

Efficacy, Safety, and Patient-Reported Outcomes (PROs) of Treatments for Relapsed/Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL): A Systematic Literature Review (SLR)

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Background

- DLBCL is the most common non-Hodgkin lymphoma in the United States and Europe^{1,2}
- Approximately 10% to 15% of patients have primary refractory disease to first-line treatment and an additional 20% to 25% relapse after an initial response, typically within 2 years after treatment completion¹
- There has been an influx of treatments with novel mechanisms of action studied or approved to treat R/R DLBCL, including chimeric antigen receptor T-cell therapy (CAR-T), antibody-drug conjugates (ADC), nuclear export inhibitors (S), aza-anthracedione analogues (P), and chemotherapy/chemoimmunotherapy (Ch) combination therapies¹
- No systematic literature reviews (SLRs) have been published specifically evaluating 3L+ treatments of R/R DLBCL despite multiple SLR publications evaluating R/R DLBCL^{3,4,5}

Objective

- To conduct a SLR evaluating the efficacy, safety, and PROs of therapies for 3L+ R/R DLBCL
 - In this poster, we specifically report on the following drug classes of interest: CAR-T, ADC, S, P, and Ch

Materials & Methods

Data sources

- The following electronic databases were searched in November 2020:
 - MEDLINE and MEDLINE® In-Process
 - Embase®
 - Cochrane
- Conference proceedings were hand-searched for the last 3 years (2018–2020) to identify abstracts of interest:
 - American Society of Clinical Oncology
 - European Society for Medical Oncology
 - American Society of Hematology
 - European Hematology Association

Study eligibility

- All studies in R/R DLBCL were included at the title/abstract screening stage, regardless of line of therapy
- During the full-text screening phase, only relevant studies in patients who had relapsed or were refractory to at least 2 prior lines of therapy, including prior anti-CD20 antibody, were included
- Intervention/comparator: systemic therapies with/without control arm; in this poster, only interventions of interest are presented as defined in the objective
- Study: randomized and non-randomized controlled trials, single-arm studies
- Outcomes: response, survival, safety, PROs
- Only material published in English were included in the SLR
- Only studies in the 3L+ setting were included for data extraction

Results

- After screening of 9,901 records, 169 publications inclusive of 45 unique studies were identified
- Seven studies (from 108 publications) reported interventions of interest in 4 drug classes. Of these, 3 studies (from 85 publications) involved CAR-T, 2 studies (from 5 publications) involved ADC, 1 (from 11 publications) involved S, 1 (5 publications) involved P. Two studies were randomized controlled trials (from 9 publications) that included Ch as the control arm and P or ADC as the active comparator

Efficacy outcomes

- Wide ranges of efficacy outcomes were reported by drug class
- Commonly reported efficacy endpoints included median duration of response (mDoR), median progression-free survival (mPFS), and median overall survival (mOS) (Table 1). Objective response rate (ORR) and complete response (CR) are shown in Figure 1

- Across drug classes, the SLR results showed higher ORRs, and CR rates did not always translate to longer mPFS or mOS. The durability of the response may be a more important predictor of survival

Safety outcomes

- Safety profiles varied by drug class. Commonly reported safety outcome categories across publications included hematological and non-hematological adverse events (AEs) and treatment-emergent adverse events (TEAEs)
- In studies with complete AE reporting, hematologic AEs were more prevalent than non-hematologic AEs. Cytokine release syndrome (CRS) and neurologic AEs are more prevalent in CAR-T studies than other drug classes
- The most common Grade ≥3 AEs are shown in Figure 2

PROs

- Two CAR-T studies reported PROs
- PRO tools utilized included the Functional Assessment of Cancer Therapy-Lymphoma and the European Organisation for Research and Treatment of Cancer questionnaires
- Health-related quality of life improvements were clinically meaningful in a notable proportion of patients, starting from month 1 onwards

Figure 1. ORR and CR rate by drug class and trial

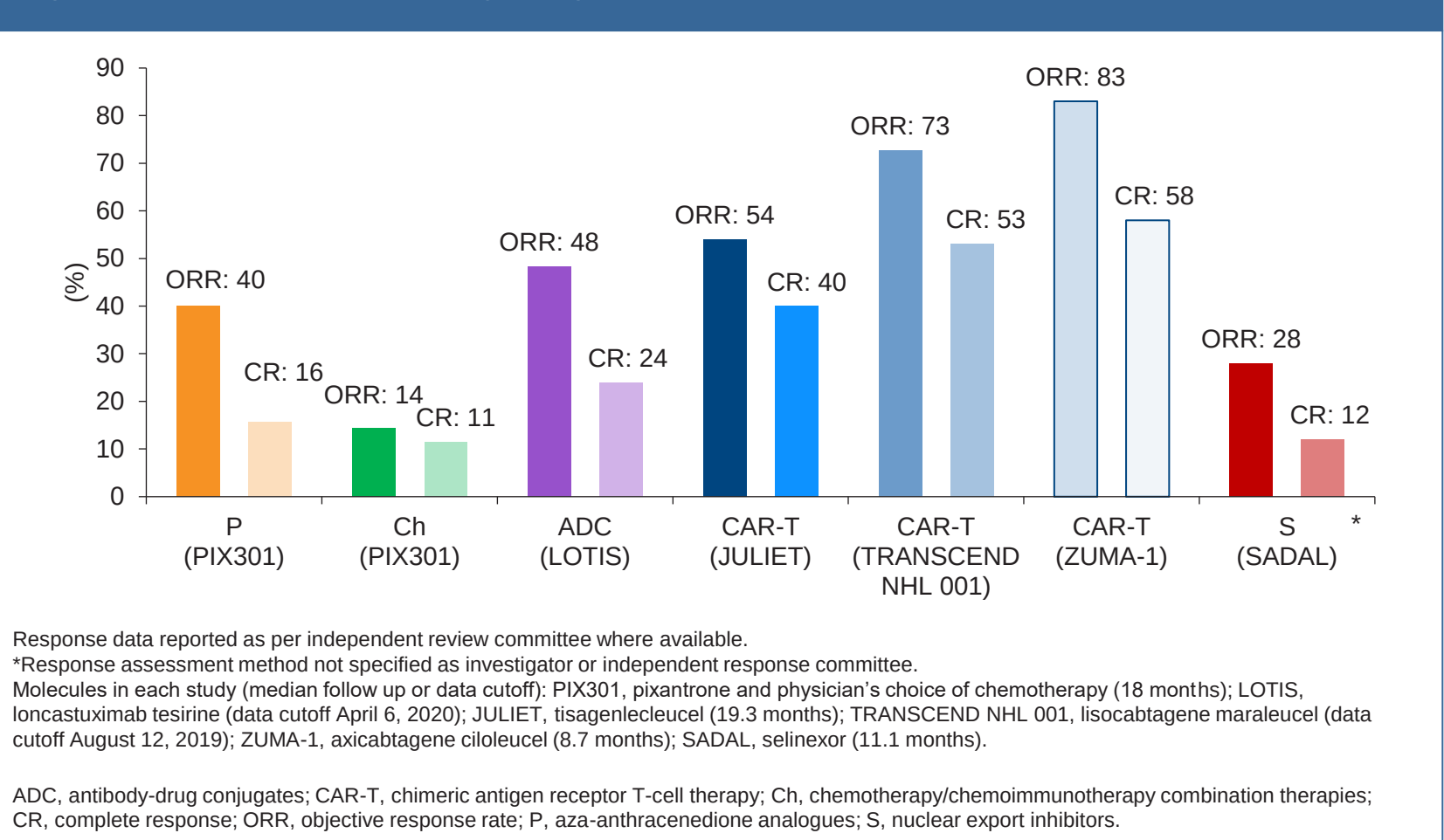


Figure 2. Incidence of Grade ≥3 adverse events by drug class and trial

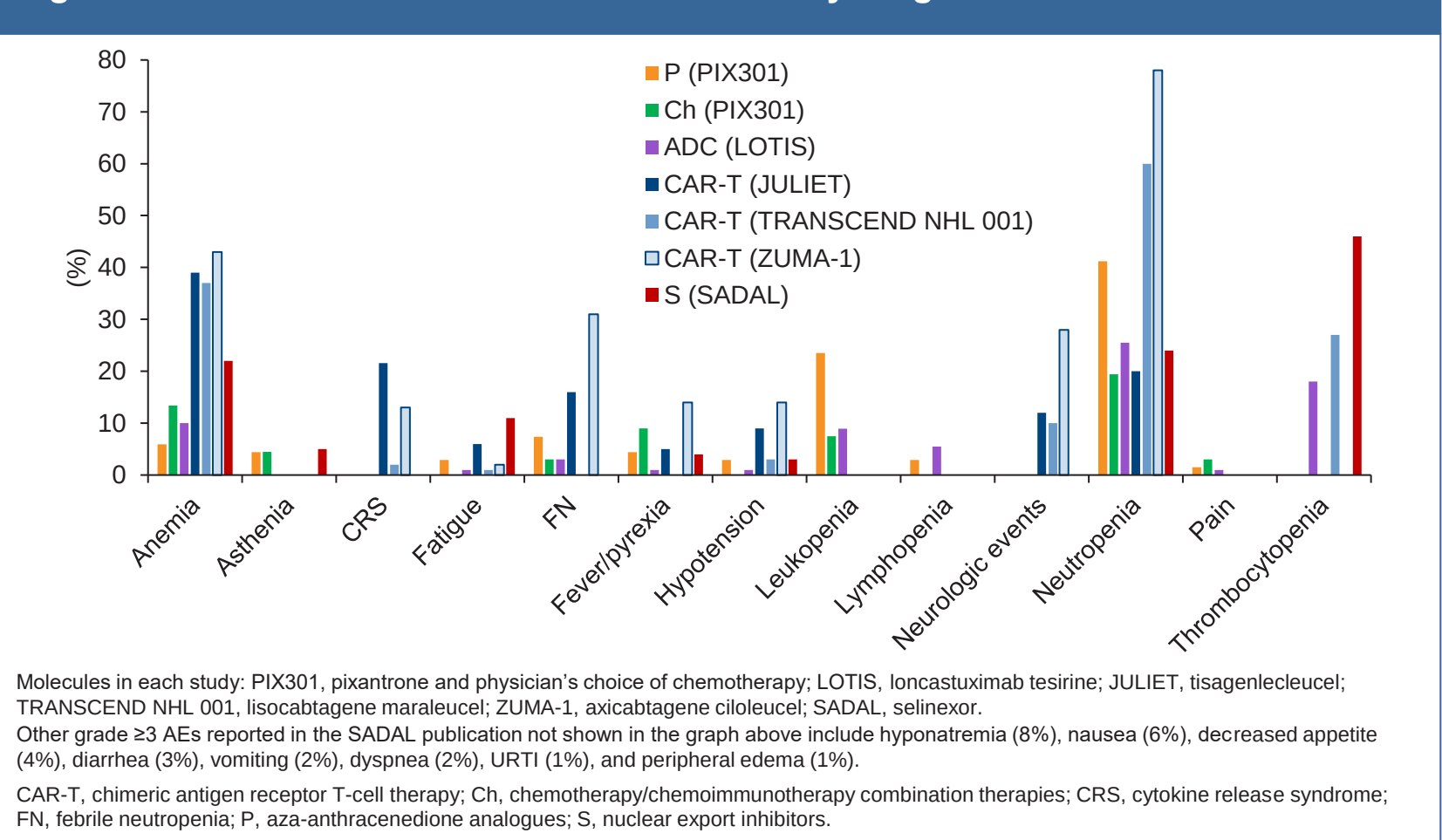


Table 1. Summary of trials reporting clinical outcomes of 3L+ treatments for R/R DLCLB								
Treatment (drug class)	Trial name (Author & Year)	Study design details; N allocated	Median FU (months); cut-off date	Median no. of prior lines of therapy (range)	Efficacy results			Safety results
					Median DoR (months) (95% CI)	Median PFS (months) (95% CI)	Median OS (months) (95% CI)	All TEAEs (Grade 3–4); most common Grade ≥3 TEAE (%); AESI, if reported separately
RCTs								
Pixantrone dimaleate (P)	PIX301 (Pettengell 2012) ⁶	Ph 3, OL, MC; N=40	18; Feb 16, 2010	3 (2–8)	9.6 (4–20.8) (ITT, IRC)	5.3 (2.3–6.2)	10.2 (6.4–15.7)	76.5% (NR) AEs: neutropenia: 41.2%; leukopenia: 23.5%; febrile neutropenia: 7.4%; anemia: 5.9%; asthenia: 4.4%; fever/pyrexia: 4.4%; fatigue: 2.9%; hypotension: 2.9%; lymphopenia: 2.9%; pain: 1.5% [data reported for ≥10% of patients]
V, O, If, Et, Mi, G, R (Ch)				3 (2–9)	4 (1–5.1)	2.6 (1.9–3.5)	7.6 (5.4–9.3)	52.2% (NR) AEs: neutropenia: 19.4%; anemia: 13.4%; fever/pyrexia: 9%; leukopenia: 7.5%; asthenia: 4.5%; pain: 3%; febrile neutropenia: 3.0% [data reported for ≥10% of patients]
Pola-BR (ADC)	GO29365 (Sehn 2020) ⁷	Ph 1/2, OL, MC; N=57	22.3; NR	2 (1–7) 2L: 27.5% ≥3L: 45.0%	10.9 (5.7–40.7) Overall population, majority of pts ≥2L	7.4	11.5	100% (87.2%) Overall population, majority of pts ≥2L
B + R (Ch)				2 (1–5) 2L: 22.5% ≥3L: 47.5%	10.6 (4.0–19.6)* Overall population, majority of pts ≥2L	3.2	3.8	97.4% (71.8%) Overall population, majority of pts ≥2L
Single-arm studies								
Tisagenlecleucel (CAR-T)	JULIET (Schuster 2019) ^{9–10}	Ph 2, OL, MC; Efficacy set N=115 ITT set N=165	19.3; May 21, 2018 OS (efficacy) updated from: 40.3; Feb 20, 2020	3 (1–6) 2L: 44% 3L: 31% 4–6L: 21%	Not reached (10–not reached) (Efficacy)	Reached based on Kaplan-Meier, value NR	11.1 (6.6–23.9) (Efficacy) 8.2 (5.8–11.7) ITT; interim results at Dec 8, 2017 data cutoff)	89% (63%) AEs: anemia: 39%; CRS: 21.6%; neutropenia: 20%; febrile neutropenia: 16%; fatigue: 6%; fever/pyrexia: 5%; hypotension: 9% [data cutoff: 13.9mo; Dec 8, 2017] [data reported for ≥10% of patients] AESI: CRS Grades 3 (14%) and 4 (8%); neurological events Grades 3 (7%) and 4 (5%); treatment-related death: 0%
Lisocabtagene maraleucel (CAR-T)	TRANSCEND NHL 001 (Abramson 2020) ¹¹	Ph 1, OL, MC; Evaluable set N=269; ITT set N=344	Ongoing; Aug 12, 2019	3 (2–4) 2L: 45% 3L: 25% ≥4L: 26%	Not reached (8.6–not reached) (Evaluable; IRC) 18.2 (8.2–not reached) (ITT; IRC) 16.8 (6–not reached) (Primary; IRC)	6.8 (3.3–14.1) (Evaluable; IRC) 4.8 (4.3–7.3) (ITT; IRC) 9 (3.1–not reached) (Primary; IRC)	21.1 (13.3–not reached) (Evaluable) 14 (11.1–21.1) (ITT) 19.9 (10.4–not reached) (Primary)	79% as TEAEs (NR) TEAEs: neutropenia: 60%; anemia: 37%; thrombocytopenia: 27%; neurological events: 10%; hypotension: 3%; CRS: 2%; fatigue: 1% [Safety set: 267, data reported for ≥3% of patients] AESI: CRS Grades 3 (1%) and 4 (1%); neurological event Grades 3 (9%) and 4 (1%); treatment-related death: <1%
Axicabtagene ciloleucel (CAR-T)	ZUMA-1 (Neelapu 2017) ^{12–14}	Ph 2, OL, MC; mITT N=101 ITT N=111	8.7; Jan 27, 2017 [Primary analysis] 15.4; Aug 11, 2017 [Updated analysis]	3 3L+: 69%	11.1 (4.2–not reached) (inv) Not reached (10.9–not reached) (IRC)	5.9 (3.3–15) (mITT, IRC)	17.4 (ITT) Not reached (12.8–not reached)	100% as TEAEs (NR) AEs: neutropenia: 78%; anemia: 43%; febrile neutropenia: 31%; neurological events: 28%; pyrexia: 14%; hypotension: 14%; CRS: 13%; fatigue: 2%; treatment-related death: 2% [data reported for ≥5% of patients]
Loncastuximab tesirine (ADC)	LOTIS-2 (Caimi 2021) ¹⁵	Ph 2, OL, MC; N=145	Data cutoff: April 6, 2020	3 (2–4) 2L: 43% 3L: 24% ≥4L: 32%	10.3 (6.9–not reached) (ITT; IRC)	4.9 (2.9–8.3) (ITT; IRC)	9.9 (6.7–11.5) (ITT)	72.4% as TEAEs (NR) TEAEs: neutropenia: 25.51%; thrombocytopenia: 18%; anemia: 10%; leukopenia: 8.96%; lymphopenia: 5.51%; febrile neutropenia: 3%; fatigue: 1%; fever/pyrexia:1%; hypotension: 1%; pain: 1% [data reported for ≥10% of patients] AESI: neutropenia Grades 3 (10%) and 4 (16%); thrombocytopenia Grades 3 (12%), 4 (6%)
Selinexor (S)	SADAL (Kalakonda 2020) ^{16,17}	Ph 2b, OL, MC; Primary set N=127; Post hoc set N=134	11.1; 14.8 post-hoc (data cut off Aug 1, 2020)	2 (2–3) 2L: 59% ≥3L: 41%	9.3 (4.8–23) (Primary; ITT; inv) 9.3 (Post-hoc; ITT; unclear)	2.6 (1.9–4) (Primary; ITT; inv)	9.1 (6.6–15.1) (Primary; ITT) 9 (Post-hoc; ITT)	98% as TEAEs (NR) TEAEs: thrombocytopenia: 46%; neutropenia: 24%; anemia: 22%; fatigue: 11%; hyponatremia: 8%; nausea: 6%; asthenia: 5%; Decreased appetite: 4%; pyrexia: 4%; diarrhea 3%; hypotension: 3%; vomiting: 2%; dyspnea: 2%; URTI: 1%; peripheral edema: 1% [data reported for ≥10% of patients]

ADC, antibody drug conjugate; AE, adverse events; AESI, adverse events of special interest; CAR-T, chimeric antigen receptor T cell therapy; Ch, chemotherapy/chemoimmunotherapy combinations; CI, confidence intervals; CR, complete response; CRS, cytokine release syndrome; DoR, duration of response; Et, etoposide; FU, follow-up; G, gemtacinibine; If, ifosfamide; inv, investigator; IRC, independent review committee; ITT, intention-to-treat; MC, multicenter; Mi, mitoxantrone; mo, months; N, number; NR, not reported; O, oxaliplatin; OL, open label; P, aza-anthracedione analogues; PFS, progression-free survival; Ph, phase; Pola-BR, polatuzumab vedotin; R, rituximab; S, nuclear export inhibitors; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; V, vinorelbine.

Conclusions

- Despite the availability of novel 3L+ therapies, wide ranges of efficacy outcomes are reported, and therapies are limited by AEs leading to treatment discontinuation
- Therefore, a high unmet need exists for additional treatment options providing a favorable benefit/risk profile for R/R DLBCL patients
- Limited PROs have been reported to date, and more studies characterizing patient reported outcomes are warranted to better elucidate benefit/risk profiles for existing and novel therapies for 3L+ R/R DLBCL

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