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SYSTEMATIC REVIEW & META-ANALYSIS

Targeted Therapies and Immunotherapies for Diffuse Large B-Cell Lymphoma Across Lines of Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Many targeted therapies and immunotherapies have been compared with standard treatment for diffuse large B-cell lymphoma (DLBCL), with discordant results across lines of therapy.

Objective: To estimate their effects on survival, response and serious toxicity and to test whether setting or mechanism modifies them.

Methods: PubMed/MEDLINE, Europe PMC, OpenAlex and Scopus were searched for randomized trials comparing a regimen containing a novel targeted agent or immunotherapy with standard therapy in adults with DLBCL. Hazard ratios (HR) and risk ratios (RR) with 95% confidence intervals (CI) were pooled with random-effects models; certainty was rated with GRADE.

Results: Thirty-eight trials (14,001 participants) were included. Progression-free survival improved in relapsed or refractory disease (HR 0.54, 95% CI 0.44 to 0.68; moderate certainty), most in transplant-ineligible patients (HR 0.42, 95% CI 0.38 to 0.47), and modestly in first-line induction (HR 0.84, 95% CI 0.76 to 0.94; moderate certainty); the setting modified the effect (p<0.001), whereas immunotherapies and targeted therapies did not differ (p=0.55). Overall survival improved in relapsed or refractory disease (HR 0.72, 95% CI 0.60 to 0.87) but not significantly in first-line induction (HR 0.88, 95% CI 0.77 to 1.01); the difference between settings was not significant (p=0.13). Grade ≥3 adverse events (RR 1.10, 95% CI 1.04 to 1.16) and fatal adverse events (RR 1.34, 95% CI 1.08 to 1.66) increased.

Conclusion: The benefit of novel agents in DLBCL differed between lines of treatment but not between mechanisms: substantial in relapsed or refractory disease and modest in first-line therapy, where it must be weighed against more fatal toxicity.

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1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma and the most frequent aggressive lymphoma in adults worldwide. Non-Hodgkin lymphoma ranks among the leading hematological malignancies by incidence and mortality in global cancer estimates,[1] and analyses of the Global Burden of Disease study show that the share of this burden attributable to high body mass index grew over three decades, is projected to keep rising and varies markedly between countries.[2] DLBCL is biologically heterogeneous. In a population-based gene-expression study, cell-of-origin subgroups and a double-hit signature separated patients whose outcomes differed widely after the same immunochemotherapy.[3] Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) cures most patients. Age, frailty and dose attenuation erode these results, as cohorts from developing countries and population-based studies of older patients showed.[4,5] Among more than 10,000 patients starting first-line therapy, 30% needed second-line treatment, and 13% died within a year without receiving it.[6]

Randomized trials have tried for two decades to improve on this standard by adding targeted agents or new immunotherapies. In first-line therapy, bortezomib, ibrutinib, lenalidomide, enzastaurin, everolimus, bevacizumab and obinutuzumab were added to R-CHOP, substituted for some of its components, or given as maintenance, and most did not improve progression-free survival in the whole population,[7–13] although post hoc analyses hinted at benefit in molecularly or clinically defined subsets.[14,15] Replacing vincristine with the anti-CD79b antibody-drug conjugate polatuzumab vedotin was the first change to improve progression-free survival in a phase 3 trial.[16,17] Trials of tafasitamab with lenalidomide and of the histone deacetylase inhibitor tucidinostat followed.[18,19] Relapsed or refractory disease changed faster. In two of three phase 3 trials, CD19-directed chimeric antigen receptor (CAR) T cells replaced salvage chemotherapy and autologous transplantation for early relapse.[20–22] Single-arm studies established bispecific T-cell engagers, antibody-drug conjugates and anti-CD19 antibodies in later lines,[23–26] and randomized trials then combined these agents with chemotherapy for patients who are not candidates for transplantation.[27–30] Outside trials, large cohorts treated with commercial CAR T cells or bispecific antibodies have fared less well than the pivotal studies suggested.[31–33]

Earlier syntheses took these questions one setting at a time: improvements of first-line R-CHOP,[34] maintenance strategies,[35] second-line CAR T cells[36] and systemic therapies

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for relapsed or refractory disease.[37] None used all the randomized evidence to ask whether the relative benefit of novel agents depends on the line of treatment, or on whether an agent acts through immune effector mechanisms or by targeting a tumor pathway. The phase 3 trials reported most recently have not yet been pooled with earlier evidence. The questions matter outside high-income health systems. Most patients treated in practice would not have met the eligibility criteria of the pivotal trials,[31] referral for CAR T-cell therapy remains limited even where it is available,[38] and its cost-effectiveness depends on national prices and pathways.[39] In Indonesia and comparable settings, cellular therapy is rarely accessible. Clinicians there need to know which classes of novel agents change outcomes, and in which setting, compared with the chemoimmunotherapy that remains the default treatment.

Three elements set this study apart from previous syntheses, including network meta-analyses of relapsed disease, none of which combined them. The first is a single analysis of every randomized trial that compared a regimen containing a novel targeted agent or immunotherapy with the standard therapy of the same setting, from first-line induction and maintenance to relapsed or refractory disease, using the most mature follow-up of each trial and the phase 3 reports published most recently. The second is a set of pre-specified tests of whether the treatment setting and the mechanism of action modify the relative effect on progression-free survival. The third is a joint appraisal of efficacy and serious toxicity, graded for certainty of evidence. The aim was to estimate the effects of targeted therapies and immunotherapies, compared with standard therapy, on progression-free survival, overall survival, complete response and serious adverse events in adults with DLBCL. It was also to determine whether these effects differ by line of treatment and by mechanism.

2. Methods

2.1 Study design

This systematic review and meta-analysis of randomized controlled trials was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement.[40] The review question, eligibility criteria, outcomes, subgroup variables and analysis plan were defined before the searches were run. The analysis used published aggregate data, so ethical approval and patient consent were not required.

2.2 Information sources and search strategy

PubMed/MEDLINE, Europe PMC, OpenAlex and Scopus were searched from inception without language restriction. MEDLINE covers the clinical journals in which randomized lymphoma trials are reported; Europe PMC adds full-text records and other biomedical sources; OpenAlex indexes scholarly works across publishers; and Scopus, limited to journal articles, adds citation-indexed journals outside MEDLINE. The strategy combined three concepts with Boolean operators: diffuse large B-cell lymphoma (Medical Subject Headings and free-text synonyms, including large B-cell and aggressive B-cell lymphoma), novel targeted or immunotherapeutic agents (subject headings for molecular targeted therapy, immunotherapy, chimeric antigen receptors, bispecific antibodies, immunoconjugates and kinase, proteasome and histone deacetylase inhibitors, together with the names of 45 individual agents) and randomized trial terms. The reference lists of 8 recent systematic reviews and network meta-analyses and of the included trials were screened. The results posted on ClinicalTrials.gov for the included trials were used to complete their outcome data. Conference abstracts were not eligible because they rarely report hazard ratios with adequate follow-up and are usually superseded by full reports; their exclusion is considered among the limitations.

2.3 Eligibility criteria

Eligible studies were randomized controlled trials of phase 2, 2/3 or 3 in adults with DLBCL. They compared a regimen containing a novel targeted agent or immunotherapy with the standard regimen of the same setting without that agent. Targeted therapies were small molecules, antibody-drug conjugates, radioimmunoconjugates and other antibodies directed at a defined tumor pathway or antigen. Immunotherapies were agents whose principal mechanism was immune effector engagement, namely CAR T cells, bispecific T-cell engagers, non-rituximab monoclonal antibodies and cytokine agonists. Two kinds of trials were not eligible because they do not test a novel agent: trials in which rituximab itself was the only difference between arms, and trials of cytotoxic drugs, radiotherapy, transplant intensity or supportive care. The criteria are detailed in Table 1.

Table 1. Eligibility criteria.

Element	Inclusion	Exclusion
Population	Adults with diffuse large B-cell lymphoma (including high-grade and transformed large B-cell lymphoma enrolled in DLBCL trials), previously untreated or relapsed/refractory; mixed-histology trials if DLBCL was at least 80% of participants or reported separately	Primary central nervous system lymphoma; pediatric trials; post-transplant lymphoproliferative disorders; mixed histologies without separable DLBCL data
Intervention	A regimen containing a novel targeted agent (antibody-drug or radioimmunoconjugate, immunomodulatory drug, BTK, proteasome, PKC-β, mTOR or histone deacetylase inhibitor, anti-angiogenic antibody, genotype-directed combination) or immunotherapy (CAR T cells, bispecific T-cell engager, non-rituximab monoclonal antibody, cytokine agonist), added to or substituted for a component of standard therapy	Rituximab, rituximab biosimilars or rituximab dose and schedule as the only difference; cytotoxic drugs, radiotherapy, transplant intensity or supportive care as the only difference
Comparator	The standard regimen of the same setting without the investigational agent (R-CHOP or the trial's anti-CD20-containing standard; placebo or observation for maintenance; salvage chemoimmunotherapy with or without autologous transplantation, R-GemOx, bendamustine-rituximab or investigator's choice)	Two novel agents without a standard arm; first-line control arm without an anti-CD20 antibody
Outcomes	Progression-free survival (primary; event-free or disease-free survival when progression-free survival was not reported), overall survival, complete response, grade ≥3 and fatal adverse events	No arm-level outcome data for any review outcome
Design and report	Randomized controlled trials (phase 2, 2/3 or 3); full peer-reviewed reports and their follow-up publications	Single-arm or non-randomized studies; conference abstracts only; trial protocols

Notes: DLBCL, diffuse large B-cell lymphoma; BTK, Bruton tyrosine kinase; PKC-β, protein kinase C-beta; mTOR, mechanistic target of rapamycin; CAR, chimeric antigen receptor; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-GemOx, rituximab, gemcitabine and oxaliplatin.

2.4 Study selection and data extraction

Records from the four databases were merged and de-duplicated by PubMed identifier, digital object identifier and normalized title. A rule-based triage marked records that were conference abstracts, non-primary publications, laboratory or animal studies, pediatric studies, studies of other lymphomas or records without any randomized comparison. In a validation set of 35 eligible trial reports assembled before screening, the rules excluded none. All remaining titles and abstracts were then screened, and potentially eligible reports were assessed in full. One

reviewer screened records and extracted data with a piloted form. A second reviewer verified every effect estimate, event count and risk-of-bias judgment against the trial reports; disagreements were resolved by discussion. For each trial the following were recorded: phase, masking, setting, population, novel-agent and standard regimens, drug class and strategy (addition, substitution, replacement or maintenance). The numbers randomized, median age, sex, median follow-up, time-to-event estimates and binary outcomes were also recorded. Companion reports of the same trial were linked, and the most mature follow-up was used for each time-to-event outcome. Every trial therefore contributed once to each analysis, and no trial contributed more than one comparison. The hazard ratio of each trial came from the population analyzed in the report used. This was the intention-to-treat population except in four trials that analyzed eligible, evaluable or molecularly classified patients (E1412, PYRAMID, REMoDL-B and A051301). These departures were considered in the risk-of-bias assessment.

Progression-free survival was the primary outcome. When a trial did not report progression-free survival, event-free or disease-free survival was used and the substitution was examined in a sensitivity analysis. Hazard ratios were oriented so that values below 1 favored the novel-agent arm. Their log values and standard errors were obtained from the reported 95% confidence intervals (Equation 1), or from 90% intervals with the corresponding normal quantile.

$$\begin{aligned} y_i &= \ln(\mathrm{HR}_i), \\ \mathrm{SE}_i &= \frac{\ln(U_i)-\ln(L_i)}{2\times 1.96}, \\ v_i &= \mathrm{SE}_i^2 \end{aligned} \tag{1}$$

When a hazard ratio was reported with a two-sided P value but no confidence interval, the standard error was derived from the P value. When only landmark survival proportions and a P value were reported, the hazard ratio was estimated from the ratio of the logarithms of the survival proportions under proportional hazards (Equation 2). When the P value was reported only as below a threshold (for example, below 0.001), the threshold itself was used, which gives a conservative, wider interval. Derived estimates are marked in the forest plots, and the reported values used to calculate them are included in the supplementary data workbook. Event counts of binary outcomes were calculated from reported percentages and denominators when counts were not given. Grade ≥3 adverse events were taken from the safety population. Trials that reported only grade 3–4 events contributed those, and trials that reported only treatment-related deaths contributed them to the fatal adverse event outcome.

$$\begin{aligned} \mathrm{SE}_i &= \frac{|y_i|}{\Phi^{-1}(1-P_i/2)}, \\ \widehat{\mathrm{HR}}_i &= \frac{\ln\left(S_{\mathrm{N},i}(t)\right)}{\ln\left(S_{\mathrm{C},i}(t)\right)} \end{aligned} \tag{2}$$

2.5 Risk of bias

Risk of bias for progression-free survival was assessed with the revised Cochrane tool for randomized trials (RoB 2) across five domains. The domains were the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result.[41] Outcome assessment by investigators in open-label trials was judged to raise some concerns unless an independent review confirmed the result. Exclusion of randomized patients from the efficacy analysis raised concerns about missing data. Estimates that had to be derived from secondary or exploratory analyses raised concerns about selection of the reported result. The overall judgment was the most severe domain-level judgment.

Overall survival and adverse events were appraised narratively. Overall survival is measured objectively, so outcome measurement was not a concern. Crossover to the novel agent and subsequent therapies after progression can dilute the effect, so trials with protocol-specified crossover were identified and examined in a sensitivity analysis. Adverse events in open-label trials depend on ascertainment and attribution. Differences in the definitions of grade ≥3 and fatal events were examined in sensitivity analyses and in the certainty ratings.

2.6 Statistical analysis

Log hazard ratios were pooled with inverse-variance random-effects models. The between-trial variance τ^2 was estimated with the DerSimonian–Laird method (Equation 3), the pooled log hazard ratio was the weighted mean with weights equal to the inverse of the within-trial variance plus τ^2 (Equation 4), and its 95% confidence interval used the Hartung–Knapp adjustment with a t distribution on k–1 degrees of freedom (Equation 5), which keeps coverage closer to nominal when trials are few or heterogeneous.[42]

$$\begin{aligned} \tau^2 &= \max\left\{0, \frac{Q-(k-1)}{\sum_i w_i - \frac{\sum_i w_i^2}{\sum_i w_i}}\right\}, \\ w_i &= \frac{1}{v_i} \end{aligned} \tag{3}$$

$$\begin{aligned} \hat{\mu} &= \frac{\sum_i w_i^* y_i}{\sum_i w_i^*}, \\ w_i^* &= \frac{1}{v_i+\tau^2}, \\ \mathrm{HR}_{\mathrm{pooled}} &= \exp(\hat{\mu}) \end{aligned} \tag{4}$$

$$\hat{\mu} \pm t_{k-1,0.975}\sqrt{\frac{\sum_i w_i^*(y_i-\hat{\mu})^2}{(k-1)\sum_i w_i^*}} \tag{5}$$

Heterogeneity was quantified with Cochran's Q, I^2 and τ^2 (Equation 6). The 95% prediction interval was calculated to show the range of effects expected in a new trial (Equation 7).[43]

$$\begin{aligned} Q &= \textstyle\sum_i w_i(y_i-\hat{\mu}_{\mathrm{FE}})^2, \\ I^2 &= \max\left\{0, \frac{Q-(k-1)}{Q}\right\}\times 100\% \end{aligned} \tag{6}$$

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$$\hat{\mu} \pm t_{k-2,0.975}\sqrt{\tau^2 + \mathrm{SE}^2(\hat{\mu})} \quad (7)$$

Pre-specified subgroup analyses compared treatment settings (first-line induction, first-line maintenance, relapsed or refractory), mechanisms (immunotherapy versus targeted therapy), the five combinations of setting and mechanism present in the data, drug classes, transplant eligibility within relapsed or refractory disease, treatment strategy, trial phase, masking and overall risk of bias, with separate random-effects models within subgroups and the Cochran Q test for differences. Mixed-effects meta-regression with Knapp–Hartung tests examined the setting (relapsed or refractory versus first line), the mechanism and their interaction (Equation 8), and, separately, publication year, trial size and median follow-up.

$$\begin{gathered} y_i = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \beta_3 x_{1i} x_{2i} + u_i + \varepsilon_i, \\ u_i \sim N(0, \tau^2), \\ \varepsilon_i \sim N(0, v_i) \end{gathered} \quad (8)$$

The setting and the mechanism were the two pre-specified effect modifiers; the other subgroup variables were exploratory. Because the setting was correlated with the comparator, publication year and trial size, multivariable meta-regressions were run. They combined the setting with publication year, with publication year and trial size, and with mechanism and publication year. The credibility of effect modification was judged from pre-specification, the size and consistency of the difference across analyses, the presence of a within-setting rather than only a between-trial comparison, and biological plausibility. The mechanism classification was tested in two sensitivity analyses. In the first, immunomodulatory drugs were classed as immunotherapy. In the second, the two regimens combining an immunotherapy with a targeted or immunomodulatory agent were excluded. With two trials in a subgroup, the Hartung–Knapp interval uses a t distribution with one degree of freedom and is therefore very wide; such subgroups were reported descriptively.

Sensitivity analyses repeated the primary analysis with a common-effect model, restricted maximum likelihood and Paule–Mandel estimators of τ^2 and Wald-type intervals, and after excluding trials with derived estimates, trials with event-free or disease-free survival in place of progression-free survival, trials with some concerns about risk of bias, phase 2 trials, open-label trials and trials with fewer than 100 participants; a leave-one-out analysis examined the influence of single trials.

Further analyses excluded the two transplant-conditioning trials and the trial of consolidation after CAR T-cell therapy. They also examined first-line induction without the trial with the largest estimated effect and repeated the overall survival analysis without trials that allowed protocol crossover.

Small-study effects were assessed with a funnel plot and the Egger regression test, with Begg rank correlation as a supplementary test. The Egger test was repeated within settings, because asymmetry could arise from the concentration of small trials in relapsed disease. The trim-and-fill method estimated the effect after imputation of potentially missing trials.[44] These tests were applied because more than ten trials contributed. Overall survival was analyzed in the same way. The association between trial-level effects on progression-free and overall survival was assessed with Spearman correlation and linear regression of log hazard ratios weighted by trial size and, alternatively, by the inverse variance of the overall-survival estimate. This descriptive analysis is not a formal evaluation of surrogacy.

Binary outcomes were pooled as risk ratios with the same random-effects model, with 0.5 added to the cells of trials with zero events and a Mantel–Haenszel common-effect model as sensitivity analysis; grade ≥3 and fatal adverse events were also analyzed after excluding trials that reported only grade 3–4 events or only treatment-related deaths; absolute differences per 1000 patients were derived from the median risk in the standard arms (Equation 9).

$$\begin{gathered} y_i = \ln\left(\frac{a_i/n_{\mathrm{N},i}}{c_i/n_{\mathrm{C},i}}\right), \\ \mathrm{ARD}_{1000} = 1000 \times p_{\mathrm{C}} \times (\mathrm{RR} - 1) \end{gathered} \quad (9)$$

The certainty of evidence for each outcome, and for progression-free and overall survival within settings, was rated with the Core GRADE approach,[45] starting at high certainty for randomized evidence and rating down for risk of bias (more than half of the weight from trials with some concerns), inconsistency (I^2 ≥50%, or I^2 ≥25% with a 95% prediction interval including no effect), imprecision (95% CI including no effect, or fewer than 300 events for binary outcomes), small-study effects (Egger p<0.10 with at least ten trials) and indirectness when outcome definitions differed in what they measured. Analyses used R 4.5.3 with the meta (8.2.1) and metafor (4.8.0) packages; all tests were two-sided with a significance level of 0.05.

3. Results

3.1 Study selection

The searches identified 5,278 records (PubMed/MEDLINE 905, Europe PMC 703, OpenAlex 2,517 and Scopus 1,153). After removal of 2,134 duplicates and 2,525 records marked ineligible by the rule-based triage, 619 titles and abstracts were screened and 50 reports were assessed in full. Three reports were excluded. One trial used a control arm without an anti-CD20 antibody. Another enrolled mixed lymphoma histologies with fewer than half DLBCL and no separate results. The third reported no arm-level outcome data. Citation searching identified no further reports. Thirty-eight randomized trials described in 47 reports were included, as shown in Figure 1.

3.2 Characteristics of the included trials

The 38 trials randomized 14,001 participants (7,234 to novel-agent regimens and 6,767 to standard therapy). Sixteen trials (8,555 participants) tested first-line induction regimens,[7–10,13,16,18,19,46–53] three (2,150 participants) tested maintenance after first-line therapy[11,12,54] and 19 (3,296 participants) enrolled patients with relapsed or refractory disease. Of these, 8 were in transplant-eligible second-line or transplant-based settings[20–22,55–59] and 11 were in patients ineligible for transplantation or in later lines.[27–30,60–66] Twenty-four trials were phase 3 and 14 were double-blind. Of the 24 open-label trials, 8 assessed the time-to-event outcome used here by independent review, and three allowed protocol-specified crossover to the novel agent. Fourteen trials tested immunotherapies (four CAR T-cell products, four bispecific T-cell engager regimens and six other antibody or cytokine regimens). The other 24 tested targeted therapies (seven antibody-drug or radioimmunoconjugates, six immunomodulatory drug regimens, two Bruton tyrosine kinase inhibitors and nine other targeted agents), as detailed in Table 2.

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Table 2. Characteristics of the included randomized trials, by treatment setting and year.

Trial	Phase; blinding	Population	Novel-agent regimen	Standard regimen	Class	n (novel / standard)	FU (months)	PFS HR (95% CI)
First-line induction								
Seymour 2014 (MAIN)	3; double-blind	Previously untreated CD20-positive DLBCL	Bevacizumab + R-CHOP	Placebo + R-CHOP	Other targeted	390 / 387	23.6	1.09 (0.85 to 1.40)
Offner 2015 (LYM-2034)	2; open-label	Previously untreated non-GCB DLBCL	Bortezomib replacing vincristine (VR-CAP)	R-CHOP	Other targeted	84 / 80	NR	1.12 (0.54 to 2.32)
Hainsworth 2016	2; open-label	Previously untreated intermediate/high-risk DLBCL	Enzastaurin + R-CHOP	R-CHOP	Other targeted	58 / 43	NR	NR
Leonard 2017 (PYRAMID)	2; open-label	Previously untreated non-GCB DLBCL	Bortezomib + R-CHOP	R-CHOP	Other targeted	92 / 91	34	0.73 (0.39 to 1.37)
Vitolo 2017 (GOYA)	3; open-label	Previously untreated advanced DLBCL	Obinutuzumab-CHOP	R-CHOP	Other antibody/cytokine	704 / 710	48	0.94 (0.78 to 1.13)
Davies 2019 (REMoDL-B)	3; open-label	Previously untreated DLBCL with gene-expression profiling	Bortezomib + R-CHOP	R-CHOP	Other targeted	459 / 459	64	0.81 (0.64 to 1.03)
Younes 2019 (PHOENIX)	3; double-blind	Previously untreated non-GCB DLBCL	Ibrutinib + R-CHOP	Placebo + R-CHOP	BTK inhibitor	419 / 419	NR	0.92 (0.71 to 1.18)
Le Gouill 2021 (GAINED)	3; open-label	Previously untreated DLBCL, 18–60 y, aaIPI ≥1	Obinutuzumab + chemotherapy (CHOP or ACVBP)	Rituximab + chemotherapy (CHOP or ACVBP)	Other antibody/cytokine	336 / 334	38.7	0.88 (0.75 to 1.04) [EFS]
Nowakowski 2021 (E1412)	2; open-label	Previously untreated DLBCL, stage II bulky-IV, IPI ≥2	Lenalidomide + R-CHOP	R-CHOP	IMiD	145 / 135	36	0.66 (0.43 to 1.01)
Nowakowski 2021 (ROBUST)	3; double-blind	Previously untreated ABC-type DLBCL	Lenalidomide + R-CHOP	Placebo + R-CHOP	IMiD	285 / 285	NR	0.85 (0.63 to 1.14)
Oberic 2021 (SENIOR)	3; open-label	Previously untreated DLBCL, age ≥80 y	Lenalidomide + R-miniCHOP	R-miniCHOP	IMiD	122 / 127	25.1	NR
Tilly 2022 (POLARIX)	3; double-blind	Previously untreated intermediate/high-risk DLBCL, 18–80 y	Polatuzumab vedotin-R-CHP	R-CHOP	ADC/radioimmunoconjugate	440 / 439	64.1	0.77 (0.62 to 0.96)
Zhang 2023 (GUIDANCE-01)	2; open-label	Previously untreated intermediate/high-risk DLBCL	Genotype-guided R-CHOP-X	R-CHOP	Other targeted	64 / 64	NR	0.28 (0.13 to 0.59)
Westin 2025	2; open-label	Previously untreated DLBCL	Mosunetuzumab + polatuzumab-CHP	Polatuzumab-R-CHP	Bispecific antibody	40 / 22	NR	1.27 (0.44 to 3.67)
Lenz 2026 (frontMIND)	3; double-blind	Previously untreated high-intermediate/high-risk DLBCL or HGBL, 18–80 y	Tafasitamab + lenalidomide + R-CHOP	Placebo + R-CHOP	Other antibody/cytokine	448 / 451	35.2	0.75 (0.59 to 0.96)
Xu 2026 (DEB)	3; double-blind	Previously untreated MYC/BCL2 double-expressor DLBCL	Tucidinostat + R-CHOP	Placebo + R-CHOP	Other targeted	211 / 212	41.3	0.78 (0.56 to 1.09)
First-line maintenance								
Crump 2016 (PRELUDE)	3; double-blind	High-risk DLBCL in CR after R-CHOP	Enzastaurin maintenance	Placebo	Other targeted	504 / 254	48	0.92 (0.69 to 1.22) [DFS]
Thieblemont 2017 (REMARC)	3; double-blind	DLBCL, 60–80 y, CR/PR after R-CHOP	Lenalidomide maintenance	Placebo	IMiD	323 / 327	39	0.71 (0.54 to 0.93)
Witzig 2018 (PILLAR-2)	3; double-blind	High-risk (IPI ≥3) DLBCL in PET-confirmed CR after rituximab-chemotherapy	Everolimus maintenance	Placebo	Other targeted	372 / 370	50.4	0.92 (0.69 to 1.22) [DFS]
Relapsed or refractory								
Shimoni 2012	2; open-label	Refractory/relapsed CD20-positive aggressive large B-cell lymphoma (DLBCL, PMBL, transformed FL)	Ibritumomab tiuxetan-BEAM	BEAM	ADC/radioimmunoconjugate	22 / 21	NR	0.53 (0.20 to 1.40)
Vose 2013 (BMT CTN 0401)	3; open-label	Chemotherapy-sensitive persistent or relapsed DLBCL	Iodine-131 tositumomab-BEAM	Rituximab-BEAM	ADC/radioimmunoconjugate	111 / 113	NR	1.02 (0.61 to 1.71)
Fayad 2015	2; double-blind	DLBCL relapsed after R-CHOP	Dacetuzumab + R-ICE	Placebo + R-ICE	Other antibody/cytokine	75 / 76	NR	NR
Czuczman 2017	2/3; open-label	R/R DLBCL after ≥2 prior therapies	Lenalidomide	Investigator's choice (gemcitabine, rituximab, etoposide or oxaliplatin)	IMiD	54 / 57	NR	NR
van Imhoff 2017 (ORCHARRD)	3; open-label	R/R CD20-positive DLBCL, transplant candidates	Ofatumumab-DHAP	Rituximab-DHAP	Other antibody/cytokine	222 / 225	NR	1.12 (0.89 to 1.41)
Kühnl 2020 (LEGEND)	2; open-label	R/R DLBCL, second line	Lenalidomide-R-GEM	Methylprednisolone-R-GEM	IMiD	18 / 16	NR	NR
Sehn 2020 (GO29365)	2; open-label	Transplant-ineligible R/R DLBCL	Polatuzumab vedotin + bendamustine-rituximab	Bendamustine-rituximab	ADC/radioimmunoconjugate	40 / 40	22.3	0.39 (0.23 to 0.66)
Bishop 2022 (BELINDA)	3; open-label	Aggressive B-cell lymphoma refractory to or progressing <=12 months after first-line therapy	Tisagenlecleucel	Salvage chemotherapy and autologous transplantation	CAR T cells	162 / 160	NR	1.07 (0.82 to 1.40) [EFS]
Kamdar 2022 (TRANSFORM)	3; open-label	LBCL refractory to or relapsed <=12 months after first-line therapy, transplant candidates	Lisocabtagene maraleucel	Salvage chemoimmunotherapy and autologous transplantation	CAR T cells	92 / 92	33.9	0.42 (0.28 to 0.64)
Locke 2022 (ZUMA-7)	3; open-label	LBCL refractory to or relapsed <=12 months after first-line therapy	Axicabtagene ciloleucel	Salvage chemoimmunotherapy and autologous transplantation	CAR T cells	180 / 179	47.2	0.51 (0.38 to 0.68)
Abramson 2024 (STARGLO)	3; open-label	Transplant-ineligible R/R DLBCL after ≥1 line	Glofitamab + GemOx	R-GemOx	Bispecific antibody	183 / 91	35.1	0.41 (0.29 to 0.58)
Song 2024	3; double-blind	Transplant-ineligible R/R DLBCL	Polatuzumab vedotin + bendamustine-rituximab	Placebo + bendamustine-rituximab	ADC/radioimmunoconjugate	28 / 14	7.5	0.50 (0.24 to 1.05)
Ahmed 2025	2; double-blind	R/R LBCL treated with CD19 CAR T cells	NKTR-255 after CAR T cells	Placebo	Other antibody/cytokine	11 / 4	NR	NR
Andreadis 2025 (A051301)	3; double-blind	R/R ABC-type DLBCL undergoing autologous transplantation	Ibrutinib with conditioning and as maintenance	Placebo	BTK inhibitor	39 / 38	30.4	0.54 (0.26 to 1.11)

Trial	Phase; blinding	Population	Novel-agent regimen	Standard regimen	Class	n (novel / standard)	FU (months)	PFS HR (95% CI)
Bartlett 2025 (ECHELON-3)	3; double-blind	R/R DLBCL after ≥2 lines, transplant-ineligible	Brentuximab vedotin + lenalidomide + rituximab	Placebo + lenalidomide + rituximab	ADC/radioimmunoconjugate	112 / 118	16.4	0.53 (0.38 to 0.73)
Budde 2025 (SUNMO)	3; open-label	Transplant-ineligible R/R LBCL	Mosunetuzumab + polatuzumab vedotin	R-GemOx	Bispecific antibody	138 / 70	23.2	0.41 (0.29 to 0.58)
Borchmann 2026 (DALY 2-EU)	2; open-label	Second-line LBCL ineligible for transplantation	Zamtocabtagene autoleucel	R-GemOx	CAR T cells	82 / 78	17	0.39 (0.27 to 0.57) [EFS]
Chavez 2026	2; open-label	R/R LBCL after ≥1 line	Mosunetuzumab + polatuzumab vedotin	Rituximab + polatuzumab vedotin	Bispecific antibody	40 / 40	NR	0.47 (0.22 to 1.00)
Matasar 2026 (POLARGO)	3; open-label	Transplant-ineligible R/R DLBCL	Polatuzumab vedotin + R-GemOx	R-GemOx	ADC/radioimmunoconjugate	129 / 126	24.6	0.37 (0.27 to 0.51)

Notes: Phase; blinding: trial phase and masking. n: randomized participants, novel-agent arm / standard arm, or the analyzed population where the hazard ratio came from a modified population (E1412, PYRAMID, A051301); the REMoDL-B hazard ratio came from the 801 patients with a molecular classification. FU, median follow-up in months of the report used for the time-to-event outcomes. PFS HR: hazard ratio for progression-free survival (novel versus standard; values below 1 favor the novel agent) with 95% CI; [EFS] or [DFS], event-free or disease-free survival used because progression-free survival was not reported; NR, not reported as a hazard ratio. ADC, antibody-drug conjugate; IMiD, immunomodulatory drug; LBCL, large B-cell lymphoma; HGBL, high-grade B-cell lymphoma; ABC, activated B-cell-like; GCB, germinal center B-cell-like; R/R, relapsed or refractory; aaIPI, age-adjusted International Prognostic Index; BEAM, carmustine, etoposide, cytarabine and melphalan; DHAP, dexamethasone, cytarabine and cisplatin; ICE, ifosfamide, carboplatin and etoposide; GemOx, gemcitabine and oxaliplatin; CHP, cyclophosphamide, doxorubicin and prednisone; R-CHOP, rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone); R-miniCHOP, R-CHOP at reduced doses; R-GEM, rituximab and gemcitabine; CAR, chimeric antigen receptor; BTK, Bruton tyrosine kinase; DLBCL, diffuse large B-cell lymphoma. Class labels are abbreviated: ADC/radioimmunoconjugate, antibody-drug or radioimmunoconjugate; Other antibody/cytokine, other antibody or cytokine immunotherapy; Other targeted, other targeted small molecule or anti-angiogenic antibody.

The first-line trials enrolled mainly patients with intermediate- or high-risk disease. Four were restricted to non-germinal center or activated B-cell-like lymphoma, one to double-expressor lymphoma and one to patients aged 80 years or older. The relapsed-setting trials ranged from transplant candidates with early relapse to heavily pretreated patients after two or more lines, and one tested a cytokine agonist as consolidation after CAR T-cell therapy. Median follow-up of the reports used ranged from 7.5 to 64.1 months; for seven trials a later follow-up or final report supplied the time-to-event outcomes.[15,17,67–72] The long-term follow-up of TRANSFORM reported the lisocabtagene maraleucel arm only.[73]

Progression-free survival was available as a hazard ratio for 32 trials. Of these, 5 contributed event-free or disease-free survival. The standard error was derived from a P value for 3, and the hazard ratio was estimated from landmark survival for 3 and one trial reported a 90% confidence interval. Six trials reported no time-to-event estimate and contributed complete response or adverse events only: SENIOR, Hainsworth 2016, Fayad 2015, Czuczman 2017, LEGEND and Ahmed 2025.[47,51,56,64–66]

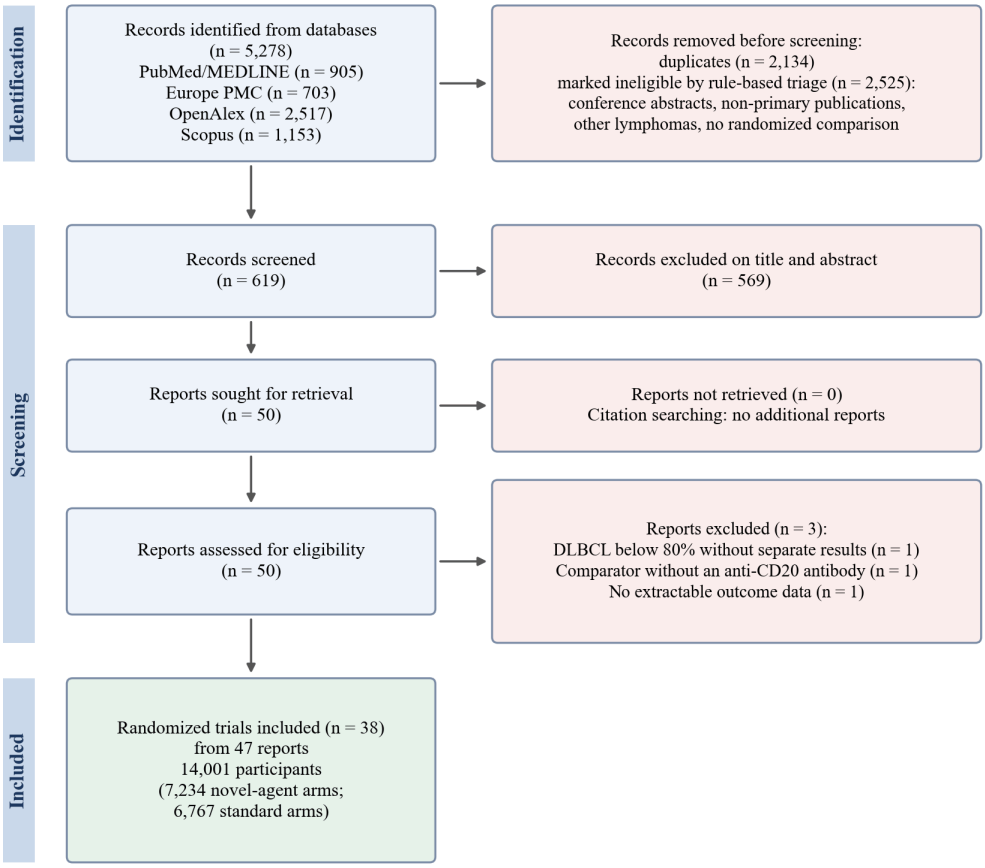


Figure 1. PRISMA 2020 flow diagram of the identification, screening and inclusion of randomized trials.

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3.3 Risk of bias

Twenty-one trials were at low risk of bias for progression-free survival and 17 raised some concerns; none was at high risk. Concerns arose mainly from investigator-assessed outcomes in open-label trials (measurement of the outcome). Other sources were exclusion of randomized patients from the efficacy analysis (missing outcome data) and hazard ratios that had to be estimated from secondary or landmark data (selection of the reported result), as illustrated in Figure 2. The reason for each judgment is given in Supplementary Table S2. Overall survival was measured objectively in all trials. Crossover in TRANSFORM and the frequent use of cellular therapy after progression in the standard arms of the transplant-eligible CAR T-cell trials could have diluted the survival effect.

3.4 Progression-free survival by treatment setting

The effect of novel agents on progression-free survival differed markedly by setting, as illustrated in Figure 3. In first-line induction the pooled hazard ratio was 0.84, 95% CI 0.76 to 0.94 (k=14; I^2=30.1%; prediction interval 0.67 to 1.06). The largest individual effects came from genotype-guided R-CHOP-X (HR 0.28, 95% CI 0.13 to 0.59), estimated from 2-year rates,[52] tafasitamab with lenalidomide (HR 0.75, 95% CI 0.59 to 0.96)[18] and polatuzumab-R-CHP (HR 0.77, 95% CI 0.62 to 0.96).[17] By contrast, obinutuzumab, ibrutinib, bortezomib and bevacizumab trials were close to no effect. Without GUIDANCE-01 the first-line estimate was 0.86, 95% CI 0.80 to 0.93 with no heterogeneity (I^2=0.0%), and in phase 3 first-line trials it was 0.87, 95% CI 0.80 to 0.95.

Maintenance after first-line therapy gave 0.84, 95% CI 0.58 to 1.23 (k=3), with lenalidomide the only agent that prolonged progression-free survival in an individual trial.[54] In relapsed or refractory disease the pooled hazard ratio was 0.54, 95% CI 0.44 to 0.68 (k=15; I^2=82.6%; prediction interval 0.21 to 1.40). The estimate was larger and homogeneous in transplant-ineligible or later-line trials (0.42, 95% CI 0.38 to 0.47; k=8; I^2=0.0%) than in transplant-eligible trials (0.72, 95% CI 0.48 to 1.07; k=7; I^2=82.4%; p for difference 0.002), where ZUMA-7 and TRANSFORM favored CAR T cells and BELINDA and ORCHARRD showed no benefit.[22,55,68,70]

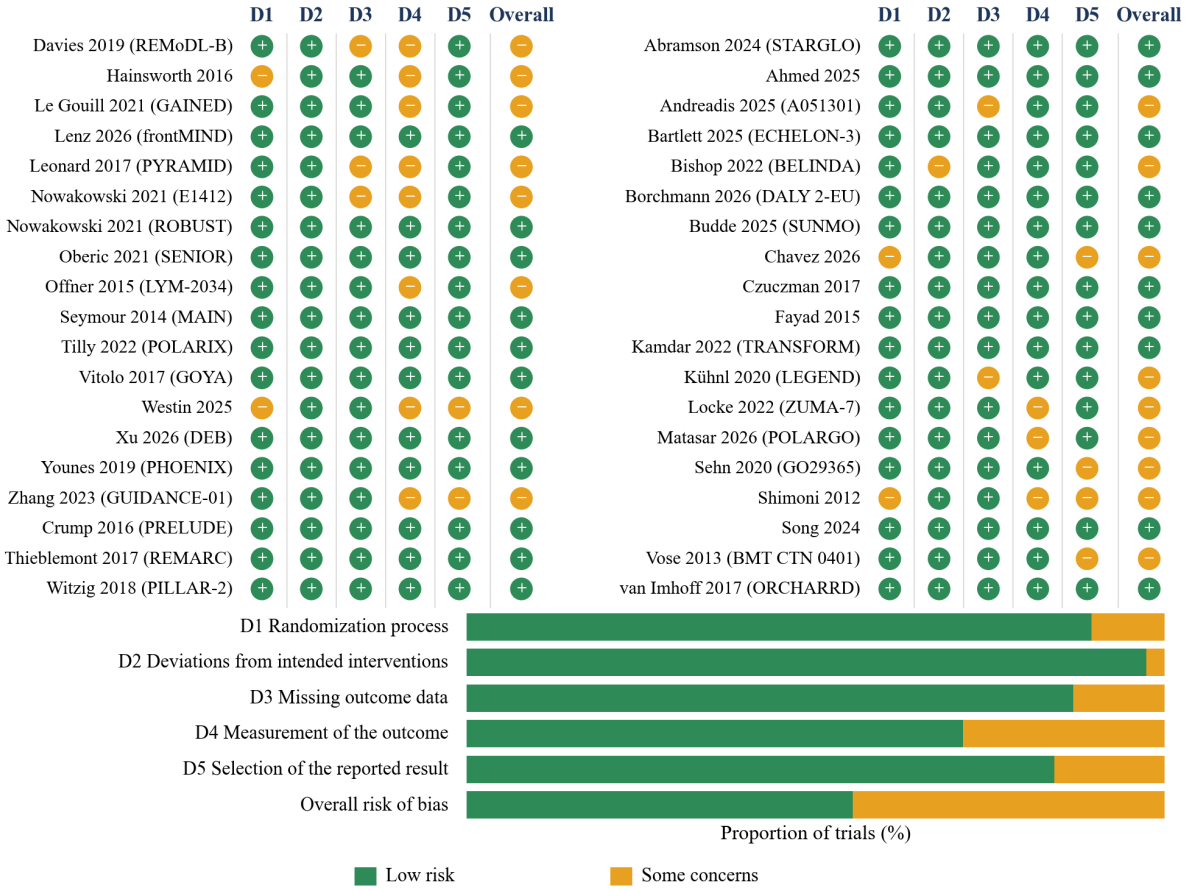


Figure 2. Risk of bias of the included trials for progression-free survival (RoB 2), grouped by treatment setting. Top: judgment for each domain and overall (green, low risk; amber, some concerns). Bottom: proportion of trials in each category. D1, randomization process; D2, deviations from the intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result.

Taken together, the 32 trials gave a pooled hazard ratio of 0.69, 95% CI 0.60 to 0.79 (I^2=77.3%; τ^2=0.087; prediction interval 0.37 to 1.28). Because this estimate averages agents, comparators and settings that are not clinically interchangeable, it is presented as a summary of a family of interventions rather than as the effect expected from any one regimen.

3.5 Effect modification and meta-regression

The treatment setting modified the effect (p for difference <0.001), whereas the mechanism did not: immunotherapies 0.66 (0.50 to 0.87) (k=12) and targeted therapies 0.72 (0.61 to 0.84) (k=20; p=0.55). Within each setting the two mechanisms gave similar estimates, as detailed in Table 3. The absence of a mechanism effect persisted when immunomodulatory drugs were classed as immunotherapy (immunotherapy 0.67, 95% CI 0.54 to 0.84; p for difference 0.74) and when the two dual-mechanism regimens were excluded (p=0.73).

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Table 3. Subgroup analyses and meta-regression for progression-free survival.

Analysis	*k*	HR (95% CI)	I^2 (%)
Treatment setting (*p* for difference <0.001)			
First-line induction	14	0.84 (0.76 to 0.94)	30.1
First-line maintenance	3	0.84 (0.58 to 1.23)	11.4
Relapsed or refractory	15	0.54 (0.44 to 0.68)	82.6
Mechanism (*p* for difference = 0.55)			
Immunotherapy	12	0.66 (0.50 to 0.87)	86.1
Targeted therapy	20	0.72 (0.61 to 0.84)	66.8
Setting and mechanism (*p* for difference <0.001)			
First-line induction: immunotherapy	4	0.88 (0.74 to 1.03)	0.0
First-line induction: targeted therapy	10	0.82 (0.68 to 0.98)	42.3
First-line maintenance: targeted therapy	3	0.84 (0.58 to 1.23)	11.4
Relapsed or refractory: immunotherapy	8	0.56 (0.38 to 0.81)	88.8
Relapsed or refractory: targeted therapy	7	0.51 (0.37 to 0.71)	48.8
Relapsed or refractory: transplant eligibility (*p* for difference = 0.002)			
Second line, transplant-eligible	7	0.72 (0.48 to 1.07)	82.4
Transplant-ineligible or later line	8	0.42 (0.38 to 0.47)	0.0
Drug class (*p* for difference <0.001)			
Bispecific T-cell engager	4	0.45 (0.27 to 0.77)	28.1
CAR T-cell therapy	4	0.55 (0.26 to 1.16)	88.8
Antibody-drug or radioimmunoconjugate	7	0.56 (0.40 to 0.79)	71.5
Immunomodulatory drug	3	0.75 (0.55 to 1.02)	0.0
BTK inhibitor	2	0.79 (0.04 to 16.61)	45.7
Other targeted small molecule or anti-angiogenic antibody	8	0.85 (0.67 to 1.09)	48.2
Other antibody or cytokine immunotherapy	4	0.91 (0.72 to 1.16)	47.8
Strategy (*p* for difference = 0.05)			
Substituted for a regimen component	9	0.83 (0.63 to 1.08)	71.8
Added to the standard regimen	15	0.65 (0.53 to 0.80)	72.0
Maintenance after first-line therapy	3	0.84 (0.58 to 1.23)	11.4
Replaced the standard regimen	5	0.52 (0.31 to 0.89)	87.2
Trial phase (*p* for difference = 0.09)			
Phase 3	23	0.73 (0.63 to 0.85)	79.3
Phase 2 or 2/3	9	0.55 (0.38 to 0.78)	47.7
Blinding (*p* for difference = 0.04)			
Open-label	20	0.63 (0.51 to 0.77)	83.3
Double-blind	12	0.80 (0.70 to 0.91)	41.7
Risk of bias (*p* for difference = 0.54)			
Low risk of bias	17	0.71 (0.59 to 0.86)	79.9
Some concerns	15	0.65 (0.52 to 0.83)	74.8
Meta-regression (ratio of hazard ratios)			
Relapsed or refractory vs first line; p = 0.001	32	0.67 (0.53 to 0.84)	R^2 29.3%
Immunotherapy vs targeted therapy; p = 0.60	32	0.93 (0.70 to 1.24)	R^2 0.0%
Setting × mechanism interaction; p = 0.90	32	1.03 (0.61 to 1.75)	R^2 26.0%
Publication year (per year); p<0.001	32	0.94 (0.92 to 0.97)	R^2 49.4%
Trial size (per log participant); p<0.001	32	1.31 (1.14 to 1.50)	R^2 47.3%
Median follow-up (per month); p = 0.010	22	1.01 (1.00 to 1.02)	R^2 19.1%

Notes: Hazard ratios for progression-free survival (novel versus standard) from random-effects models (DerSimonian–Laird, Hartung–Knapp) fitted within each subgroup; p for difference from the Cochran Q test between subgroups. Meta-regression: mixed-effects models with Knapp–Hartung tests; the ratio of hazard ratios expresses how much the hazard ratio changes per unit of the moderator; R^2, relative reduction in τ^2 compared with the model without moderators. Subgroups with k = 2 give wide intervals because the t distribution has one degree of freedom.

Drug classes differed (p<0.001), from bispecific T-cell engager regimens (0.45, 95% CI 0.27 to 0.77) and antibody-drug or radioimmunoconjugates (0.56, 95% CI 0.40 to 0.79) to other antibody or cytokine immunotherapies (0.91, 95% CI 0.72 to 1.16). Class and setting were closely linked, however, because bispecific and conjugate regimens were tested mainly in relapsed disease. Subgroups with two trials, such as the two BTK-inhibitor trials, had very wide intervals and are described only, as shown in Figure 4.

In univariable meta-regression, relapsed or refractory disease was associated with a lower hazard ratio than first-line therapy (ratio of hazard ratios 0.67, 95% CI 0.53 to 0.84; p=0.001; R^2=29.3%), with no interaction between setting and mechanism (p=0.90). Later publication year was also associated with larger effects (ratio 0.94 per year), and larger trials showed smaller effects (ratio 1.31 per log participant; p<0.001). After adjustment for publication year the setting remained associated with the effect (ratio 0.76, 95% CI 0.61 to 0.94; p=0.01), and mechanism remained unassociated (p=0.11). When trial size was added, the setting coefficient was attenuated (ratio 0.90; p=0.43), reflecting the strong correlation between setting, year and size.

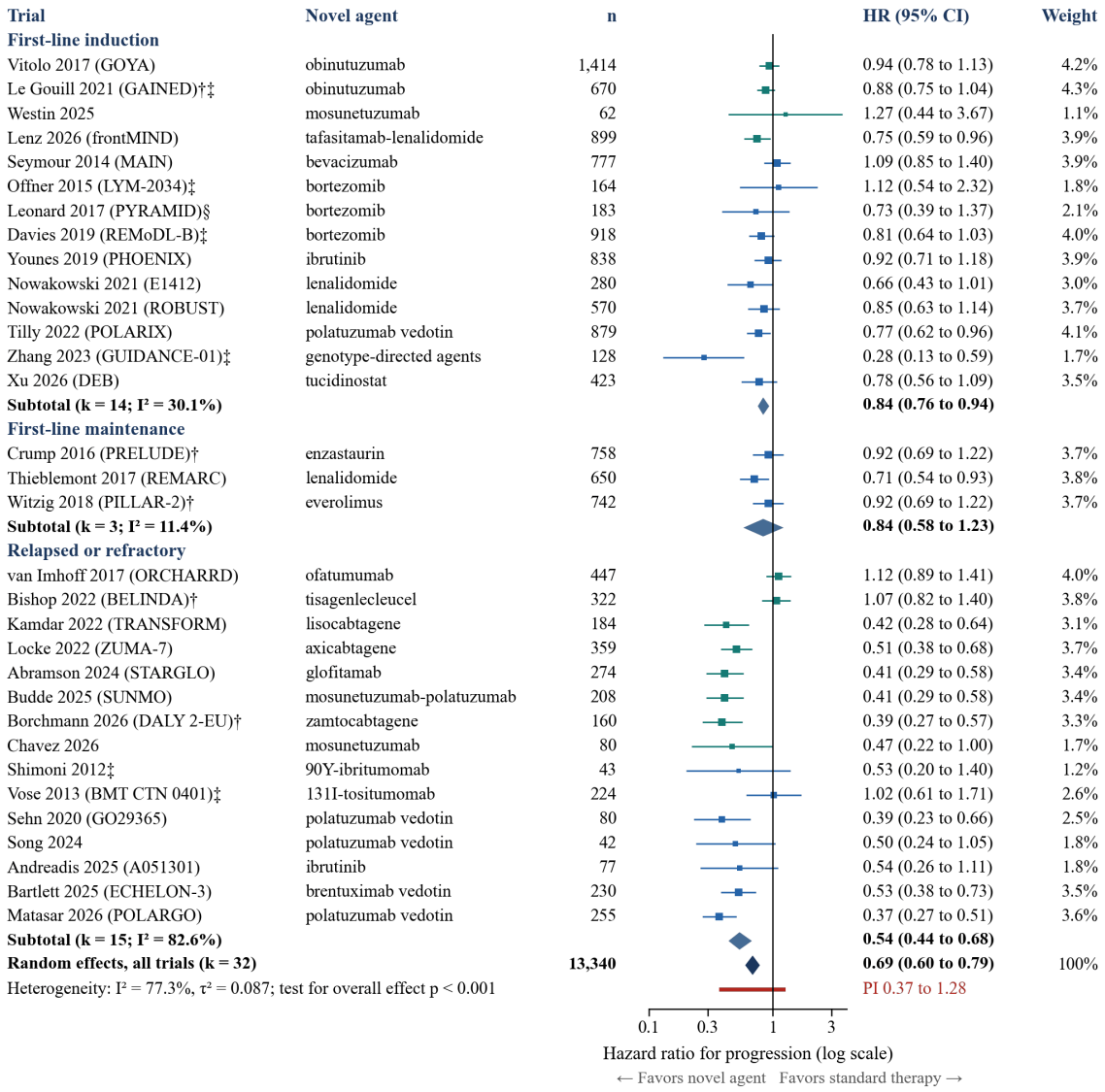
3.6 Sensitivity analyses and small-study effects

The pooled hazard ratio was stable across estimators and trial sets, ranging from 0.54 to 0.80, as detailed in Table 4. It was 0.67, 95% CI 0.58 to 0.79 without derived estimates, 0.66, 95% CI 0.57 to 0.77 without event-free or disease-free substitutes. It was 0.71, 95% CI 0.59 to 0.86 in trials at low risk of bias. Omitting single trials gave estimates between 0.68, without ORCHARRD,[55] and 0.71, without POLARGO.[29] In relapsed or refractory disease the estimate was 0.52, 95% CI 0.41 to 0.66 without the transplant-conditioning trials and 0.52, 95% CI 0.42 to 0.65 without event-free survival substitutes. Across all settings it was 0.69, 95% CI 0.59 to 0.79 without the transplant-conditioning trials and the trial of consolidation after CAR T-cell therapy.

Table 4. Sensitivity analyses for progression-free survival.

Analysis	*k*	HR (95% CI)	I^2 (%)
Primary model (DerSimonian–Laird, Hartung–Knapp)	32	0.69 (0.60 to 0.79)	77.3
Common-effect (inverse variance)	32	0.76 (0.72 to 0.80)	77.3
REML τ^2, Hartung–Knapp	32	0.69 (0.60 to 0.79)	77.3
Paule–Mandel τ^2, Hartung–Knapp	32	0.69 (0.60 to 0.79)	77.3
DerSimonian–Laird, Wald-type CI	32	0.69 (0.61 to 0.78)	77.3
Reported hazard ratios with CI only (derived estimates excluded)	26	0.67 (0.58 to 0.79)	79.7
Progression-free survival only (EFS/DFS substitutes excluded)	27	0.66 (0.57 to 0.77)	76.4
Low risk of bias only	17	0.71 (0.59 to 0.86)	79.9
Phase 3 trials only	23	0.73 (0.63 to 0.85)	79.3
Double-blind trials only	12	0.80 (0.70 to 0.91)	41.7
Trials with at least 100 participants	26	0.71 (0.61 to 0.83)	80.0
Leave-one-out: range of pooled HR (omitting van Imhoff 2017 (ORCHARRD) to omitting Matasar 2026 (POLARGO))	31	0.68 to 0.71	74.2–78.0
Trim-and-fill (9 trials imputed)	41	0.83 (0.70 to 0.98)	–

Notes: Pooled hazard ratio for progression-free survival under alternative estimators and trial sets. Derived estimates: standard errors obtained from P values or hazard ratios estimated from landmark survival (Equation 2). REML, restricted maximum likelihood.



Test for subgroup differences by setting: Q = 15.35, df = 2, p < 0.001. Teal, immunotherapy; blue, targeted therapy. † Event-free or disease-free survival (progression-free survival not reported). ‡ Standard error derived from the P value (or hazard ratio estimated from landmark survival and P value). § 90% confidence interval reported.

Figure 3. Forest plot of the hazard ratio (HR) for progression-free survival, novel-agent regimen versus standard therapy, grouped by treatment setting. Squares are trial estimates (area proportional to the random-effects weight; teal, immunotherapy; blue, targeted therapy) with 95% confidence intervals; diamonds are random-effects pooled estimates (DerSimonian–Laird, Hartung–Knapp) and the red bar the 95% prediction interval. n, randomized participants. † Event-free or disease-free survival. ‡ Standard error derived from the P value or hazard ratio estimated from landmark survival. § 90% confidence interval reported.

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The funnel plot was asymmetrical (Egger p=0.012), with smaller relapsed-setting trials showing larger effects, as illustrated in Figure 5. Within settings the Egger test was not significant (first-line induction p=0.25; relapsed or refractory p=0.18). This suggests that much of the overall asymmetry reflected the concentration of small trials in relapsed disease. Trim-and-fill imputed 9 trials and gave an adjusted hazard ratio of 0.83, 95% CI 0.70 to 0.98.

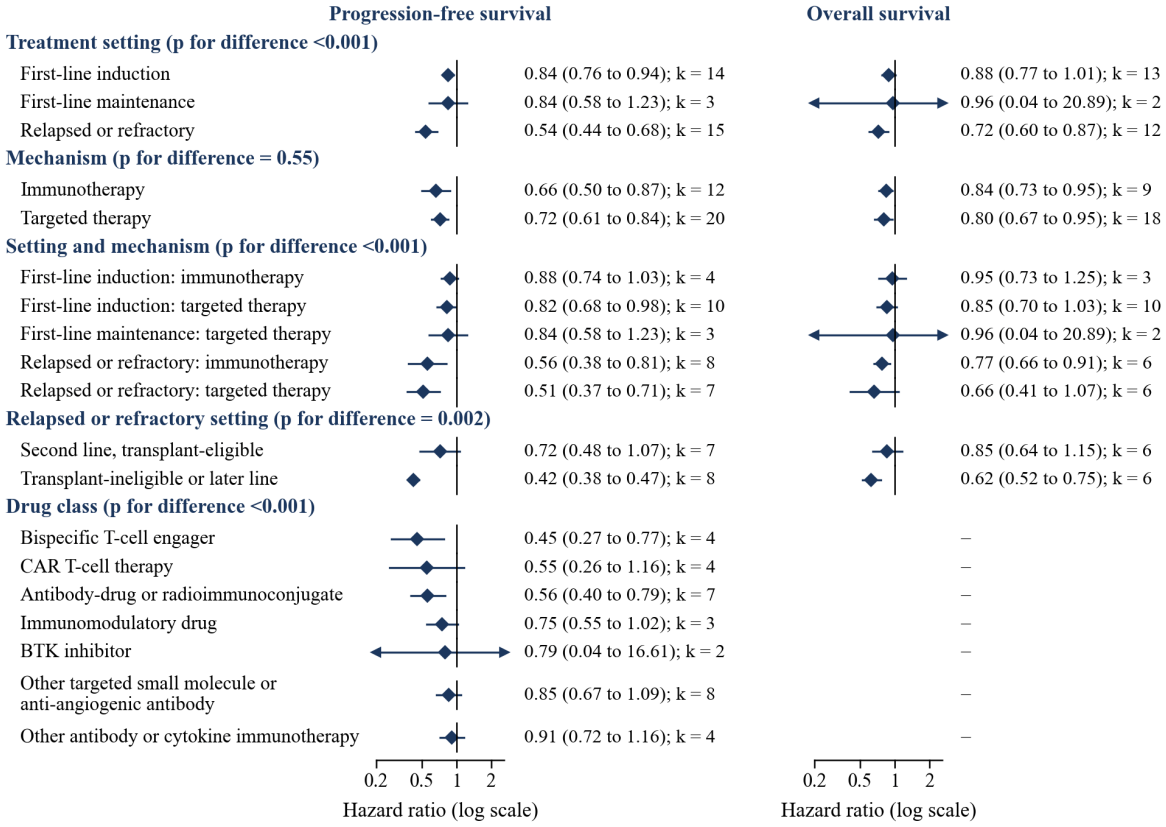


Figure 4. Subgroup estimates of the hazard ratio for progression-free survival (left) and overall survival (right) by treatment setting, mechanism, setting and mechanism combined, transplant eligibility in relapsed or refractory disease and drug class; p values test differences between subgroups for progression-free survival; k, number of trials. Subgroups with two trials have very wide Hartung–Knapp intervals (one degree of freedom) and are described only; drug classes are exploratory.

3.7 Overall survival

Twenty-seven trials (11,388 participants) reported overall survival. The hazard ratio was 0.72, 95% CI 0.60 to 0.87 in relapsed or refractory disease (k=12) and 0.88, 95% CI 0.77 to 1.01 in first-line induction (k=13; p for difference between settings 0.13), as illustrated in Figure 6. Across all trials it was 0.81, 95% CI 0.73 to 0.91 (I^2=42.2%; prediction interval 0.57 to 1.15). Excluding the trial with protocol crossover gave 0.81, 95% CI 0.72 to 0.91 overall and 0.72, 95% CI 0.59 to 0.88 in relapsed or refractory disease. TRANSFORM reported a crossover-adjusted hazard ratio of 0.566 (95% CI 0.359 to 0.895), lower than its unadjusted estimate of 0.757,[70] and survival data were interim in several trials reported most recently.[18,28]

Trial-level effects on progression-free and overall survival were strongly correlated (Spearman ρ=0.75; p<0.001). The slope was 0.55 when weighted by trial size and 0.51 (95% CI 0.32 to 0.70) when weighted by the precision of the survival estimate, as shown in Figure 7.

3.8 Complete response and adverse events

Complete response was more frequent with novel agents (RR 1.27, 95% CI 1.10 to 1.47; k=24). The increase was mainly in relapsed or refractory disease (RR 1.68) rather than in first-line induction (RR 1.05; p for difference <0.001). Grade ≥3 adverse events increased (RR 1.10, 95% CI 1.04 to 1.16; k=21), as did fatal adverse events (RR 1.34, 95% CI 1.08 to 1.66; k=17; I^2=0.0%), with no difference between settings or mechanisms, as shown in Figure 8. At the median risk in the standard arms (4.0%), this corresponds to about 14 additional fatal adverse events per 1000 patients (95% CI 3 to 26). The increases persisted when the analyses were restricted to trials using the review definitions (grade ≥3 RR 1.09, 95% CI 1.04 to 1.15; fatal RR 1.37, 95% CI 1.08 to 1.74). Two trials with no fatal event in one arm contributed with the 0.5 continuity correction. Trial-level counts are given in Supplementary Table S4.

3.9 Certainty of evidence

Certainty was moderate for progression-free survival within first-line induction and within relapsed or refractory disease, and low for the summary across all settings because of inconsistency and small-study effects. For overall survival it was moderate in relapsed or refractory disease and low in first-line induction, where the confidence interval included no effect. Certainty was moderate for grade ≥3 and fatal adverse events and very low for complete response, whose heterogeneity was explained largely by setting, as summarized in Table 5.

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Table 5. Summary of findings: novel targeted therapies and immunotherapies versus standard therapy in diffuse large B-cell lymphoma.

Outcome	*k*	Participants	Relative effect (95% CI)	Standard vs novel per 1000 (difference; 95% CI)	Certainty	Reasons for rating down
Progression-free survival, all settings	32	13,340	HR 0.69 (0.60 to 0.79)	–	Low	Inconsistency (I^2 77.3%; prediction interval includes no effect); possible small-study effects (Egger p=0.012)
Progression-free survival, first-line induction	14	8,205	HR 0.84 (0.76 to 0.94)	–	Moderate	Inconsistency (I^2 30.1%; prediction interval includes no effect)
Progression-free survival, first-line maintenance	3	2,150	HR 0.84 (0.58 to 1.23)	–	Moderate	Imprecision (95% CI includes no effect)
Progression-free survival, relapsed or refractory	15	2,985	HR 0.54 (0.44 to 0.68)	–	Moderate	Inconsistency (I^2 82.6%; prediction interval includes no effect)
Overall survival, all settings	27	11,388	HR 0.81 (0.73 to 0.91)	–	Low	Inconsistency (I^2 42.2%; prediction interval includes no effect); possible small-study effects (Egger p=0.023)
Overall survival, first-line induction	13	7,535	HR 0.88 (0.77 to 1.01)	–	Low	Imprecision (95% CI includes no effect); possible small-study effects (Egger p=0.048)
Overall survival, relapsed or refractory	12	2,461	HR 0.72 (0.60 to 0.87)	–	Moderate	Inconsistency (I^2 43.9%; prediction interval includes no effect)
Complete response	24	7,298	RR 1.27 (1.10 to 1.47)	425 vs 538 per 1000 (+113; +40 to +198)	Very low	Very serious inconsistency (I^2 80.2%, effects in both directions); possible small-study effects (Egger p=0.003)
Grade ≥3 adverse events	21	8,164	RR 1.10 (1.04 to 1.16)	726 vs 797 per 1000 (+71; +28 to +117)	Moderate	Inconsistency (I^2 61.8%; prediction interval includes no effect)
Fatal adverse events	17	6,898	RR 1.34 (1.08 to 1.66)	40 vs 54 per 1000 (+14; +3 to +26)	Moderate	Indirectness (grade 5 adverse events and treatment-related deaths combined)

Notes: Certainty assessed with Core GRADE (randomized trials start at high certainty). Absolute effects for binary outcomes use the median risk in the standard arms (per 1000 patients; Equation 9). HR, hazard ratio; RR, risk ratio; I^2, between-trial heterogeneity.

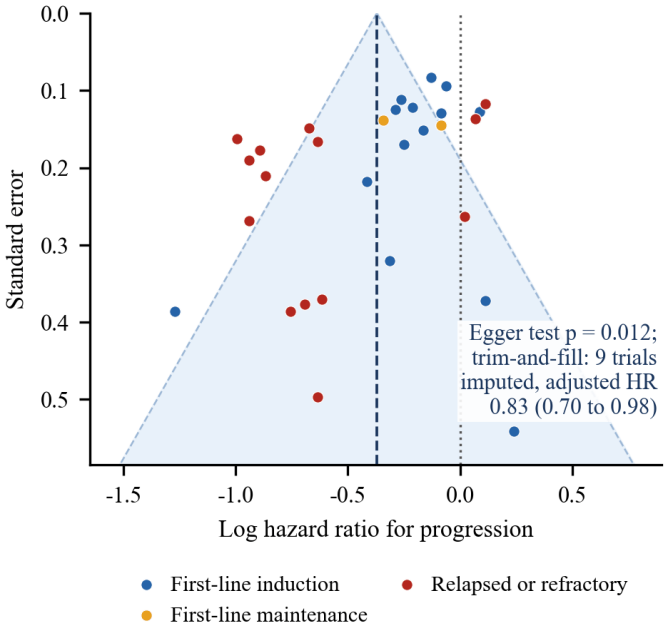


Figure 5. Funnel plot of trial log hazard ratios for progression-free survival against their standard errors, colored by treatment setting. The dashed line marks the pooled estimate, the dotted line no difference and the shaded region the pseudo 95% confidence limits.

4. Discussion

4.1 Principal findings

This meta-analysis of 38 randomized trials found that the benefit of adding or substituting a targeted therapy or an immunotherapy in DLBCL differed between lines of treatment. In relapsed or refractory disease, novel-agent regimens reduced the hazard of progression by almost half (HR 0.54) and the hazard of death by more than a quarter (HR 0.72). The effect was largest and most consistent in patients who could not undergo transplantation (HR 0.42). First-line induction behaved differently. The reduction in the hazard of progression was modest (HR 0.84), and the effect on overall survival was not statistically significant (HR 0.88). Within a setting, it made no measurable difference whether the agent engaged immune effector cells or targeted a tumor pathway, and this held under alternative classifications. More grade ≥3 and fatal adverse events accompanied the gains, and the increase was similar across settings and mechanisms.

4.2 Comparison with previous evidence

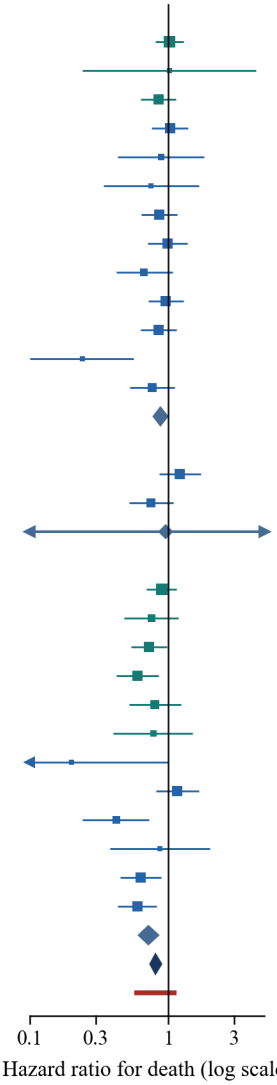
Earlier meta-analyses reached compatible conclusions within single settings. A synthesis of 21 first-line trials found that few modifications of R-CHOP improved survival,[34] although it also included chemotherapy intensification and rituximab-schedule trials, which were not eligible here because they do not test a novel agent. A network meta-analysis of maintenance found no survival benefit.[35] Analyses of second-line CAR T cells and network comparisons of systemic therapies for relapsed disease favored cellular therapy and bispecific or antibody-drug conjugate combinations over salvage chemotherapy.[36,37] Those network analyses compared regimens with each other within relapsed disease. They did not test whether the relative benefit of novel agents differs between first-line and relapsed settings or between mechanisms. That is the question addressed here. The

present analysis adds the phase 3 trials reported most recently, namely frontMIND, DEB, POLARGO, SUNMO and the randomized zamtocabtagene trial,[18,19,28,29,60] and uses the mature follow-up of POLARIX, TRANSFORM, ZUMA-7 and STARGLO,[17,68,70,71] so that all settings are placed on one scale and their difference is estimated rather than inferred.

4.3 First-line therapy: a ceiling effect and the role of biology

A modest first-line effect is plausible. R-CHOP cures most patients, so an added agent can act only on the minority destined to relapse, and its effect is diluted across the whole trial population. Without the small genotype-guided trial, the first-line estimate was HR 0.86 with no heterogeneity, and in phase 3 trials it was HR 0.87. The benefit was therefore carried mainly by polatuzumab substitution and by tafasitamab with lenalidomide, not by the class as a whole.[17,18] The strongest first-line signals came from trials that enriched for biology or risk. These were genotype-guided R-CHOP-X, tucidinostat in double-expressor lymphoma, and the activated B-cell-like and molecular high-grade subgroups of REMoDL-B.[15,19,52] The benefit of ibrutinib in younger patients with MCD and N1 genetic subtypes shows both the promise and the limits of this approach.[8,14] Population-based profiling found a double-hit gene-expression signature in about a fifth of germinal center B-cell-like tumors,[3] a group in which enrichment designs could test whether targeted additions overcome the poor results of standard therapy.

Age modified both benefit and harm. In PHOENIX, ibrutinib improved event-free, progression-free and overall survival in patients younger than 60 years but worsened all three in older patients, in whom it reduced the delivery of R-CHOP and increased serious adverse events.[8] In SENIOR, lenalidomide added to R-miniCHOP did not improve survival in patients aged 80 years or older. Grade 3–4 adverse events rose from 53% to 81%.[47] Attenuated chemotherapy is already a compromise in older and frail patients, as population-based data show,[4,5] so the margin for added toxicity is narrow in the patients who make up much of the DLBCL population in Indonesia and elsewhere.



Trial	Novel agent	n	HR (95% CI)	Weight
First-line induction				
Vitolo 2017 (GOYA)	obinutuzumab	1,414	1.02 (0.81 to 1.29)	6.4%
Westin 2025	mosunetuzumab	62	1.02 (0.24 to 4.32)	0.5%
Lenz 2026 (frontMIND)	tafasitamab-lenalidomide	899	0.85 (0.63 to 1.14)	5.3%
Seymour 2014 (MAIN)	bevacizumab	777	1.03 (0.76 to 1.40)	5.1%
Offner 2015 (LYM-2034)‡	bortezomib	164	0.89 (0.43 to 1.82)	1.6%
Leonard 2017 (PYRAMID)§	bortezomib	183	0.75 (0.34 to 1.67)	1.4%
Davies 2019 (REMoDL-B)‡	bortezomib	918	0.86 (0.64 to 1.16)	5.3%
Younes 2019 (PHOENIX)	ibrutinib	838	0.99 (0.71 to 1.38)	4.7%
Nowakowski 2021 (E1412)‡	lenalidomide	280	0.67 (0.42 to 1.08)	3.1%
Nowakowski 2021 (ROBUST)	lenalidomide	570	0.96 (0.72 to 1.30)	5.3%
Tilly 2022 (POLARIX)	polatuzumab vedotin	879	0.85 (0.63 to 1.15)	5.2%
Zhang 2023 (GUIDANCE-01)‡	genotype-directed agents	128	0.24 (0.10 to 0.56)	1.2%
Xu 2026 (DEB)	tucidinostat	423	0.77 (0.53 to 1.12)	4.1%
Subtotal (k = 13; I² = 16.6%)			**0.88 (0.77 to 1.01)**	
First-line maintenance				
Thieblemont 2017 (REMARC)	lenalidomide	650	1.22 (0.86 to 1.72)	4.5%
Witzig 2018 (PILLAR-2)	everolimus	742	0.75 (0.52 to 1.09)	4.2%
Subtotal (k = 2; I² = 71.6%)			**0.96 (0.04 to 20.89)**	
Relapsed or refractory				
van Imhoff 2017 (ORCHARRD)	ofatumumab	447	0.90 (0.70 to 1.15)	6.1%
Kamdar 2022 (TRANSFORM)	lisocabtagene	184	0.76 (0.48 to 1.19)	3.2%
Locke 2022 (ZUMA-7)	axicabtagene	359	0.73 (0.54 to 0.98)	5.3%
Abramson 2024 (STARGLO)	glofitamab	274	0.60 (0.42 to 0.85)	4.4%
Budde 2025 (SUNMO)	mosunetuzumab-polatuzumab	208	0.80 (0.52 to 1.24)	3.4%
Chavez 2026	mosunetuzumab	80	0.78 (0.40 to 1.51)	1.8%
Shimoni 2012‡	90Y-ibritumomab	43	0.20 (0.04 to 1.00)	0.4%
Vose 2013 (BMT CTN 0401)‡	131I-tositumomab	224	1.17 (0.82 to 1.67)	4.4%
Sehn 2020 (GO29365)	polatuzumab vedotin	80	0.42 (0.24 to 0.73)	2.4%
Andreadis 2025 (A051301)	ibrutinib	77	0.87 (0.38 to 2.00)	1.3%
Bartlett 2025 (ECHELON-3)	brentuximab vedotin	230	0.63 (0.45 to 0.89)	4.6%
Matasar 2026 (POLARGO)	polatuzumab vedotin	255	0.60 (0.43 to 0.83)	4.8%
Subtotal (k = 12; I² = 43.9%)			**0.72 (0.60 to 0.87)**	
Random effects, all trials (k = 27)		**11,388**	**0.81 (0.73 to 0.91)**	100%
Heterogeneity: I² = 42.2%, τ² = 0.027; test for overall effect p < 0.001			PI 0.57 to 1.15	

Test for subgroup differences by setting: Q = 4.06, df = 2, p = 0.13. Teal, immunotherapy; blue, targeted therapy. ‡ Standard error derived from the P value (or hazard ratio estimated from landmark survival and P value). § 90% confidence interval reported. The two-trial subtotal (k = 2) is shown as an interval running past the axis.

Figure 6. Forest plot of the hazard ratio for overall survival, novel-agent regimen versus standard therapy, grouped by treatment setting; layout and symbols as in Figure 3.

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4.4 Relapsed or refractory disease: weak comparators and non-cross-resistant mechanisms

Comparators are weak in relapsed disease. In a recent cohort treated in community practice, R-GemOx produced complete responses in about a fifth of patients,[74] and many patients die before they can receive later-line therapy.[6] Agents whose mechanisms are not cross-resistant with chemotherapy, such as T-cell redirection by CAR T cells and bispecific antibodies or antibody-delivered cytotoxic payloads, therefore produce larger relative effects. The homogeneity of the transplant-ineligible trials is notable. Glofitamab and mosunetuzumab-based regimens, polatuzumab and brentuximab combinations and zamtocabtagene all reduced the hazard of progression by roughly half or more compared with chemoimmunotherapy alone.[28–30,60,61,71,72]

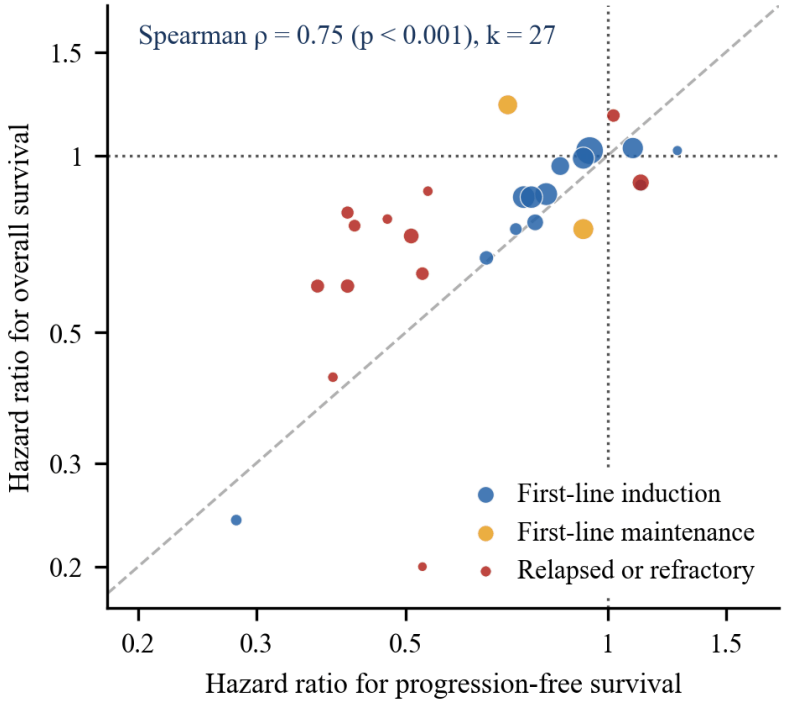


Figure 7. Trial-level hazard ratios for progression-free survival and overall survival (log scales). Circle area is proportional to trial size; the dashed diagonal marks equal effects on both end points.

The transplant-eligible trials were more heterogeneous, and the differences among the three CAR T-cell trials are informative. BELINDA stands apart. The median interval from leukapheresis to infusion was 52 days, bridging chemotherapy was frequent, the tisagenlecleucel arm included more high-grade lymphoma (24.1% versus 16.9%) and a quarter of its patients had progressed by week 6; event-free survival also counted stable disease at or after the week-12 assessment as an event.[22] ZUMA-7 and TRANSFORM, by contrast, showed large benefits.[20,69] These features of BELINDA, rather than the CAR T-cell mechanism itself, explain most of the inconsistency in this subgroup. In ORCHARRD, replacing rituximab with ofatumumab did not overcome rituximab refractoriness. A new antibody against the same antigen is not a new mechanism in this setting.[55]

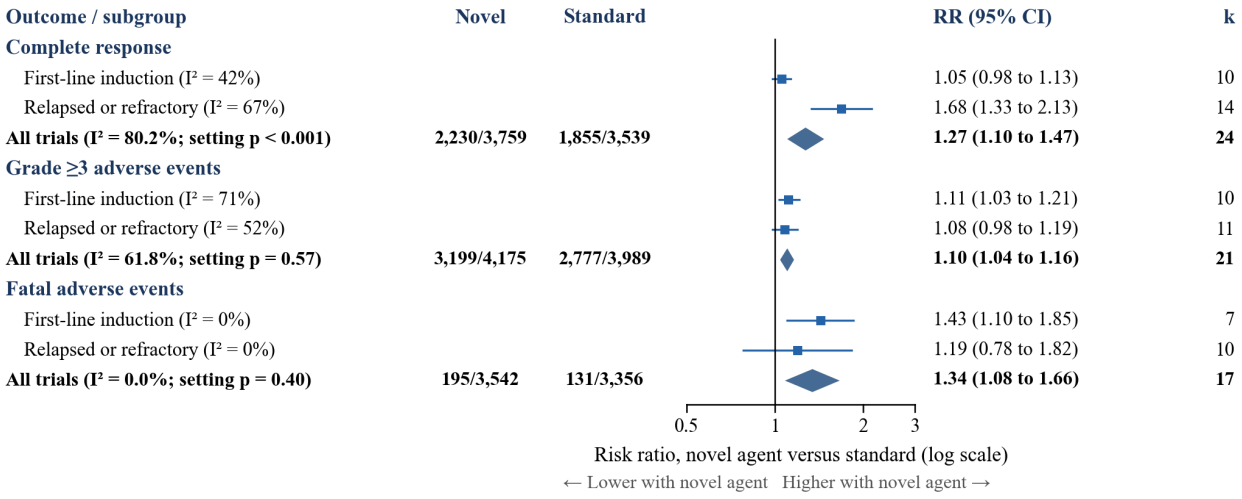


Figure 8. Pooled risk ratios (RR, log scale) for complete response, grade ≥3 adverse events and fatal adverse events, overall and by treatment setting; counts are events/participants; k, number of trials.

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4.5 Why the mechanism did not matter

The absence of a mechanism effect should not be read as evidence that all novel agents are equivalent. Within a setting, effective and ineffective agents existed in both mechanistic groups. In first-line therapy, polatuzumab and tafasitamab with lenalidomide helped, whereas obinutuzumab, ibrutinib and bevacizumab did not. In relapsed disease, CAR T cells, bispecific antibodies and antibody-drug conjugates all improved outcomes over chemotherapy. The credibility of the setting effect is moderate. It was pre-specified, large, consistent across sensitivity analyses and biologically plausible, and it persisted after adjustment for publication year (ratio of hazard ratios 0.76), but it rests on comparisons between trials and was attenuated when trial size was added (ratio 0.90), because setting, era and size were closely correlated. Comparisons between drug classes are exploratory.

4.6 Survival, response and toxicity

The effect on overall survival was smaller than that on progression-free survival. This is expected when effective subsequent therapies, including crossover to CAR T cells, are available after progression. Trial-level effects on the two end points were correlated, and the slope of about one half indicates that survival gains were roughly half the size of progression-free gains on the log scale; this descriptive association does not validate progression-free survival as a surrogate. Complete response followed the pattern of progression-free survival and increased substantially only in relapsed disease. The increase in fatal adverse events was consistent across settings and mechanisms, with no heterogeneity, and was attributed in the source reports mainly to infections with anti-CD20 antibody substitution and with polatuzumab and bispecific combinations, and to the toxicity of ibrutinib and lenalidomide in older patients.[8,29,47,67,71] With a baseline risk of about 4%, the absolute excess was small. In first-line therapy, however, it is of the same order as the absolute survival gain and should be part of shared decisions.

4.7 Heterogeneity and small-study effects

Setting explained about 29% of the between-trial variance in progression-free survival. Residual heterogeneity reflected differences between agents within a setting, the use of event-free or disease-free survival in five trials and the composite design of some regimens. Funnel-plot asymmetry was not apparent within settings. This suggests that it arose largely because small trials were concentrated in relapsed disease, where effects may genuinely be larger: small phase 2 trials of polatuzumab and of mosunetuzumab-based regimens were later confirmed by larger phase 3 trials.[28,29,61,72] Trim-and-fill, which assumes that asymmetry is due to missing studies, attenuated the summary estimate. This uncertainty was carried into the certainty ratings.

4.8 Strengths and limitations

This review has clear strengths. It is restricted to randomized comparisons with a contemporary standard arm, includes 38 trials and more than 14,000 participants, and uses the most mature follow-up. It also offers pre-specified tests of setting and mechanism with multivariable meta-regression, conservative Hartung–Knapp intervals, extensive sensitivity analyses and graded certainty.

Several limitations apply. First, the agents and comparators were clinically diverse, so the summary across settings describes a family of interventions rather than the effect of any single drug. Second, Embase and Cochrane CENTRAL were not searched and trials reported only as conference abstracts were not eligible, so phase 3 trials still awaiting full publication are missing. Third, the analysis used aggregate data, and patient-level modifiers such as age, cell of origin and timing of relapse could not be examined directly. Fourth, five trials used event-free or disease-free survival in place of progression-free survival, hazard ratios were derived for six, and four trials analyzed modified populations, although excluding these trials did not change the conclusions. Fifth, many trials were open-label with investigator-assessed outcomes. Sixth, crossover and subsequent therapies affected overall survival, which was immature in the trials reported most recently. Seventh, toxicity definitions differed between trials. Eighth, one reviewer screened the records and a second verified all extracted data, rather than both working in full duplicate. Finally, two transplant-conditioning trials and a 15-patient trial of consolidation after CAR T cells are atypical, but excluding them did not change the estimates, and very few participants came from South-East Asia.

4.9 Implications for practice and research

For patients with relapsed or refractory DLBCL who are not candidates for transplantation, the consistent benefit of adding a bispecific antibody, an antibody-drug conjugate or another novel agent to chemoimmunotherapy supports considering these combinations as options where they are available. Access to CAR T-cell therapy is limited even in high-income systems, and its value depends on national prices and pathways.[38,39] In Indonesia and comparable settings, these off-the-shelf combinations therefore deserve consideration in national formularies and access programs. Their availability and cost in the region were not assessed in this review. In first-line therapy, the small average gain and the increase in fatal adverse events (RR 1.34) argue for selecting patients by risk and biology rather than adding agents broadly, and for particular caution in older patients.[8,47] Future trials should enrich for biological subgroups, report toxicity with uniform definitions, include patients from Asia and other under-represented regions, and use overall survival or adequately validated surrogate end points. Less restrictive eligibility criteria would make their results more applicable to routine practice.[31]

Translating these findings into practice also requires attention to patients treated outside trials. In a multicenter cohort receiving commercial bispecific antibodies, most patients would have been ineligible for the pivotal trials, and responses and progression-free survival were lower than in those trials.[31] Relapse after second-line CAR T cells occurred in a third of patients in a national cohort and was difficult to salvage.[33] The randomized estimates are therefore likely to represent the upper range of what services new to these agents can expect. For hematologists in Indonesia, the practical implications are clear. Access should be prioritized for agents that have shown benefit in randomized trials for transplant-ineligible patients. Early referral pathways should be built where cellular therapy becomes available. The small average gain and the increase in fatal adverse events argue against adding novel agents to first-line therapy outside selected high-risk or biologically defined groups; cost was not assessed in this review.

5. Conclusion

In adults with diffuse large B-cell lymphoma, regimens containing targeted therapies or immunotherapies improved progression-free survival compared with the standard therapy of the same setting, but the size of the benefit differed between lines of treatment rather than between mechanisms of action. In relapsed or refractory disease, the hazard of progression fell by almost half and the hazard of death by more than a quarter. The largest and most consistent effects were in patients who were not candidates for transplantation. The certainty of this evidence was moderate. In first-line induction the reduction in the hazard of progression was modest, was carried mainly by polatuzumab substitution and tafasitamab with lenalidomide, and did not translate into a statistically significant survival benefit. Maintenance strategies showed no clear benefit (progression-free survival

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HR 0.84, 95% CI 0.58 to 1.23; overall survival was reported in two trials only, HR 0.96, 95% CI 0.04 to 20.89). Immunotherapies and targeted therapies did not differ significantly within each setting (p=0.55 overall). This may suggest that the strength of the standard comparator and the biology of the disease at each stage matter more than the class of drug, a hypothesis these data cannot test.

These gains came with more grade ≥3 and fatal adverse events in all settings. For clinical practice, the findings support novel-agent combinations, including bispecific antibodies and antibody-drug conjugates, as options to consider in relapsed or refractory disease, particularly where cellular therapy is unavailable. In first-line therapy they support selective use of novel agents, guided by biology and age. Future trials should be designed around biological subgroups, report toxicity uniformly, use overall survival or validated surrogate end points, and enroll patients from Asia and other under-represented regions.

Declarations

Ethics approval and consent to participate

Not applicable; this review analyzed published aggregate data.

Consent for publication

Not applicable. This study analyzed only previously published aggregate data and contains no individual person's data.

Use of artificial intelligence

None.

Author contributions

I.P.H.M.: Conceptualization, Methodology, Software, Investigation, Data curation, Formal analysis, Visualization, Writing – original draft. K.S.: Conceptualization, Validation, Supervision, Writing – review & editing. Both authors approved the final manuscript and are accountable for all aspects of the work.

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Conflict of interest

The authors declare no competing interests.

Data availability

All data analyzed were extracted from published reports.

Reporting guideline

This review followed PRISMA 2020; the completed checklist is provided as supplementary material.

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None.

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