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INVITED REVIEW

# Diffuse large B-cell lymphoma

Allison Barraclough[1,2] | Eliza Hawkes[3,4] | Laurie H. Sehn[5] | Sonali M. Smith[6]

[1]Department of Haematology, Fiona Stanley Hospital, Perth, Western Australia, Australia

[2]University of Melbourne, Medical School, Melbourne, Victoria, Australia

[3]Olivia Newton John Cancer Research Centre, Austin Health, Melbourne, Victoria, Australia

[4]Monash University School of Public Health & Preventive Medicine, Melbourne, Victoria, Australia

[5]BC Cancer Centre for Lymphoid Cancer, The University of British Columbia, Vancouver, British Columbia, Canada

[6]The University of Chicago Medicine, Section of Hematology/Oncology, The University of Chicago, Chicago, Illinois, USA

**Correspondence**
Sonali M. Smith, Section of Hematology/Oncology, Department of Medicine, The University of Chicago, Chicago, IL, USA.
Email: smsmith@bsd.uchicago.edu

## Abstract

Large B-cell lymphoma, the prototype of aggressive non-Hodgkin lymphomas, is both the most common lymphoma and accounts for the highest global burden of lymphoma-related deaths. For nearly 4 decades, the goal of treatment has been "cure", first based on CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), and subsequently with rituximab plus CHOP. However, there is significant clinical, pathologic, and biologic heterogeneity, and not all patients are cured. Understanding and incorporating this biologic heterogeneity into treatment decisions unfortunately is not yet standard of care. Despite this gap, we now have significant advances in frontline, relapsed, and refractory settings. The POLARIX trial shows, for the first time, improved progression-free survival in a prospective randomized phase 3 setting. In the relapsed and refractory settings, there are now many approved agents/regimens, and several bispecific antibodies poised to join the arsenal of options. While chimeric antigen receptor T-cell therapy is discussed in detail elsewhere, it has quickly become an excellent option in the second-line setting and beyond. Unfortunately, special populations such as older adults continue to have poor outcomes and be underrepresented in trials, although a new generation of trials aim to address this disparity. This brief review will highlight the key issues and advances that offer improved outcomes to an increasing portion of patients.

KEYWORDS
antibody-drug conjugates, diffuse large B-cell lymphoma, older adults, treatment

## 1 | INTRODUCTION

Large B-cell lymphoma is a heterogeneous group of lymphomas. The updated World Health Organization (WHO) Classification and International Consensus Classification recognize an expanding group of discrete entities, with diffuse large B cell lymphoma, not otherwise specified (DLBCL, NOS) being the most common.[1,2] Within DLBCL, NOS (herein referred to as DLBCL), two molecular subtypes have been recognized by gene expression profiling: germinal-center B cell-like (GCB) and activated B cell-like (ABC).[3] These subtypes represent lymphomas arising from different stages of lymphoid differentiation (cell-of-origin) and driven by distinct oncogenic mechanisms.[4] While the ABC subtype generally has an inferior outcome (3-year progression-free survival (PFS) of approximately 45% versus 75% in the GCB subtype), a higher risk subset within GCB-DLBCL has been recognized characterized by a high-grade molecular signature.[5,6] Moving beyond cell-of-origin, novel DLBCL classifications have been proposed based on detailed genetic analyses.[7,8] The LymphGen

algorithm identifies at least six genetic subtypes (EZB, ST2, BN2, A53, N1, and MCD), classifying approximately 63% of DLBCL cases.[8] Although these genetic classifications require further validation prior to clinical application, they may enable better precision care in the future. The majority of front-line studies focus on DLBCL, whereas many trials studying relapsed or refractory disease include other aggressive B-cell lymphomas such as high-grade B-cell lymphomas (including those with concurrent *MYC* and *BCL2* rearrangements) and primary mediastinal B-cell lymphoma.

## 2 | FRONTLINE TREATMENT FOR DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Despite greater biological insight, most patients with DLBCL continue to be treated the same. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) has been the standard of care for 2 decades, as trials evaluating more intensive or alternative chemotherapy combinations have not yielded additional benefit. Recent phase 3 clinical trials have explored novel agents combined with R-CHOP in an attempt to overcome chemoresistant disease (Table 1). The phase 3 GOYA trial evaluated the use of obinutuzumab in combination with CHOP (G-CHOP) with no significant difference in PFS compared to R-CHOP.[9] Novel agents with presumed preferential activity within cell-of-origin subtypes have required patient enrichment based on biomarker selection. The REMoDL-B trial compared bortezomib-R-CHOP with R-CHOP in patients with DLBCL, stratified by cell-of-origin. While this trial was initially reported as negative, a recent 5-year analysis suggested benefit for patients with ABC subtype, as well as those with GCB subtype and high grade molecular signature.[10,14] The PHOENIX trial randomized patients with non-GCB DLBCL to receive R-CHOP with or without ibrutinib.[11] The addition of ibrutinib to R-CHOP did not improve outcomes in the intent-to-treat population; however, a pre-planned subgroup analysis revealed a survival benefit in patients younger than 60 years and increased toxicity in older patients. A retrospective analysis evaluating outcomes according to genetic subtyping suggested that MCD and N1 subtypes (which typically fall within ABC DLBCL) appeared to benefit the most from the addition of ibrutinib.[15] Clinical trials incorporating second-generation Bruton's tyrosine kinase inhibitors such as acalabrutinib (NCT05820841, NCT04529772) and zanubrutinib (NCT05164770) are underway to further validate this observation. The combination of lenalidomide and R-CHOP (R2-CHOP) has also been studied in the phase 3 ROBUST trial for patients with ABC DLBCL, which showed no significant difference in PFS as compared to R-CHOP.[12] However, the combination of lenalidomide and the CD19-directed antibody, tafasitamab, is active in the relapsed setting, and is now being evaluated with R-CHOP in the frontline setting (NCT04824092).

**TABLE 1** Recent phase 3 clinical trials of novel agents in frontline diffuse large B-cell lymphoma (DLBCL).

| Reference<br>Author<br>Journal (year) | Study inclusion | Study arm | *N* | PFS | OS |
|---|---|---|---|---|---|
| GOYA[9] | ≥18 years with DLBCL, IPI ≥ 2 or IPI 1 and ≤ 60years or IPI 0 with bulky disease | Obinutuzumab + CHOP | G-CHOP: 704 | 3 years: 69.6% | 3 years: 81.2% |
| Vitolo et al. | | | R-CHOP: 710 | 66.9% | 81.4% |
| J Clin Oncol (2017) | | | | ($p = 0.39$) | ($p = 1.00$) |
| REMoDL-B[10] | ≥18 years with DLBCL, bulky stage I or stage II–IV | Bortezomib + R-CHOP | RB-CHOP: 459 | 30 m: 74.3% | 30 m: 83.6% |
| Davies et al. | | | R-CHOP: 459 | 70.1% | 82.7% |
| Lancet Oncol (2019) | | | | ($p = 0.28$) | ($p = 0.52$) |
| PHOENIX[11] | ≥18 years with non-GCB DLBCL, stage II–IV, R-IPI ≥ 1 | Ibrutinib + R-CHOP | Ibrutinib: 419 | 3 years: 70.8% | 3 years: 82.8% |
| Younes et al. | | | Placebo: 419 | 68.1% | 81.4% |
| J Clin Oncol (2019) | | | | ($p = 0.502$) | ($p = 0.959$) |
| ROBUST[12] | 18–80 years with ABC DLBCL, stage II–IV, IPI ≥ 2 | Lenalidomide + R-CHOP | Lenalidomide: 285 | 2 years: 67% | 2 years: 79% |
| Nowakowski et al. | | | Placebo: 285 | 64% | 80% |
| J Clin Oncol (2021) | | | | ($p = 0.29$) | ($p = 0.64$) |
| POLARIX[13] | 18–80 years with DLBCL, IPI ≥ 2 | Polatuzumab vedotin + R-CHP | Pola-CHP-R: 440 | 2 years: 76.7% | 2 years: 88.7% |
| Tilly et al. | | | R-CHOP: 439 | 70.2% | 88.6% |
| New Engl J Med (2021) | | | | ($p = 0.02$) | ($p = 0.75$) |

The series of negative phase 3 trials has yielded important lessons. Restrictive clinical trial eligibility criteria, along with the delay required for biomarker testing, has led to the exclusion of the highest risk patients. In addition, due to the biological heterogeneity within cell-of-origin subtypes, patient selection may have lacked sufficient granularity to assess the benefit of novel agents. Future trials will need to incorporate adaptive designs to minimize these limitations.

More recently, the POLARIX phase 3 trial evaluated the anti-CD79b antibody-drug conjugate polatuzumab vedotin as a replacement for vincristine (pola-R-CHP) versus R-CHOP in patients with DLBCL and an International Prognostic Index (IPI) score of ≥2.[13] With a median follow-up of 28.2 months, the primary endpoint of investigator-assessed PFS was significantly improved with pola-R-CHP compared to R-CHOP; 2-year PFS 76.7% versus 70.2% (HR 0.73, 95% CI 0.57–0.95, $p = 0.02$), respectively. Although there was no difference in overall survival at the time of analysis, patients receiving R-CHOP were more likely to require secondary therapies, including stem cell transplantation and chimeric antigen receptor (CAR) T-cell therapy. Importantly, the safety profile was similar between the two arms, with no compromise in the delivery of chemotherapy. There was a slight increased incidence of febrile neutropenia in patients receiving pola-R-CHP. Although CD79b is expressed regardless of molecular subtype, exploratory subgroup analyses did not show clear benefit in patients with GCB subtype, patients ≤60 years of age, patients with bulky disease (≥7.5 cm) and patients with an IPI score of 2. However, subgroup analyses represent only univariate comparisons and were not powered to draw definitive conclusions. Thirty-month follow-up data has confirmed a sustained improvement in PFS with pola-R-CHP.[16] Based on the positive findings of the POLARIX trial, pola-R-CHP has earned regulatory approval and represents a new standard of care option for frontline treatment of DLBCL.

## 3 | EMERGING AGENTS AND NOVEL COMBINATIONS

Most patients with DLBCL not cured by R-CHOP face dismal survival. Improved biological knowledge of DLBCL has expanded the armamentarium via a diverse suite of novel agents. In only 5 years, a number of new treatments have received regulatory approval for relapsed/refractory DLBCL (RR-DLBCL), all with different mechanisms of action. Of note, CAR-T is covered elsewhere in this series, but is clearly a breakthrough in the treatment armamentarium of relapsed/refractory DLBCL. Selecting between chimeric antigen receptor T-cell therapy (CAR-T) and non-CAR-T options (including autologous stem cell transplant) is a complex discussion, and often driven by comorbidities, financial/logistical considerations, and access. Although a full discussion on patient selection is beyond the scope of this review, non-CAR-T therapies have the advantage of ease of administration in a community setting and can be given to a more frail patient. An oft-forgotten option for relapsed/refractory DLBCL is allogeneic hematopoietic stem cell transplant; in the era of CAR-T, this has declined in use and remains limited by issues related to age, comorbidities, availability of a suitable donor, and persistent high non-relapse mortality. Nevertheless, it is a worthy point of discussion with a subset of patients.[17] Here, we focus on the latest advancements in non-CAR-T-based drug therapies for RR-DLBCL.

### 3.1 | B-cell directed therapies

The early success of targeting CD20 cell surface receptors with rituximab has been replicated with newer monoclonal antibodies (mAbs) and antibody drug conjugates (ADCs) targeting CD19 and CD79b.

Polatuzumab vedotin (pola), an anti-CD79b ADC, was the first FDA-approved novel therapy for RR-DLBCL. Compared to bendamustine-rituximab (BR) alone, six cycles of pola-BR demonstrated superior complete responses, (CR: 40% vs. 18%), median PFS (9.5 vs. 3.7 months) and OS (12.4 vs. 4.7 months).[18] This was a transplant-ineligible RR-DLBCL population exposed to at least 1 prior treatment. Although pola-BR caused more cytopenias, it did not translate into higher infection or hospitalization rates.

Tafasitamab, a humanized anti-CD19 mAb, has limited single-agent activity but in a phase II study, tafasitamab delivered continuously until progression combined with 12 months of lenalidomide demonstrated an overall response rate (ORR) of 57.5% (CR 40%) with a median PFS and OS of 11.6 and 34 months respectively.[19] This transplant-ineligible population was relatively favorable as refractory and high grade B-cell lymphomas were excluded. Subsequent "real-world" studies including poorer risk groups have described significantly inferior results with CR in 8.7%–17% and median OS of 6.6–6.8 months.[20,21]

Loncastuximab tesirine, a CD19-targeting ADC with a pyrrolobenzodiazepine dimer payload was associated with an ORR of 47% (CR 40%) in RR-DLBCL including high grade and transformed lymphomas, when given for 12 months or longer if deriving clinical benefit.[22] The main toxicities reported in the pivotal phase II study were cytopenias, liver enzyme elevation, fluid retention and photosensitivity. The latter adverse events are distinctive to pyrrolobenzodiazepine and managed with a combination of modified dosing approaches and supportive care therapies which significantly improved the toxicity profile.

### 3.2 | Immunotherapeutic agents

Overcoming a cancer's ability to suppress the immune system has been a focus of drug development for decades. MAbs blocking immune inhibitory signals such as programmed cell death-1, have revolutionized therapy of some lymphoma subtypes, but proved disappointing in studies recruiting unselected, heavily pre-treated RR-DLBCL. Newer checkpoint inhibitors directed at LAG3, TIGIT and TIM3 are in early development but preliminary data demonstrate no significant efficacy signals in DLBCL.

Modest success, however, has been reported with CD47-sirp-alpha axis antagonists. Malignant cells upregulate this potent "do not eat me" myeloid signaling pathway to evade detection and destruction by macrophages and other innate immune cells. Several CD47 and SIRP-alpha therapies are in phase I/II development including magrolimab,[23] CC-95251,[24] ALX148,[25] TTI-622[26] and lemzoparlimab.[27] RR-DLBCL monotherapy results have been variable, thus most have been combined with rituximab yielding ORR between 29% and 64%. There are ongoing trials combining magrolimab with chemotherapy (NCT02953509). Reversible, predominantly mild cytopenias are the most common toxicity of this therapeutic class.

### 3.3 | Bispecific antibodies

T-cell engaging agents with a B-cell binding domain have yielded some of the most promising results in RR DLBCL to date. Bispecific antibodies (bsAb) combine B cell-surface targeting via CD20, CD19 or CD22 most commonly with T-cell engagement via CD3. These drugs offer very effective "off-the-shelf" T-cell manipulation with manageable toxicity.

Efficacy of CD3/CD19 therapy was first demonstrated with blinatumomab for B-lymphocytic leukemia, however RR-DLBCL populations met challenges with continuous 4–8 weeks long infusions and prohibitive neurotoxicity.[28] Newer bsAbs such as TNB486[29] are aiming to address these barriers.

The most advanced in development are the CD3/CD20 agents (Table 2). The phase II study of fixed-duration glofitamab in RR-DLBCL, after 2 or more treatment lines, yielded ORR and CR of 52% and 39% respectively, with the majority (78%) of CR ongoing at 12 months.[31] Median duration of response, PFS and OS were 18.4, 4.9 and 11.5 months. In a similar population, subcutaneous epcoritamab led to ORR and CR of 63% and 39% respectively with durable responses again noted. Unlike glofitamab however, epcoritamab was continued until disease progression or unacceptable toxicity.[32] These results led to FDA filing for both glofitamab and epcoritamab.

Studies of T-cell engagers binding CD3/CD22 for example, JNJ-75348780, (NCT04540796), IgM CD3/CD20 bsAbs such as IGM2323[40] (NCT04082936) and expansion to so-called "trispecifics", which include either one T-cell and two inhibitory B-cell binding domains, or co-stimulatory T-cell signals with one B-cell signal are ongoing.[41-43]

Toxicities of these T-cell engagers typically reflect the dual T-cell *stimulation* and B-cell *inhibition* thus manifest most commonly as cytokine release syndrome (CRS), cytopenias and infections related to hypogammaglobulinaemia. High-grade neurotoxicity is rare. Dose ramping to target dose over weeks coupled with supportive medications, close monitoring, and early employment of mitigating anti-cytokine therapies such as tocilizumab have reduced side-effects significantly. Corticosteroids are also an important means of mitigating toxicity. These treatments, however, continue to require specialized multidisciplinary toxicity management with prolonged observation periods, particularly during the first weeks of commencement. Newer studies are focused on fixed duration treatment and antimicrobial prophylaxis with viral monitoring to reduce the B-cell-directed associated toxicities.

TG1801 is a first-in-class CD47/CD19 bsAb.[35] RR-DLBCL patients treated within the phase I study experienced an ORR 56% and CR 40% in combination with the anti-CD20 agent ublituximab. Main toxicities were mild and included anemia, thrombocytopenia, fatigue and infusion reactions. This strategy continues to be explored with the addition of agents co-targeting CD47/CD20.

### 3.4 | Other

Selinexor, an oral selective XPO1-mediated nuclear export inhibitor, received FDA approval in 2020 for RR-DLBCL based on efficacy described in the Phase II SADAL trial.[30] The ORR of 28% (CR 12%), median PFS and OS of 2.1 and 9.1 months respectively is comparatively low, despite refractory populations being largely excluded. Additionally, the challenging toxicities has limited use in RR-DLBCL treatment.

Several other newer therapies still under evaluation include the ROR1 antibody-drug conjugate zilovertamab vedotin,[44] CELMoD (cereblon E3 ligase modulator) CC282[45] and MALT1 protease inhibitors.[46] The latter may be more potent in specific DLBCL subsets, but this is yet to be confirmed.

### 3.5 | Principles of combination and future directions

Although more choice for RR-DLBCL has improved outcomes overall, meaningful benefits of single-agent new therapies are limited to a minority of patients. Building on the success of polydrug chemotherapy and the diverse mechanisms of action plus manageable toxicity of established novel agents, early studies of "chemo-free" combinations are surfacing (Table 2).

Phase I/II combination trials of small molecules, immunomodulators and immunotherapy have largely failed to shift the treatment paradigm yet, either due to limited additive efficacy or more rarely, unexpected toxicities.[47-49] The most promising to date are bsAb combinations, with numerous randomized trials underway.

A major hurdle of future success is the complete absence of useful biomarkers predicting response or resistance in RR-DLBCL for any current agents. This is despite the recognition of DLBCL biological heterogeneity, evolution and host immune activity. In fact, several of the most active approaches, such as CAR-T and bsabs, are agnostic of mechanistic drivers. Knowledge gains are also required in optimal sequencing, particularly with current treatments such as CAR-T and bsabs. There are also gaps in defining optimal surveillance for detecting relapse. The next generation of combination trials should be based on strong biological rationale, low toxicity, patient preferences, and most importantly, inclusion of patients that adequately reflect diverse clinical populations.

**TABLE 2** Current agents in treatment of relapsed/refractory diffuse large B-cell lymphoma (RR-DLBCL).

| Therapy | Treatment length and delivery | *n* | Prior lines | ORR (%) | CR (%) | mDOR (months) | PFS (months) | OS (months) | Comments |
|---|---|---|---|---|---|---|---|---|---|
| FDA approved therapies (as of Mar 2023) | | | | | | | | | |
| Polatuzumab Bendamustine Rituximab[18] | 6 cycles (24 weeks) IV | 40 | ≥1 | 45 | 40 | 12.6 | 9.5 | 12.4 | |
| Tafasitamab + lenalidomide[19] | Tafasitamab: Continuous 2 weekly IV lenalidomide up to 12 cycles (4-weekly oral) | 81 | 1–3 | 57 | 40 | 34.1 | 11.6 | 33 | |
| Loncastuximab[22] | 12 months (or longer if deriving benefit) 3-weekly IV | 145 | ≥2 | 48 | 24 | 10.3 | 4.9 | 9.9 | |
| Selinexor[30] | Continuous oral until progression | 127 | 2–5 | 28 | 12 | 9.3 | 2.0 | 9.1 | Good prognosis patients. Required disease stability for 8 (if prior CR/PR) or 14 weeks (if prior SD/PD) prior to study entry. |
| Bispecific therapies | | | | | | | | | |
| Glofitamab[31] | 3-weekly (12 cycles) IV | 155 | ≥2 | 52 | 39 | 18.4 | 4.9 | 11.5 | Pretreatment with obinutuzumab to reduce CRS. |
| Epcoritamab[32] | Weekly C2-3, 2 weekly cycles 4–9 then 4-weekly until PD subcut | 157 | ≥2 | 63 | 39 | 12.0 | 4.4 | Not reached | Frequency of drug administration differs with cycle number. |
| Mosunetuzumab[33] | 3-weekly IV | 129 | ≥1 | 35 | 19 | 7. | 1.4 m | NR | For 8 or 17 cycles based on response. |
| Odronextamab[34] | Continuous weekly IV for 12 weeks, then 2 weekly IV until PD | 85 | ≥1 | 53*/33** | 53*/27** | Not reached | 11.5*/ 2.0** | NR | *With no prior CAR-T. **With prior CAR-T. |
| TG-1801[35] | Up to 24 cycles IV | 14 | ≥1 | 56 | 0 | NR | NR | NR | Frequency of drug administration differs with cycle number. |
| Newer combination therapies | | | | | | | | | |
| Rituximab Polatuxumab Lenalidomide[36] | 12 months (6 cycles pola) 3 weekly IV/oral | 57 | ≥1 | 39 | 29 | 8. | 6.3 | 10.9 | |
| Mosunetuzumab polatuzumab[37] | 8 cycles 3 weekly IV mosun, 6 cycles pola | 60 | ≥1 | 62 | 48 | NR | 8.9 | NR | |

(Continues)

TABLE 2 (Continued)

| Therapy | Treatment length and delivery | n | Prior lines | ORR (%) | CR (%) | mDOR (months) | PFS (months) | OS (months) | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Glofitamab Polatuzumab[38] | 3-weekly (12 cycles) IV glofitamab, 6 cycles pola | 33 | ≥1 | 73 | 51 | NR | NR | NR | HGBL, transformed FL and DLBCL eligible. Median follow up only 3.2 months. |
| Epcoritamab-chemotherapy GemOx or R-DHAX/C[39] | Epcoritamab continuous, 4 cycles GemOx/ 4 cycles R-DHAX/C | 27 | ≥1 | 92 | 60 | NR | NR | NR | Frequency of drug administration differs with cycle number. Median follow up 6–9 months. |
| | | 29 | ≥1 | 85 | 65 | Not reached | NR | NR | |

Abbreviations: CAR-T, chimeric antigen receptor T-cell therapy; CR, complete response rate; FL, follicular lymphoma; GemOx, gemcitabine, oxaliplatin; HGBL, high grade B cell lymphoma; mDOR, median duration of response; NR, not reported; ORR, overall response rate; OS, overall response rate; PFS, progression free survival; pola, polatuzumab; R-DHAX/C rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin.

### 3.6 | Access and patient selection

For patients ineligible for or relapsed post CAR-T cell therapy, there is no clear guidance on the next best therapy of choice. Uncertainties remain with respect to the value of sequential CD19-targeting treatments, optimal order of immunotherapy with immunosuppressive agents, feasibility of community bispecific delivery and cost-effectiveness of newer combinations. In many countries, access to these medications is restricted and decisions must be based on availability alone. For those with ease of access, decisions are influenced by patient preference, mode and location of delivery, toxicity profile, treatment duration, prior therapy and antigenic expression (e.g., CD19 and CD20) on the relapsed tumor sample. Ultimately, further research is needed to provide the best strategies moving forward in this difficult to treat population.

## 4 | SPECIAL POPULATIONS: OLDER ADULTS WITH DLBCL

As described above, the goal of therapy in DLBCL is to achieve a durable remission that translates into cure with time. Unfortunately, curative potential is lower in certain populations, especially the older adult (here defined as ≥75 years) and those with significant comorbidities. From an epidemiologic perspective, older adults constitute the majority of patients with DLBCL and, yet, are profoundly underrepresented in clinical trials. The Surveillance, Epidemiology, and End Results (SEER) database from the United States reports that more than half of all DLBCL occurs in people ≥65 years, and nearly one-third of patients are ≥75 years old (https://seer.cancer.gov/statfacts/html/dlbcl.html). Unfortunately, both PFS and OS decrease with age, and this is observed in clinical trials as well as in observational datasets.

Prospective data on treating older DLBCL patients has historically been limited to single arm trials, with R-mini-CHOP setting a modern standard for patients over age 80 years with an expected 2-year PFS and OS of 47% and 59%, respectively.[50] Key observations from this pivotal trial include that there is early and overall mortality, with 12/149 (8%) percent of patients dying of treatment-related effects despite attenuated dosing. Furthermore, efficacy is modest, with 33/149 (22%) of patients dying of lymphoma. So, this is "a" standard, but one that requires significant improvement. More recently, randomized trials are building on this backbone. The SENIOR trial showed that lenalidomide plus R-mini-CHOP unfortunately did not improve outcomes with 2-year OS 66% in both arms.[51] There are ongoing trials testing the addition of oral azacitidine (NCT04799275) or polatuzumab (NCT04332822) to R-mini-CHOP. Other trials have moved away from chemotherapy entirely, albeit likely in a more selected population[52]; in this study, the combination of ibrutinib, lenalidomide and rituximab was prospectively tested in patients with a median age of 64 years, with one-third of patients over age 70 years. The early data shows impressive complete response rates (94%) and PFS and OS. However, it is not clear that "chemo-free" will equate to "toxicity-free", and more investigation is needed.

The bispecific agent targeting CD20 and CD3, mosunetuzumab, also has promising single agent activity in frail/unfit older DLBCL patients in the frontline setting.[53] Among 40 patients with a median age of 84 years (range, 67–100 years) and significant comorbidities, nearly two-thirds of patients had an objective response with manageable toxicity. The results are quite preliminary at this time, and we await mature data.

A key challenge is determining which older adult is "fit" for anthracycline-based treatment, or even any treatment at all. A series of earlier Italian studies have led to a recent international analysis proposing a simplified geriatric assessment (sGA) and "Elderly Prognostic Index" (EPI) to assist in decision-making.[54] The sGA classifies patients into three categories of fit, unfit, and frail with important differences in 3-year OS of 75%, 58%, and 43%, respectively. The EPI combines this sGA, the IPI, and hemoglobin level to define three risk

groups with disparate survival. The prospective randomized S1918 US Intergroup trial (NCT04799275) will be the first to prospectively stratify patients based on frailty.

## 5 | CONCLUSIONS

Major progress has been achieved in treating large B-cell lymphomas in the past decade, both in the front-line and especially in the relapsed/refractory settings where there are now a plethora of options. R-CHOP has been a highly successful backbone and sets a high bar. While it has been difficult to show incremental improvements on this backbone, the recent POLARIX trial is encouraging and has led to approvals in many parts of the world. In the relapsed and refractory settings, we have more options than ever before, ranging from cellular therapy (discussed in a separate chapter) to antibody-drug conjugates and better combinations. The emerging class of bispecific antibodies promises to add to the arsenal of relapsed/refractory management options, and is also being tested as part of initial treatment.

Overall, several hurdles in the front-line management of DLBCL are to incorporate biologic heterogeneity if we are to attain a precision approach, develop response-adapted treatment (either via imaging or blood-based testing), and reduce the toxicity of current strategies in vulnerable populations. Furthermore, even as there are increasing options with improved survival, it is clear that major gaps in access, even within wealthier nations, persist. The glaring lack of diversity in the majority of therapeutic trials leading to regulatory approval highlights disparities in racial groups as well as socioeconomically disadvantaged patient populations.[55] This latter point is a critical topic that limits true progress and sets an important goal for the next generation of trials.

### CONFLICT OF INTEREST STATEMENT

Allison Barraclough has received honoraria from Gilead, Janssen, Roche. Eliza Hawkes has research funding paid to her institution from Roche, Bristol-Myers Squibb, Merck KgA, Astra Zeneca; has advisory boards BMS, Astra Zeneca, and advisory fees (paid to institution) from Roche, Gilead, Antengene, Link, Novartis, Beigene and Merck Sharpe & Dohme, speakers fees from Roche, Regeneron, Janssen, AstraZeneca (paid to institution). Sonali M. Smith has consulting fees from Gilead and Ono Pharmaceuticals; institutional research funding from Epizyme, TG Therapeutics, Pharmacyclics, FortySeven, Karyopharm, BMS, Acerta, Genentech, Portola, Curis, Celgene.

### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

### ORCID

*Sonali M. Smith* https://orcid.org/0000-0002-9893-4949

### PEER REVIEW

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