

Frontline treatment for diffuse large B-cell lymphoma in 2026: Lessons from targeted and immune-based approaches

Tycel Phillips

Department of Hematology & Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA, USA

<https://doi.org/10.17925/OHR.2026.22.2.7>

The addition of the Cluster of Differentiation (CD)20 antibody rituximab (R) to the cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy backbone has significantly improved outcomes in patients with diffuse large B-cell lymphoma (DLBCL). Despite the efficacy of this regimen, approximately one-third of patients who receive it will either relapse or not respond. Efforts to improve outcomes by adding novel agents to R-CHOP have, until recently, not resulted in substantial improvements over R-CHOP alone. The cumulative effect of numerous clinical trials that failed to demonstrate a survival benefit over R-CHOP challenged the perception that the key to improving outcomes in frontline DLBCL would be solely through the addition of a novel agent. Although the POLARIX study was the first to change this trend, several on-going and completed immune-based approaches look primed to follow the success of polatuzumab. For older patients with DLBCL, the ability to administer full-intensity treatment has been impacted by age, fitness and pre-existing comorbidities present at diagnosis. R-mini-CHOP remains the standard of care, despite having a 2-year overall survival (OS) rate close to 50%. We have struggled to improve outcomes in this patient population, mainly due to the difficulty of balancing the efficacy of new agents against the risk of additional toxicity when combined with R-mini-CHOP. This has recently led to the exploration of regimens that alter the CHOP backbone or are devoid of chemotherapy entirely. The fundamental basis of these strategies is to achieve an improvement in efficacy while limiting additive toxicity in this difficult-to-treat patient population. Based on early results from these studies, it appears that we may be in the midst of another immunotherapeutic evolution in the frontline standard of care for DLBCL.

Keywords

Aged 80 and over, antineoplastic agents, diffuse large B-cell lymphoma (DLBCL), immunotherapy, novel agents, R-CHOP chemotherapy

Disclosures: Tycel Phillips has received grants or contracts from Blood Cancer United Cures Within Reach; consulting fees from Abbvie, ADC, AZ, Bayer, BeOne, BMS, Caribou, Genmab, Genentech, Gilead, Immunomune, Incyte, Janssen, J & J, Kite, Legend, Lily, Merck, Miltenyi, Pharmacocyclical, Pfizer, Regeneron, Xencor; participation on data safety monitoring board/advisory board from Genentech, Xencor; leadership of fiduciary role in other board, society, committee or advocacy group, paid or unpaid from LRF MCL executive committee, Chair MCLA SAB; research support from Genentech, Abbvie, Sobi and BMS.

Acknowledgements: No artificial intelligence (AI) or large language model (LLM) tools were used in the development of this article.

Review process: Double-blind peer review.

Compliance with ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the writing of this article.

Authorship: The named author meets the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, takes responsibility for the integrity of the work as a whole and has given final approval for the version to be published.

Access: This article is freely accessible at touchONCOLOGY.com. ©Touch Medical Media 2026.

Received: 4 August 2026

Accepted: 20 October 2026

Published online: 29 October 2026

Citation: *touchREVIEWS in Oncology & Haematology*. 2026;22(2):50–54

Corresponding author: Tycel Phillips, Hematology and Bone Marrow Transplantation, City of Hope National Medical Center, Duarte, CA 91010, USA.
E: tphillips@coh.org

Support: No funding was received in the publication of this article.

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma in the USA and Western Europe.^{1,2} DLBCL is treated with curative intent given the aggressive nature of the disease. Rituximab (R), cyclophosphamide (C), doxorubicin (H), vincristine (O) and prednisone (P) (R-CHOP) has been the bedrock of therapy for patients with DLBCL since the pivotal study by Coiffier et al.³ This was the first study in DLBCL that introduced an immunotherapeutic agent (rituximab) into the treatment of lymphoma. Although highly effective for most patients, approximately one-third of those who receive this regimen will have primary refractory disease or experience a late relapse. Additionally, patients must have adequate cardiac function to safely receive doxorubicin, which is one of the most effective components of this regimen.

Attempts at improving outcomes in frontline DLBCL have mostly focused on the R-CHOP + X model, which is rooted in the belief that adding novel treatments (X) that have demonstrated single-agent activity in DLBCL could further enhance the efficacy of R-CHOP. This approach led to the enrollment and completion of several studies, as illustrated in *Table 1*, including a cooperative study from the USA that sought to establish rituximab (R), dose-adjusted etoposide phosphate (E), prednisone (P), vincristine sulfate (Oncovin; O), cyclophosphamide (C), doxorubicin hydrochloride (Hydroxydaunomycin; H) or R-DA-EPOCH as the new standard of care.^{4–11} Unfortunately, with the exception of small, selected populations in some of these studies, these trials failed to demonstrate any benefit over R-CHOP, despite the great initial enthusiasm for some of the regimens that demonstrated impressive phase II data.

This metric changed with the completion of the POLARIX study (A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Polatuzumab Vedotin in Combination With Rituximab and CHP [R-CHP] Versus Rituximab and

Table 1: Clinical trials discussing R-DA-EPOCH^{4–11}

Trial name	Phase	Experimental arm	Population	Total n	Results	Met primary endpoint
POLARIX (A Study Comparing the Efficacy and Safety of Polatuzumab Vedotin With Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone (R-CHP) Versus Rituximab-Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone [R-CHOP] in Participants With Diffuse Large B-Cell Lymphoma; ClinicalTrials.gov identifier: NCT03274492) ⁵	III	Pola-R-CHP	Untreated DLBCL, IPI 2–5, aged 18–80 years	879	5-year PFS 64.9% versus 59.1%; HR, 0.77 (CI 0.62–0.97); OS HR, 0.85 (0.63–1.15)	Yes
frontMIND (Tafasitamab + Lenalidomide + R-CHOP Versus R-CHOP in Newly Diagnosed High-intermediate and High Risk DLBCL Patients; ClinicalTrials.gov identifier: NCT04824092) ⁶	III	Tafasitamab + lenalidomide + R-CHOP	Untreated high-intermediate/high-risk DLBCL (IPI 3–5 or 60 years or younger with aalPI 2–3)	899	2-year PFS 71.1% versus 62.9%; HR, 0.75 (CI 0.59–0.96); p=0.019; interim OS HR, 0.85 (0.63–1.14)	Yes
GOYA (A Study of Obinutuzumab in Combination With CHOP Chemotherapy Versus Rituximab With CHOP in Participants With CD20-Positive Diffuse Large B-Cell Lymphoma; ClinicalTrials.gov identifier: NCT01287741) ^{4,7}	III	Obinutuzumab + CHOP	Untreated advanced DLBCL	1,418	5-year PFS 63.8% versus 62.6%; HR, 0.94 (CI 0.78–1.12); p = 0.48	No
CALGB 50303 (Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance; ClinicalTrials.gov identifier: NCT00118209) ⁸	III	R-DA-EPOCH	Untreated advanced DLBCL	491	2-year PFS 78.9% versus 75.5%; HR, 0.93 (CI 0.68–1.27); p=0.65; OS HR, 1.09	No
PHOENIX (Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non-Germinal Center B-Cell Diffuse Large B-Cell Lymphoma; ClinicalTrials.gov identifier: NCT01855750) ⁹	III	Ibrutinib + R-CHOP	Untreated non-GCB DLBCL	838	3- year EFS 69.6% versus 67.4%; HR, 0.934 (ABC HR, 0.949)	No
ROBUST (Efficacy and Safety Study of Lenalidomide Plus R-CHOP Chemotherapy Versus Placebo Plus R-CHOP Chemotherapy in Untreated ABC Type Diffuse Large B-cell Lymphoma; ClinicalTrials.gov identifier: NCT02285062) ¹⁰	III	Lenalidomide + R-CHOP	Untreated ABC-DLBCL (GEP-confirmed)	570	2-year PFS was 67% for R2-CHOP and 64% for placebo/R-CHOP; HR, 0.85 (CI 0.63–1.14); p=0.29	No
REMoDL-B (A Randomised Evaluation of Molecular Guided Therapy for Diffuse Large B-cell Lymphoma With Bortezomib; ClinicalTrials.gov identifier: NCT01324596) ¹¹	III	Rituximab + bortezomib + CHOP	Untreated DLBCL, GEP-stratified	918	30-month PFS 74.3% versus 70.1%; HR, 0.86; p=0.28	No

aalPI = age-adjusted International Prognostic Index; ABC = activated B-cell; CHOP = cyclophosphamide (C), doxorubicin (H), vincristine (O) and prednisone (P); DLBCL = diffuse large B-cell lymphoma; EFS = event-free survival; GCB = germinal center B-cell; GEP = gene expression profiling; HR = hazard ratio; IPI = International Prognostic Index; OS = overall survival; PFS = progression-free survival; Pola-R-CHP = polatuzumab vedotin (P), rituximab (R), cyclophosphamide (C), doxorubicin (H), prednisolone (P); R-CHOP = rituximab (R), cyclophosphamide (C), doxorubicin (H), vincristine (O) and prednisone (P); R-DA-EPOCH = rituximab (R), dose-adjusted etoposide phosphate (E), prednisone (P), vincristine sulfate (Oncovin; O), cyclophosphamide (C), doxorubicin hydrochloride (Hydroxydaunomycin; H).

CHOP [R-CHOP] in Previously Untreated Patients With Diffuse Large B-Cell Lymphoma; ClinicalTrials.gov identifier: NCT03274492), which substituted the antibody–drug conjugate (ADC) polatuzumab (pola) for vincristine.⁵ This study enrolled 879 patients who were subsequently randomized in

a 1:1 ratio to receive either polatuzumab vedotin (Pola), rituximab (R), cyclophosphamide (C), doxorubicin (H), prednisolone (P) (Pola-R-CHP) or R-CHOP. This study demonstrated a progression-free survival (PFS) benefit over R-CHOP. The most recent update, after a median follow-up

Table 2: Ongoing randomized studies in frontline DLBCL^{18–23}

Name	Phase	Experimental arm	Control arm	Total n	Primary endpoint
OLYMPIA-3 (NCT06091865) ¹⁸	III	Odronektamab + CHOP	R-CHOP	904	Incidence of dose limiting toxicities (timeframe: up to 35 days) Incidence of TEAEs (timeframe: up to 2 years) Severity of TEAEs (timeframe: up to 2 years) Part 1A PFS, assessed by independent central review (timeframe: up to 5 years) Part 2
EPCORE DLBCL-2 (NCT05578976) ¹⁹	III	Epcoritamab + R-CHOP	R-CHOP	900	Number of participants with PFS and an International Prognostic Index of 3–5 (timeframe: up to approximately 46 months)
SKYGLO (NCT06047080) ²⁰	III	Glofitamab + Pola-R-CHP	Pola-R-CHP	1,130	PFS, as determined by an independent review facility (timeframe: from randomization to the first occurrence of disease progression or relapse, or death due to any cause, whichever occurs first (up to approximately 65 months)
GOLSEEK-1 (NCT06356129) ²²	III	Golcadomide + R-CHOP	R-CHOP	850	PFS, assessed by the investigator (timeframe: approximately 24 months after the last participant's first treatment)
ESCALADE (NCT04529772) ²¹	III	Acalabrutinib + R-CHOP	R-CHOP	611	PFS, per the Lugano Classification for NHL (timeframe: at every visit, up to 60 months)
waveLINE-010 (NCT06717347) ²³	III	Zilovetamab vedotin + R-CHP	R-CHOP	1,046	PFS (timeframe: up to ~50 months)

CHOP = cyclophosphamide (C), doxorubicin (H), vincristine (O) and prednisone (P); NHL = non-Hodgkin's lymphoma; PFS = progression-free survival; Pola-R-CHP = polatuzumab vedotin (P), rituximab (R), cyclophosphamide (C), doxorubicin (H), prednisolone (P); R-CHOP = rituximab (R), cyclophosphamide (C), doxorubicin (H), vincristine (O) and prednisone (P); TEAEs = treatment-emergent adverse events.

Table 3: Studies using bispecific antibodies alone or in combination with ADC, pola or mini-CHOP/CVP^{29–33}

Study name	Experimental drug	Regimen	Patient population	Total n	Results	Adverse events
EPCORE DLBCL-3 (NCT04628494) ³⁰	Epcor	Epcor monotherapy	Older (≥75 years) pts who are ineligible for anthracycline-based treatment with previously untreated large B-cell lymphoma	66	ORR was 70% in the response-evaluable population (n=53), and the CR rate was 58%. Median DOR and DOCR were NR. Median PFS was 13 months (95% CI, 5.4–NR), and median OS was NR (95% CI, 13.0–NR)	TEAEs of any grade occurred in 94% of pts, with CRS (70%), diarrhea (23%) and fatigue (21%) being the most frequent. Grade ≥3 TEAEs occurred in 61% of pts. CRS events were primarily low grade (G1: 38%; G2: 27%; G3: 5%). ICANS occurred in 18% of pts (G1: 8%; G2: 8%; G3: 3%); 10 of 12 cases had resolved by the data cutoff. Infections of any grade occurred in 59% of pts, and grade ≥3 infections occurred in 18%. Two additional grade 5 TEAEs (pneumonia and death) were reported
MorningSun study (NCT05207670) ³¹	Mosun	Mosun monotherapy	Pts aged ≥80 years or aged 65–79 and considered ineligible for chemioimmunotherapy	49	ORR and CR rates were 73.5% and 59.2%, respectively. The 12-month PFS rate was 68.8% (95% CI, 52.1–80.6), and the 12-month OS rate was 77.2% (95% CI, 61.1–87.3). The 12-month DOR and DOCR rates were 84.6% (95% CI, 66.8–93.3) and 95.0% (95% CI, 69.5–99.3), respectively. Two events occurred, all of which resolved	The most common AE of any grade was injection-site reaction (n=25, 51.0%). Grade 3/4 AEs occurred in 65.3% of pts (n=32), most commonly infections (16.3% [n=8]) and decreased neutrophil count (10.2% [n=5]). Serious AEs occurred in 42.9% of pts (n=21). Four pts experienced grade 5 AEs (congestive heart failure, volvulus, unexplained death and intracranial hemorrhage; n=1 each). Infections occurred in 46.9% (n=23) of pts (G1/2: 30.6% [n=15]; G3: 16.3% [n=8]); no grade 4/5 infections were reported
EPCORE NHL-2 trial (NCT04663347) ³²	Epcor	Epcor + mini-R-CHOP	Pts aged ≥75 years or aged ≥65 years with comorbidities	28	ORR was 89%, and the CR rate was 86%. Median DOR and DOCR were NR. Median PFS and OS were NR. The estimated 2-year PFS and OS rates were 76% and 82%, respectively	Eight pts (29%) had grade ≥3 infections. TEAEs led to treatment discontinuation in 3 (11%) pts, including grade 2 rhinitis, grade 2 CRS and grade 5 confusional state and cytomegalovirus infection reactivation in a 90-year-old pt who was also diagnosed with an acute cerebrovascular accident
R-Pola-Glo trial (NCT05798156) ²⁹	Glo + pola	Rituximab + pola + glo	80 previously untreated pts with DLBCL who are older, frail or otherwise medically unfit for full-dose R-CHOP	80	ORR was 90%, and the CMR rate was 81%. The 1-year PFS rate was 94.7% (95% CI, 68–99%)	Grade 3–5 AEs occurred in 34% (27/80) of pts. Common toxicities included infections, which were grade 3–5 in 22% of pts (G3: 15; G5: 3), including three fatal infections (COVID: 1; COVID + RSV: 1; unknown focus: 1). CRS occurred in 31% of pts (G3: 1; no G4/5 events) and ICANS in 4% of pts (G2: 2; G3: 1)
Phase II trial of epcoritamab in combination with rituximab-mini-CVP for adults who are older, unfit or frail or anthracycline ineligible with newly diagnosed DLBCL (NCT06045247) ³³	Epcor	Epcor + R- mini-CVP	Eligible pts have histologically confirmed DLBCL and are classified as unfit or frail per the FLI simplified geriatric assessment, are ineligible for anthracyclines due to reduced ejection fraction (<50%) or have received prior anthracycline therapy	22 of planned 40	ORR was 100%, and the CMR rate was 86%	CRS occurred in 12 pts (55%). One pt developed grade 2 neurotoxicity

ADC = antibody drug conjugate; AE = adverse event; CHOP = cyclophosphamide (C), doxorubicin (H), vincristine (O) and prednisone (P); CI = confidence interval; CMR = complete metabolic response; COVID = coronavirus disease; CR = complete response; CRS = cytokine release syndrome; CVP = cyclophosphamide, vincristine and prednisone; DLBCL = diffuse large B-cell lymphoma; DOCR = duration of complete response; DOR = duration of response; epcor = epcoritamab; FIL = Fondazione Italiana Linfomi; G = grade; glo = glofitamab; ICANS = immune cell associated neurotoxicity syndrome; mosun = mosunetuzumab; NR = not reached; ORR = overall response rate; PFS = progression-free survival; pola = polatuzumab; pt = patient; R-CHOP = rituximab (R), cyclophosphamide (C), doxorubicin (H), vincristine (O) and prednisone (P); RSV = respiratory syncytial virus; TEAEs = treatment-emergent adverse events.

of 64.1 months, reported a 64.9% PFS in the Pola-R-CHP group versus 59.1% in the group treated with R-CHOP, with a corresponding hazard ratio (HR) of 0.78.^{5,12} Despite the PFS benefit, even with longer follow-up, this study has yet to demonstrate an overall survival (OS) benefit with Pola-R-CHP. Data continue to suggest that the regimen is most effective in patients diagnosed with the nongerminal center B-cell (non-GCB)/activated B-cell (ABC) subtype and has an equivalent outcome to R-CHOP in those with a germinal center (GC) subtype of DLBCL. Those in favor of Pola-R-CHP have often raised the issue of the difficulty of accurately classifying all patients based on cell of origin (COO). The gold standard for determining COO, gene expression profiling (GEP), is seldom, if ever, used outside of Canada. Currently, the most widely used method to determine COO in most other countries, immunohistochemical staining, has an approximately 20% discordance rate compared with GEP. As such, treating all patients with Pola-R-CHP would provide a benefit to all patients with the non-GCB/ABC subtype while providing equivalent efficacy to those with the GC subtype. This approach is further supported by the similar toxicity profiles between the two regimens, despite the inclusion of pola. Further subgroup analysis indicates that several other patient subsets appear to obtain a PFS benefit over R-CHOP when treated with Pola-R-CHP. The argument against utilization of Pola-R-CHP in all patients has centered on the lack of an OS benefit despite several years of follow-up, as well as the cost-effectiveness of the regimen versus R-CHOP. The latter has been evaluated in three studies, whose results have mostly supported the role of Pola-R-CHP in frontline DLBCL, with the data indicating that it would continue to be cost-effective as long as it maintained at least a 5% PFS benefit over R-CHOP.

The combination of tafasitamab (tafa), a CD19 monoclonal antibody, and lenalidomide (len), an immunomodulatory agent, (tafa-len), was shown to be an effective regimen in the L-MIND study (A Phase II, Single-Arm, Open-Label, Multicentre Study to Evaluate the Safety and Efficacy of Lenalidomide Combined With MOR00208 in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma [R-R DLBCL]; ClinicalTrials.gov identifier: NCT02399085), which enrolled patients with relapsed DLBCL.¹³ Given the results of this study, especially in those treated after only one prior line of therapy, the tafa-len regimen was further explored in combination with R-CHOP in patients with newly diagnosed DLBCL. The frontMIND study (A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Comparing the Efficacy and Safety of Tafasitamab Plus Lenalidomide in Addition to R-CHOP Versus R-CHOP in Previously Untreated, High-intermediate and High-risk Patients With Newly-diagnosed Diffuse Large B-cell Lymphoma [DLBCL]; ClinicalTrials.gov identifier: NCT04824092) enrolled patients aged 18–80 years with high-risk DLBCL and an International Prognostic Index (IPI) score of 3–5 or patients aged 60 years or younger with an age-adjusted IPI score of 2–3.⁶ In this double-blind study, patients were randomized to receive either R-CHOP plus placebo or R-CHOP in combination with 25 mg of len on days 1–10 and 12 mg/kg of intravenous (IV) tafa on days 1, 8 and 15. With 899 patients randomized, tafa-len-R-CHOP demonstrated a 3-year PFS rate of 71.1% versus 62.9% for those who received R-CHOP, with a corresponding HR of 0.79. At this early readout, this regimen has not yet demonstrated an OS benefit but currently appears to be agnostic to COO. Like Pola-R-CHP, the frontMIND regimen presents some unique challenges that might limit universal adoption. The inclusion of len is covered differently from the IV medicines, must be obtained through a specialty pharmacy and is therefore subject to patient-to-patient variability in copay costs. The regimen also introduces additional treatment burden compared with Pola-R-CHP and R-CHOP, as tafa is given weekly throughout the entirety of treatment. Lastly, unlike Pola-R-CHP, the toxicity profile of tafa-len-R-CHOP raises some concerns about tolerability in older patients.

The POLARIX and frontMIND regimens have demonstrated that immunotherapy-based treatments may improve the efficacy of R-CHOP in patients aged 80 years or younger. Several studies building upon this theme have completed enrollment in phase III trials and are awaiting formal results. These studies have incorporated T-cell-engaging antibodies, which have recently made an impact on the management of relapsed/refractory DLBCL. Epcoritamab and glofitamab have received accelerated approval based on phase I/II studies in the USA (both are approved in the European Union [EU]), whereas odronextamab has approval in the EU and Asia based on the ELM-2 study.^{14–17} These three agents, combined with a CHOP, R-CHOP or Pola-R-CHP backbone, are being evaluated in separate randomized studies in frontline DLBCL, in comparison with R-CHOP or Pola-R-CHP.^{18–20} Given the single-agent activity of these molecules in third-line or later DLBCL, there is an expectation that these studies will usher in the next advancement in frontline therapy for DLBCL. To this point, the EPCORE DLBCL-2 study (A Phase 3, Randomized, Open-Label Study to Evaluate Safety and Efficacy of Epcoritamab in Combination With R-CHOP Compared to R-CHOP in Subjects With Newly Diagnosed Diffuse Large B-Cell Lymphoma [DLBCL]; ClinicalTrials.gov identifier: NCT05578976) has reported a 51% reduction in the risk of progression or death (HR, 0.49; $p < 0.001$) with epcoritamab plus R-CHOP compared with R-CHOP. We look forward to further details being reported to fully assess the role of this regimen in frontline DLBCL.

Efforts to improve outcomes in this patient population are not limited to immunotherapeutic modalities. ESCALADE (Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Acalabrutinib in Combination With Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone [R-CHOP] in Subjects ≤ 75 Years With Previously Untreated Non-GCB DLBCL; ClinicalTrials.gov identifier: NCT04529772) and GOLSEEK-1 (A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Comparing the Efficacy and Safety of Golcadomide Plus R-CHOP Chemotherapy vs Placebo Plus R-CHOP Chemotherapy in Participants With Previously Untreated High-risk Large B-cell Lymphoma; ClinicalTrials.gov identifier: NCT06356129) are active studies aimed at improving upon the results reported in PHOENIX (PHOENIX DDR/Anti-PD-L1 Trial: A Pre-surgical Window of Opportunity and Post-surgical Adjuvant Biomarker Study of DNA Damage Response Inhibition With or Without Anti-PD-L1 Immunotherapy in Patients With Neoadjuvant Treatment Resistant Residual Triple Negative Breast Cancer; ClinicalTrials.gov identifier: NCT03740893) and ROBUST (Phase 3 Randomized, Double-Blind, Placebo Controlled, Multicenter Study to Compare the Efficacy and Safety of Lenalidomide [CC-5013] Plus R-CHOP Chemotherapy [R2-CHOP] Versus Placebo Plus R-CHOP Chemotherapy in Subjects With Previously Untreated Activated B-cell Type Diffuse Large B-cell Lymphoma; ClinicalTrials.gov identifier: NCT02285062), respectively, through the incorporation of novel second-generation agents related to ibrutinib and len, respectively.^{8,9,21,22} The ESCALADE study will randomize patients aged 65 years or younger with non-GCB DLBCL (the ABC subtype will be centrally confirmed after enrollment) to acalabrutinib 100 mg twice a day (BID) + R-CHOP versus R-CHOP, with PFS as the primary endpoint. The GOLSEEK-1 study will randomize patients with newly diagnosed DLBCL to golcadomide, a novel cereblon E3 ligase modulatory drug (CELMoD) reported to promote the degradation of Ikaros and Aiolos more effectively than len, at a dose of 0.4 mg on days 1–7 of each cycle in conjunction with R-CHOP versus R-CHOP. This study will also have PFS as its primary endpoint. A list of all on-going randomized studies in frontline DLBCL is provided in Table 2.^{18–25}

Using an alternative approach from the group at MD Anderson has slowly adapted a series of phase II studies in an attempt to eliminate

chemotherapy in patients who achieve a complete response to an induction regimen composed of immunotherapeutic agents and small-molecule inhibitors.^{24,25} The most recent iteration, Smart Stop, demonstrated that some patients could achieve remission without having to receive CHOP. Long-term follow-up is needed to determine whether this induction regimen can induce a cure without chemotherapy consolidation.

Although we have had promising changes in the landscape of frontline DLBCL treatment for younger patients, this has not been the case for older patients (>80) and/or those with comorbidities that preclude the use of full-intensity therapy in frontline DLBCL. For this patient population, there has been a heterogeneous mix of regimens used, although none have matched the efficacy of R-CHOP. The most commonly used regimen for this patient population is R-mini-CHOP, which, unfortunately, has not demonstrated OS rates equivalent to that in younger patients treated with R-CHOP.²⁶ Several studies evaluating whether to replace R-mini-CHOP or add novel agents to a mini-CHOP backbone have been hampered by increased toxicity in the experimental arms. Some of this is understandably attributable to the novel agent included, but some of this is undoubtedly due to the frailty of this patient population.

Recent efforts to improve outcomes in this patient population have again used immunotherapeutic approaches. The most mature study is the phase III POLAR BEAR study (R-MINI-CHOP Versus R-MINI-CHP in Combination With Polatuzumab-vedotin, as Primary Treatment for Patients With Diffuse Large B-cell Lymphoma, ≥80 Years, or Frail ≥75

Years - an Open Label Randomized Nordic Lymphoma Group Phase III Trial; ClinicalTrials.gov identifier: NCT04332822), which is evaluating Pola-R-mini-CHP versus R-mini-CHOP.²⁷ Although mature data from this study are not yet available, some of the early data again hint at increased toxicity in the experimental arm.²⁸

As illustrated in Table 3, several other studies have sought to improve outcomes in this patient population using bispecific antibodies alone, in combination with the ADC, pola or mini-CHOP/CVP. The results of these phase II studies have demonstrated promising efficacy and acceptable toxicity.^{29–33} The next steps in the development of these regimens will be to evaluate them against R-mini-CHOP in a randomized phase III study. We look forward to seeing whether any of these regimens will provide the first improvement in this population since the introduction of rituximab.

Treatment approaches for frontline DLBCL remain an area of great interest, given the limitations of current standard-of-care regimens. Despite significant progress, approximately one-third of patients will relapse or have primary resistance to R-CHOP or Pola-R-CHP. Unfortunately, despite substantial efforts, only one randomized study had demonstrated a PFS benefit over R-CHOP until the recently reported frontMIND study. Unfortunately, neither the POLARIX nor the frontMIND regimen, despite meeting their prespecified primary endpoints, is likely to completely displace R-CHOP, given the concerns raised about both studies. There is hope that some of the currently on-going studies have the potential, based on their known safety and efficacy profiles, to establish a new standard of care for all patients with newly diagnosed DLBCL. □

1. Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *CA Cancer J Clin*. 2016;66:443–59. DOI: 10.3322/caac.21357.
2. Freedman A. Follicular lymphoma: 2015 update on diagnosis and management. *Am J Hematol*. 2015;90:1171–8. DOI: 10.1002/ajh.24200.
3. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346:235–42. DOI: 10.1056/NEJMoa011795.
4. Sehnh LH, Martelli M, Trnėný M, et al. A randomized, open-label, phase III study of obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large b-cell lymphoma: final analysis of GOYA. *J Hematol Oncol*. 2020;13:71. DOI: 10.1186/s13045-020-00900-7.
5. Morschhauser F, Salles G, Sehnh LH, et al. Five-year outcomes of the POLARIX study comparing pola-r-CHP and r-CHOP in patients with diffuse large b-cell lymphoma. *J Clin Oncol*. 2025;43:3698–705. DOI: 10.1200/JCO.25-00925.
6. Vitolo U, Nowakowski GS, Burke JM, et al. Poster: ABCL-023 frontMIND: A phase III, randomized, double-blind study of tafasitamab + lenalidomide + R-CHOP versus R-CHOP alone for newly diagnosed high-intermediate and high-risk diffuse large B-cell lymphoma. *Clin Lymphoma Myeloma Leuk*. 2022;22:S163. DOI: 10.1016/S2152-2650(22)00999-5.
7. Vitolo U, Trnėný M, Belada D, et al. Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large B-cell lymphoma. *J Clin Oncol*. 2017;35:3529–37. DOI: 10.1200/JCO.2017.73.3402.
8. Younes A, Sehnh LH, Johnson P, et al. Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. *J Clin Oncol*. 2019;37:1285–95. DOI: 10.1200/JCO.18.02403.
9. Nowakowski GS, Chiappella A, Gascoyne RD, et al. ROBUST: A phase III study of lenalidomide plus R-CHOP versus placebo plus R-CHOP in previously untreated patients with ABC-type diffuse large B-cell lymphoma. *J Clin Oncol*. 2021;39:1317–28. DOI: 10.1200/JCO.20.01366.
10. Leonard JP, Kolibaba KS, Reeves JA, et al. Randomized phase II study of R-CHOP with or without bortezomib in previously untreated patients with non-germinal center B-cell-like diffuse large B-cell lymphoma. *J Clin Oncol*. 2017;35:3538–46. DOI: 10.1200/JCO.2017.73.2784.
11. Davies A, Cummin TE, Barrans S, et al. Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large b-cell lymphoma (remod-b): An open-label, randomised, phase 3 trial. *Lancet Oncol*. 2019;20:649–62. DOI: 10.1016/S1473-0458(18)30935-5.
12. Tilly H, Morschhauser F, Sehnh LH, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. *N Engl J Med*. 2022;386:351–63. DOI: 10.1056/NEJMoa2115304.
13. Duell J, Abrisqueta P, Andre M, et al. Tafasitamab for patients with relapsed or refractory diffuse large B-cell lymphoma: Final 5-year efficacy and safety findings in the phase II L-MIND study. *Haematologica*. 2024;109:553–66. DOI: 10.3324/haematol.2023.283480.
14. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 bispecific T-cell-engaging antibody, in relapsed or refractory large B-cell lymphoma: Dose expansion in a phase I/II trial. *J Clin Oncol*. 2023;41:2238–47. DOI: 10.1200/JCO.22.01725.
15. Thieblemont C, Karimi YH, Ghesquieres H, et al. Epcoritamab in relapsed/refractory large B-cell lymphoma: 2-year follow-up from the pivotal EPCORE NHL-1 trial. *Leukemia*. 2024;38:2653–62. DOI: 10.1038/s41375-024-02410-8.
16. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2022;387:2220–31. DOI: 10.1056/NEJMoa2206913.
17. Kim WS, Kim TM, Cho SG, et al. Odonexetamab monotherapy in patients with relapsed/refractory diffuse large B-cell lymphoma: Primary efficacy and safety analysis in phase 2 ELM-2 trial. *Nat Cancer*. 2025;6:528–39. DOI: 10.1038/s43018-025-00967-6.
18. Hawkes EA, Kim TM, Donato Martin EM, et al. Phase 3 trial evaluating the efficacy and safety of odronexetamab versus standard-of-care (SOC) therapy in relapsed/refractory (r/r) aggressive b-cell non-hodgkin lymphoma (b-NHL; OLYMPIA-4). *J Clin Oncol*. 2024;42(Suppl.):TPS7093. DOI: 10.1200/JCO.2024.42.16_suppl.TPS7093.
19. Sehnh LH, Chamuleau M, Lenz G, et al. Phase 3 trial of subcutaneous epcoritamab + R-CHOP versus R-CHOP in patients (pts) with newly diagnosed diffuse large B-cell lymphoma (DLBCL): EPCORE DLBCL-2. *J Clin Oncol*. 2023;41(Suppl.):TPS7592. DOI: 10.1200/JCO.2023.41.16_suppl.TPS7592.
20. Advani RH, Dickinson MJ, Fox CP, et al. SKYGLO: a global phase III randomized study evaluating glofitamab plus polatuzumab vedotin + rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-r-CHP) versus pola-r-CHP in previously untreated patients with large b-cell lymphoma (LBCL). *Blood*. 2024;144(Suppl.1):1718. DOI: 10.1182/blood-2024-194000.
21. Sehnh LH, Kahl BS, Matasar MJ, et al. ESCALADE: A phase 3 study of acalabrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for patients <65y with untreated non-germinal center B-cell-like (non-GCB) diffuse large B-cell lymphoma (DLBCL). *J Clin Oncol*. 2021;39(Suppl.15):TPS7572. DOI: 10.1200/JCO.2021.39.15_suppl.TPS7572.
22. Vassilakopoulos T, Munoz J, Huang H, et al. Golsseek-1: A phase 3, double-blind, randomized study of golcadomide (GOLCA), a potential, first-in-class, oral celmold. *Blood*. 2025;146(Suppl.1):3704. DOI: 10.1182/blood-2025-3704.
23. Armand P, Lee ST, Jurczak W, et al. WaveLINE-003: Phase 2/3 trial of zilvertamab vedotin plus standard of care in relapsed/refractory diffuse large B-cell lymphoma. *J Clin Oncol*. 2025;43(Suppl.16):7005. DOI: 10.1200/JCO.2025.43.16_suppl.7005.
24. Westin J, Davis RE, Feng L, et al. Smart start: Rituximab, lenalidomide, and ibrutinib in patients with newly diagnosed large B-cell lymphoma. *J Clin Oncol*. 2023;41:745–55. DOI: 10.1200/JCO.22.00597.
25. Westin J, Fayad L, Steiner R, et al. Primary analysis of the smart stop trial: Lenalidomide, tafasitamab, rituximab, and acalabrutinib alone and with combination chemotherapy in newly diagnosed diffuse large B-cell lymphoma. *Blood*. 2025;(Suppl. 1):477. DOI: 10.1182/blood-2025-477.
26. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: A multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2011;12:460–8. DOI: 10.1016/S1473-0458(11)70069-9.
27. Jerkeman M, Leppä S, Hamfjord J, et al. S227: Initial safety data from the phase 3 POLAR BEAR trial in elderly or frail patients with diffuse large cell lymphoma, comparing R-Pola-mini-CHP and R-mini-CHOP. *Hemasphere*. 2023;7(Suppl.):e91359ec. DOI: 10.1097/01.HS9.0000967820.91359.ec.
28. Jerkeman M, Maria Ferreri AJ, Brown P. Safety data and initial pooled efficacy data from the nordic lymphoma group phase 3 POLAR BEAR trial in elderly or frail patients with diffuse large cell lymphoma: R-pola-mini-CHP vs r-mini-CHOP. Presented at: European Hematology Association (EHA) 2026 Congress, Stockholm, Sweden, 12, June, 2026. Abstr S238.
29. Chapuy B, Wurm-Kuczer R, Michael R, et al. Phase II frontline chemolight R-pola-glo trial induces high and durable response rates in elderly and medically unfit/frail patients with aggressive B-cell lymphoma. *Blood*. 2025;146(Suppl.1):61. DOI: 10.1182/blood-2025-61.
30. Vitolo U, Duell J, Bergua Burgues JM, et al. Fixed-duration epcoritamab monotherapy induces high response and MRD-negativity rates in elderly patients with newly diagnosed large b-cell lymphoma (LBCL) and comorbidities: Results from EPCORE DLBCL-3. *Blood*. 2025;146(Suppl.1):63. DOI: 10.1182/blood-2025-63.
31. Sharmar J, Tun A, Villasboas Bisneto J, et al. Fixed treatment duration subcutaneous mosunetuzumab monotherapy in elderly/unfit patients with previously untreated diffuse large B-cell lymphoma: Interim results from the phase II morningsun study. *Blood*. 2025;146(Suppl.1):62. DOI: 10.1182/blood-2025-62.
32. Cheah C, Đuraš J, Belada D, et al. Epcoritamab + R-mini-CHOP results in 2-year remissions and high MRD negativity rates in elderly patients with newly diagnosed DLBCL: Results from the EPCORE NHL-2 trial. *Blood*. 2025;(Suppl.1):64. DOI: 10.1182/blood-2025-64.
33. Chihara D, Chauhan A, Lin R, et al. Phase 2 trial of epcoritamab in combination with rituximab-mini CVP for older unfit/frail or anthracycline-ineligible adult patients with newly diagnosed diffuse large B-cell lymphoma: Interim futility analysis. *J Clin Oncol*. 2026;44(Suppl.16):7002. DOI: 10.1200/JCO.2026.44.16_suppl.7002.