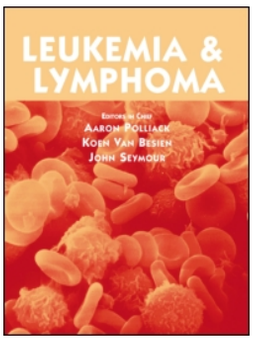

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REVIEW

Treatment of aggressive B-cell non-Hodgkin lymphoma beyond frontline therapy in patients not eligible for stem cell transplantation: a structured review

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ABSTRACT

Aggressive B-cell non-Hodgkin lymphoma (aNHL) accounts for ~50% of all NHL cases. The only potentially curative, broadly available treatment for patients with relapse, failing frontline treatment, is high-dose therapy followed by autologous stem cell transplantation (ASCT); patients ineligible for/who have failed ASCT have limited standard-of-care options. We conducted a structured review of treatments for relapsed/refractory patients with aNHL based on literature published between 2006 and 2017. Of the 22 publications identified for inclusion, most described phase II, single-arm trials ($N = 25$–217), and only three were randomized studies (phase II [$N = 96$], phase II/III [$N = 111$] and phase III [$N = 338$]). The majority of treatments evaluated resulted in only modest efficacy (median progression-free survival, 2.1–20.0 months) and ultimately poor health outcomes (median overall survival, 25 weeks–15.5 months). In conclusion, there is an unmet need for novel, effective, and tolerable treatments for patients with relapsed/refractory aNHL who are ineligible for/have failed ASCT.

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Introduction

Aggressive B-cell non-Hodgkin lymphoma (aNHL) represents ~50% of all NHL cases [1]. The most common type of aNHL is diffuse large B-cell lymphoma (DLBCL), which comprises ~30–58% of NHL cases with an incidence of 3.8/100,000/year in Europe [2,3]. Approximately 60–70% of patients with aNHL are diagnosed at advanced stages of the disease, representing a treatment challenge for clinicians [1].

Frontline treatment for aNHL consists of rituximab and anthracycline-based chemotherapy [2], leading to a cure for ~67% of patients with DLBCL [4]. For patients who relapse after, or are refractory to, frontline chemotherapy, the only option for long-term survival is high-dose chemotherapy (HDT), followed by autologous stem cell transplantation (ASCT). However, about 50% of patients with relapsed or refractory aNHL are not eligible to receive HDT/ASCT because of a range of reasons including advanced age, comorbidities, social issues, or personal choice [4]. Most patients who do not obtain a complete response (CR) to first-line chemotherapy do not respond to treatment with HDT/ASCT [5] and therefore, ASCT is recommended only in patients that are chemosensitive [6]. Furthermore, a proportion of patients relapse following this treatment; 47% of patients with relapsed DLBCL in a study reported by Gisselbrecht and colleagues had progressed three years after HDT/ASCT [7]. Allogeneic stem cell transplantation (allo-SCT) can also be considered for selected patients who have refractory or relapsed disease, or who have failed ASCT [2]. However, this treatment has its own constraints (response to further salvage therapy, donor availability, and toxicities), and only ~40% of patients did not have disease progression 3 years after allo-SCT following relapse after ASCT [8]. Treatment options for patients with DLBCL who are ineligible for or who have failed HDT/SCT are limited [2], hence their prognosis is poor [4]. ESMO guidelines recommend such patients receive platinum- and/or gemcitabine-based regimens or palliative care, or that they participate in clinical trials testing novel drugs [2].

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The objective of this review was to identify the scope and quality of information available from peer-reviewed, published articles on the efficacy and safety of treatments for patients with relapsed or refractory aggressive B-cell NHL who are not eligible for or have failed SCT.

Materials and methods

Search strategy and data extraction

The literature review followed the guidelines laid out in The Joanna Briggs Institute Reviewers' Manual: Methodology for JBI Scoping Reviews [9]. The research question we aimed to address was: 'What efficacy and safety outcomes have been reported for therapeutic agents used to treat patients with relapsed or refractory aNHL who have either failed or who are not candidates for stem cell transplantation?' Inclusion and exclusion criteria used to set up the search strategy are shown in Table 1 (pre-specified screening). Since rituximab was approved as a treatment for patients with DLBCL in 2006, this date was chosen as a cutoff for the literature searches; the literature was searched for publications appearing between 1 January 2006 and 17 November 2017. Based on the search strategy, only fully peer-reviewed manuscripts were included; congress abstracts were excluded from the searches. A full list of search terms is shown in the Appendix.

Table 1. Eligibility criteria for screening publications.

Pre-specified screening: 'identification'
Inclusion criteria
Population
• Human participants; female or male
• Adults (≥18 years of age)
Concept
• Any therapeutic agent used to treat relapsed or refractory aggressive B-cell NHL
• Patients who were not eligible for, or who had failed SCT
Context
• Geography: no limitations
• Original, peer-reviewed research articles
• Number of prior treatments: no limitations
• Publication: between 1 January 2006 and 17 November 2017 (after rituximab approval)
Exclusion criteria
• Reviews, case studies, congress abstracts
• Publications in language other than English
Additional screening: 'filter-based review'
Automated filter: exclusion criteria
• Embase publications without NHL/DLBCL in the title
Manual filter: exclusion criteria
• Studies including patients who were ineligible for or who had failed SCT but which did not report specific data on these subpopulations
• Phase I studies with safety as primary endpoint and efficacy a secondary endpoint
• Retrospective studies
• Studies including <30 patients for the patient population of interest
Additional screening: 'in-depth manual review'
In-depth review: exclusion criteria
• Any of the above exclusion criteria identified when full text of the article was examined

DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin lymphoma; SCT: stem cell transplantation.

The full literature screening process is shown in Figure 1 and the detailed screening criteria for each step are shown in Table 1. The screening process included three steps: 'identification,' 'filter-based review' and 'in-depth manual review.' As described above, the 'identification' step used a pre-specified literature search strategy of the PubMed, Embase, and Cochrane library databases. The records returned then underwent 'filter-based review.' As the Embase search had returned a larger number of publications than expected, the first stage of the 'filter-based review' step was an 'automated filter' to exclude records which did not include NHL or DLBCL in their title, run on Embase records only. The subsequent 'manual filter' screened remaining PubMed, Embase, and Cochrane library records based on information contained within their titles and abstracts. Studies not including patients who were ineligible for or who had failed SCT, or that included patients who were ineligible for or who had failed SCT, but did not show the necessary data on these specific subpopulations, were excluded. The 'manual filter' also excluded phase I studies that primarily reported safety (where efficacy was a secondary endpoint), retrospective studies and studies including <30 patients for the patient population of interest.

For abstracts not containing sufficient information to determine whether the publication fulfilled the 'manual filter' eligibility criteria (designated 'unclear' publications), full-text articles were obtained. During the 'in-depth review' step, 'unclear' publications were either discarded at 'review 1' on the basis of the information in the full-text articles, or retained for 'review 2.' 'Review 2' required a detailed reading of the publications to confirm the remaining papers were indeed eligible for inclusion. The data extracted from the eligible papers ('extraction'; Figure 1) were: study design and patient population details, sample size, treatment(s) studied, inclusion/exclusion criteria, primary and secondary efficacy/safety endpoints, patient baseline characteristics, efficacy outcomes (objective response rate [ORR], CR rates, median duration of response, median progression-free survival [PFS], median overall survival [OS]), and safety outcomes (patients with ≥1 adverse event [AE], most common AEs, most common grade ≥3 AEs, treatment-related deaths).

Results

Identification and inclusion of studies

In total, 2067 records were identified through electronic databases. Following filtering of literature search

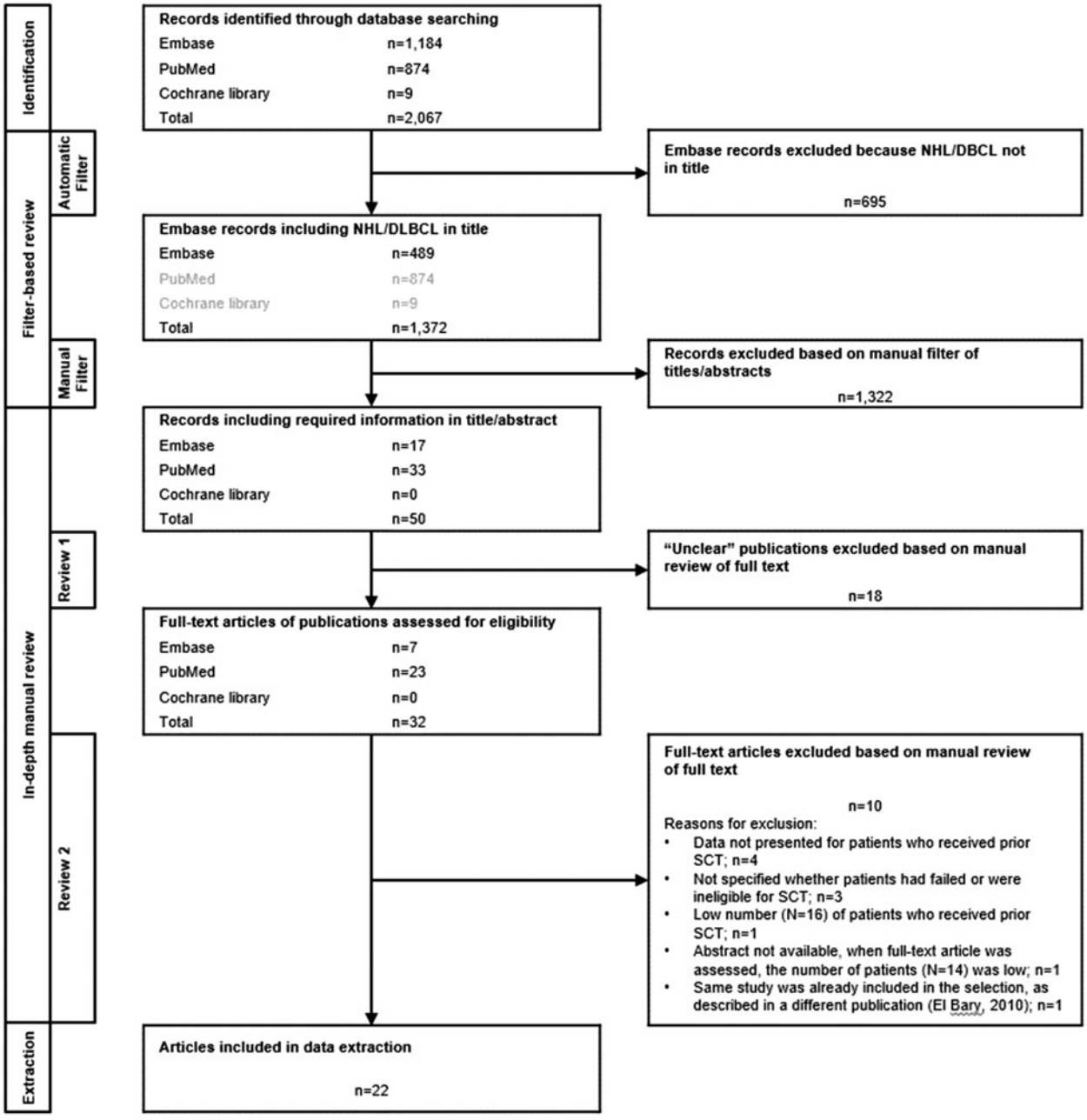

Figure 1. Literature search results and study selection. 'Keep' publications: based on abstract content, these publications were selected during the 'manual filter'. 'Unclear' publications: based on abstract content, it was not clear whether these publications fulfilled eligibility criteria during the 'manual filter'. The full text of these manuscripts was reviewed manually to identify those publications fulfilling the eligibility criteria. During the 'in-depth filter', it was found that two publications reported data from the same study. The publication by Abdel-Bary et al. was discarded ($N = 40$) [50], while the publication by El Bary et al. ($N = 41$) was included in the selected publications [24]. DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin lymphoma; SCT: stem cell transplantation

results and screening, the full text of 32 articles was assessed for eligibility. Of these publications, 22 fulfilled the criteria for inclusion in the review, while 10 were rejected at the 'Screen 2' step. The majority of publications excluded at the final screen step were rejected because they did not disclose details on SCT eligibility for patients in the study (Figure 1).

Characteristics of included studies

The majority of the 22 studies eligible for inclusion were phase II, single-arm trials (19 studies). Only three studies were randomized; one phase II [10], one phase II/III [11] and one phase III study [12]. Furthermore, although one study was originally designed as a

Table 2. Study design and populations (patients ineligible for or who have failed SCT) in the 22 studies included in the analysis.

First author, date	Sample size (total number of patients)	Patient population	Study design	Treatment/mechanism of action	Primary endpoint
Monotherapy					
Batlevi, 2017 [45]	$N = 72$	Adults with pathological confirmation of relapsed/refractory DLBCL or relapsed/refractory FL	Phase II, open-label, single-arm, multicenter trial	Mocetinostat (HDAC inhibitor)	ORR (CR, CRu, PR)
Churpek, 2015 [21]	$N = 51$	Adults with histologically confirmed relapsed or refractory aNHL	Phase II, single-arm, multicenter trial	Ixabepilone (microtubule stabilization agent)	ORR (CR, CRu, PR)
Coiffier, 2013 [46]	$N = 81$	Adults with relapsed or progressive $CD20^+$ DLBCL	Phase II, open-label, single-arm, multicenter trial	Ofatumumab (anti-CD20 IgG1κ agent)	ORR (CR, PR)
Czuczman, 2017 DLC-001 study [11]	$N = 102$	Adults with histologically confirmed relapsed or refractory DLBCL	Phase II/III, open-label, randomized, multicenter trial	Lenalidomide (immunomodulatory agent) vs. IC (gemcitabine, rituximab, etoposide or oxaliplatin)	ORR (CR, CRu, PR)
Flinn, 2016 [13]	$N = 68$	Adults with relapsed or refractory DLBCL	Phase II, single-arm[a], multicenter trial	Fostamatinib (Syk inhibitor)	ORR (CR, PR)
Robertson, 2007 [27]	$N = 55$	Adults with relapsed or refractory DLBCL	Phase II, single-arm, multicenter trial	Enzastaurin (PKCβ inhibitor)	FFP (CR, PR, SD) for $\geq$ two cycles[b]
Wiernik, 2008 [15]	$N = 49$	Adults with relapsed or refractory aNHL	Phase II, single-arm, multicenter trial	Lenalidomide (immunomodulatory agent)	ORR (CR, CRu, PR)
Witzig, 2011a [14]	$N = 217$	Adults with relapsed or refractory aNHL	Phase II, open-label, single-arm, multicenter trial	Lenalidomide (immunomodulatory agent)	ORR (CR, CRu, PR)
Witzig, 2011b [20]	$N = 77$	Adults with relapsed or refractory aNHL	Phase II, single-arm, multicenter trial	Everolimus (mTOR inhibitor)	ORR (CR, CRu, PR)
Combination chemotherapy					
Aribi, 2010 [10]	$N = 96$	Adults with relapsed or refractory DLBCL	Phase II, randomized, single-blind, monocentric trial	Etoposide (inhibits DNA synthesis), cisplatin (alkylating agent), methylprednisolone (glucocorticoid receptor agonist), cytarabine (DNA damage) vs. gemcitabine (cytidine analog), cisplatin (alkylating agent), dexamethasone (immunomodulatory agent)	ORR, 3-year mean survival
Buckstein, 2006 [22]	$N = 35$	Adults with relapsed or refractory aNHL	Phase II, single-arm, multicenter trial	Low dose cyclophosphamide (immunomodulatory agent) and high-dose celecoxib (COX-2 inhibitor)	ORR, CR rates
Di Renzo, 2006 [23]	$N = 69$	Adults with relapsed or refractory aNHL	Phase II, single-arm trial	Gemcitabine (cytidine analog), vinorelbine (inhibits microtubule dynamics), procarbazine (alkylating agent) and prednisone (glucocorticoid receptor agonist)	3-year RFS
El Bary, 2010 [24]	$N = 41$	Adults with relapsed or refractory DLBCL	Phase II, single-arm, monocentric trial	Cyclophosphamide, methotrexate (immunomodulatory agents) and high-dose celecoxib (COX-2 inhibitor)	Response rates
Combination therapy with biologics					
Dang, 2017 [12]	$N = 338$	Adults with refractory/relapsed $CD20^+$/$CD22^+$ aggressive B-cell NHL	Phase III, two-arm, randomized, open-label, multicenter trial	Rituximab (anti-CD20 agent)-Inotuzumab ozogamicin (anti-CD22 agent) vs. investigator's choice of rituximab-bendamustine (alkylating agent) or rituximab-gemcitabine (cytidine analog)	Median OS
Coiffier, 2016 [47]	$N = 52$	Adults with refractory/relapsed $CD19^+$/$CD20^+$ DLBCL	Phase II, open-label , single-arm, multicenter trial	Rituximab (anti-CD20 agent) and coltuximab ravtansine (anti-CD19 agent)	ORR
El Gnaoui, 2007 [16]	$N = 46$	Adults with refractory/relapsed $CD20^+$ B-cell lymphoma	Phase II, open-label, single-arm, monocentric trial	Rituximab (anti-CD20 agent), gemcitabine (cytidine analog) and oxaliplatin (alkylating agent)	ORR after 4 cycles of treatment
Morschhauser, 2007 [25]	$N = 104$	Adults with refractory/relapsed $CD20^+$ DLBCL	Phase II, single-arm, multicenter trial	Rituximab (anti-CD20 agent) and ^{90}Y-ibritumomab (radioimmunotherapy agent)	ORR, CR rate
Mounier, 2013 [17]	$N = 49$	Adults with refractory/relapsed $CD20^+$ DLBCL	Phase II, open-label, single-arm, multicenter trial	Rituximab (anti-CD20 agent), gemcitabine (cytidine analog) and oxaliplatin (alkylating agent)	ORR after four cycles of treatment

Table 2. (Continued).

First author, date	Sample size (total number of patients)	Patient population	Study design	Treatment/mechanism of action	Primary endpoint
Papadopoulos, 2015 [48]	$N = 43$	Adults with relapsed aggressive $CD20^+$ B-cell aNHL	Phase II, open-label, single-arm, multicenter trial	Rituximab (anti-CD20 agent) and YM155 (survivin suppressant)[c]	ORR (CR, PR)
Straus, 2015 [26]	$N = 30$	Adults with relapsed or refractory DLBCL or transformed low-grade NHL	Phase I/II, open-label, single-arm, monocentric trial	Rituximab (anti-CD20 agent), cyclophosphamide (immunomodulatory agent), vorinostat (HDAC inhibitor), etoposide (inhibits DNA synthesis), prednisone (glucocorticoid receptor agonist) and filgrastim or pegfilgrastim (G-CSF)	CR rate
Ohmachi, 2013 [19]	$N = 63$	Adults with relapsed or refractory $CD20^+$ DLBCL	Phase II, open-label, single-arm, multicenter trial	Rituximab (anti-CD20 agent) and bendamustine (alkylating agent)	ORR (CR, PR)
Vacirca, 2014 [18]	$N = 61$	Adults with refractory/relapsed $CD20^+$ DLBCL	Phase II, single-arm, multicenter trial	Rituximab (anti-CD20 agent) and bendamustine (alkylating agent)	ORR (CR, PR)

aNHL: aggressive non-Hodgkin lymphoma; CD20: cluster of differentiation 20; CI: confidence interval; CR: complete response; CRu: complete response unconfirmed; DLBCL: diffuse large B-cell lymphoma; FFP: freedom from progression; FL: follicular lymphoma; G-CSF: granulocyte colony-stimulating factor; HDAC: histone deacetylase; IgG1κ: immunoglobulin G1κ; mTOR: mechanistic target of rapamycin; NHL: non-Hodgkin lymphoma; ORR: objective response rate; OS: overall survival; PR: partial response; RFS: relapse-free survival; SCT: stem cell transplantation; Syk: spleen tyrosine kinase.
[a]The trial was originally designed as a two-arm randomized, double-blind study of two doses of fostamatinib (100 mg and 200 mg); however, preliminary results showed limited efficacy of fostamatinib (following enrollment of 35 patients) and the protocol was amended to treat all patients with fostamatinib 200 mg. Patients who were assigned to fostamatinib 100 mg were given the opportunity to receive fostamatinib 200 mg.
[b]One cycle: 28 days.
[c]Sepantronium bromide.

two-arm, randomized, double-blind trial of two doses of fostamatinib, because of limited treatment efficacy following enrollment of the first 35 patients, the trial design was amended to include only the highest dose of the drug and thus became a single-arm study [13]. The sample sizes in the randomized phase II/III [11] and phase III [12] studies were $N = 111$ and $N = 338$, respectively, while the phase II randomized study [10] included 96 patients. Most single-arm studies had a small sample size ($N = 25$–104), with the exception of one study with 217 patients [14].

Of the included studies, 12 recruited patients with DLBCL only and the others recruited patients with different aNHL subtypes, although the most common subtype overall was DLBCL. In 13 studies, patients had received only 1 or 2 treatments prior to study entry, while 9 studies included heavily pretreated patients ($\geq$3 prior treatments). The majority of treatment regimens studied were only represented once within the final set of publications included in the analysis, with the exception of lenalidomide [14,15]; rituximab, gemcitabine, and oxaliplatin (R-GemOx) [16,17]; and rituximab and bendamustine [18,19] each of which were evaluated in two studies.

Characteristics of the 22 studies included in our analysis are summarized in Table 2.

Studies describing monotherapy

Efficacy outcomes

The only randomized study describing monotherapy was a phase II/III trial comparing the outcomes of patients treated with lenalidomide vs. investigator's choice (IC: gemcitabine, rituximab, etoposide, or oxaliplatin) [11]. In this study, there were no significant differences in ORR, duration of response, and median OS between lenalidomide-treated patients and IC-treated patients (Table 3). Only median PFS was significantly higher for lenalidomide vs. IC (13.6 weeks vs. 7.9 weeks, $p = .041$) [11]. Both single-arm studies evaluating lenalidomide as monotherapy reported an ORR of 35% [14,15], which was similar to that (27.5%) reported for lenalidomide in the randomized study [11]. Median PFS was similar between the two single-arm studies and the randomized study evaluating lenalidomide (4 months, 3.7 months, and 13.6 weeks, respectively) [11,14,15]. Among the remaining single-arm monotherapy studies, the ORR ranged from 3% with fostamatinib treatment [13] to 30% with everolimus treatment [20], while median PFS ranged from 5.3 weeks with fostamatinib 200 mg [13] to 3.7 months

Table 3. Efficacy outcomes among patients who are ineligible for or who have failed SCT in the 22 studies included in the analysis.

First author, date	Treatment	Number of patients-efficacy population (% patients who had received prior SCT)	Median age (range), years	Median number of prior treatments (range)	Patients with ≤2 / ≥3 prior treatments, %	ORR (95% CI)[a], % / CR rates, %	Median duration of response (95% CI), months	Median PFS (95% CI), months	Median OS (95% CI), months
Monotherapy									
Batlevi, 2017 [45]	Mocetinostat	$N = 41$ (34.1)	60 (31–80)	3 (NR)[b]	NR	18.9 (7.2–32.2) / 2.7	90 days	2.1 (1.6–3.6)	12.3 (5.8–17.8)
Churpek, 2015 [21]	Ixabepilone	$N = 51$ (12 patients)	66 (44–90)	3 (NR)	1 prior treatment: 27 2–3 prior treatments: 43 ≥4 prior treatments: 29	27 (16–42) / 12	9.7	3.7	15.5
Coiffier, 2013 [46]	Ofatumumab	$N = 81$ (31)	68 (22–87)	3 (1–7)[b]	83[c]/22[c]	11 / 1 patient	9.5	2.6	NR[d]
Czuczman, 2017 [11]	Lenalidomide vs. IC	$N = 102$ Lenalidomide: $n = 51$ (25) IC: $n = 51$ (33.3)	Lenalidomide: 69 (28–84) IC: 65 (20–84)	NR (NR)	Lenalidomide: 51[c] / 49[d] IC: 37.2[d] / 62.7[d]	Lenalidomide: 27.5 (15.9–41.7) / 9.8 IC: 11.8 (4.4–23.9) / 2.0 [d]p=.079	Lenalidomide: 73.9 weeks (16.4, not yet reached) IC: 29.2 weeks (7.0–43.9) [d]p=.138	Lenalidomide: 13.6 weeks IC: 7.9 weeks HR (95% CI), 0.64 (0.41–0.99) [d]p=.041	Lenalidomide: 31 weeks IC: 24.6 weeks HR (95% CI), 0.91 (0.59–1.41) [d]p=.673
Flinn, 2015 [13]	Fostamatinib	$N = 68$[f] 100 mg: $n = 21$ 200 mg: $n = 47$ (NR)	Overall: 65 (29–86) 100 mg: 64 (31–84) 200 mg: 67 (29–86)	Overall: 3 (1–8) 100 mg: 3 (1–8) 200 mg:3 (1–6)	NR	3[f] / 1.5[g]	100 mg: >41 weeks[g] 200 mg: >57 weeks[g]	100 mg: 7.3 weeks (4.1–7.9) 200 mg: 5.3 weeks (3.7–6.1)	NR
Robertson, 2007 [27]	Enzastaurin	$N = 55$ (11)	68 (31–87)	2 (1–5)[b]	73[b] / 28[b]	FFP for ≥2 cycles: 22 (13–46) FFP for ≥4 cycles: 15 (6–27) FFP for ≥20 cycles: 7 (2–18)	NR	NR	NR
Wiernik, 2008 [27]	Lenalidomide	$N = 49$ (29)	65 (23–86)	4 (NR)	24 / 75	35 / 2 patients	6.2 (0–12.8)	4.0 (0–14.5)	NR
Witzig, 2011a [20]	Lenalidomide	$N = 217$ (33.6)	66 (21–87)	3 (1–13)	NR	35 (29.1–42.2) / 13 (9.1–18.6)	10.6 (7.0–NR)	3.7 (2.7–5.1)	NR
Witzig, 2011b [20]	Everolimus	$N = 77$ (32)	70 (36–92)	3 (1–15)	NR	30 (20–41) / 3 patients	5.7 (3.6–12.3)	3.0 (2.1–3.9)	8.1 (5.3–12.5)
Combination chemotherapy									
Aribi, 2010 [10]	Etoposide, cisplatin, methylprednisolone, cytarabine vs. gemcitabine, cisplatin, dexamethasone	ESHAP: $N = 48$ GDP: $N = 48$ (NR)	Mean (SE) ESHAP: 65 (3.6) GDP: 66 (2.5)	NR	NR	ESHAP: 55 / 38 GDP: 63 / 29 [d]p=.01	NR	3-year PFS ESHAP: 10.9% (8.2–13.7) GDP: 20.5% (16.3–24.0) [d]p=.0003	3-year OS ESHAP: 11.8% (8.9–14.6) GDP: 20.5% (16.5–24.5) [d]p=.001
Buckstein, 2006 [22]	Low dose cyclophosphamide and high-dose celecoxib	$N = 32$ (34)	64 (22–83)	3 (1–7)[h]	NR	37.5 / 2 patients	8.2 (0–29)	4.7 (2.5–9.2)	14.4 (6.2–23)
Di Renzo, 2006 [23]	Gemcitabine, vinorelbine, procarbazine and prednisone	$N = 66$ (NR)	64 (25–80)	2 (1–7)	NR	40.0 / 23	NR	NR	3-year OS: 25% (16%–36%)
El Bary, 2010 [24]	Cyclophosphamide, methotrexate and high-dose celecoxib	$N = 41$ (NR)	57 (38–78)	NR (NR)	49 / 7	NR / 2.4	NR	20 (13.9–26.0)	NR
Combination therapy with biologics									
Dang, 2017 [12]	Rituximab–Inotuzumab ozogamicin vs. investigator's choice of rituximab–bendamustine or rituximab–gemcitabine	R-InO: $N = 166$ IC: $N = 172$ (NR)	R-InO: 72 (18–92) IC: 69 (28–91) Total: 70 (18–92)	NR (NR)[i]	R-InO: 88 / 11 IC: 87 / 14	R-InO: 41 (33–49) IC: 44 (36–51) [d]p=.714	R-InO: 11.6 (7.8–NR) IC: 6.9 (5.5–10.8)[d]p=.142)	R-InO: 3.7 (2.9–5.0) IC: 3.5 (2.8–4.9)	R-InO: 9.5 (7.0–14.5) IC: 9.5 (7.7–14.1)

Table 3. (Continued).

First author, date	Treatment	Number of patients-efficacy population (% patients who had received prior SCT)	Median age (range), years	Median number of prior treatments (range)	Patients with ≤2 / ≥3 prior treatments, %	ORR (95% CI)[a], % / CR rates, %	Median duration of response (95% CI), months	Median PFS (95% CI), months	Median OS (95% CI), months
Coiffier, 2016 [47]	Rituximab and coltuximab ravtansine	$N = 45$ (13.5)	67 (38–85)	2 (0–5)	59.6 / 40.3	31.1 (80% CI: 22.0–41.6) / 8.9	8.6 (0–18)	3.9 (80% CI: 3.22–3.98)	9.0 (80% CI: 6.47–13.67)
El Gnaoui, 2007 [16]	Rituximab, gemcitabine and oxaliplatin	$N = 46$ (30)[j]	64 (43–78)	2 (1–5)	NR	ORR after 4 cycles: 83 (69–92) / 10 patients	NR	2-year EFS: 43% (27–60)	2-year OS: 66% (50–82)
Morschhauser, 2007 [25]	Rituximab and ^{90}Y-ibritumomab	N = 104[k] Group A Stratum AI: n = 33 Stratum AII: n = 43 Group B: n = 28 (NR)	Mean (SD) Group A Stratum AI: 73 (7.3) Stratum AII: 71 (5.6) Group B: 72 (6.0)	NR (NR)[l]	NR	Group A Stratum AI: 52 / 21 Stratum AII: 53 / 32.5 Group B: 19 / 4	NR	Group A Stratum AI: 5.9 Stratum AII: 3.5 Group B: 1.6	Group A Stratum AI: 21.4 Stratum AII: 22.4 Group B: 4.6
Mounier, 2013 [49]	Rituximab, gemcitabine and oxaliplatin	$N = 48$ (35)	69 (41–77)	NR (NR)[m]	NR	ORR after 4 cycles: 61 (45–74) / 44	10	5	11
Papadopoulos, 2016 [48]	Rituximab and YM155[c]	$N = 41$ (36.6)	64 (29–82)	3 (1–7)[n]	NR	43.9 (30.6–57.9) / 17.1 (8.3–29.7)	NR[m]	8.5 (4.4–not estimable)	NR[o]
Straus, 2015 [26]	Rituximab, cyclophosphamide, vorinostat, etoposide, prednisone and filgrastim or pegfilgrastim	$N = 23$ (NR)	76 (69–88)	1 (1–2)[h]	NR	57 / 35	NR	9.2 (5.5–12.9)	17.5 (13.6–21.5)
Ohmachi, 2013 [19]	Rituximab and bendamustine	$N = 59$ (13.6)	67 (36–75)	1 (1–3)[h]	86.4 / 13.6	62.7 (49.1–75.0) / 37.3 (25–50.9)	NR	6.7 (3.6–13.7)	NR
Vacirca, 2014 [18]	Rituximab and bendamustine	$N = 59$ (8)	74 (25–90)	1 (1–9)	72 / 28	45.8 (41–70) / 15.3	17.3 (4.2, not reached)	3.6 (2.7–7.2)	NR[o]

CHOP: cyclophosphamide hydroxydaunorubicin oncovin prednisone; CI: confidence interval; CR: complete response; EFS: event-free survival; ESHAP: etoposide, cisplatin, methylprednisolone, cytarabine; GDP: gemcitabine, dexamethasone, cisplatin; IC: investigator's choice; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; R-InO: Rituximab-Inotuzumab ozogamicin; SCT: stem cell transplantation; SD: standard deviation.

[a]CIs shown where they are reported.

[b]Systemic therapies.

[c]Rituximab-containing therapies.

[d]OS could not be determined because follow-up data were not collected for patients following their withdrawal from the study.

[e]*p* values are for comparison between treatment arms.

[f]The trial was originally designed as a two-arm randomized, double-blind study of two doses of fostamatinib (100 mg and 200 mg); however, preliminary results showed limited efficacy of fostamatinib (following enrollment of 35 patients) and the protocol was amended to treat all patients with fostamatinib 200 mg. Patients who were assigned to fostamatinib 100 mg were given the opportunity to receive fostamatinib 200 mg.

[g]Referring to the two clinical responses reported, which were still continuing at the time of manuscript preparation.

[h]Systemic chemotherapies.

[i]Eligibility criteria were for patients to have had 1–3 prior chemotherapy-based regimens.

[j]Prior high-dose therapy.

[k]Group A: patients previously treated with chemotherapy. Group B: patients treated with chemotherapy plus rituximab. Group A included patients who had failed induction therapy (stratum AI) and patients who had relapsed after achieving CR (stratum AII).

[l]Eligible patients had to have received one prior treatment with CHOP or a CHOP-like regimen.

[m]Patients had to be in first or second relapse, previously treated with a chemotherapy regimen containing anthracycline with or without rituximab.

[n]Chemotherapy or biologic therapy.

[o]Not reached as remaining subjects were censored at data cutoff.

with ixabepilone [21]. Approximately half of the monotherapy studies did not report OS data (Table 3).

Safety outcomes

Among the monotherapy studies evaluating lenalidomide, neutropenia was consistently reported, with a similar incidence, as the most common grade ≥3 AE (Czuczman et al: 43%, Wiernik et al: 33% and Witzig et al: 41%; Table 4) [11,14,15]. Neutropenia and thrombocytopenia were the most common grade ≥3 AEs across all monotherapy studies. Two treatment-related deaths were reported in the study evaluating fostamatinib (intercurrent pneumonia and treatment-related pneumonitis) [13]. Most studies in this category did not report any treatment-related deaths or did not specify if the deaths were due to treatment (Table 4).

In conclusion, single agents studied in patients with relapsed or refractory aNHL showed either limited (mocetinostat, ixabepilone, ofatumumab, everolimus, enzastaurin [ORR: 11–27%]) or poor (fostamatinib) efficacy. In addition, lenalidomide treatment was not associated with better efficacy vs. IC by ORR; however, a significant treatment difference using PFS as an efficacy outcome was shown. Adequate toxicity was reported for all studies.

Studies describing combination chemotherapy only

Efficacy outcomes

Amongst studies describing combination chemotherapy alone, the only randomized study was a phase II trial comparing gemcitabine, dexamethasone, cisplatin (GDP) with etoposide, cisplatin, methylprednisolone, and cytarabine (ESHAP; Table 3). The ORR, 3-year PFS and 3-year OS were significantly higher in patients treated with GDP compared with patients treated with ESHAP (63% vs. 55%, $p = .01$; 20.5% vs. 10.9%, $p = .0003$; 20.5% vs. 11.8%, $p = .001$, respectively) [10]. The ORR in both single-arm studies that reported this endpoint was lower than that for either the GDP or ESHAP arms in the randomized study: low-dose cyclophosphamide and high-dose celecoxib; ORR: 37.5% [22], vinorelbine, gemcitabine, procarbazine, and prednisone (ViGePP); ORR: 40% [23]. However, patients in the randomized study only had a median of 1 prior treatment vs. 3 and 2 for patients in the study of low dose cyclophosphamide and high-dose celecoxib, and the study of ViGePP, respectively [22,23]. In the study of low dose cyclophosphamide and high-dose celecoxib and the study of cyclophosphamide, methotrexate, and high-dose celecoxib, the median PFS was 4.7 and 20 months, respectively [22,24]. A 3-year PFS rate of 20.5% and 10.9% for the GDP and ESHAP arms, respectively, was observed in the randomized study [10]. In the study of ViGePP, the 3-year OS rate was 25% [23], compared with 20.5% and 11.8% for GDP and ESHAP regimens, respectively in the randomized study [10]. Treatment with cyclophosphamide and celecoxib resulted in a median OS of 14.4 months [22].

Safety outcomes

Among those patients receiving combination chemotherapy only, grade ≥3 AEs were common. The most common grade 2–4 AEs that were reported following ViGePP treatment were neutropenia, anemia, thrombocytopenia, and nausea and vomiting [23]. In the phase II, randomized study, the most common grade ≥3 AE was thrombocytopenia (41%) for GDP-treated patients and leukopenia (63%) for ESHAP-treated patients [8]. One death due to treatment toxicity was reported following ViGePP therapy (no further details were disclosed) [23] (Table 4).

In conclusion, combination chemotherapy regimens demonstrated modest efficacy (ORR: 37.5–63%) and an adequate safety profile in patients with relapsed or refractory aNHL. The phase II, randomized study demonstrated that GDP was associated with better efficacy compared with ESHAP among patients who had received a median of 1 prior treatment [10].

Studies describing combination therapy with biologics

Efficacy outcomes

All treatments in studies describing combination therapy with biologics contained rituximab. The only randomized study describing combination therapy with biologics was a phase III study comparing rituximab-inotuzumab ozogamicin (R-InO) vs. IC (rituximab-bendamustine or rituximab-gemcitabine; Table 3) [12]. No significant difference was detected in ORR and duration of response in patients treated with R-InO vs. patients who received IC. Median PFS and OS were also similar between treatment groups at 3.7 (95% CI: 2.9–5.0) vs. 3.5 (95% CI: 2.8–4.9) months and 9.5 (95% CI: 7.0–14.5) vs. 9.5 (95% CI: 7.7–14.1) months, respectively [12]. Among the single-arm studies describing combination therapy with biologics, the ORR ranged from 19% in the subgroup of patients treated with rituximab and ^{90}Y-ibritumomab and who had previously been treated with chemotherapy plus rituximab

Table 4. Safety outcomes among patients who are ineligible for or who have failed SCT in the 22 studies included in the analysis.

First author, date	Treatment	Number of patients (safety population)	Patients with ≥1 AE	Most common Aes (any grade)	Grade ≥3 AEs, ≥20%	Treatment-related deaths, *n*
Monotherapy						
Batlevi, 2017 [45]	Mocetinostat	$N = 72$	98.6%	Fatigue (75%), nausea (69%), diarrhea (61%) and vomiting (38%)	Fatigue (24%)	0
Churpek, 2015 [21]	Ixabepilone	$N = 51$	Patients with ≥1 AE grade 3/4: 67%	Grade ½ Sensory neuropathy (49%), nausea (47%), anemia (45%) and fatigue (41%)	Grade ¾ Neutropenia (33%), leukopenia (29%), fatigue (20%) and lymphopenia (20%)	NR
Coiffier, 2013 [46]	Ofatumumab	$N = 81$	96%	Diarrhea (15%), fatigue (15%), neutropenia (15%) and peripheral edema (12%)	–[a]	0
Czuczman, 2017 [11]	Lenalidomide vs. IC	$N = 109$ Lenalidomide: $n = 54$ IC: $n = 55$	Lenalidomide: 100% IC: 100%	Lenalidomide: Neutropenia (43%), anemia (33%), fatigue (33%), pyrexia (30%) and constipation (30%) IC: Anemia (47%), thrombocytopenia (44%), neutropenia (36%) and nausea (36%)	Lenalidomide: Neutropenia (43%) IC: Anemia (31%), thrombocytopenia (26%) and neutropenia (26%)	NR
Flinn, 2015 [13]	Fostamatinib	$N = 68$ 100 mg: $n = 21$ 200 mg: $n = 47$	100 mg: 100% 200 mg: 94%	Overall: Diarrhea (21%), nausea (19%), fatigue (18%) and thrombocytopenia (13%) 100 mg: Thrombocytopenia (19%), neutropenia (19%), fatigue (14%) and nausea (14%) 200 mg: Diarrhea (30%), nausea (21%), fatigue (19%), constipation (13%) and vomiting (13%)	NR	2
Robertson, 2007 [27]	Enzastaurin	$N = 55$	NR	Fatigue ($n = 8$), diarrhea ($n = 7$) and nausea or vomiting ($n = 5$)[b]	–[a]	0
Wiernik, 2008 [27]	Lenalidomide	$N = 49$	NR	Neutropenia (53%), thrombocytopenia (53%), fatigue (49%) and anemia (41%)	Neutropenia (33%), thrombocytopenia (19%)	NR
Witzig, 2011a [14]	Lenalidomide	$N = 217$	NR	NR	Neutropenia (41%)	NR
Witzig, 2011b [20]	Everolimus	$N = 77$	NR	NR	Thrombocytopenia (38%)	NR
Combination chemotherapy						
Aribi, 2010 [10]	Etoposide, cisplatin, methylprednisolone, cytarabine vs. gemcitabine, cisplatin, dexamethasone	ESHAP: $N = 48$ GDP: $N = 48$	NR	NR	ESHAP: leukopenia (63%), vomiting (31%) and infection (20%) GDP: thrombocytopenia (41%), vomiting (29%) and infection (29%)	NR
Buckstein, 2006 [22]	Low dose cyclophosphamide and high-dose celecoxib	$N = 32$	NR	Fatigue or weakness ($n = 23$), skin rash ($n = 13$), anemia ($n = 7$), edema ($n = 7$)	–[a]	NR
Di Renzo, 2006 [23]	Gemcitabine, vinorelbine, procarbazine and prednisone	$N = 66$	NR	NR	Grade 2–4 TEAEs: Neutropenia (49%), anemia (38%), thrombocytopenia (38%), nausea and vomiting (20%)	1
El Bary, 2010 [24]	Cyclophosphamide, methotrexate and high-dose celecoxib	$N = 41$	NR	Fatigue or weakness (61%), dyspepsia (24%), anemia (22%) and nausea (22%)	–[a]	NR

Table 4. (Continued).

First author, date	Treatment	Number of patients (safety population)	Patients with ≥1 AE	Most common Aes (any grade)	Grade ≥3 AEs, ≥20%	Treatment-related deaths, *n*
Combination therapy with biologics						
Dang, 2017 [12]	Rituximab-Inotuzumab ozogamicin vs. investigator's choice of rituximab-bendamustine or rituximab-gemcitabine	R-InO: $N = 164$ IC: $N = 167$	R-InO: 90% IC: 87%	R-InO: thrombocytopenia (60%), neutropenia (35%) and nausea (24%) IC: neutropenia (47%), thrombocytopenia (35%) and leukopenia (31%)	R-InO: thrombocytopenia (48%) and neutropenia (24%) IC: neutropenia (40%), leukopenia (23%) and lymphopenia (22%)	2
Coiffier, 2016 [47]	Rituximab and coltuximab ravtansine	$N = 52$	98%	Anemia (78%), lymphopenia (71%), hepatic and renal abnormalities: AST (57%) and leukopenia (53%)	Lymphopenia (37%)	0
El Gnaoui, 2007 [16]	Rituximab, gemcitabine and oxaliplatin	$N = 46$	NR	NR[c]	NR	0
Morschhauser, 2007 [25]	Rituximab and ^{90}Y-ibritumomab	$N = 102$[d] Group A Stratum AI: $n = 33$ Stratum AII: $n = 43$ Group B: $n = 28$	NR	Hematologic toxicity (60%)	Hematologic toxicity (43%)	2
Mounier, 2013 [49]	Rituximab, gemcitabine and oxaliplatin	$N = 48$	NR	Low neutrophil counts (98%) and platelet toxicity (92%)	Neutropenia (73%) and platelet toxicity (44%)	1
Papadopoulos, 2016 [48]	Rituximab and YM155[c]	$N = 41$	93%	Pyrexia (34%), fatigue (32%), cough (29%), anemia (24%), diarrhea (24%), nausea (24%) and vomiting (24%)	Neutropenia (20%)	NR
Straus, 2015 [26]	Rituximab, cyclophosphamide, vorinostat, etoposide, prednisone and filgrastim or pegfilgrastim	$N = 29$	NR	NR	Lymphopenia (90%), leucopenia (66%), neutropenia (52%), thrombocytopenia (41%), hyperglycemia (38%), anemia (31%), hypophosphatemia (28%) and hypokalemia (21%)	NR
Ohmachi, 2013 [19]	Rituximab and bendamustine	$N = 59$	NR	Neutropenia (88%), leukopenia (83%), lymphopenia (78%) and thrombocytopenia (70%)	Neutropenia (76%), leukopenia (73%), lymphopenia (78%), CD4 lymphopenia (66%) and thrombocytopenia (22%)	0
Vacirca, 2014 [18]	Rituximab and bendamustine	$N = 59$	NR	Neutropenia (44%), anemia (44%), thrombocytopenia (44%) and leukopenia (34%)	Neutropenia (36%), leukopenia (24%) and thrombocytopenia (22%)	NR

AE: adverse event; AST: aspartate aminotransferase; ESHAP: etoposide, cisplatin: methylprednisolone, cytarabine; GDP: gemcitabine, dexamethasone, cisplatin; IC: investigator's choice; NR: not reported; R-InO: Rituximab-Inotuzumab ozogamicin; SCT: stem cell transplantation.

[a]AEs reported had <20% incidence.

[b]One patient had both nausea and vomiting.

[c]Safety data reported by cycle, not patient. Neutropenia grades 2, 3 and 4 were reported in 23%, 27% and 17% of cycles, respectively, whereas thrombocytopenia grades 2, 3 and 4 were reported in 12%, 19% and 4% of cycles, respectively. Febrile neutropenia was reported in 4% of cycles and grade 2 neurotoxicity was observed in 9% of cycles. Grade 3/4 neurotoxicity was not reported.

[d]Group A: patients previously treated with chemotherapy. Group B: patients treated with chemotherapy plus rituximab. Group A included patients who had failed induction therapy (stratum AI) and patients who had relapsed after achieving CR (stratum AII).

(group B) [25], to 83% (after 4 cycles) in patients who received R-GemOx [16]. In the study of rituximab and ^{90}Y-ibritumomab, patients in group B might have had refractory disease, which would explain the low ORR [25]. In addition, in this study, enrolled patients had a higher median age than the patients in the study by El Gnaoui et al who received R-GemOx (median age: 72.1 years vs. 64 years) [25]. In the other study that evaluated the effect of R-GemOx, 61% of patients demonstrated an ORR after 4 cycles [17]. Median PFS ranged from 3.5 months in patients treated with rituximab and ^{90}Y-ibritumomab and who had previously received chemotherapy and had relapsed after achieving CR (group A; stratum AII) [25], to 9.2 months in patients treated with rituximab, cyclophosphamide, vorinostat, etoposide, and prednisone [26]. Median OS ranged from 4.6 months (rituximab and ^{90}Y-ibritumomab, group B; see above) to 22.4 months (rituximab and ^{90}Y-ibritumomab, group A, stratum AII; see above) [25]. In the study by El Gnaoui (R-GemOx), 43% and 66% of patients achieved a 2-year event-free survival and 2-year OS, respectively [16] (Table 3).

Safety outcomes

Most common (≥20%) AEs of grade ≥3 were hematological, including neutropenia, lymphocytopenia, and leukopenia. Two treatment-related deaths were reported the in phase III, randomized study (R-InO, pneumonia [$n = 1$]; IC, fungal pneumonia, febrile neutropenia, and septicemia [$n = 1$]) [12], and one death was reported in the study of R-GemOx by Mounier, which was caused by thrombotic microangiopathy and was probably related to gemcitabine [17]. Two patients died from thrombocytopenic cerebral bleeding following administration of rituximab and ^{90}Y-ibritumomab [25] (Table 4).

In conclusion, with the exception of R-GemOx, combination therapy with biologics demonstrated modest efficacy (ORR: 19–62.7%) in patients with relapsed or refractory aNHL, while toxicity associated with the different therapies was adequate. Treatment with R-InO was not associated with better efficacy compared with IC [12].

Discussion

Despite aNHL accounting for approximately half of all NHL cases, the standard of care is limited for patients with relapsed or refractory disease who are not eligible for or have failed SCT [2]. Therefore, we searched the literature for publications evaluating treatments for this patient population to assess the number and quality of such studies. To our knowledge, this is the first structured review, reporting on treatments for patients with relapsed or refractory aNHL who are ineligible for or have failed SCT.

Following filtering and screening of literature searches, we identified an unexpectedly small number of publications that met the eligibility criteria and were included in the review. Additionally, most publications identified described single-arm trials; only three studies reported data from randomized trials. The number of novel biologic therapies included was also small, with most studies assessing the efficacy and safety of chemotherapeutic agents alone or combination therapy with rituximab. Sample sizes of the included studies were mostly small and the majority of the studies were proof-of-concept trials. A substantial proportion of studies included heavily pretreated patients (≥3 prior treatments). Eligibility criteria for SCT were also different across the included studies, and some studies included both patients who were ineligible for SCT and those who had failed SCT, while other studies included only patients who were ineligible for SCT. Thus patient populations were heterogeneous across the studies, making it difficult to draw any meaningful comparisons between trials.

Among the three randomized trials included in the review, only the study by Aribi et al. demonstrated that a treatment regimen (GDP) resulted in better efficacy for patients with relapsed or refractory DLBCL compared with another treatment (ESHAP) [10]. The other two randomized trials failed to demonstrate that patients benefited from lenalidomide or R-Ino treatment vs. IC [11,12]. Overall, therapies that were evaluated in the single-arm studies demonstrated only limited clinical benefit for patients with relapsed or refractory aNHL. Although direct comparisons between the different trials are not appropriate, treatment with R-GemOx as described by El Gnaoui et al. resulted in the highest ORR after 4 cycles (83%) [16]; however, the same regimen yielded a lower ORR (61%) in the study described by Mounier et al. [17]. In this study, 86% of patients were refractory or in first relapse [17] vs. 39% of patients in the study by El Gnaoui [16], which could explain the difference in ORR. Of note, enzastaurin, a protein kinase C β inhibitor that was studied by Robertson et al. [27], has since failed a phase III trial in patients with DLBCL in complete remission and at a high risk of relapse after first-line therapy [28].

No safety concerns were identified in the included studies. Most common grade ≥3 AEs reported were

hematological and the majority of studies did not report treatment-related deaths.

Based on the efficacy and safety data included in this review, the outcomes for patients with relapsed or refractory aNHL who are ineligible for or have failed SCT are poor, and new, effective treatments are urgently needed. Once promising therapies are identified, large, randomized trials are required to generate robust evidence and establish the beneficial effect of these therapies over the standard of care.

The publications included in this review were identified following a strict search strategy which excluded retrospective studies, hence, key publications on the CORAL and SCHOLAR-1 studies did not meet the eligibility criteria. However, these studies report data on the patient population studied in this review. In a retrospective analysis of data from the CORAL study, a phase III, multicenter, randomized trial evaluating the efficacy of three rituximab, ifosfamide, carboplatinum, etoposide or rituximab, dexamethasone, cytarabine, cisplatinum cycles followed by ASCT with or without rituximab, the outcomes of 75 patients with DLBCL who had relapsed after ASCT were analyzed [29]. The ORR to third-line chemotherapy was 44% and the median OS was 10 months; the median OS was shorter for patients who relapsed $<$6 months compared with $\geq$12 months following SCT [29]. In a different retrospective analysis of the CORAL study, which reviewed the outcomes of 203 patients who were ineligible for ASCT, the ORR following third-line chemotherapy was 39%, the median OS was 4.4 months and 32% of patients eventually underwent SCT [30]. Similarly, in SCHOLAR-1, a large retrospective study of pooled data from two phase III randomized trials and two academic databases, patients with refractory DLBCL previously treated with an anti-CD20 monoclonal antibody and an anthracycline who had relapsed $\leq$12 months after ASCT experienced an ORR of 34% and a median OS of 6.2 months following next-line treatment [31]. These analyses highlight that third/next-line chemotherapy can be beneficial for a subset of patients who relapse after or are not eligible for SCT, but that outcomes are generally poor. These data can be used as a baseline for assessing new treatments in this difficult-to-treat patient population. A key consideration when evaluating new therapies is that outcomes of patients with relapsed or refractory DLBCL differ based on response to initial treatment, timing of relapse and access to ASCT [32]. In line with this, patients with DLBCL who have primary refractory disease or who experience early relapse (within 1 year of diagnosis following a CR) have poor outcomes compared with patients who show partial response after the end of first-line therapy, requiring further treatment (residual disease). Specifically, in a retrospective analysis of patients with refractory DLBCL, the 2-year event-free survival rates were 13%, 14%, and 42% ($p = .044$), and the 2-year OS rates were 27%, 25%, and 52% ($p = .062$), for patients with primary refractory, early relapse and residual disease, respectively [33].

A systematic review assessed the efficacy and safety data that were available between August 1997 and August 2012 for patients with relapsed or refractory DLBCL and who were ineligible for SCT [34]. This analysis identified 55 publications and, in line with our results, most studies included were single-arm trials and had small sample sizes. It was concluded that the limited number of randomized trials hindered the identification of optimal therapies. Randomized trials are needed to provide evidence for the benefit of therapies in patients with relapsed or refractory DLBCL [34].

Trials that study relapsed or refractory patients with aNHL, but do not specify if the patients are ineligible for or have failed SCT, could also provide valuable insight into promising treatment options. A randomized, phase III trial comparing single-agent pixantrone vs. physicians choice of treatment in heavily pretreated patients with relapsed or refractory aNHL reported significantly more participants achieving a CR or an unconfirmed CR and a higher overall response rate among patients receiving pixantrone compared with those receiving comparator treatment (20% vs. 6%; $p = .021$ and 37% vs. 14%; $p = .003$, respectively). Pixantrone-treated patients also had a significantly longer median PFS than those receiving comparator treatment (5.3 months vs. 2.6 months; $p = .005$) [35]. In a phase IIa study, MOR208 demonstrated antitumor activity in patients with relapsed or refractory B-cell NHL; for patients with DLBCL, the 12-month PFS rate was 39% and 26% of patients showed responses. In this study, 50% of patients had received $\geq$3 prior treatments [36]. Additionally, in the phase II ZUMA-1 study, treatment of patients with refractory DLBCL with the chimeric antigen receptor [CAR] T-cell therapy axicabtagene ciloleucel resulted in an ORR of 82% and an 18-month-OS rate of 52%; 69% of patients had received $\geq$3 prior treatments [37]. In the phase II ROMULUS study, polatuzumab vedotin and pinatuzumab vedotin plus rituximab demonstrated similar efficacy to each other in patients with relapsed or refractory DLBCL (median number of prior treatments: 3) [38]. In another key trial in patients with relapsed or

refractory DLBCL, ibrutinib has demonstrated selective efficacy in those patients with the ABC subtype of DLBCL vs. patients with the GCB subtype (CR or PR: 37% vs. 5%, $p = .0106$) (median number of prior treatments: ABC: 3; GCB: 3.5) [39].

Our literature search included only manuscripts that had been published up to November 2017 and excluded congress abstracts; however, interesting novel therapies are in development. In a preliminary analysis of a phase II study, MOR208, an anti-CD19 antibody, in combination with lenalidomide, demonstrated efficacy in patients with relapsed or refractory DLBCL who were ineligible for SCT; ORR: 52%, preliminary median PFS: 11.3 months [40]. In addition, in the preliminary analysis of the JULIET study, tisagenlecleucel, a CAR T-cell therapy, produced the best ORR of 53%, while the 6-month probability of OS was 64.5% in patients with relapsed or refractory DLBCL who were ineligible for or had failed SCT [41]. Based on these data, tisagenlecleucel has recently been approved as a treatment for patients with relapsed or refractory DLBCL [42]. However, CAR T-cell therapy is also associated with limitations, such as toxicities, high cost and required infrastructure for large-scale production; in addition, questions remain regarding the position of CAR-T in the current treatment algorithm and inhibition by the tumor microenvironment [43]. Addition of polatuzumab vedotin to bendamustine plus rituximab in a similar patient population resulted in greater efficacy compared with bendamustine plus rituximab alone; best ORR: 70% vs. 33%; median PFS: 6.7 months vs. 2 months [44].

Limitations of this review included the strict search strategy that was applied and the timeframe of the searches (1 January 2006–17 November 2017), meaning that some relevant publications might have been excluded. Also, as with any pre-specified search terms, those used here will have limited the number of publications identified, as other search terms or synonyms capturing publications of interest might exist. Finally, only including publications in English means that relevant studies in other languages would have been excluded.

In conclusion, in this structured review, we assessed the scope and quality of published data from primary manuscripts reporting on efficacy and safety outcomes of patients with relapsed or refractory aNHL who were ineligible for or had failed SCT. Most of the studies identified described single-arm trials. Furthermore, among the studies identified, the majority of treatments demonstrated modest efficacy, suggesting a lack of effective options for this patient population. Our results highlight an unmet need for novel, efficacious and tolerable treatments for patients with relapsed or refractory aNHL who are ineligible for or have failed SCT. In addition, well-designed, randomized trials are necessary to evaluate new treatments, taking into account the clinical heterogeneity of patients with aNHL. Promising, new biologic therapies, such as MOR208, CAR T-cell therapy, and polatuzumab vedotin are in clinical development and could be integrated into future standard-of-care treatments for patients with relapsed or refractory aNHL.

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Appendix

Table: Search terms used in literature searches.

Search	Search title	Query
#1	NHL - 1	Search "Lymphoma, Non-Hodgkin"[Mesh] OR "non-Hodgkin lymphoma"[tiab] OR "non Hodgkin lymphoma"[tiab] OR "nonHodgkin lymphoma"[tiab] OR NHL[tiab]
#2	NHL - 2	Search "Non-Hodgkins Lymphoma"[tiab] OR "Nonhodgkins Lymphoma"[tiab] OR "Non-Hodgkin Lymphoma"[tiab] OR "Non Hodgkin Lymphoma"[tiab] OR "Non-Hodgkin's Lymphoma"[tiab] OR "Non Hodgkin's Lymphoma"[tiab] OR "Diffuse Small Cleaved-Cell Lymphoma"[tiab] OR "Diffuse Small Cleaved Cell Lymphoma"[tiab] OR "Nonhodgkin's Lymphoma"[tiab] OR "High-Grade Lymphoma"[tiab] OR "High-Grade Lymphomas"[tiab] OR "Intermediate-Grade Lymphoma"[tiab] OR "Intermediate-Grade Lymphomas"[tiab] OR "Reticulum-Cell Sarcoma"[tiab] OR "Reticulum-Cell Sarcomas"[tiab] OR "Reticulum Cell Sarcoma"[tiab] OR "Reticulosarcoma"[tiab] OR "Reticulosarcomas"[tiab] OR "Mixed Lymphocytic-Histiocytic Lymphoma"[tiab] OR "Mixed Lymphocytic-Histiocytic Lymphomas"[tiab] OR "Mixed-Cell Lymphoma"[tiab] OR "Mixed Cell Lymphoma"[tiab] OR "Mixed-Cell Lymphomas"[tiab] OR "Mixed Lymphoma"[tiab] OR "Mixed Lymphomas"[tiab] OR "Diffuse Mixed-Cell Lymphoma"[tiab] OR "Diffuse Mixed Cell Lymphoma"[tiab] OR "Diffuse Mixed-Cell Lymphomas"[tiab] OR "Diffuse Mixed Small and Large Cell Lymphoma"[tiab] OR "Small Non-Cleaved-Cell Lymphoma"[tiab] OR "Small Non Cleaved Cell Lymphoma"[tiab] OR "Small Non-Cleaved-Cell Lymphomas"[tiab] OR "Diffuse Undifferentiated Lymphoma"[tiab] OR "Diffuse Undifferentiated Lymphomas"[tiab] OR "Small Noncleaved-Cell Lymphoma"[tiab] OR "Small Noncleaved Cell Lymphoma"[tiab] OR "Small Noncleaved-Cell Lymphomas"[tiab] OR "Undifferentiated Lymphoma"[tiab] OR "Undifferentiated Lymphomas"[tiab] OR "Pleomorphic Lymphoma"[tiab] OR "Pleomorphic Lymphomas"[tiab] OR "Diffuse Lymphoma"[tiab] OR "Diffuse Lymphomas"[tiab] OR "Lymphosarcoma"[tiab] OR "Lymphosarcomas"[tiab] OR "Lymphatic Sarcoma"[tiab] OR "Lymphatic Sarcomas"[tiab] OR "Low-Grade Lymphoma"[tiab] OR "Low-Grade Lymphomas"[tiab] OR "transformed follicular lymphoma"[tiab] OR "transformed low-grade lymphoma"[tiab]
#3	NHL Combined	Search #1 OR #2
#4	Aggressive	Search Aggressive[tiab]
#5	Aggressive NHL - 1	Search #3 AND #4
#6	Aggressive NHL - 2	Search "Lymphoma, Large B-Cell, Diffuse"[Mesh] OR "Diffuse large B-cell lymphoma"[tiab] OR "Diffuse large B-cell lymphomas"[tiab] OR "Diffuse large B cell lymphoma"[tiab] OR "Diffuse large B cell lymphomas"[tiab] OR "Histiocytic Lymphoma"[tiab] OR "Histiocytic Lymphomas"[tiab] OR "Diffuse Histiocytic Lymphoma"[tiab] OR "Diffuse Histiocytic Lymphomas"[tiab] OR "Diffuse Large-Cell Lymphoma"[tiab] OR "Diffuse Large Cell Lymphoma"[tiab] OR "Diffuse Large-Cell Lymphomas"[tiab] OR DLBCL[tiab] OR aNHL[tiab]
#7	Aggressive NHL Combined	Search #5 OR #6
#8	Recurrent/Relapsed Terms	Search "Recurrence"[Mesh] OR Recurrent[tiab] OR Recurrence[tiab] OR Reoccurring[tiab] OR Relapse[tiab] OR Relapsed[tiab] OR Relapsing[tiab] OR Refractory[tiab]
#9	Recurrent/Relapsed NHL	Search #7 AND #8
#10	Stem Cell Transplantation (SCT) Terms	Search "Stem Cell Transplantation"[Mesh] OR "Stem Cell Transplantation"[tiab] OR "Stem Cell Transplantations"[tiab] OR "bone marrow transplant"[tiab] OR "bone marrow transplantations"[tiab] OR "bone marrow transplantation"[tiab] OR SCT[tiab] OR ASCT[tiab] OR alloSCT[tiab] OR autoSCT[tiab]
#11	Qualifier Terms	Search Fail[tiab] OR failed[tiab] OR "not a candidate for"[tiab] OR "not suitable"[tiab] OR "not an option"[tiab] OR unsuitable[tiab] OR "not eligible"[tiab]
#12	Qualified Stem Cell Transplantation (SCT)	Search #10 AND #11
#13	Failed/not eligible SCT NHL	Search #7 AND #12
#14	Recurrent OR Failed/not eligible SCT NHL	Search #9 OR #13
#15	Drug Therapy Terms	Search "Drug Therapy"[Mesh] OR "Drug Therapy"[tiab] OR "Drug Therapies"[tiab] OR "drug treatment"[tiab] OR "Chemotherapy"[tiab] OR "Chemotherapies"[tiab] OR "Pharmacotherapy"[tiab] OR "Pharmacotherapies"[tiab]
#16	Interim Output - Recurrent OR Failed/not eligible SCT NHL Treated with Drug Therapy	Search #14 AND #15
#17	All Reviews	Search "review"[tiab] OR review[Publication Type] OR Comment[Publication Type] OR Editorial[Publication Type] OR Letter[Publication Type] OR News[Publication Type]
#18	Systematic Reviews Only	Search systematic review[Publication Type] OR ("systematic"[tiab] AND "review"[tiab])
#19	Reviews minus Systematic Reviews	Search #17 NOT #18
#20	Selection for Reviews in Interim Output	Search #16 AND #19
#21	Interim Output with All Non-Systematic Reviews Removed	Search #16 NOT #20
#22	Output - Selected for Humans only	Search #21 NOT ("Animals"[Mesh] NOT "Humans"[Mesh])
#23	Output - Unwanted Types of Publication Removed	Search #22 NOT (Editorial[pt] OR Letter[pt] OR Case Reports[pt] OR Comment[pt])
#24	Final Output(1); Date restriction added	Search #22 NOT (Editorial[pt] OR Letter[pt] OR Case Reports[pt] OR Comment[pt]) Filters: Publication date from 2006/01/01
#25	Final Output(2); Date restriction, language restriction added	Search #22 NOT (Editorial[pt] OR Letter[pt] OR Case Reports[pt] OR Comment[pt]) Filters: Publication date from 2006/01/01; English