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Real-world outcomes following third or subsequent lines of therapy: A Danish population-based study on 189 patients with relapsed/refractory large B-cell lymphomas

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Summary

Outcome data of patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) beyond the second line are scarce outside of clinical trials. Novel therapies in the R/R setting have been approved based on single-arm trials, but results need to be contextualized by real-world outcomes. Medical records from 3753 Danish adults diagnosed with DLBCL were reviewed. Patients previously treated with rituximab and anthracycline-based chemotherapy who received the third or later line (3 L+) of treatment after 1 January 2015, were included. Only 189 patients with a median age of 71 years were eligible. The median time since the last line of therapy was 6 months. Patients were treated with either best supportive care (22%), platinum-based salvage therapy (13%), low-intensity chemotherapy (22%), in clinical trial (14%) or various combination treatments (32%). The 2-year OS-/PFS estimates were 25% and 12% for all patients and 49% and 17% for those treated with platinum-based salvage therapy. Age ≥70, CNS involvement, elevated LDH and ECOG

≥2 predicted poor outcomes, and patients with 0–1 of these risk factors had a 2-year OS estimate of 65%. Only a very small fraction of DLBCL patients received third-line treatment and were eligible for inclusion. Outcomes were generally poor, but better in intensively treated, fit young patients with limited disease.

KEYWORDS
chemotherapy, clinical research, epidemiology, lymphomas, malignant lymphomas

BACKGROUND

Approximately a quarter of diffuse large B-cell lymphoma (DLBCL) cases relapse within 5 years from the time of diagnosis,[1] and up to 70% of these cases are primary refractory (i.e. stable or progressive disease or relapse within 12 months from diagnosis).[1,2] Until recently, the most commonly used, potentially curative approach for patients with R/R DLBCL was platinum-based chemotherapy, followed by high-dose therapy (HDT) and autologous stem cell transplantation (ASCT).[3,4] However, more than half of all R/R patients are ineligible for ASCT merely due to age (>70 years),[5] and even in trial setting, 48%–68% of patients planned for HDT/ASCT do not reach consolidation mainly due to the insufficient response and toxicity of induction treatment.[6–9] For the minority completing HDT/ASCT, half achieve durable responses and are still alive at 2 years.[5,6]

Historically, patients with R/R DLBCL after two or more lines of therapy have been offered palliative rather than curative intent treatment. As a result, the interest in reporting outcomes in DLBCL after two or more lines of therapy has generally been low. However, in 2017, the first CD19-directed chimeric antigen receptor T-cell (CAR-T) therapy, axicabtagene ciloleucel, was approved by the FDA for use in adult patients with R/R large B-cell lymphoma, followed by other CAR-T treatments.[10] In 2018, the European Medicines Agency approved tisagenlecleucel and axicabtagene ciloleucel for the same indications.[10,11] The response rates reported in the registrational trials have later been confirmed in real-world data studies, with demonstrated CR rates of 40%–53% and with more than half of patients alive after 15 months.[10–14] Most recently, a significant survival benefit was also demonstrated in the second line in early relapsed or primary refractory patients, compared to HDT/ASCT.[15] However, CAR-T therapies are expensive, and access is limited on a global scale. Even within Europe, there is significant regional variation in access. Despite approval by the European Medical Agency (EMA), cost–benefit evaluations for introduction and public reimbursement are performed on a per-country basis with variable conclusions. In Denmark, CAR-T treatment is currently not publicly reimbursed in any treatment line, while other countries have significant practical experience and a well-established structural foundation, including visitation and treatment procedures.[16,17] As a possible alternative to CAR-T therapy, T-cell engaging bispecific antibodies have also demonstrated promising efficacy in the 3L+ setting.[18–20] Glofitamab was recently approved in Canada for patients with R/R DLBCL, transformed follicular lymphoma and primary mediastinal B-cell lymphoma. It was recommended for approval with the EMAs Committee for Medicinal Products for Human Use, and both glofitamab and epcoritamab were recently approved by the FDA.[21] The registrational studies for tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel, epcoritamab and glofitamab were all single-arm trials,[10,11,14,21,22] which carries inherent bias in terms of patient selection and interpretation of time-to-event data. There is a need for detailed data on the real-world outcomes of R/R DLBCL commencing conventional 3L+ therapy to contextualize the results of these registrational trials.

In the present Danish population-based study, we report nationwide data on outcomes of DLBCL in the 3L+ setting by type of therapy and trial eligibility status.

PATIENTS AND METHODS

This retrospective study was based on the population-based Danish Lymphoma Registry (LYFO), which has high coverage (>95%).[23] Adult patients (≥18 years) diagnosed with DLBCL between 1 January 2012 and 31 December 2019 were screened for eligibility. DLBCL not otherwise specified (NOS), high-grade B-cell lymphoma (HGBL) and primary mediastinal B-cell lymphoma (PMBCL) were eligible. Primary central nervous system (CNS) lymphoma, post-transplant lymphoproliferative disorder and Burkitt or Burkitt-like lymphoma were not eligible. Patients initiating the third or later line of therapy (3L+) between 1 January 2015 and 31 August 2021 were included if treatment failure had occurred after immunochemotherapy, including CD20 monoclonal antibodies and anthracyclines (i.e. CHOP/CHOEP/DA-EPOCH). The first eligible line of therapy after 1 January 2015 was used as the index line. The displacement between the screening period (time of initial diagnosis) and inclusion period (time of index line) was chosen to balance the population, as fully overlapping periods would lead to a higher proportion of early relapses and a lower proportion of late relapses. Medical records were reviewed by local haematologists or haematologists in training for eligibility and to collect detailed clinical information on baseline characteristics prior to commencing treatment, response to treatment, relapse and survival outcomes. A dedicated review of the diagnosis by haematopathologists was not performed, as all patients were diagnosed at centres with access to pathologists

with experience in lymphoma diagnostics. Clinical stage and end-of-treatment response were assessed according to criteria in place at the time.[24,25] Fluorescence in situ hybridization (FISH) results for relevant translocations (MYC, BCL2 and BCL6) were recorded. Up to seven lines of therapy were recorded for each patient with best supportive care (BSC), considered a line of therapy on its own. BSC was defined as no lymphoma-directed therapy aside from steroid alone or other symptom-directed medications. Refractory disease was defined as a stable or progressive disease with the best response or relapse/progression within 12 months from the start of the previous line of treatment. The date of death was collected from the Danish Civil Registration System, with the last follow-up on 31 August 2021. Trial eligibility status was defined as no CNS involvement at relapse, an Eastern Cooperative Oncology Group performance score (PS) ≤2 and no organ dysfunction. Organ dysfunctions prior to treatment were recorded if a patient had a known history of left ventricular ejection fraction (LVEF) <45%, a New York Heart Association score (NYHA) >2, creatinine >1.5 times the upper limit of normal (ULN), bilirubin >1.5 times the ULN, alanine transaminase (ALT) >3 times the ULN or a significant pulmonary disorder affecting physicians' choice of treatment. A recent (<180 days) biopsy-verified disease was included in a sensitivity analysis.

The study was compliant with national regulations for non-interventional, retrospective studies (record numbers: 2021-221 and 2021-040892).

Statistical analyses

OS was defined as the time between the start of the index treatment line and death from any cause or censoring if alive on the last follow-up. Progression-free survival (PFS) was until non-response/progression/relapse, death from any cause or censoring. Survival probabilities were estimated using the Kaplan–Meier estimator. The objective response rate (ORR) was defined as the proportion of patients achieving partial remission (PR) or complete remission (CR).

Prognostic factors for OS among patients receiving therapies beyond BSC and palliative radiotherapy were explored in Cox proportional hazards models with (1) bidirectional stepwise regression with AIC as a measure of model performance. The model was obtained using the R-function step AIC from the MASS package and (2) LASSO penalization with the optimal lambda value found by cross-validation and Harrell's C as a performance measure. Both models were fitted using 1000 bootstrap samples.

In a sensitivity analysis, the robustness of results when choosing another line of therapy for each patient (if available) was tested using a resampling method. For each patient, a random eligible line of treatment (between 3 and 7) was selected (REL-3+), and all patients were combined to form 1000 separate datasets ($D_{1\ldots1000}$). Outcome measures were calculated for each dataset, and the outcomes and characteristics of all datasets were combined by computing medians and 2.5/97.5 percentiles. The statistical programming language 'R' (version 4.2.2, Vienna, Austria, http://www.R-project.org) was used for all statistical analyses.

RESULTS

A total of 3753 patients with DLBCL diagnosed between 1 January 2012 and 31 December 2019 were screened for eligibility and 189 patients (5%) were included (Data S1 and S2). Clinical characteristics at the time of the index line are outlined in Table 1. The index line equalled third-line (3L) therapy in 182 out of 189 patients.

Advanced-stage disease, extra-nodal involvement, B symptoms and elevated LDH were common. PS was available in 144 patients; 56 of those (39%) had PS ≥2. CNS involvement was present in 32 patients, of whom 16 also had verified CNS involvement at a previous relapse or diagnosis.

Of the 189 patients, 143 (76%) were refractory to the previous line of therapy. After a median follow-up of 31 months, median OS and PFS estimates after the start of the index line were 5.8 months (95% CI: 4.6–7.8) and 2.8 months (95% CI: 2.0–3.2). The 2-year OS and PFS estimates were 25.1% (95% CI: 18.5–31.7) and 11.7% (95% CI: 6.8–16.7) (Table 1; Figure 1). Patients who were refractory to the most recent treatment line prior to the index line had 2-year OS and PFS of 22.2% (95% CI: 14.9–29.4) and 7.3% (95% CI: 2.7–11.9) respectively. In a sensitivity analysis, we used a random eligible line (REL-3L+) as an index line, and the outcomes remained largely unchanged. Across all 1000 random samples, the median 2-year OS was 23.1% (2.5–97.5 percentile: 21.3–24.8), and the median 'median survival' was 3.7 months (2.5–97.5 percentile: 3.1–4.6). Demography and outcomes are provided in the Data S4.

Treatment patterns in the first, second and index lines are shown in Table 2 and Figure 2 (Sankey plot). Most patients received R-CHOP/R-CHOEP as first-line therapy, and the most commonly used second-line therapies were ICE/DHAP/GDP. Rituximab was administered to 83.1% of the patients in the second line. The index-line therapies (3L for 96%) were most often BSC (20%), platinum-based salvage therapy (ICE/DHAP/GDP, 13%) and pixantrone–rituximab–etoposide–bendamustine (PREBen, 8%). Ibrutinib or lenalidomide as a single agent or in combination with chemotherapy, CNS-directed chemotherapy and RTx monotherapy were less frequently used and grouped in an 'Other' category (Table 2; Table S5). Fourteen percent of the patients were enrolled in clinical trials. Rituximab was part of the index-line therapy in 79 patients (42%). Seven patients (4%) received HDT/ASCT, and six patients received allogeneic stem cell transplantation (SCT) in 3L. Two patients received allogeneic SCT in a later line.

Outcomes by treatment are outlined in Table 1 and Figure 3, and responses to treatment are described in the Data S9. The 2-year OS for patients treated with ICE/DHAP/

TABLE 1 Demography and clinicopathological information at the time of index-line treatment for 189 R/R DLBCL patients.

	All patients (*n* = 189)	DHAP/ICE/GDP (*n* = 24)	BSC (*n* = 37)	Clinical trial (*n* = 25)	Low-intensive chemo (*n* = 42)	Other treatments (*n* = 61)
Age, median (range)	71.0 (20.0–90.0)	66.0 (20.0–81.0)	76.0 (47.0–87.0)	69.0 (42.0–80.0)	71.0 (50.0–90.0)	72.0 (44.0–90.0)
Months since diagnosis	20.5 (2.6–107.4)	13.8 (3.2–89.4)	18.5 (4.9–83.0)	24.2 (6.9–75.0)	19.8 (4.9–84.5)	21.7 (2.6–107.4)
Months since prev. line	5.9 (0.5–61.0)	3.4 (1.3–36.8)	5.4 (0.5–50.7)	6.0 (1.1–55.3)	6.1 (0.5–47.2)	6.7 (0.7–61.0)
Ann Arbor stage, *n* (%)						
I–II	51 (27.0)	4 (16.7)	6 (16.2)	5 (20.0)	8 (19.0)	28 (45.9)
III–IV	124 (65.6)	19 (79.2)	23 (62.2)	19 (76.0)	33 (78.6)	30 (49.2)
Unknown	14 (7.4)	1 (4.2)	8 (21.6)	1 (4.0)	1 (2.4)	3 (4.9)
Performance status, *n*(%)						
0–1	88 (46.6)	14 (58.3)	7 (18.9)	22 (88.0)	18 (42.9)	27 (44.3)
2–4	56 (29.6)	3 (12.5)	25 (67.6)	0 (0.0)	11 (26.2)	17 (27.9)
Unknown	45 (23.8)	7 (29.2)	5 (13.5)	3 (12.0)	13 (31.0)	17 (27.9)
B symptoms, *n* (%)						
Yes	30 (15.9)	1 (4.2)	8 (21.6)	2 (8.0)	9 (21.4)	10 (16.4)
No	117 (61.9)	17 (70.8)	17 (45.9)	23 (92.0)	22 (52.4)	38 (62.3)
Unknown	42 (22.2)	6 (25.0)	12 (32.4)	0 (0.0)	11 (26.2)	13 (21.3)
Extra-nodal sites, *n* (%)						
0	60 (31.7)	10 (41.7)	9 (24.3)	9 (36.0)	15 (35.7)	17 (27.9)
1	66 (34.9)	9 (37.5)	13 (35.1)	6 (24.0)	10 (23.8)	28 (45.9)
>1	53 (28.0)	4 (16.7)	9 (24.3)	9 (36.0)	17 (40.5)	14 (23.0)
Unknown	10 (5.3)	1 (4.2)	6 (16.2)	1 (4.0)	0 (0.0)	2 (3.3)
LDH, *n* (%)						
Normal	73 (38.6)	9 (37.5)	9 (24.3)	11 (44.0)	16 (38.1)	28 (45.9)
Elevated	108 (57.1)	14 (58.3)	22 (59.5)	14 (56.0)	26 (61.9)	32 (52.5)
Unknown	8 (4.2)	1 (4.2)	6 (16.2)	0 (0.0)	0 (0.0)	1 (1.6)
IPI, *n* (%)						
0–2	87 (46.0)	15 (62.5)	6 (16.2)	15 (60.0)	15 (35.7)	36 (59.0)
3–5	98 (51.9)	9 (37.5)	27 (73.0)	10 (40.0)	27 (64.3)	25 (41.0)
Unknown	4 (2.1)	0 (0.0)	4 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)
CNS involvement, *n* (%)						
No	153 (81.0)	20 (83.3)	24 (64.9)	25 (100.0)	41 (97.6)	43 (70.5)
Yes	32 (16.9)	4 (16.7)	10 (27.0)	0 (0.0)	1 (2.4)	17 (27.9)
Unknown	4 (2.1)	0 (0.0)	3 (8.1)	0 (0.0)	0 (0.0)	1 (1.6)
Histology, *n* (%)						
DLBCL	95 (50.3)	10 (41.7)	12 (32.4)	19 (76.0)	25 (59.5)	29 (47.5)
HGBL	7 (3.7)	2 (8.3)	1 (2.7)	2 (8.0)	0 (0.0)	2 (3.3)
Not repeated at index*	87 (46.0)	12 (50.0)	24 (64.9)	4 (16.0)	17 (40.5)	30 (49.2)
Index treatment line, *n* (%)						
Third	182 (96.3)	24 (100.0)	33 (89.2)	25 (100.0)	41 (97.6)	59 (96.7)
Fourth	5 (2.6)	0 (0.0)	3 (8.1)	0 (0.0)	1 (2.4)	1 (1.6)
Fifth	1 (0.5)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)
Seventh	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Refractory to prior line, *n* (%)						
No	46 (24.3)	3 (12.5)	9 (24.3)	6 (24.0)	12 (28.6)	16 (26.2)
Yes	143 (75.7)	21 (87.5)	28 (75.7)	19 (76.0)	30 (71.4)	45 (73.8)
2-year OS (95% CI)	25.1 (18.5–31.7)	49.3 (27.9–70.7)	5.4 (0.0–12.7)	27.7 (7.4–48.0)	21.5 (8.2–34.8)	28.6 (16.5–40.6)
Median OS (months)	5.8 (4.6–7.8)	19.8 (10.7-NA)	1.2 (0.8–1.7)	13.5 (7.3–21.3)	6.0 (3.5–9.9)	6.7 (4.3–13.5)
2-year PFS (95% CI)	11.7 (6.8–16.7)	17.4 (0.5–34.3)	5.4 (0.0–12.7)	13.7 (0.0–30.0)	10.6 (0.9–20.4)	13.0 (4.2–21.8)
Median PFS (months)	2.8 (2.0–3.2)	2.9 (1.1–9.3)	1.2 (0.8–1.7)	3.3 (2.8–5.2)	2.8 (2.0–4.2)	3.4 (1.9–4.4)

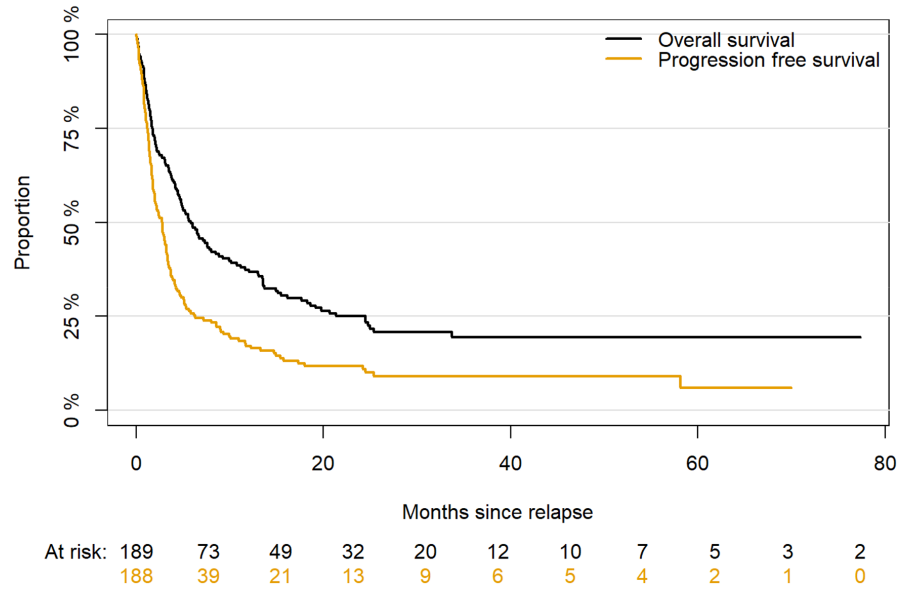

FIGURE 1 Overall survival and progression-free survival for all patients measured from the time of index-line treatment.

GDP in 3L+ was 49.3% (95% CI: 27.9–70.7). In comparison, survival was significantly worse for patients treated with BSC (HR = 8.63, 95% CI: 4.40–16.95), low-intensive regimens (HR = 2.23, 95% CI: 1.14–4.35) and 'other treatments' (HR = 2.12, 95% CI: 1.12–4.01) (Figure 3).

Prognostic factors in the 3L setting (not including BSC and palliative radiotherapy)

An International Prognostic Index (IPI) of 0–2 at the time of index treatment was associated with a 2-year OS of 40.1% (95% CI: 28.8–51.5) vs. 12.6% (95% CI: 5.4–19.7) for IPI 3–5 ($p < 0.001$, Figure 4). Age ≥70, PS ≥2, CNS involvement and elevated LDH were the most frequently selected prognostic factors in both the stepwise regression and LASSO penalty Cox models (Data S3 and S7). Among 101 patients with available data on all risk factors, those with <2 risk factors had a significantly better 2-year OS of 64.6% (95% CI: 47.7–81.6) vs. 14.6% (95% CI: 5.5–23.7%) for patients with ≥2 risk factor (Figure 5; Figure S8).

Outcome of 3L trial candidates (not including BSC and palliative radiotherapy)

Sixty-eight of 182 patients (37%) fulfilled the defined trial eligibility criteria, of whom 19 (of 68 eligible patients) were enrolled in clinical trials. The remaining were treated with DHAP/GDP/ICE ($n = 12$; 7%), low-intensive regimens ($n = 17$; 9%) or 'other' treatment ($n = 20$; 11%). The median age was 70.5 years, and 49% had an IPI >2. The 2-year OS and PFS were 34.5% (95% CI: 22.3–46.8) and 14.4% (95% CI: 5.3–23.5) respectively. Median OS was 13 months (95% CI: 7.6–19.8) (Data S6). In a sensitivity analysis, patients without biopsy confirmation of diagnosis within 180 days prior to the start of index therapy were excluded. In the remaining 57 patients, survival was identical with a 2-year OS of 35.1% (95% CI: 21.8–48.4).

DISCUSSION

In this Danish population-based retrospective study of patients with DLBCL after the third or subsequent lines of therapy, we report on the clinical characteristics, treatment patterns and outcomes. Of the 3753 patients identified with newly diagnosed DLBCL and screened for inclusion, only 189 (5%) were eligible for this study. More than half of the included patients had an IPI >2. CAR-T therapy was not available to any patient in their index line. Outcomes were generally dismal, with 2-year OS and PFS estimates of 25% and 12%, respectively, and the minority of patients that received platinum-based salvage therapy had a 2-year OS and PFS of 49% and 17% respectively.

Nearly 20% of patients only received BSC, and less than 13% received platinum-based salvage regimens. Of all 189 patients, only 24% achieved CR/PR, and less than 7% were consolidated with HDT/ASCT or allogenic SCT. In the CORAL trial,[6] 203 patients were excluded due to toxicity or insufficient response, and a follow-up study reported on the outcomes of these patients following third-line treatment. In these trial-eligible patients with a median age of 55, 60% received second salvage intensive regimens. However, only 28% and 4% reached HDT/ASCT or allogenic SCT respectively.[26] Similarly, a recent Swedish population-based study reported on R/R DLBCL after initial curative intent treatment. The median age was 71 years, only 27% received intensive salvage therapies as second-line therapy, and only 17% were consolidated with HDT/ASCT.[5] That is, despite the significant

TABLE 2 Treatment patterns in the first, second and index lines.

First-line		Second-line		Index-line	
Chemotherapy. *n* (%)		Chemotherapy. *n* (%)		Chemotherapy. *n* (%)	
R-CHOP/R-CEOP	130 (68.8)	CHOP	8 (4.2)	DHAP/ICE/GDP	24 (12.7)
R-CHOEP	26 (13.8)	DHAP/ICE/GDP	82 (43.4)	Gemcitabine/GemOX	8 (4.2)
Clinical trial	6 (3.2)	Low-intensity chemo	46 (24.3)	Bendamustin	6 (3.2)
R-CHOP/CHOEP plus MTX and or HD-AraC	20 (10.5)	Clinical trial	6 (3.2)	PREBEN	15 (7.9)
R-BFM/R-CODOX-M/Other	7 (3.7)	Others	47 (24.9)	CCVP	13 (6.9)
				BSC	37 (19.6)
Number of cycles. *n* (%)				Clinical trial	25 (13.2)
1–2	8 (4.3)			Other (BTK-i. IMiD. CNS. RTx)	61 (32.3)
3–5	19 (10.2)				
6	134 (71.7)	Consolidation. *n* (%)		Consolidation. *n* (%)	
>6	26 (13.9)	No consolidation	122 (64.9)	No consolidation	165 (87.3)
		Radiotherapy	29 (15.4)	HDT + ASCT	7 (3.7)
Consolidation. *n* (%)		ASCT ± RTx	33 (17.5)	Allo	7 (3.7)
No consolidation	153 (81.0)	Unknown	4 (2.1)	Unknown	10 (5.3)
Radiotherapy/ASCT	36 (19.0)				
		Response evaluation. *n* (%)		Response evaluation. *n* (%)	
Response evaluation. *n* (%)		CR/CRu	54 (28.6)	CR/CRu	33 (18.4)
CR/CRu	115 (60.8)	PR	20 (10.6)	PR	13 (7.3)
PR	16 (8.5)	SD or PD	99 (52.4)	SD or PD	82 (45.8)
SD or PD	51 (27.0)	Unknown or Tox	16 (8.5)	Discontinued due to tox or unknown	7 (3.7)
Unknown	7 (3.7)			Dead before response assessment	44 (24.6)

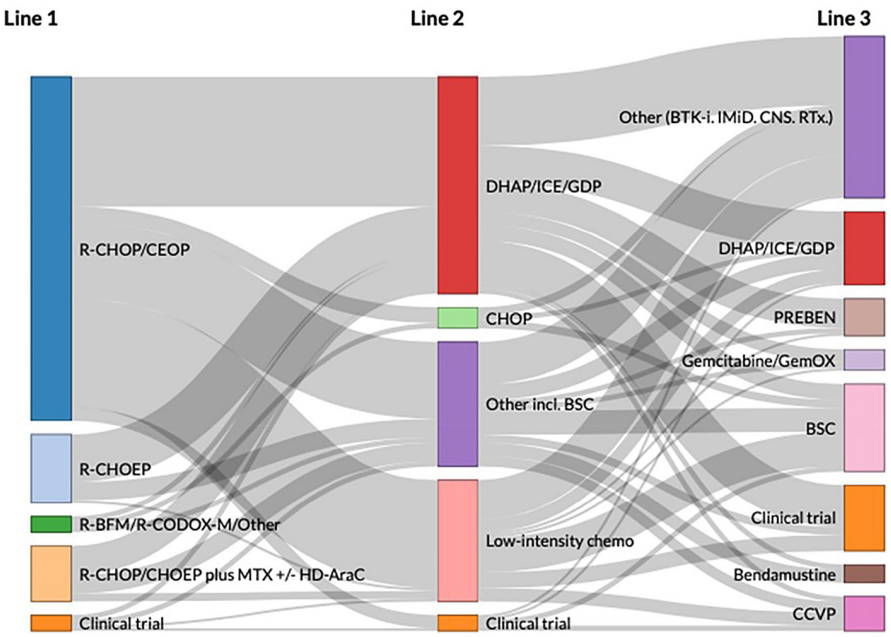

FIGURE 2 Sankey plot of the first three lines of treatment in the 189 included 3L+ patients. Importantly, the index line corresponded to the third line for the majority (183/189) but not all patients. [Corrections made on 21 December 2023, after first online publication: Figures 2, 3, 4 and 5 were previously wrongly swapped and were corrected in this version.]

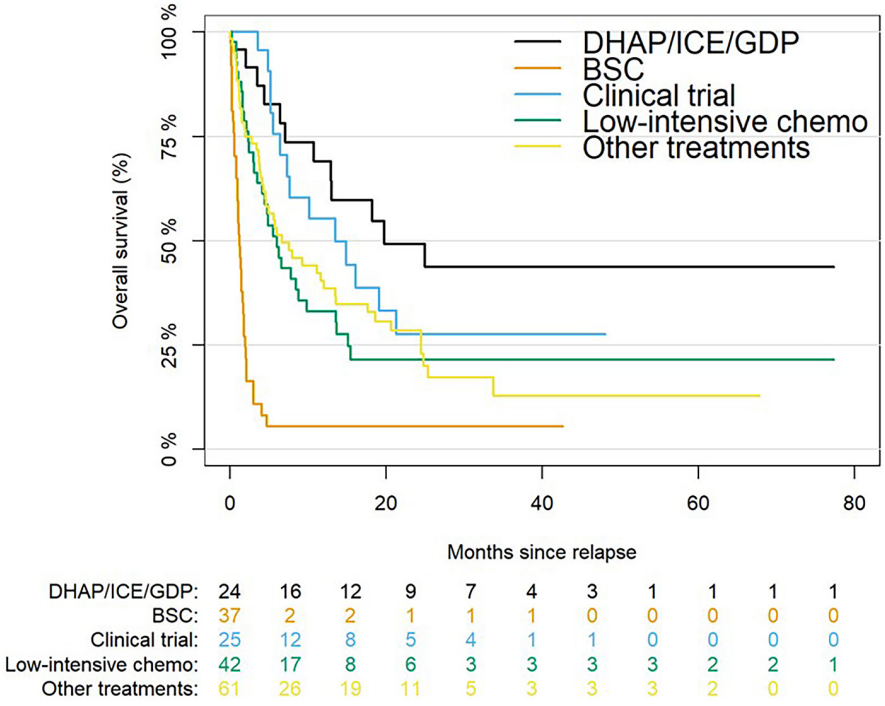

FIGURE 3 Treatment stratified overall survival. 'Low-intensive chemo' included PREBEN, CCVP, gemcitabine, Gem/Ox and bendamustine, whereas 'other treatments' included mostly IMiDs, BTK-I, CNS-guided treatment and RTx monotherapy.

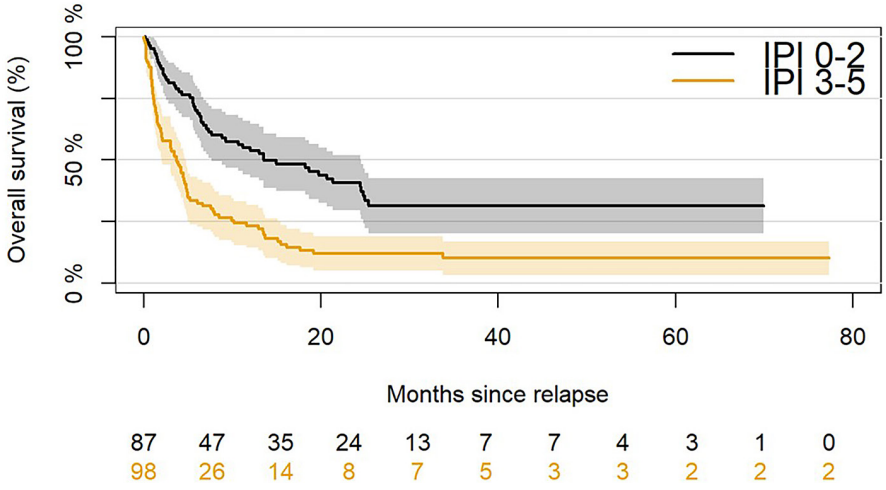

FIGURE 4 Overall survival stratified by International Prognostic Index (IPI) at the time of index-line treatment in 185 patients with available IPI. Shaded areas indicate pointwise confidence intervals.

demographic difference between these three populations, outcomes are surprisingly similar with regards to SCT consolidation rates following intensive salvage therapy.

To our knowledge, there are no published population-based data on outcomes after the third or later lines of treatment in DLBCL. In our cohort, outcomes were very poor and similar to the SCHOLAR-1 study, despite fundamental differences in study design. SCHOLAR-1 pooled data from two clinical trials and two observational cohorts[10] and included patients that achieved PD as the best response after the first line, SD/PD as the best response after the second or later lines and patients that relapsed within 12 months from the time of HDT/ASCT.[27] The median age of the cohort was only 55 years, and 73% had a PS of 0–1. More than 75% were refractory to second line or later or had an early relapse within 12 months from ASCT. Excluding the patients that experienced early relapse following ASCT, 36% were primary refractory. SCHOLAR-1 reported a response rate of 26%, a median OS of 6.3 months and a 2-year OS of 20% vs. 26%, 5.8 months

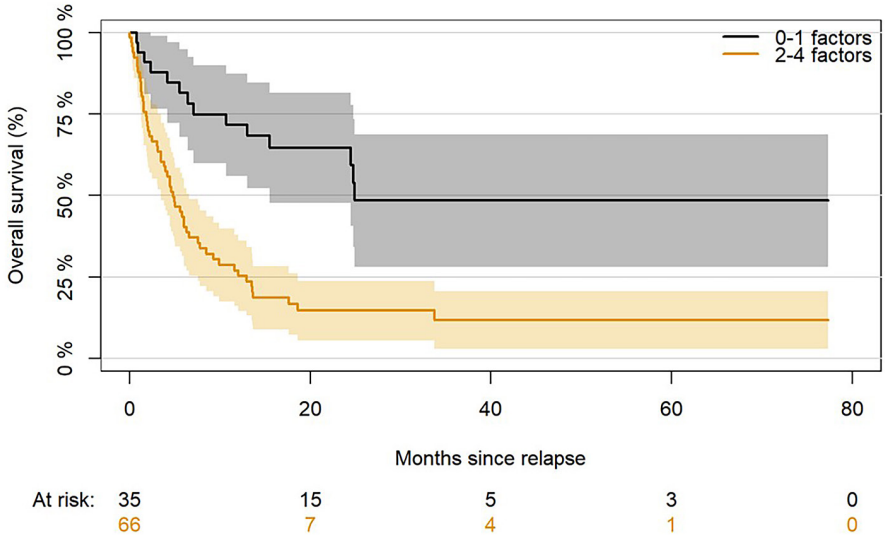

FIGURE 5 Overall survival stratified by the number of present risk factors (age >70, PS ≥2, CNS involvement, elevated LDH) in 101 patients with sufficient data on the risk factors. Patients treated with BSC and palliative RTx are excluded.

and 25%, respectively, in the current study. These results were similar to the 6.5 months reported by Sermer et al. in a retrospective single-centre study of 146 patients with R/R DLBCL between 2001 and 2017.[12] The results of the present study were also consistent with the 7.7 months reported by Hamadi et al. in a multicentre registry-based study of 174 patients after 3L treatment for DLBCL.[28] These universally low response rates and poor treatment outcomes across different study populations warrant continued research into non-chemotherapy treatment options for this group of patients where conventional therapies have proven unsuccessful.[26,29,30]

We were able to identify four adverse prognostic factors: CNS involvement, elevated LDH, age ≥70 and PS ≥2. Patients in the low-risk category (0–1 risk factor) had a 2-year OS and 5-year OS of 65% and 49%, respectively, in contrast to patients with >2 risk factors with a dismal 2-year OS of 15%. The low-risk category identifies a group of patients where the pursuit of long-term remission, even following two or more failed lines of treatment, remains within reach.

Outside clinical trials, there is a paucity of knowledge on treatment patterns and outcomes in the third line and beyond settings. In recent years, several CAR-T treatments have demonstrated remarkable efficacy. The ZUMA-1 trial reported a 2-year OS of 50% following treatment with axicabtagene ciloleucel in a single-arm phase 1/2 trial.[31] The Transcend trial found similar outcomes for lisocabtagene maraleucel, with a median OS of 21.1 months.[14] The efficacy of CAR-T was confirmed in a 'real-world' study by Sermer et al., which reported a median OS of 19.3 months.[12] However, access is still limited in many parts of the world due to cost and logistical challenges. This is an issue even in some northern European countries, such as Denmark, where CAR-T treatments are not publicly reimbursed in any treatment line as of 1 September. T-cell engaging bispecific antibody treatments may be a promising, accessible alternative to CAR-T therapy, with reported high overall response rates of more than 50% as well as durable remissions.[21,22] Glofitamab demonstrated a median survival of 12 months in a single-arm phase 2 trial, similar to a phase 2 study with epcoritamab.[21,22] However, these pivotal data need to be interpreted and contextualized by real-world data on comparable patient populations. In an attempt to provide this context, we identified all patients treated in the third line that fulfilled a prespecified list of criteria related to trial eligibility defined as no CNS involvement, no history of significant cardiac, pulmonary, renal or hepatic comorbidity and a PS ≤2 and treated with anything but BSC. Only 68 of 189 patients fulfilled these criteria, highlighting the disparity between real-world patients and typical trial-eligible populations. The trial-eligible patients in this study had a 2-year OS of 35% and a median survival of 13 months. While inferior to the CAR-T trials, the outcomes of our trial-eligible patients were similar to those reported in 'bispecific' trials. Of course, comparison between single-arm trials and retrospective cohorts should be done with caution. While the CAR-T and bispecifics trials all included young patients (median age 58–64 vs. 70 in our cohort), they were also heavily pretreated, and 50%–70% had received three or more lines of previous therapy. Arguably, the patients in these clinical trials may be less chemo-sensitive than the trial-eligible patients in the current study, where all patients had received only two previous lines of treatment. Finally, the treatment patterns in our cohort of multiple R/R DLBCL were heterogeneous and may not be representative in all countries where other treatment options are available.

Limitations

This study has several limitations inherent to the retrospective design. The screening and inclusion period were

designed to create a heterogeneous 'real-world' cohort at the expense of homogeneity. Due to the format of data collection, we are not able to discern how many patients were excluded because they never experienced third relapse from those that experienced a third relapse but outside the inclusion period. While this study is population-based, the exclusion of CD20/anthracycline-naïve patients in the first and second lines precludes generalizability of the study results to a broader population of elderly/frail patients that were not candidates for standard immunochemotherapy. However, for this group, an increasing number of trials are now available in the first or later lines. Patients perceived as clinically high-risk may have been allocated to more intensive regimens or suboptimal treatments (including BSC) due to treatment bias. This could potentially confound the comparison of different treatment regimens as well as impact the detected prognostic factors. Patients with 'high-risk' features based on the identified prognostic markers may have experienced worse outcomes due to confounding by indication, and these results should be interpreted with caution.

CONCLUSION

In this study, we provide a granular description of characteristics and outcomes in 189 patients with R/R DLBCL treated in the third or later line in a contemporary Danish population-based setting. Response rates were poor, and only a few patients received consolidating stem cell transplants. Although some patients with low-risk disease achieved long-term remission, survival was generally very poor, with a median OS of less than 6 months and a 2-year OS of only 25%. We speculate that the outcomes would have been improved for some patients in the presence of readily available CAR-T therapy. Our data highlight the need for accessible novel treatments in patients with multiple R/R DLBCL.

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AUTHOR CONTRIBUTIONS

Thomas Stauffer Larsen and Ahmed Ludvigsen AL-Mashhadi designed the study and formulated the study protocol. All authors contributed to the data collection. Lasse Hjort Jakobsen and Ahmed Ludvigsen AL-Mashhadi performed data management and statistical analysis. Ahmed Ludvigsen AL-Mashhadi and Thomas Stauffer Larsen wrote the first draft of the manuscript; all authors participated in the interpretation and reviewing the manuscript; and all authors accepted the submitted paper.

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CONFLICT OF INTEREST STATEMENT

LHJ reports Honoria from Roche and employment at Novo Nordisk A/S. PDB reports participation on the advisory board for Incyte, Roche, Gilead and Novartis. JMJ reports participation on the advisory board/consultancy for Abbvie, Celgene/BMS, Roche, Incyte, Gilead, Novartis and SOBI. MRC reports participation on the advisory board for Astra Zeneca, Incyte, Genmab, Abbvie, Kite and Janssen. TSL reports advisory board/consultancy for Roche, Gilead, Novartis, Celgene/BMS.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not available due to Danish privacy regulations.

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