinations.[24] Results of rituximab–gemcitabine–oxaliplatin (R-GemOx) and bendamustine–rituximab (BR) represent relevant comparators, applied in patients not eligible for dose intensification. Both treatments were

TABLE 3 Adverse events (number of patients with at least one event)

		Total	
		Grade 1–2	Grade 3–5
System organ class	Preferred term	*N* (%)	*N*
Blood and lymphatic system disorder[a]	Anaemia	11 (16.2%)	9 (13.2%)
	Leukopenia	5 (7.4%)	44 (64.7%)
	Neutropenia	4 (5.9%)	46 (67.7%)
	Thrombocytopenia	6 (8.8%)	14 (20.6%)
Gastrointestinal disorder	Constipation	11 (16.2%)	1 (1.5%)
	Diarrhoea	14 (20.6%)	1 (1.5%)
	Nausea	13 (19.1%)	2 (2.9%)
	Vomiting	4 (5.9%)	–
	Stomatitis	3 (4.4%)	1 (1.5%)
General disorders	Fatigue	17 (25%)	2 (2.9%)
	Mucosal inflammation	3 (4.4%)	–
	Oedema peripheral	8 (11.8%)	1 (1.5%)
	Pyrexia	8 (11.8%)	–
Infections of special interest	Pneumonia	–	6 (8.8%)
	Urinary tract infection	7 (10.3%)	1 (1.5%)
	Sepsis	–	2 (2.9%)
	Any infectious complication	29 (42.7%)	13 (19.1%)
Investigations	γ-GT increased	2 (2.9%)	4 (5.9%)
Metabolism and nutrition disorders	Hypokalaemia	4 (5.9%)	3 (4.4%)
Nervous system disorders	Polyneuropathy	4 (5.9%)	1 (1.5%)
Respiratory, thoracic and mediastinal disorders	Cough	10 (14.7%)	–
	Dyspnoea	11 (16.2%)	1 (1.5%)
Skin and subcutaneous tissue disorders	Pruritus	5 (7.4%)	–
	Rash	7 (10.3%)	–
Vascular disorders	Hypertension	1 (1.5%)	4 (5.9%)
Renal and urinary disorders	Acute kidney injury	–	3 (4.4%)
Neoplasms	Acute myeloid leukaemia	2 (2.9%)	–
	Neuroendocrine carcinoma of the skin	1 (1.5%)	–

Selective: only events grade 3/4 (>5%) or with a frequency >10% or events of special interest are selected.

[a]Lymphopenia was an expected adverse reaction in the treatment with obinutuzumab and pixantrone and was therefore not documented as an adverse event.

investigated in prospective and retrospective studies; however, there is no randomized comparison of these regimens. While early results of e.g. (R-)GemOx demonstrated high response rates, many of the patients treated within these trials had not received rituximab previously.[25,26] In contrast, later series, including patients with prior rituximab exposure, had inferior ORR and CR rates; a recent retrospective series revealed an ORR of 43% and a median OS of eight months only.[27] BR gave conflicting results in retrospective series, but a recent controlled randomized trial showed an ORR of 25% with a PFS of 2.0 months (investigators' results; 3.7 months by independent review) and an OS of 4.7 months.[8] Taking these prospective data into account, pixantrone–obinutuzumab achieved, albeit with comparable response rates, prolonged disease control as compared to results reported for (R-)GemOx or BR. In addition, compared to other data, results for patients at first relapse are promising. A recent large retrospective series of patients with DLBCL (ReMIND2) analysed the results of patients with only one prior line for BR and R-GemOX: PFS and OS for these regimens were 8.8 and 7.1 months and 12 and 16.8 months, as compared to not reached in our series.[28] Other combinations incorporating pixantrone have also been explored, supporting the efficacy of pixantrone -based combinations. For example, the PREBEN trial explored pixantrone, rituximab, etoposide and bendamustin in pretreated AL patients. In this mixed-bag trial, an ORR of 53% was observed. An analysis of the Polish group evaluating efficacy in a more homogenous group of patients confirmed the promising efficacy, but follow-up was short in both trials, which does not allow comparing long-term results.[29,30] The Pix306 trial tested rituximab–pixantrone versus rituximab–pixantrone,

without demonstrating superiority of R-Pix over R-Gem. Focussing on the R-Pix arm, there was a comparably higher ORR and prolonged OS as demonstrated in our study. However, primary refractory patients had been excluded and most of the patients had received only one prior regimen, which limits the comparison between trials. Consequently, a potential benefit of obinutuzumab versus rituximab cannot be assumed from comparison with this trial.[19]

Recently, a variety of non-chemotherapy treatment regimen has been introduced into the treatment of relapsed lymphoma. For patients with sufficient fitness, chimeric antigen receptor (CAR) T-cells are of special interest and polatuzumab in combination with BR has been approved.[31] OS for this combination was 12.4 months, which compares favourably to the regimen tested here. However, the number of patients with long-term disease control remains low, requiring other treatment options. Amongst these, together with bispecific antibodies or the anti-CD19 antibody tafasitamab, the combination of pixantrone and obinutuzumab may be considered a reasonable treatment option for RR aNHL.

In summary, the combination of pixantrone and obinutzumab is able to induce remissions in patients with RR DLBCL. Longer disease control is observed especially in patients with more beneficial characteristics. With the increasing number of therapeutic options for relapsed DLBCL, further efforts are needed to define a role in the increasingly complex algorithm.

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CONFLICT OF INTERESTS

Georg Hess received research support from Pfizer, Janssen and Roche. He has received advisory or speaker honoraria from Roche, Janssen, Gilead/Kite, Novartis, Morphosys, Abbvie, AstraZeneca, Genmab, Incyte. Georg Lenz declares the following potential conflict of interests with respect to the current study: he has received honoraria from Abbvie, Bayer, BMS, AstraZeneca, CTI Pharma, Genmab, Karyopharm NanoString, Novartis Celgene, Gilead, Incyte, Janssen, Morphosys, Roche, Takeda, and has received research funding from AQUINOX, AGIOS, AstraZeneca, Bayer, Celgene, Gilead, Janssen, Morphosys and Roche. Ulrich Keller:Takeda: Consultancy; MSD: Consultancy; Janssen-Cilag: Consultancy; Roche: Consultancy; BMS: Consultancy; Celgene: Research Funding; Consultancy;. AstraZneneca: Consultancy; Abbvie: Consultancy; Gilead: Consultancy; Pentixapharm: Consultancy; Hexal: Consultancy; Marcel Trautmann received research support from NanoString, and Roche. He received advisory or speaker honoraria from Novartis, and BMS. Mathias Witzens-Harig received research support from Roche. Andreas Viardot: Consultancy: Kite/Gilead, Novartis, BMS, Roche, Amgen, Takeda; Honoraria: Kite/Gilead, Novartis, BMS, Roche, Amgen, Astrazeneca. Martin Dreyling received research support from Abbvie, Bayer, Celgene, Janssen and Roche. He received advisory or speaker honoraria from Amgen, Astra Zeneca, Bayer, Beigene, Celgene, Gilead, Incyte, Janssen, Roche, Janssen, Novartis, Roche. All remaining authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

The study was planned by Matthias Theobald, Georg Hess and Georg Lenz. Georg Hess, Andreas Hüttman, Mathias Witzens-Harig, Martin Dreyling, Ulrich Keller, Reinhard Marks, Thomas Ernst, Christiane Pott, Andreas Viardot and Georg Lenz contributed patients to the trial, read and approved the protocol. Fabian Frontzek and Marcel Trautmann performed the molecular analysis, Andreas Rosenwald performed central pathology review, Oliver Deuster managed the trial, Christian Ruckes performed the statistical analysis. Matthias Theobald, Georg Lenz and Georg Hess wrote the manuscript.

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SUPPORTING INFORMATION

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