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2021 Update on Diffuse large B cell lymphoma: A review of current data and potential applications on risk stratification and management

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Abstract

Diffuse large B cell lymphoma (DLBCL), the most common type of Non-Hodgkin lymphoma (NHL), comprises a heterogeneous group of diseases with different biology, clinical presentations, and response to treatment. R-CHOP remains the mainstay of therapy and can achieve long-term disease control in nearly 90% of patients presenting with limited-stage and in up to 60% of those presenting with advanced stages. Advances on the understanding of the genetic landscape and molecular features of DLBCL have identified high-risk subsets with poor outcomes to chemo-immunotherapy that are actively being studied in clinical trials. Novel therapies could potentially improve outcomes for patients with high-risk disease. Studies evaluating risk-adapted therapy based on classification by cell of origin (COO) and molecular features are ongoing. Developments in the fields of immunotherapy, mostly with adoptive T-cell therapy, have significantly improved the outcomes of patients with relapsed refractory disease. In this review, we will summarize the recent data and discuss ongoing efforts to improve DLBCL treatment in the frontline and relapsed refractory settings.

1 | INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the most common hematological malignancy, with an estimated number of 77 240 new cases in the US in 20 201.[1] DLBCL, the most frequent NHL subtype, accounts for 30%–40% of cases. DLBCL itself comprises a heterogeneous group of biologically distinct entities resulting in the clonal proliferation of a germinal or post-germinal malignant B cell. The disease is usually aggressive, and the diagnosis is commonly made by biopsy of a suspicious lymph node or an extranodal tumor where the normal architecture is replaced by sheets of large cells that stain positive for pan-B cell antigens, such as CD20 and CD79a.

The standard treatment of DLBCL in 2021 remains chemo-immunotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). Though this modality is safe and effective, up to 45%–50% of patients will relapse. Ongoing efforts in

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the understanding of the genomic and transcriptomic landscape of DLBCL have identified subsets of patients with poor prognosis to chemo-immunotherapy. These advances guide the design of novel trials evaluating novel combinatory regimens in the upfront and relapsed settings and inform patient selection. In this review, we will summarize the recent data and discuss the use of new agents in the frontline treatment of DLBCL and in the management of the relapsed or refractory disease.

2 | CLASSIFICATION

Over the last two decades, multidisciplinary efforts from pathologists, molecular scientists, and clinicians have identified unique DLBCL subtypes by either cell of origin (COO) or molecular characteristics. These classification systems are now routinely used to identify subsets of patients with high-risk disease and poorer outcomes to up-front standard R-CHOP therapy.

2.1 | Cell of origin

A landmark study evaluated the gene expression profiling (GEP) of 96 normal and DLBCL lymphocytes and identified three unique genetic signatures with distinct patterns of somatic mutations[2] Germinal center B cell-like (GCB) DLBCL has a gene expression profile characteristic of normal germinal center B cells with intraclonal heterogeneity, ongoing somatic hypermutation, and CD10 and BCL6 expression. The activated B-cell like (ABC) subtype has a gene expression of post-germinal or activated B cells with high expression and constitutive activity of the nuclear factor kappa B (NF-KB) complex and expression of IRF4 and BCL2. The third subtype is the unclassified subtype, and accounts for 10%–15% of cases. The capacity to perform GEP routinely on fresh frozen samples is limited, and immunohistochemical (IHC) algorithms have been the most common method to determine COO in clinical practice. The IHC algorithm developed by Hans and Tally is the most widely used. More recently, novel platforms such as the Lymph2Cx allow for digital GEP on fixed, paraffin-embedded tissue. Though its use is restricted mostly to research, several studies have shown better concordance with GEP than IHC[3,4]

2.2 | Molecular features

C-MYC is a proto-oncogene located in chromosome 8q24. Ten to fifteen % of patients with newly diagnosed DLBCL have an underlying MYC rearrangement, resulting in dysregulated cellular survival and proliferation. Approximately half of these cases also carry a rearrangement of the anti-apoptotic proto-oncogene BCL2 and/or its transcription repressor BCL6. These genetic rearrangements are identified by fluorescent in-situ hybridization (FISH). Their presence defines a DLBCL subset known as double-hit or triple-hit lymphoma, recognized in the most recent WHO classification as High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (HGBCL-DH/TH).[5] These patients account for 8%–10% of de novo DLBCL diagnoses, have more aggressive disease and a worse prognosis after frontline treatment with R-CHOP, especially in patients with advanced-stage disease.[6,7] However, even within this group, there is further heterogeneity. More recently, Ennishi et al. performed a comprehensive analysis of RNA sequencing data from 157 patients with GCB DLBCL treated with up-front R-CHOP.[8] They established a

Double-Hit gene expression signature (DHITsig) able to identify a high-risk subset of GCB cases (27%). This DHITsig group had a 5-year time to progression rate of 57% compared with 81% for the rest of the cohort. HGBCL-DH/TH with BCL2 rearrangements accounted for only 50% of the high-risk DHITsig group. A subsequent study using whole-genome sequencing showed the presence of cryptic rearrangements of MYC or BCL2 not detectable by routine testing within the DHITsig+ that may account for underlying MYC dysregulation in these patients.[9] Also, patients with DLBCL can have a double expresser lymphoma (DEL), characterized by overexpression of the c-MYC oncogene and BCL2 detected by IHC (≥40% and > 50%, respectively). DELs account for approximately a third of de novo cases and have an intermediate prognosis with up-front R-CHOP therapy. DELs can also be detected in up to 50% of relapsed refractory DLBCL, where they are also associated with poorer outcomes with salvage chemotherapy treatment.[7] Notably, GCB is enriched for DH/TH subtypes and ABC for DEL.[10] In sum, this data highlights the need to routinely perform both IHC and FISH studies at the time of diagnosis and preferentially also at the time of recurrence.

2.3 | Genetic subtypes

The use of whole-exome sequencing further identified new genetic subtypes of disease characterized by frequently recurrent mutations. Schmitz et al. analyzed 574 pre-treatment DLBCL biopsy samples and identified four distinct genetic subtypes of disease with different recurring high-frequency mutations.[11] These categories include the MCD, BN2, N1, and EZB subtypes. The MCD subtype was characterized by the co-occurrence of MYD88(L265P) and CD79 mutations, the BN2 subtype by BCL62 fusions and NOTCH2 mutations, the N1 subtype had frequent NOTCH1 mutations, and the EZB subtype had EZH2 and BCL2 translocations. The MCD and N1 subtypes corresponded to ABC disease, while the BN2 and EZB subtypes corresponded to the GCB subtype. These groups portend different outcomes to upfront therapy. BN2 and EZB subtypes conferred a good prognosis, while the other subtypes conferred a poor prognosis. In parallel, Chapuy and colleagues[12] classified 304 primary, previously untreated DLBCLs into five different DLBCL clusters. These include two distinct subsets of a low-risk ABC-DLBCL (C1 associated with MYD88 mutations), a poor prognosis ABC-DLBCL (C5 that resembles the MCD subtype with MYD88-L265P and CD79 mutations), an ABC/GCB-independent group (C2 characterized by mutations and deletions of the chromosome 17p), a GCB-DLBCL with poor and good risk (C3 and C4, respectively).

3 | RISK STRATIFICATION

Over the last three decades, the International Prognostic Index (IPI) has been used to predict prognosis in aggressive NHL treated with doxorubicin-containing regimens. This score has been validated in the rituximab era (R-IPI), where patients with a score of 0–1, 2, 3, and 4–5 had a 3-year OS of 91%, 81%, 65% and 59%, respectively.[13] More recently, classifications based on COO and molecular features allow the identifications of patient subsets with poor prognosis. In addition, several studies have reported the utility of PET imaging and circulating tumor DNA in the prognostication of patients with lymphoma.

3.1 | Positron emission tomography – Computed tomography (PET/CT)

PET-CT is a valuable tool to accurately determine baseline stage in lymphoma. However, its use in the assessment of response to therapy has limitations due to situations leading to false positives results in the setting of concomitant inflammation or infection, or false-negative results due to its inability to detect microscopic disease. These limitations are demonstrated by the mixed results using the Deauville score visual assessment in determining early response to therapy.[14] Other measurements than the commonly used Deauville score may provide more accuracy. For example, the retrospective evaluation of the 360 patients from the phase 3 REMARC trial, which evaluated the addition of lenalidomide maintenance vs. placebo in DLBCL patients age ≥ 60 years old treated with upfront R-CHOP, used total metabolic tumor volume (TMTV) calculated as the sum of the metabolic volumes of all nodal and extranodal lesions.[15] A high TMVT, defined as >220 at baseline PET, was able to identify patients with inferior EFS (HR 2.3, $p = .0002$) and OS (HR 3.3, $p = .0001$) when compared with those with lower TMVT. The prognostic ability of high TMVT was maintained across the different treatment groups, and after adjustment for LDH, B2-microglobulin, performance status, and clinical risk scores (IPI and NCCN-IPI).

Another quantitative approach, the delta SUVmax, compares the SUV value of the most FDG-avid lesions on baseline and interim scans and may improve reproducibility during response assessments. To this point, Schoder et al. recently reported the results of a prospective analysis of PET-CT serial evaluations of 504 patients studied in the phase 3CALGB 50303 trial. They performed a comparison between visual Deauville 5-point scale with percent change in FDG uptake (delta SUV).[16] With a median follow-up of 5 years, a delta SUV ≥66% on interim-PET, measured after two cycles of chemotherapy, was predictive of OS (HR 0.21, $p = .02$) but not PFS. In contrast, visual assessment by Deauville score did not predict either outcome. The delta SUV value was also assessed in a phase 2 study of 1073 patients with newly diagnosed CD20+ lymphoma, including 609 with DLBCL.[17] Patients were treated with two cycles of R-CHOP followed by an interim PET CT (iPET). A negative scan was defined as delta SUVmax >66%. If the iPET was negative, patients were randomized to R-CHOPx4 arm vs. R-CHOPx4 plus two cycles of rituximab arm. If the interim scans were positive, patients were randomized to an escalated Burkitt protocol arm or R-CHOP × 6 arms. The iPET negative was negative in 87.5% of patients and positive in 12,5%. The post-hoc analysis compared the deltaSUV method with the Deauville 5-point scale. The study reported that iPET scan assessed by deltaSUV but not Deauville score accurately predicted better 2-year PFS (79.4% vs. 36.7%, $p < .0001$) and 2-year OS (88.2%vs 59% $p < .0001$) in those patients with negative scans across all lymphoma types. However, escalation of treatment based on positive iPET did not translate into improved outcomes, similarly to several earlier trials, demonstrating the limitations of interim PET CT in guiding therapy in DLBCL.[18]

3.2 | Circulating tumor DNA (ctDNA)

Circulating cell-free DNA is continuously released into the peripheral bloodstream by normal or tumor cells undergoing cell death. Novel Minimal Residual Disease strategies use next-generation sequencing (NGS) techniques to identify clonal tumor immunoglobulin heavy chain sequences (eg ClonoSeq®; Adaptive Biotechnologies) or tumor-specific

mutations from a panel of disease-specific genes—cancer personalized profiling by deep sequencing (CAPP-Seq).[19] Advantages of monitoring cfDNA are its non-invasive nature with the potential to track clonal evolution and detect new mutations that arise during treatment, which could be potentially exploited using targeted agents. In a landmark study, Rochewski and colleagues retrospectively analyzed ctDNA in pre-treatment tumor specimens, and serial serum samples of 126 patients with untreated DLBCL enrolled in three trials of upfront R-EPOCH vs. EPOCH.[20] CtDNA was analyzed using NGS by clonal VDJ rearrangements. After completion of treatment, patients were monitored with serial CT scans and concurrent serial serum samples. With a median of 11 years, positive ctDNA during surveillance had a positive predictive value of 88.2% and a negative predictive value of 97.8% for relapse. Patients developed detectable ctDNA with a lead time of 3.5 months prior to clinical progression. The ability of circulating tumor DNA (ctDNA) to detect early relapse has been confirmed since in several others studies, including in high-risk patients,[19] post-allo-HSCT,[21] and in the RR setting in patients receiving CART-therapy[22] or other novel therapies (Herrera ASH 2020).

4 | UPFRONT THERAPY

DLBCL is an aggressive but curable disease for most patients, with survival rates similar to the general population in patients who have remained disease-free for 2 years after frontline therapy.[23,24]

The standard frontline treatment of DLBCL remains chemo-immunochemotherapy with R-CHOP +/− radiation according to disease stage and clinical risk factors. For treatment purposes, patients with untreated DLBCL are generally classified as having either limited-stage disease (Ann Arbor stage I or II without bulky disease or B symptoms) or advanced-stage disease.

4.1 | Limited stage DLBCL

Early- or limited-stage diffuse large B-cell lymphoma (DLBCL) accounts for approximately 30% of all DLBCL cases. In the pre-rituximab era, the SWOG S8736 trial established the use of a combined modality of abbreviated chemotherapy (CHOP x3) plus consolidative radiation therapy over CHOP x8 as the standard of care for these patients.[25] However, long-term follow-up revealed a continued risk of relapse in both groups. With a median follow-up time of more than 17 years, the PFS and OS of CHOP8 and CHOP3-RT were similar (12 vs. 11.1 years, $p = .73$ and 13.0 vs. 13.7 years, $p = .38$).[26] The addition of rituximab to CHOP3-RT in SWOG S0014 improved outcomes with a 2-year PFS of 92% and a 4-year OS of 92%.[27] Though the long-term follow-up data have not been published, the median PFS and OS were not reached at a median follow-up time of 12 years.[26] Several trials have recently informed a positron emission tomography scan (PET) guided approach of abbreviated chemotherapy without radiation. In a LYSA/GOELAMS trial, 334 patients with stage I/II DLBCL, non-bulky disease who achieved complete metabolic response (CMR) by PET after treatment with R-CHOPx4 were randomized to receive consolidative radiation with 40Gy versus observation. The 5-year survival was comparable in the radiation versus observation arms (PFS 92% vs. 89% and OS 92% vs. 96%).[28] Underscoring that an abbreviated course

of RCHOP alone without radiation may be sufficient for a select group of patients has been the FLYER study,[29] a phase 3, multicenter non-inferiority trial that enrolled 592 young patients (≤60 years) with stages I-II, non-bulky disease, normal LDH, and ECOG performance status of 0–1. The investigators compared R-CHOP × 6 vs. R-CHOP × 4 followed by two doses of rituximab without radiation consolidation. After a median follow-up of 5.5 years, the three-year-PFS for patients was 93% vs. 96% for those treated with R-CHOP × 6 vs. R-CHOP × 4 followed by two doses of rituximab, establishing four cycles of RCHOP as the standard of care for these low-risk patients.

Using PET-CT after three cycles of RCHOP, 158 patients with non-bulky stage I/II DLBCL were enrolled and either received one further cycle of RCHOP of the iPET3 was negative, or involved field radiation therapy followed by ibritumomab tiuxetan radioimmunotherapy. Eight-nine percent of participants achieved a negative iPET3 and, with abbreviated therapy with R-CHOP × 4 alone, achieved a 5-year PFS of 87% and a 5-year- OS of 89%.[30] As opposed to FLYER, S1001 included elderly patients (54% of study subjects were older than 60 years) and patients with adverse clinical characteristics (elevated LDH in 14% and smIPI score ≥ 1 in 73%). However, a retrospective study of patients with limited-stage DLBCL with MYC rearrangements showed a lower two-year PFS and OS of 78% and 86%, respectively in patients receiving R-CHOP or intensified immunochemotherapy regimens with or without consolidative radiation per physician discretion without clear association of survival and therapy intensity.[31] Nevertheless, current data support the option for an abbreviated course of chemo-immunotherapy for patients with limited-stage DLBCL in the majority of patients.

4.2 | Advanced stage DLBCL

Advanced stage DLBCL accounts for 60%–70% of patients with DLBCL. The standard upfront treatment of advanced-stage DLBCL has remained R-CHOP for the last two decades. This modality can be curative in up to 60% of de novo DLBCL cases.[32] Multiple attempts to improve the R-CHOP backbone, including intensification of dose intensity (eg, R-CHOP14 vs. RCHOP-21),[33,34] other CD20 monoclonal antibodies (eg, rituximab for obinutuzumab),[35] infusional vs. bolus (eg, CALGB50303),[36] or dose-dense rituximab[37] have so far not translated into improved patient outcomes, especially for those with high-risk disease identifying an area of unmet need.

4.3 | Treatment options in DLBCL in high-risk DLBCL – up-front therapy

Over the last three decades, ongoing efforts to better understand the disease biology have identified subsets at high-risk for failure to upfront R-CHOP. Risk-adapted therapy informed by lymphoma pathobiology is an attractive approach aimed to improve outcomes for these patients.

4.3.1 | Non-GCB—ABC DLBCLs are characterized by the activation of the NF-κB pathway and chronic BCR signaling. In a retrospective study of 157 de novo DLBCL cases treated with an up-front rituximab chemo-immunotherapy regimen, patients with the ABC subtype as identified by GEP had worse 5-year PFS and OS compared to those with GCB subtype (31% vs. 76% and 45% vs. 80%, respectively).[4] Another study of 344 patients with

de novo DLBCL treated with R-CHOP evaluated the impact of COO determined by Lymph2Cx assay on FFPE reported similar results with the 5-year PFS and OS of the ABC subtype group was 48% and 56% versus 73% and 78% in GCB subtype.[3]

Efforts to improve up-front therapy in non-GCB DLBCL have combined R-CHOP with different biologic agents targeting BCR signaling and NF-κB pathway activation, including ibrutinib, bortezomib, and lenalidomide, but these have not translated into improved patient outcomes. Despite promising early results, prospectively conducted randomized, double-blinded placebo control Phase III trials evaluating the combination of R-CHOP plus ibrutinib for stage I-IV non-GCB/ABC DLBCL (PHOENIX trial)[38] and R-CHOP plus lenalidomide (R2CHOP) in non-GCB/ABC IPI 2–5 DLBCL (ROBUST trial) failed to demonstrated significant improvement in outcomes over RCHOP alone. These results probably reflect the wider heterogeneity within the COO subgroup. However, additional subgroup analyses of these studies suggested that younger patients and/or those with overexpression of Bcl-2 and Myc may have better outcomes with the addition of ibrutinib, but potential improvements in lymphoma-specific outcomes may have been negated by increased toxicities and less R-CHOP dose intensity in older patients. Similarly, the addition of lenalidomide may provide more benefit to patients with clinically higher-risk disease (IPI score of 3–5). Of note, the randomized phase II trial E1412 found a significant reduction of risk of death or progression in patients with DLBCL treated with R2CHOP (HR 0.66; $p = .03$), including patients with ABC and GCB subtypes. This apparent discrepancy may be explained by patient selection or statistical power, casting residual uncertainty on the role of lenalidomide in upfront DLBCL management. Preliminary Data from the SMART-START (NCT02636322) suggests combining two cycles of rituximab, lenalidomide, and ibrutinib (RLI) followed by CHOP or EPOCH may be a safe and potentially effective option. In this study, 60 patients with non-GCB DLBCL were enrolled, and results in 58 evaluable patients showed an ORR of 100% (CR 95%, PR 5%) with a 1-year PFS of 92.5% at the 16 months follow-up. Notably, one patient had a fatal fungal infection (CNS aspergillosis) attributed to concomitant use of high dose corticosteroids, leading to the prohibition of corticosteroids during the RLI only cycles with no further fungal infections identified.[39]

4.3.2 | DLBCL with MYC and BCL2 and/or BCL6 rearrangements (Double hit and triple hit lymphoma)—High-grade B-cell lymphomas with MYC and BCL2 and or/BCL6 rearrangements are usually identified in the GCB subtype and have consistently shown poor outcomes with upfront R-CHOP.[7,40] Despite this knowledge, its relative infrequency and the often highly aggressive clinical behavior have hindered prospective studies aimed at identifying the optimal upfront management, which up to now has been mainly informed by retrospective series with their inherent limitations.

A multicenter prospective study treated 53 patients with MYC rearrangement (45% HGBCL-DH/TH, 19% HGBCL, and 34% DLBCL) with six cycles of DA-EPOCH-R. After a median follow-up of 55.6 months, the 4-year EFS was 71.0% (95% CI, 56%–81%) with a 4-year OS of 76.7% (95% CI, 63%–86%), both of which significantly better compared to historical controls.[41] Another prospective multicenter phase II trial by the HOVON group studied the addition of lenalidomide to R-CHOP (R2CHOP) × 6 in 82 newly diagnosed MYC+ large B cell lymphoma (LBCL) patients. At the end of treatment, 67% of patients

achieved a complete response, and the 2-year estimates for OS, DFS, EFS of 73%, 75%, and 63%, respectively, after a median follow-up of 25.4 months were encouraging. In addition to modifications of an anthracycline-containing chemoimmunotherapy backbone, non-cytotoxic treatment strategies hold promise. ZUMA-12,[42] a phase 2, multicenter, open-label, single-arm study, explores the utility of the CD19-directed chimeric antigen receptor T cell (CAR T) product, Axicabtagene ciloleucel (axi-cel, Yescarta®), in the upfront management for patients with high-risk LBCL (DHL/THL or LBCL) with IPI score ≥ 3 at baseline and a positive interim PET scans per Lugano Classification. All patients undergo leukapheresis prior to systemic therapy. Patients with positiveiPET after 2 cycles of induction therapy undergo conditioning chemotherapy (cyclophosphamide 500 mg/m2/d and fludarabine 30 mg/m2/d for 3 days) followed by a single axi-cel infusion (target dose, two × 106 CAR T cells/kg). The preliminary data of 32 evaluable patients showed an impressive overall response rate of 85% and a CR rate of 74%, with 70% of participants having an ongoing response after a median follow-up of 9.3 months. Notably, all patients developed cytokine release syndrome (CRS), mostly grade 1–2. Neurological toxicity developed in 69% of the patients, with 25% having grade 3 or higher. Interestingly, the median peak CAR T cell levels, CAR T cell expansion, and frequency of CD45 or a CCR7-positive phenotype were greater in ZUMA-12 vs. ZUMA-1 Cohort 1, suggesting better T cell fitness. The results of these correlative studies are in line with a prior study suggesting better T cell fitness in myeloma patients at earlier stages of their disease.[43] At the annual ASH meeting in 2020, investigators showed that the addition of mosunetuzumab, a CD20xCD3 bispecific antiboty (BiTE), to CHOP (M-CHOP) resulted in an impressive ORR of 96%, with 85% CR in 27 patients with untreated DLBCL with a favorable toxicity profile. CRS events seen in Cycle 1 were mild, transient, and required minimal intervention, and no Grade ≥3 CRS events were reported. No neurotoxicity was observed.[44]

In addition to molecularly agnostic therapies, early phase studies evaluating the combination of DA-EPOCH-R with targeted therapies as Venetoclax [NCT03036904][45] and ixazomib [NCT02481310][46] are currently ongoing.

4.3.3 | DLBCL with overexpression of BCL-2—BCL-2 overexpression identifies another subset of patients with inferior outcomes to upfront R-CHOP. A multicenter, open-label phase 1b/2 study (CAVALLI trial) showed that the addition of venetoclax to R-CHOP in 206 patients with untreated advanced-stage DLBCL significantly increased 2-year PFS rate in Bcl-2–positive patients (78% vs. 62%; HR, 0.55) when compared with a contemporary historical control (GOYA study) despite a higher incidence of hematological toxicity, mainly neutropenia, which was managed with the use of growth factors.[47]

Additional select ongoing upfront trials in DLBCL are listed in Table 1.

5 | RELAPSED REFRACTORY DISEASE

5.1 | Salvage chemotherapy and ASCT

Salvage chemotherapy with autologous stem cell transplant (ASCT) consolidation is the current standard of care for transplant-eligible patients who have chemotherapy-sensitive disease. In the pre-rituximab era, approximately 50% of patients with relapsed DLBCL were

cured with this appraoch. In the rituximab era however, the benefit of ASCT is less pronounced. In the CORAL study, the 3-year PFS of patients previously treated with rituximab who received either R-ICE or R-DHAP prior to ASCT, was only 21%.[53] Maintenance rituximab did not improve the outcomes after ASCT compared to placebo. In addition, patients undergoing ASCT for relapsed DLBCL experienced excess death for at least 5 years after ASCT, mainly owing to progressive lymphoma. Maintenance strategies after ASCT in several other studies have so far not shown improvement in overall survival.[54–56]

Frigault et al. evaluated the use of the anti–PD-1 monoclonal antibody pembrolizumab after ASCT in patients with chemosensitive DLBCL in a phase 2, multicenter, single-arm study.[57] Of a total of 29 patients treated, only 62% completed all eight planned cycles of pembrolizumab, and 79% experienced grade 3 or higher adverse event and 34% grade 2 or higher immune-related adverse event. This study failed to meet its primary endpoint with an 18-PFS month of 59% and an 18-month OS of 93%.

5.2 | Treatment options in DLBCL for RR disease – tumor agnostic approach

In relapsed disease, the prognostic impact of COO remains less clear. The Bio-CORAL study suggested improved 3 year-PFS in GCB DLBCL treated with R-DHAP compared to those treated with R-ICE,[58] but multiple other studies have failed to reproduce these results.[59–61] In addition, novel immunotherapies are revolutionizing the therapy landscape of RR DLBCL, with the available data suggesting that their effectiveness is not determined by the molecular profile of the tumor. Before the advent of CAR T cell therapies, transplant-ineligible patients had a median OS of 3.3 months.[62] Similarly, patients with chemo-resistant disease or early relapse (<12 months) after ASCT have a median OS of 6 months.[63]

5.2.1 | Chimeric antigen receptor T-cell therapy—CARs are autologous genetically modified T cells formed by combining the antigen-binding site of an antibody with the intracellular domain of a T-cell activation receptor. The CAR gene is introduced into the T cell genome using a gammaretroviral or lentiviral vector. Upon encountering the surface antigen of interest in the target cell, the T-cell receptor's intracellular domain is directly stimulated independently of the HLA-complex.[64] Currently, there are 3 FDA-approved autologous CAR-T cell products for the treatment of relapsed or refractory large B-cell lymphoma after ≥2 lines of systemic therapy: axicabtagene ciloleucel (axi-cel, Yescarta ®), tisagenlecleucel (tisa-cel, Kymriah ®), and lisocabtagene maraleucel (liso-cel, Breyanzi ®). The ZUMA-1 trial led to the approval of axi-cel with a reported ORR of 83% and a CR rate of 54%, with ongoing responses observed in 42% of patients.[65] The approval of tisa-cel was based on the JULIET trial reporting an ORR of 52% with a CR rate of 40%.[66] The approval of liso-cel was based on the phase 1 TRANSCEND NHL 001 trial in which liso-cel induced an ORR of 73% and a CR in 53% of patients with heavily pretreated large B-cell lymphoma.[67] At a median follow-up of 12 months, the median DOR had not yet been reached. The toxicity profile of CAR therapy includes cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Notably, therapy is generally reasonably well tolerated by a broad range of patients, including those traditionally considered unfit for transplant because of advanced age. Recent real-world data publications

corroborate the results reported in the Juliet and ZUMA-1 trials, with durable responses occurring in approximately 30%–40% of patients.[68,69] In a retrospective study of commercial anti-CD19 CAR-T in patients with RR DLBCL, 49% of relapses after CAR T-cell treatment occur within the first month. Risk factors for early progression were ≥ two extranodal sites, increased CRP, and high total metabolic tumor volume at the time of treatment.[70] The association between disease burden and early relapse raises the possibility that CAR T cells may be more effective and safer if used as consolidation and/or earlier on in the disease course since CAR T cell efficacy relies on the fitness of the endogenous T cell repertoire, which can be compromised by extensive prior therapy and high disease burden. Selected studies of novel CAR-T therapies in RR DLBCL are listed in Table 2.

5.2.2 | Bispecific T-cell engager therapy (BiTEs)—BiTEs are antibodies formed by two single-chain variable fragments, one of which binds to a tumor antigen and the other onto T cells (mostly CD3), which then leads to T-cell mediated killing of tumor cells independent of MHC class I. BiTEs, similarly to CAR T cells, can stimulate the secretion of cytokines and potentially modify the tumor microenvironment, thereby restoring effective anti-tumor immunity.[75–77]

Mosunetuzumab: GO40515, is a humanized IgG1 BiTE targeting CD3 and CD20. In a phase 1/1b study of 270 heavily pretreated FL and DLBCL patients, single-agent therapy resulted in a ORR and CR rate of 42.2 and 18.6%, respectively. Notably, responses were also seen in the subgroup who had previously received CAR T-cell therapy, with an ORR of 39% and CR in 22%. The treatment was well tolerated with ICANS and CRS reported in 44% and 28.4% of patients, respectively. Both were mostly grades 1–2, transient and reversible.[78] An ongoing phase I/Ib dose-escalation study evaluating subcutaneous Mosunetuzumab reported ORRs and CR rates of 60% and 20% in 15 patients with RR aggressive NHL pts. CRS events were mild, transient, and required minimal intervention, and no Gr ≥3 CRS events were reported.[44] Consistent with reduced CRS, lower peak IL-6 levels were observed with SC dosing, with delayed onset versus IV administration.[79]

Glofitamab: Glofitamab is a novel 2-to-1 format BiTE with two CD20-binding molecules and one CD3-binding molecule. At the 2020 ASH meeting, an ongoing Phase I dose-escalation and expansion study in R/R NHL (NCT03075696) using a step-up dosing of glofitamab with obinituzumab pre-treatment reported an ORR of 60.7% and CMR rate of 53.6%, respectively, in the aggressive NHL group (n = 28). CRs were usually achieved early and observed at the first or second response assessment. Most patients had ongoing responses, including 13 of 15 responders with aggressive NHL. The safety profile of glofitamab was manageable, mostly ≤ grade 2 CRS. The step-up dosing of glofitamab can be used as a CRS mitigation strategy in addition to obinituzumab pre-treatment, allowing administration of a high target dose (30 mg).[80]

Epcoritamab: Epcoritamab is a novel subcutaneous CD3xCD20 bispecific antibody. In a Phase I/II study of patients with R/R CD 20+ NHL, epcoritamab achieved an ORR of 66.7% and CR of 33.3% at a dose of ≥12 mg; the response rate was higher at a dose ≥48 mg in the subset of patients with RR DLBCL (ORR 100%; CR of 28.6%). The responses seemed

durable, with median DOR not reached after a median follow-up of 10.2 months for patients in CR.[81]

5.2.3 | Antibody-drug conjugates (ADCs)—ADCs are complex molecules that selectively deliver cytotoxic agents to tumor cells by conjugation of a monoclonal antibody directed toward a target antigen expressed on the cancer cell surface to a cytotoxic payload via a chemical linker.[82] Two ADCs, brentuximab vedotin (BV) and polatuzumab vedotin (PoV), are FDA-approved for the treatment of NHL.

Brentuximab Vedotin consists of an anti-CD30 antibody, a cleavable linker, and a monomethyl auristatin E (MMAE) payload. In RR CD30+ DLBCL, single-agent BV showed an ORR of 44%.[83] BV-RCHP was tested for the frontline treatment of CD30+ B cell lymphoma, including DLBCL, with promising results (ORR 100%; 85% CR) and few excess toxicities.[84]

Polatuzumab Vedotin is a humanized anti-CD79b monoclonal antibody also conjugated to MMAE. A phase II trial randomized of 80 transplant-ineligible RR DLBCL patients after a least one prior line of therapy to either polatuzumab-vedotin in addition to rituximab-bendamustine (BR) or BR alone. At a median follow-up of 27 months, the study reported an ORR rate of 45% in Pola-BR vs 17.5% in the BR arm alone, with a CR of 40% vs 15% and a median DOR of 12.6 months v. 7.7 months.[85] Early phase studies of polatuzumab-vedotin with lenalidomide and obinutuzumab [NCT02600897], or lenalidomide, obinutuzumab and venetoclax [NCT02611323] are ongoing in RR DLBCL. Results of the upfront POLARIX study (Pola-RCHOP) are eagerly awaited [NCT03274492].

Loncastuximab Tesirine (ADCT-402) is a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer (PBD) toxin. In a single-arm open-label Phase 2 study (NCT03589469) in 183 patients with RR B-NHL who had failed ≥two therapies were evaluated. The study reported outcomes for 138 evaluable DLBCL patients with an ORR of 42.3% and a median DOR of 4.5 months. Notably, the ORR in DLBCL patients ≥75 years old, with primary refractory disease or DHL/THL was 55.6%, 23.3%, and 21.7%, respectively.[86] Early phase studies of loncastuximab with ibrutinib [NCT03684694] or rituximab [NCT04384484] in RR DLBCL are ongoing. Novel ADCs against CD22, CD25, and CD27 are currently being tested.

5.2.4 | Tafasitamab (MOR208, MONJUVI)—MOR208 is an Fc-enhanced monoclonal antibody against CD19 with direct cytotoxicity and enhanced antibody-dependent cell-mediated toxicity and phagocytosis. A phase II study of 81 patients with RR DLCBL evaluated the combination of MOR208 with lenalidomide (L-MIND study).[87] At a median follow-up of 13.2 months, the ORR was 60% (43% CR, 14% PR) with a median DOR of 21.7 months. Among CR patients, the median DOR had not been reached, with 93% of responses lasting ≥12 months. At a median follow-up of 17.3 months, the median PFS was 12.1 months. Toxicities of the combination were most commonly neutropenia, thrombocytopenia, and anemia, followed by diarrhea and fatigue. These results led to the FDA approval of tafasitamab in combination with lenalidomide. A phase II/III study of MOR208 with bendamustine compared to rituximab and bendamustine in RR DLBCL is

ongoing [NCT02763319]. Additionally, the FIRST MIND trial explores the role of tafasitamab in combination with R-CHOP plus lenalidomide or placebo in up-front therapy of untreated DLBCL.

5.2.5 | Checkpoint inhibitors—Checkpoint inhibitors have been studied in RR DLBCL with generally disappointing results. In a phase 2 study 121 patients with RR DLBCL, who were ineligible or progressed after ASCT, received nivolumab monotherapy at 3 mg/kg. The study reported an ORR of 3% in the transplant-ineligible and 10% in the "auto-HCT failed" cohort.[88] More recently, a retrospective evaluation of 59 patients with NHL suggests that treatment with checkpoint inhibitors could sensitize lymphoma to subsequent chemotherapy based on the finding that ORR to post-CBT (checkpoint blockade treatment) was 51%, and median DOR was significantly longer than to pre-CBT (310 vs. 79 days, $p = 0005$). At a median follow-up of 126 months, 20 patients (34%) remain in remission from their post-CBT therapy, with a median PFS of 63 months. The median OS to post-CBT therapy was not reached.[89] Furthermore, checkpoint inhibition may overcome treatment resistance to CAR T cell therapy in some patients, a strategy that is currently under investigation in the PORTIA study.[90–92]

5.2.6 | Selinexor—Selinexor is the latest FDA-approved agent for RR DLBCL. Selinexor is an oral selective inhibitor of exportin 1 (XPO1) that induces the nuclear accumulation and activation of tumor suppressor proteins and reduces Bcl2, Bcl-XL, and c-Myc oncoprotein levels. A phase II trial of 267 RR DLBCL patients after a least two prior lines of therapy evaluated the safety and efficacy of selinexor monotherapy. At a median follow-up of 27 months, the study reported an ORR rate of 28% with a CR of 12% and a median DOR of 9.3 months. The median DOR for patients in CR was 23.0 months.[93] An early phase study of selinexor in combination with different backbone therapies in RR DLBCL is actively recruiting [NCT04607772].

5.3 | Treatment options in DLBCL for RR disease by COO

Multiple combination approaches using multiple targeted agents are currently being studied in RR DLBCL. For example, the PCYC-1123 study (NCT02077166), a phase 1b/2 study, evaluates the combination of ibrutinib, lenalidomide, and rituximab (iR2) in 89 SCT-ineligible adults aged ≥18 y with RR non-GCB classified by IHC per the Hans algorithm. They reported an ORR of 47% with 28% of patients achieving a CR and 19% PR; 16% had stable disease. The median DOR, PFS, and OS were 18, 5, and 14 months, respectively.[94]

At ASH 2020 annual meeting, Melani and colleagues reported the preliminary results of the ViPOR study.[95] This regimen combines different targeted therapies directed at key survival pathways in B-cell lymphomas, such as regulation of apoptosis (BCL-2; venetoclax), B-cell receptor signaling (BTK; ibrutinib), and NF-κB survival pathways (IRF4/SPIB; lenalidomide). In a phase 1b/2 study, patients were treated with 4 dose-levels (DLs) of dose-escalated venetoclax (200 mg, 400 mg, 600 mg, and 800 mg) PO D2–14 (starts cycle 2 for DL1) in combination with fixed-dose ibrutinib 560 mg PO D1–14, prednisone 100 mg PO D1–7, obinutuzumab 1000 mg IV D1–2, and lenalidomide 15 mg PO D1–14. The regimen was well tolerated and a dose of venetoclax 800 mg was used for the phase 2 study. After the

first cycle, the ORR in 53 patients was 90%. Based on DLBCL subtype by IHC, ORR and CR rate was 62% and 54% in non-GCB and 50% and 21% in GCB DLBCL. Notably, ORR was 40% with 30% CR in 10 patients who failed prior CAR-T and completed ViPOR therapy. Selected studies of RR DLBCL according to COO are presented in Table 3.

6 | CONCLUSIONS

DLCBL is a highly heterogeneous disease with variable clinical presentation and outcomes. While our understanding of the genetic and molecular landscape of DLBCL has improved significantly over the last two decades, limited progress has been made leveraging this gained knowledge into improved upfront therapies, particularly for high-risk patients. Nevertheless, molecularly and genetically agnostic immunotherapeutics have positively impacted outcomes in patients with relapsed disease. The addition of immunotherapy to the arsenal treatment of DLBCL is poised to define a new standard of care in the upfront and relapsed setting. Furthermore, integrating these agents early on, when immune health in the host is still preserved, may significantly change how we approach upfront management. Strategies to better define suboptimal treatment responses early on will need to evolve to identify treatment failures outside of established high-risk features.

Nevertheless, the rapidly evolving armamentarium available to treat relapsed or refractory DLBCL offers an abundance of options in that setting. While this richness in available therapies in DLBCL provides exciting opportunities, this needs to be followed by strategies on how to best sequence and prioritize available treatments on and off clinical trials. As these agents are tested in earlier stages, research effort will need to focus on more standardized molecular profiling to more easily identify predictive biomarkers that may inform patient selection and clinical trial design.

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TABLE 1

Selected studies in upfront therapy

Title / NCT	Trial population	Patients	Intervention	Primary outcome
ZUMA-12/ NCT03761056[42]	HGBL, with MYC and BCL2 and/or BCL6 translocations, or LBCL with IPI score ≥ 3 and positive iPET	37	Conditioning Chemotherapy Flu/Cy + Axi-Cel Infusion	CR Preliminary data: ORR 85%, (74% CR and 11% PR)
NCT02481310[46]	Aggressive MYC-aberrant NHL (MYC-overexpression by IHC (> 40%), MYC-amplification (>4 copies) by FISH, and/or MYC-rearrangement by FISH)	38	Ixazomib + DA-EPOCH-R x6 followed by ixazomib maintenance	Safety and 12 month-PFS After induction, ORR 89%, CR 61%. Estimated 24-months PFS and OS were 66.9 and 78.7%, respectively.
ACCEPT/ NCT03571308[87]	Untreated CD20+ DLBCL	39	R-CHOP and acalabrutinib	Safety and ORR. No DLT events. Of 24 patients, ORR 95%, CR 82%, 12-month PFS and OS 100%.
NCT03147885[88]	Untreated stage III/IV DLBCL	44	Selinexor + R-CHOP followed by Selinexor maintenance for 1 year	PFS In 10 pts at Median follow up of 476 days, ORR 100%: CR 90%, PR 10%
NCT03995147[89]	Previously untreated DLBCL, transformed lymphoma and grade 3 B follicular lymphoma	30	Pembrolizumab +R-CHOPx6	PFS. At median follow-up of 32 months, 3-year estimated PFS is 83% and OS is 86% irrespective of COO by OHC
POLARIX/ NCT03274492[90]	Untreated CD20-positive DLBCL, IPI 2–5	1000	Polatuzumab with R-CHP vs R-CHOP	Investigator-assessed PFS
NCT04231877	Untreated aggressive B-cell large-B cell lymphoma (non-Hodgkin lymphoma) with adverse features per investigator assessment	18	Polatuzumab plus DA-EPCH-R	Safety
NCT03677141[44]	Previously untreated DLBCL, IPI 2–5	160	Monetuzumab plus CHOP or CHP-Polatuzumab Vedotin vs R-CHP-Polatuzumab	Safety and CR
First-MIND / NCT04134936[91]	Previously untreated DLBCL, IPI 2–5	60	Tafasitamab +R-CHOPx6 or R2-CHOPx6	Safety

Abbreviations: COO, cell of origin; CR, complete response; DLBCL, diffuse large B cell lymphoma; DLT, dose-limiting toxicity; Flu/Cy, fludarabine and cyclophosphamide; iPET, interim PET; IPI, international prognostic index; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; RR, relapsed and/or refractory.

TABLE 2

Select ongoing novel chimeric antigen receptor T-cell trials

In first relapse						
Title/NCT	**Target**	**Phase**	**Additional agents**	**Primary endpoint**	**Preliminary data**	**Status**
ZUMA-7 / NCT03391466*	CD19	3		EFS		Recruiting completed
BELINDA / NCT03570892*	CD19	3		EFS		Recruiting
TRANSFORM NCT03575351*	CD19	3		EFS		Recruiting
*Comparator arm: Platinum-based immunochemotherapy followed by high dose chemotherapy and autoSCT in responding patients						
In RR disease						
Novel targets and constructs						
NCT03277729	CD20	1/2		Safety		Recruiting
NCT04088890	CD22	1		Rate of successful manufacture, safety		Recruiting
NCT03870945[92]	CD19/CD20	1/2		Safety	ORR 75% in 12 patients, CR 42%.	Phase 2 recruiting
NCT04215016	CD19/CD20	1		Safety		Recruiting
NCT04007029	CD19/CD20			Safety		Recruiting
NCT03233854	CD19/CD22	1		Safety		Recruiting
Combinations with CPIs and targeted agents						
ZUMA-6 / NCT02926833[93]	CD19	1/2	Followed by atezolizumab	Phase 1:safety Phase 1 and 2: CR	No DLT seen in 3 patients treated	Recruiting completed
ALEXANDER (NCT03287817) [94]	CD19/CD22	1/2	Followed by pembrolizumab	Phase 1: safety Phase 2: ORR	No DLT seen in phase 1. ORR 69%; CRR 52%.	Recruiting completed
NCT02706405	CD19	1	Followed by durvalumab	Safety and pharmacokinetics		Recruiting
NCT04257578	CD19	1/2	BTK inhibitor acalabrutinib prior	Safety		Recruiting
ZUMA-19 (NCT04314843)[95]	CD19	1/2	Prior Lenzilumab, a humanized anti-GM-CSF MoAb	Incidence of Grade ≥ 2 NEs within 28 days of axi-cel administration		Recruiting

Abbreviations: CRR, complete response rate; DLBCL, diffuse large B cell lymphoma; DLT, dose-limiting toxicities; EFS, event-free survival; MoAb, monoclonal antibody; NE: neurological side-effects; ORR, overall response rate; RR, relapsed and/or refractory.

TABLE 3

Selected studies of targeted agents for relapsed refractory disease

NCT	Trial population	Patients	Intervention	Primary endpoint	Results
NCT02077166[85]	RR non-GCB DLBCL, SCT-ineligible	89	Ibrutinib, lenalidomide, and rituximab (iR2)	ORR	ORRR 47%, CR 28%, PR 19%, median DOR 18 months
NCT02628405[96]	RR DLBCL, SCT-eligible	68	Lenalidomide + R-ICE (R2-ICE)	Safety and ORR	Phase 1 completed. RP2D lenalidomide 20 mg.
NCT04305444[97,98]	RR NHL: five cohorts: ABC DLBCL, GCB DLBCL, Richter's transformation, transformed FL, and RR CLL	33	DRM-555 (DTRMWXHS-12, everolimus and pomalidomide)	CR, PR	In 10 DLBCL pts, ORR 60% (CR 20%, PR 40%), estimated mDOR 15 months
NCT02611323[99]	RR DLBCL	57	Polatuzumab-Venetoclax-Rituximab × 6	Safety and efficacy (CR at end of induction)	CR rate at EOI 31%, mDOR 5.8 months, m PFS 4.4 months, mOS 11.0 months
NCT03223610[86]	RR B cell lymphomas	53	ViPOR (venetoclax, ibrutinib, prednisone, obinutuzumab, lenalidomide) × 6	CR, ORR	In the DLBCL cohort: ORR 25.6%, CR 12.8%, mPFS 7.0 months, mOS 9.1 months

Abbreviations: ABC, activated B cell; CRR, complete response rate; DLBCL, diffuse large B cell lymphoma; GCB, germinal B cell; EFS, event-free survival; FL, follicular lymphoma; ORR, overall response rate; RP2D, recommended phase 2 dose; RR, relapsed and/or refractory; SCT, stem cell transplant.