International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Network meta-analysis of first-line R-CHOP-based regimens in MYC/BCL2 double-expressor diffuse large B-cell lymphoma

INPLASY202630036

doi: 10.37766/inplasy2026.3.0036

Received: 10 March 2026

Published: 10 March 2026

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ADMINISTRATIVE INFORMATION

Support - This work was supported by grant No. 82260042 from the National Natural Science Foundation of China (C.L.); by grant 2018GXNSFBA281026 from the Natural Science Foundation of Guangxi Zhuang Autonomous Region (C.L.); by grant No. 2024GXNSFAA010016 from the Natural Science Foundation of Guangxi Zhuang Autonomous Region (C.L.); and by the First-class Discipline Innovation-Driven Talent Program of Guangxi Medical University (C.L.).

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202630036

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 March 2026 and was last updated on 10 March 2026.

INTRODUCTION

Review question / Objective To compare the relative efficacy and safety of novel R-CHOP-based regimens (Pola-R-CHP, Ven-R-CHOP, VR-CHOP, CR-CHOP) versus standard R-CHOP in treatment-naive patients with MYC/BCL2 double-expressor diffuse large B-cell lymphoma (DEL) using a frequentist network meta-analysis framework, with the aim of informing evidence-based first-line treatment selection for this high-risk population.

Rationale Double-expressor lymphoma (DEL), defined by concurrent immunohistochemical overexpression of MYC (≥40%) and BCL2 (≥50%) without gene rearrangements, accounts for 20–30% of newly diagnosed DLBCL and is associated with inferior outcomes with standard R-CHOP. Several phase 2/3 trials have evaluated novel R-CHOP-based regimens in DLBCL with DEL subgroup analyses reported (POLARIX, CAVALLI, DEB, REMoDL-B). However, no head-to-head trials directly compare these novel regimens specifically in DEL patients, and no existing network meta-analysis has focused exclusively on the DEL population. This review addresses this evidence gap by synthesizing subgroup-level data from landmark trials using network meta-analysis.

Condition being studied Double-expressor lymphoma (DEL) is a clinically distinct subtype of diffuse large B-cell lymphoma (DLBCL) characterized by concurrent immunohistochemical overexpression of MYC (≥40%) and BCL2 (≥50%) proteins without corresponding gene rearrangements. DEL accounts for 20–30% of newly diagnosed DLBCL cases and confers

significantly inferior outcomes compared to non-DEL DLBCL when treated with standard R-CHOP immunochemotherapy.

METHODS

Search strategy PubMed, EMBASE, Cochrane Library, and Web of Science were searched from database inception through December 2025. Search terms included: "diffuse large B-cell lymphoma," "double-expressor," "MYC," "BCL2," "R-CHOP," "polatuzumab vedotin," "venetoclax," "bortezomib," "tucidinostat," "chidamide," combined using Boolean operators. Conference abstracts from ASH and EHA annual meetings (2020–2024) were hand-searched. The search strategy was reviewed by a medical librarian.

Participant or population Treatment-naive adult patients with diffuse large B-cell lymphoma (DLBCL) who meet criteria for double-expressor lymphoma (DEL), defined as concurrent immunohistochemical overexpression of MYC (≥40%) and BCL2 (≥50%) without MYC and/or BCL2 gene rearrangements, as per WHO 2016 classification criteria.

Intervention Novel R-CHOP-based regimens: (1) Polatuzumab vedotin plus R-CHP (Pola-R-CHP); (2) Venetoclax plus R-CHOP (Ven-R-CHOP); (3) Bortezomib plus R-CHOP (VR-CHOP); (4) Tucidinostat (chidamide) plus R-CHOP (CR-CHOP).

Comparator Standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), used as the common comparator in the network meta-analysis.

Study designs to be included Randomized controlled trials (RCTs) and prospective interventional studies with concurrent or historical controls reporting DEL subgroup data.Randomised controlled trials (RCTs), primarily phase III clinical trials.

Eligibility criteria Inclusion: (1) RCTs or prospective interventional studies with concurrent/historical controls; (2) treatment-naive DLBCL patients with DEL subgroup data; (3) R-CHOP or modified R-CHOP interventions; (4) HRs with 95% CIs reported or extractable for PFS/OS; (5) minimum 12-month follow-up.
Exclusion: (1) observational studies without controls, case reports, case series; (2) relapsed/refractory DLBCL; (3) inability to extract DEL subgroup survival data; (4) duplicate publications; (5) non-English and non-Chinese publications.

Information sources PubMed, EMBASE, Cochrane Library, Web of Science. Hand-searching of conference abstracts from American Society of Hematology (ASH) and European Hematology Association (EHA) annual meetings (2020–2024). Reference lists of included studies and relevant systematic reviews.

Main outcome(s) Primary outcomes: (1) Progression-free survival (PFS), measured as hazard ratio (HR) with 95% confidence interval; (2) Overall survival (OS), measured as HR with 95% CI. Treatment rankings determined using SUCRA and P-scores.

Additional outcome(s) Secondary outcomes: Grade 3–4 adverse events from intention-to-treat populations, including thrombocytopenia, neutropenia, anemia, pneumonia, peripheral neuropathy, and treatment-related mortality, measured as odds ratios (ORs) with 95% CIs.

Data management Two independent investigators extracted data using standardized forms. Hazard ratios were extracted directly from publications or estimated from Kaplan-Meier curves using the Tierney method. Discrepancies were resolved by consensus or third-party adjudication.

Quality assessment / Risk of bias analysis Risk of bias was assessed using the Cochrane RoB 2 tool for randomized controlled trials. Evidence quality was rated using the GRADE framework adapted for network meta-analysis.

Strategy of data synthesis Frequentist random-effects network meta-analysis using the netmeta package in R (version 4.3.2). HRs were log-transformed; between-study heterogeneity estimated using restricted maximum likelihood. Supplementary Bayesian NMA performed with uninformative and informative priors. SUCRA used for treatment ranking. Safety NMA performed using odds ratios from ITT population data.

Subgroup analysis Subgroup analyses were not applicable due to the limited number of eligible studies (n=4 for efficacy). All efficacy analyses were conducted on DEL subgroup-level data from included trials.

Sensitivity analysis Three pre-specified sensitivity analyses: (1) exclusion of CAVALLI (non-randomized historical control design); (2) alternative DEL ascertainment for REMoDL-B using a random forest prediction model trained on GSE117556 gene expression data (n=125 vs

primary n=207); (3) complete exclusion of REMoDL-B.

Country(ies) involved China.

Keywords Double-expressor lymphoma; Diffuse large B-cell lymphoma; Network meta-analysis; R-CHOP; Pola-R-CHP; Polatuzumab vedotin; MYC; BCL2; Progression-free survival; Systematic review.

Dissemination plans Results will be submitted for publication in a peer-reviewed hematology or oncology journal and presented at relevant international conferences.

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