THERAPEUTIC ADVANCES in
Hematology

Review

Current options and future perspectives in the treatment of patients with relapsed/refractory diffuse large B-cell lymphoma

Ther Adv Hematol

2022, Vol. 13: 1–19

DOI: 10.1177/20406207221103321

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***Abstract*:** Diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of aggressive lymphoma. Depending on individual risk factors, roughly 60–65% of patients can be cured by chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). However, patients with primary refractory disease or relapse (R/R) after an initial response are still characterized by poor outcome. Until now, transplant-eligible R/R DLBCL patients are treated with intensive salvage regimens followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) which, however, only cures a limited number of patients. It is most likely that in patients with early relapse after chemoimmunotherapy, chimeric antigen receptor (CAR) T-cells will replace high-dose chemotherapy and ASCT. So far, transplant-ineligible patients have mostly been treated in palliative intent. Recently, a plethora of novel agents comprising new monoclonal antibodies, antibody drug conjugates (ADC), bispecific antibodies, and CAR T-cells have emerged and have significantly improved outcome of patients with R/R DLBCL. In this review, we summarize our current knowledge on the usage of novel drugs and approaches for the treatment of patients with R/R DLBCL.

Keywords: ADC, ASCT, bispecific antibodies, CAR T-cells, DLBCL, monoclonal antibodies, targeted therapies

Received: 23 December 2021; revised manuscript accepted: 10 May 2022.

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Introduction

Diffuse large B-cell lymphoma (DLBCL) represents the most common lymphoma entity accounting for roughly 40% of all cases.[1] In the revised World Health Organization (WHO) classification, several subtypes previously summarized under the term 'DLBCL' now represent own entities such as primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma with *MYC* and *BCL2* and *BCL6* rearrangement, T-cell histiocyte-rich B-cell lymphoma, or Epstein-Barr virus (EBV)-positive DLBCL to mention some of them.[1] In this review, we focus on the entity of 'DLBCL not otherwise specified (NOS)'. However, it must be taken into account that various clinical DLBCL studies encompassed additional aggressive B-cell lymphoma subtypes which may have influenced the results of these trials.

Comprehensive molecular analyses showed that DLBCL represents a heterogeneous diagnostic category. Gene expression profiling defined two distinct subtypes derived from activated B-cell-like (ABC) or germinal center B-cell-like (GCB) DLBCL while roughly 15% of all DLBCL cases remained unclassifiable.[2,3] Additional molecular subtypes within and beyond ABC and GCB DLBCL have been identified based on recurrent somatic mutations, copy number alterations, and structural variants.[4–6]

Despite these advances in the understanding of DLBCL lymphomagenesis, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) still represents the internationally accepted standard therapy of untreated DLBCL patients. Until recently, large

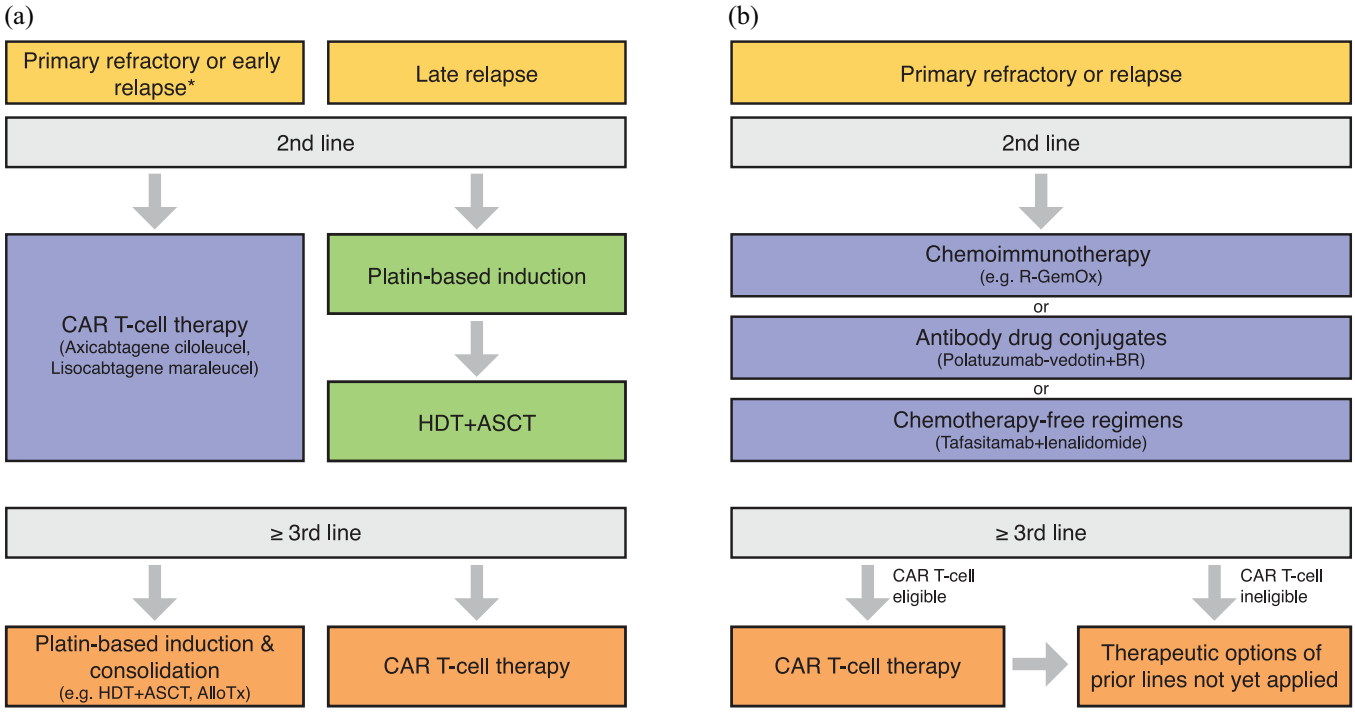

Figure 1. Therapeutic algorithm for patients with R/R DLBCL. (a) For transplant-eligible patients, depending on the time point of relapse, either an anti-CD19 CAR T-cell therapy (using axicabtagene ciloleucel or lisocabtagene maraleucel) or platin-based induction followed by high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) represent the standard approach (*within 12 months after completion of first-line therapy). (b) For transplant-ineligible patients, chemoimmunotherapy, antibody drug conjugates, as well as chemotherapy-free regimens represent potential therapeutic options in second line. Third-line therapy using anti-CD19–directed CAR T-cells represents a potentially curative option for eligible patients.

phase III studies adding different agents to R-CHOP failed to significantly improve patients' outcome.[7–11] However, very recently, encouraging results of the POLARIX trial (NCT03274492) have been reported.[12] The combination of rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) and the antibody drug conjugate (ADC) polatuzumab-vedotin significantly improved progression-free survival (PFS) of untreated DLBCL patients with an international prognostic index (IPI) of 2–5 compared with R-CHOP. Also based on the evaluation and potential approval by the medical agencies, R-CHP and polatuzumab-vedotin might become the new standard of care of untreated DLBCL patients with an IPI of 2–5.

Overall, while roughly two-thirds of DLBCL patients can be cured by first-line therapy, one-third of the patients will be primary refractory or will relapse (R/R DLBCL) after an initial response.[13] These patients are characterized by poor outcome with the majority of patients succumbing to their disease. With a plethora of novel agents available, treatment algorithms become more and more complex and the sequencing of these approaches remains poorly studied. To this end, this review provides an overview of the current therapeutic algorithms for patients with R/R DLBCL (Figure 1).

Transplant-eligible patients

Primary refractory or patients relapsing after an initial response are characterized by adverse outcome.[14] Up to now, the clinical management of R/R patients largely depends on their eligibility for high-dose therapy (HDT) and autologous stem cell transplantation (ASCT). As of today, R/R patients considered transplant-eligible will normally receive platinum-based salvage chemoimmunotherapy with rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP); rituximab, ifosfamid, carboplatin, and etoposide (R-ICE); or rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP). All three regimens have been investigated prospectively achieving very similar results for the investigated

outcome parameters.[14,15] In the multicenter phase III CORAL trial, 396 DLBCL patients in first relapse or with primary refractory disease were assigned to either R-ICE or R-DHAP followed by HDT/ASCT.[14] Response rates for both regimens were 63.5% *versus* 62.8%, respectively. Overall, 3-year PFS and the overall survival (OS) were 37% and 49%, respectively, with no significant differences between the treatment arms.

In the NCIC-CTG LY.12 trial, 619 patients with R/R aggressive lymphoma were assigned to R-GDP or R-DHAP. Response rates following R-GDP were 45.2% and 44% after R-DHAP, respectively, while R-GDP showed a better toxicity profile with less febrile neutropenia and nausea.[15]

If a partial remission (PR) or complete remission (CR) is achieved, consolidation with HDT/ASCT is recommended. The most often used HDT regimens are rituximab, carmustine, etoposide, cytarabine, and melphalan (R-BEAM) or rituximab, cyclophosphamide, etoposide, and carmustine (R-CVB). In the CORAL study, patients who underwent HDT/ASCT reached a 3-year PFS of 53%.[14] Importantly, survival significantly depended on the time between end of first-line therapy and relapse; patients with early relapse within the first 12 months after diagnosis had adverse outcome with 3-year OS of 39% compared with 64% for patients with a later relapse underscoring that especially patients with longer remissions and chemo-sensitive disease benefit from HDT/ASCT.[14] Patients not responding or relapsing after salvage therapy should be re-evaluated if cure remains the therapeutic goal. These patients frequently represent prime candidates for novel approaches, in particular for chimeric antigen receptor (CAR) T-cell therapies.

Very recently, the final results of three prospective randomized trials directly comparing the current standard of HDT/ASCT to CAR T-cell therapy in second-line therapy of transplant-eligible patients refractory to or relapsing early after R-CHOP-like therapy have been presented.[16–18] In two out of three of these trials, CAR T-cell therapy was superior to HDT/ASCT so that in near future CAR T-cells might become the new standard of second-line therapy for patients with large B-cell lymphoma refractory to or relapsing early after R-CHOP-like therapy. Detailed results of these trials are presented in the section 'Third-line therapy – Chimeric antigen receptor T cells'.

Transplant-ineligible patients

Chemoimmunotherapy

In the past, the vast majority of transplant-ineligible patients were treated in palliative intent with chemoimmunotherapeutic regimens such as rituximab, gemcitabine, and oxaliplatin (R-Gem-Ox) or bendamustine and rituximab (BR). However, these therapies most often failed to induce durable remissions. In a multicenter phase II trial, 59 R/R DLBCL patients received BR as salvage therapy. The overall response rate (ORR) was 62.7% with a CR rate of 37.3% and the median PFS was 6.7 months.[19] In an initial phase II trial including 46 transplant-ineligible R/R DLBCL patients, R-Gem-Ox showed very promising results with an ORR of 83% and a 2-year OS of 66%.[20] However, almost half of the included patients had not received prior rituximab treatment explaining the rather favorable outcome of these patients.[20] Accordingly, in another phase II trial including 49 transplant-ineligible R/R DLBCL patients who were pretreated with rituximab in 63% of cases, the 5-year OS rate following R-Gem-Ox salvage therapy was reported to be only 14%.[21]

New monoclonal antibodies

The introduction of rituximab resulted in a significant improvement in survival of DLBCL patients.[10,22–24] Besides, it also triggered the development of other monoclonal antibodies.

While the use of the anti-CD20 antibody obinutuzumab did not improve therapy of DLBCL patients,[25] the anti-CD19 antibody tafasitamab has been recently approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in combination with the immunomodulatory drug lenalidomide for transplant-ineligible patients with R/R DLBCL (Figure 2).[26] This approval is based on the recently published L-MIND trial (Table 1).[26] In this study, the combination of tafasitamab and lenalidomide was administered for up to 12 cycles every 28 days. Patients without progression after cycle 12 continued with a tafasitamab monotherapy until progression. Median age of the included study patients was 72 years and these patients had received a median of two prior lines of therapy with roughly half of patients being refractory to their last treatment. However, importantly, patients with primary refractory disease and patients with a

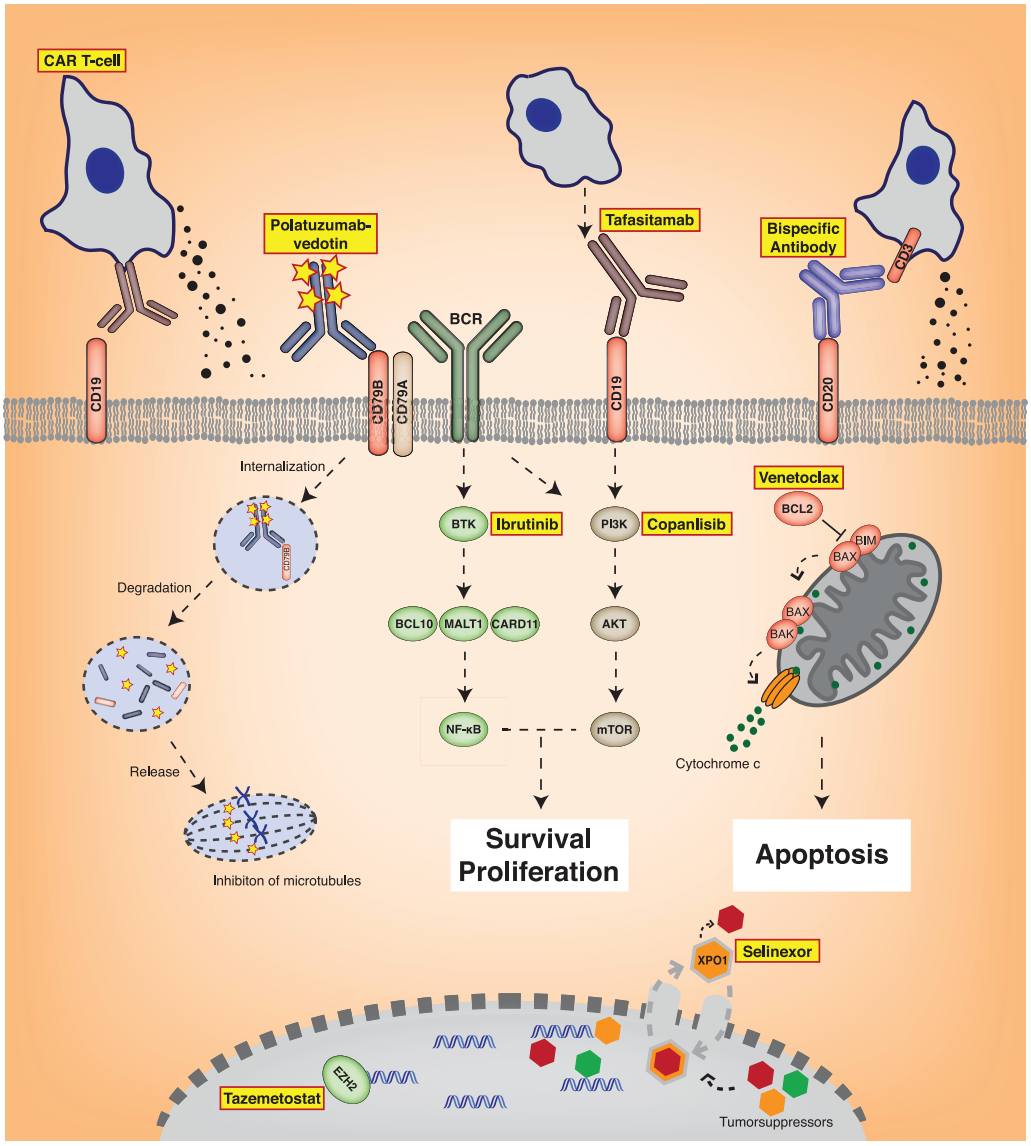

Figure 2. Novel agents for the treatment of patients with R/R DLBCL. Depicted are targets of novel therapeutic approaches. The surface antigen CD19 can be recognized by CD19-targeting CAR T-cells or by novel antibodies such as tafasitamab. Polatuzumab-vedotin binds to CD79B associated with the B-cell receptor (BCR). Bispecific antibodies can directly link B- and T cells mediating T-cell activation. Targeted small-molecule inhibitors such as ibrutinib or copanlisib inhibit BCR or PI3K signaling, respectively. Venetoclax inhibits the anti-apoptotic protein BCL2 inducing apoptosis. Tazemetostat targets the oncogenic methyltransferase EZH2. Selinexor interrupts the export of diverse tumorsuppressor proteins out of the nucleus by inhibition of XPO1 leading to nuclear accumulation and activation of these tumor suppressors.

lymphoma harboring a *MYC* and *BCL2* and/ or *BCL6* rearrangement were excluded from this study, indicating a bias toward good risk patients. Nevertheless, 48 of 80 patients (60%) showed an objective response with 43% achieving a CR and 18% a PR.[26] In a recently published follow-up study, the median duration of response was 43.9 months and median OS was 33.5 months.[27] Therapy was generally well tolerated with the most common nonhematological side effects being rash, diarrhea, asthenia, cough, peripheral edema, and fever. For the majority of transplant-ineligible patients, the combination of tafasitamab and lenalidomide represents a promising new treatment option. To what extent the anti-CD19 therapy might impair the efficacy of following CD19-targeting CAR T-cells needs further studies.

Table 1. Overview of novel therapeutic options in the management of R/R DLBCL patients.

Class and agent	Target	Study	Trial phase	Number of patients	ORR (%)	CRR (%)	Median PFS (months)	Median DOR (months)	Most frequent adverse events[a]
Monoclonal antibodies									
Tafasitamab + lenalidomide	CD19	Salles *et al.*[26]	II	80 (incl. transformation)	60	43	12.1	21.7	TEAEs (grade ⩾3): neutropenia (48%), thrombocytopenia (17%), febrile neutropenia (12%), rash (9%), anemia (7%)
Antibody drug conjugates									
Polatuzumab-vedotin + BR	CD79B	Sehn *et al.*[28]	II	40	45	40	9.5	12.6	AEs (grade 3–4): neutropenia (46%), thrombocytopenia (41%), anemia (28%), febrile neutropenia (10%)
Loncastuximab-tesirine	CD19	Caimi *et al.*[29]	II	145 (incl. PMBL, HGBCL)	48.3	24.1	–	10.3	TEAEs (grade ⩾3): neutropenia (26%), thrombocytopenia (18%), anemia (10%)
CAR T-cell therapy									
Axicabtagene ciloleucel	CD19	Neelapu *et al.*[30]	II	101 (incl. PMBL, transformed FL)	82	54	–	8.1	AEs (grade ⩾3): neutropenia (78%), anemia (43%), thrombocytopenia (38%), febrile neutropenia (31%), neurologic events (28%), CRS (13%), hyponatremia (10%)
Tisagenlecleucel	CD19	Schuster *et al.*[31]	II	93 (incl. transformed FL, HGBCL)	52	40	–	Not reached	AEs (grade 3–4, <8 weeks after infusion): cytopenia (not resolved by day 28) (32%), CRS (22%), infections (20%), febrile neutropenia (15%), neurologic events (12%)
Lisocabtagene maraleucel	CD19	Abramson *et al.*[32]	II	256 (incl. transformed FL, HGBCL)	73	53	6.8	Not reached	TEAEs (grade ⩾3): neutropenia (60%), anemia (37%), thrombocytopenia (27%), hypophosphatemia (6%); neurologic events (10%), CRS (grade 3–4) (2%)

(Continued)

Table 1. (Continued)

Class and agent	Target	Study	Trial phase	Number of patients	ORR (%)	CRR (%)	Median PFS (months)	Median DOR (months)	Most frequent adverse events[a]
Bispecific T-cell engagers									
Blinatumomab	CD19/CD3	Viardot *et al.*[33]	II	21 (incl. transformation)	43	19	3.7	13.5	AEs (grade ⩾3): neurologic events (22%), leukopenia (17%), thrombocytopenia (17%), pneumonia (13%), hyperglycemia (9%)
Mosunetuzumab	CD20/CD3	Schuster *et al.*[34]	I/Ib	124 (R/R aggressive lymphoma)	37.1	19.4	–	–	AEs (grade 3): neurologic events (3%), CRS (1%)
Glofitamab	CD20/CD3	Hutchings *et al.*[35]	I	73	41.1	28.8	2.9[b]	5.5[b]	AEs (grade ⩾3): neutropenia (25%), thrombocytopenia (8%), anemia (8%), CRS (4%)
Epcoritamab	CD20/CD3	Hutchings *et al.*[36]	I/II	22	68	45	9.1	–	TEAEs (grade ⩾3): anemia (13%), pyrexia (6%), hypotension (6%), fatigue (6%)
Immune checkpoint inhibitors									
Nivolumab	PD-1	Ansell *et al.*[37]	II	121 (incl. transformation)	10/3[c]	3/0[c]	1.9/1.4[c]	11.4/8[c]	Drug-related AEs (grade 3–4): neutropenia (4%), thrombocytopenia (3%), lipase increased (3%), fatigue (2%)
Magrolimab	CD47	Advani *et al.*[38]	Ib	15 (incl. transformation, HGBCL)	40	33	–	Not reached	SAEs (all grades): infections (18%), anemia (5%), dyspnea (5%), pyrexia (5%), lactic acidosis (5%), retroperitoneal mass (5%), pulmonary embolism (5%), infusion-related reaction (5%)
Other targeted approaches									
Ibrutinib	BTK	Wilson *et al.*[39]	I/II	80	25	10	1.6	–	TEAEs (grade ⩾3): fatigue (8%), hyponatremia (7%), thrombocytopenia (6%), anemia (5%)

(Continued)

Table 1. (Continued)

Class and agent	Target	Study	Trial phase	Number of patients	ORR (%)	CRR (%)	Median PFS (months)	Median DOR (months)	Most frequent adverse events[a]
Lenalidomide	Immunomodulatory	Czuczman *et al.*[40]	II/III	51	27.5	9.8	3.4	18.5	TEAEs (grade ⩾3): neutropenia (43%), anemia (19%), infections (19%), respiratory/thoracic/mediastinal disorders (19%), thrombocytopenia (17%), gastrointestinal disorders (17%), febrile neutropenia (7%)
Copanlisib	PI3K	Lenz *et al.*[41]	II	67 (incl. transformed FL, HGBCL)	19.4	7.5	1.8	4.3	TEAEs (grade ⩾3): hypertension (33%), hyperglycemia (31%), neutropenia (13%), hypokalemia (6%)
Venetoclax	BCL2	Davids *et al.*[42]	I	34 (incl. PMBCL)	18	12	1.0	–	Emergent AEs (grade 3–4): anemia (15%), neutropenia (11%), fatigue (7%)
Tazemetostat	EZH2	Ribrag *et al.*[43]	II	157	17	3/9[d]	4/2[d]	11/7[d]	TEAEs (all grades): thrombocytopenia (20%), nausea (17%), anemia (15%), neutropenia (15%), vomiting (15%), cough (14%), diarrhea (12%), fatigue (12%), pyrexia (12%), abdominal pain (11%), asthenia (10%)
Selinexor	XPO1	Kalakonda *et al.*[44]	II	127 (incl. transformation, HGBCL)	28	12	2.6	9.3	TEAEs (grade 3–4): thrombocytopenia (46%), neutropenia (25%), anemia (22%), fatigue (11%), hyponatremia (8%)

AE, adverse event; BR, bendamustine and rituximab; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; CRR, complete response rate; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma with rearrangement of *MYC* and *BCL2* and/ or *BCL6*; incl., including; MCL, mantle cell lymphoma; ORR, overall response rate; PD, programmed cell death proteins; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PMBL, primary mediastinal B-cell lymphoma; R/R, primary refractory/relapsed; SAE, severe adverse event; TEAE, treatment-emergent adverse event; XPO1, exportin 1.
[a]Percentages refer to the whole study population treated with the respective drug of interest.
[b]Referring to patients with aggressive lymphoma including DLBCL, FL grade 3B, MCL, PMBCL, transformation.
[c]Transplant-failed/transplant-ineligible patients.
[d]Mutated/wild-type *EZH2*.

ADC

ADC represent a novel class of anticancer agents. The first ADC integrated into routine treatment of lymphoma patients was brentuximab-vedotin that targets the CD30 antigen which is commonly expressed on Hodgkin lymphoma or anaplastic large T-cell lymphoma cells.[45]

Polatuzumab-vedotin is an ADC binding to CD79B, a B-cell receptor (BCR)-associated protein expressed by more than 95% of DLBCLs.[46] The molecule is linked to the cytotoxic anti-microtubule agent monomethyl auristatin E (MMAE). Upon binding to CD79B, polatuzumab-vedotin is internalized and MMAE is released causing cell death (Figure 2).[46] In a phase II study, 39 patients with R/R DLBCL were treated with polatuzumab-vedotin combined with rituximab until either disease progression or until unacceptable toxicities occurred.[47] The ORR was 54% with 21% of patients achieving a CR while the median duration of response was 13.4 months. Most common adverse events were hematological toxicities and diarrhea.[47] Based on these favorable results, 80 transplant-ineligible DLBCL patients with R/R disease were randomized in a phase II trial to either the combination of polatuzumab-vedotin, rituximab, and bendamustine or to rituximab and bendamustine alone (Table 1).[28] Patients included in the trial had received a median of two prior lines of therapy and 80% of patients were refractory to the last treatment. The addition of polatuzumab-vedotin to rituximab and bendamustine significantly improved both PFS and OS. The median OS was improved from 4.7 months in patients treated with rituximab and bendamustine alone to 12.4 months in the polatuzumab-vedotin, rituximab, and bendamustine arm. The median duration of response was improved by the addition of polatuzumab-vedotin to 12.6 months compared with 7.7 months. The combination of polatuzumab-vedotin, rituximab, and bendamustine was associated with a higher rate of cytopenias. However, this did not lead to more infections or increased need of transfusions. The polyneuropathy caused by polatuzumab-vedotin was in general manageable and reversible.[28] Based on these results, the combination of polatuzumab-vedotin, rituximab, and bendamustine has recently been approved by both EMA and FDA.

Another ADC that has shown promising activity in the treatment of patients with R/R DLBCL is loncastuximab-tesirine (ADCT-402). Loncastuximab-tesirine comprises anti-CD19 antibody and pyrrolobenzodiazepine (PBD) dimers.[48] PBD is a cytotoxic sequence-selective DNA cross-linking agent. In a recently completed phase II study including 145 DLBCL patients with R/R disease, nearly half of patients showed a response (ORR = 48.3%) with 24.1% of patients achieving a CR (Table 1).[29] Most common side effects were cytopenia and increase of liver enzymes. Loncastuximab-tesirine was subsequently approved by the FDA for the treatment of patients previously treated with at least two prior systemic lines with R/R large B-cell lymphoma including DLBCL NOS, DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma.

Third-line therapy–CAR T-cells

CAR T-cells represent a new therapeutic concept for the treatment of patients with different B-cell lymphomas. CAR T-cells are curative for R/R DLBCL patients having either relapsed after ASCT or for transplant-ineligible patients. Thus, CAR T-cells represent the current standard of care for patients having received two previous lines of therapy.

Autologous T cells are genetically modified to express a CAR.[49] Each CAR consists of an antibody-derived single-chain variable fragment targeting a specific tumor antigen, a spacer and linker region, as well as a cytoplasmatic domain inducing T-cell response and regulating the persistence of CAR T-cells.[49] The currently licensed and clinically available CAR T-cells all target the CD19 antigen, but differ by their cytoplasmatic co-stimulatory domains (Figure 2). Unfortunately, early CAR T-cell experience showed that harvesting sufficient numbers of viable patients' T cells may be compromised by previous therapies. Furthermore, organizational and process-related problems can prolong the time from leukapheresis to product delivery to an extent unacceptable for R/R DLBCL patients with rapidly progressing disease in need of immediate therapy. Therefore, allogeneic CAR T-cells which can be used 'off the shelf' are also under investigation.[50] Before infusion of CAR T-cells, a T cell–depleting chemotherapy mostly consisting of fludarabine and cyclophosphamide is administered.[51,52] When infused to patients, the CAR T-cells can induce multiple side effects, the most significant being the so-called cytokine release syndrome (CRS) as a

form of systemic inflammatory response syndrome (SIRS) and neurologic symptoms ranging from mild cognitive impairment to unconsciousness and coma.[30–32] These symptoms in most instances are fully reversible and can be controlled by the early use of glucocorticoids and the interleukin 6 (IL-6) receptor antagonist tocilizumab.[30–32]

Three different autologous CAR T-cells have been investigated in larger clinical studies. The efficacy and safety of axicabtagene ciloleucel, which was approved in 2017 by the FDA and 2018 by the EMA, were tested in the multicenter single-arm phase II trial ZUMA-1 (Table 1).[30] In the ZUMA-1 trial, axicabtagene ciloleucel was administered to 101 patients with R/R DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma. The median age of patients was 58 years, 69% had received more than three prior lines of therapy, and roughly 80% of patients had refractory disease. The median time from leukapheresis to delivery was 17 days and a bridging therapy was not allowed. Overall, 82% of patients showed an objective response with 54% reaching a CR.[30] In a recently presented long-term follow-up, the 3-year OS still was 47% and the median OS was 25.8 months.[53] With respect to safety, 13% of patients developed a CRS of grade 3 or higher, whereas 28% of patients showed neurologic symptoms of grade 3 or higher.[30] The median time from infusion to onset of CRS and neurologic symptoms was 2 and 5 days, respectively. Nearly all CRS and neurologic events resolved.[30]

Tisagenlecleucel represents another CAR T-cell product approved by FDA and EMA.[31] As axicabtagene ciloleucel, tisagenlecleucel received approval for adult patients with R/R DLBCL after two previous lines of systemic therapy by EMA. In the multicenter, international phase II JULIET trial, 93 patients with R/R DLBCL, transformed follicular lymphoma, or high-grade B-cell lymphoma with *MYC*, *BCL2*, and *BCL6* rearrangement ineligible for or progressive after HDT/ASCT were treated with tisagenlecleucel (Table 1). The median age of patients was 56 years, 52% had received at least three prior lines of therapy, and 55% showed refractory disease. The median time from trial enrollment to infusion of CAR T-cells was 54 days. Best ORR was 52%, 40% of patients achieved a CR. CRS and neurologic events (both ⩾grade 3) occurred in 22% and 12% of patients, respectively. In total, 97% of all CRS events had resolved at the time of data cutoff.[31] In a recently published long-term follow-up, the median duration of response was not reached with a median follow-up of 40.3 months and the proportion of patients maintaining their response at 36 months was estimated at 60.4%.[54]

Various real-life data sets confirm the promising data from the ZUMA-1 and the JULIET trials.[55–57] In a recent retrospective analysis, 275 patients were treated with axicabtagene ciloleucel across 17 US centers.[55] Median time from apheresis to start of conditioning chemotherapy was 21 days. In contrast to patients treated in the ZUMA-1 trial, 53% of patients received a bridging therapy. The ORR was 82% while 64% of patients achieved a CR. With a median observation time of 12.9 months, the median PFS was 8.3 months. Rates of CRS and neurologic events were comparable with the frequency and severity observed in the ZUMA-1 trial. Patients with elevated lactate dehydrogenase (LDH) were characterized by significantly inferior PFS and OS suggesting that tumor burden and dynamics of progressive disease before CAR T-cells is an important prognostic factor.[55] Recently, data from the French national registry DESCAR-T have been presented.[57] In total, 463 patients who received commercial CAR T-cells at 14 French centers were included in this analysis. Median age was 63 years and patients received a median number of three prior lines of therapy. Overall, 65% of patients received axicabtagene ciloleucel and 35% were treated with tisagenlecleucel. Best ORR was 70.2% with 38% of patients achieving a CR and 27% showing a PR at day 30 after CAR T-cell infusion. Of patients who achieved CR at day 30, 61% maintained their CR at day 90.[57]

Finally, lisocabtagene maraleucel represents the third CAR T-cell product that has been approved by the FDA in February 2021 for patients with R/R large B-cell lymphoma after two lines of therapy. In the single-arm, multicenter TRANSCEND trial, 256 patients with R/R DLBCL (including transformation from any indolent lymphoma) or high-grade B-cell lymphoma with *MYC*, *BCL2*, and *BCL6* rearrangement were infused with lisocabtagene maraleucel and included in the efficacy analysis (Table 1).[32] The median age of patients was 63 years. In total, 73% of patients showed an objective response and 53% achieved a CR. Median PFS

was 6.8 months. With a median follow-up of 12 months, median duration of response was not reached. Severe CRS or neurologic events (⩾grade 3) occurred in 2% and 10% of patients, respectively. Median time from leukapheresis to product delivery was 24 days.[32] In a recent presentation, preliminary data of the phase II OUTREACH trial showed comparable results in terms of efficacy and safety when lisocabtagene maraleucel was administered in an in- or outpatient setting.[58]

Recently, the available CAR T-cell therapies have prospectively been compared with the current standard care of HDT/ASCT in second-line therapy. The ZUMA-7 trial was an international phase III trial randomly assigning 180 patients with refractory large B-cell lymphoma or early relapse within 12 months after front-line chemoimmunotherapy to axicabtagene ciloleucel and 179 patients to receiving standard care therapy.[16] Standard care was defined as two or three cycles of salvage therapy followed by HDT/ASCT for responding patients. As in the ZUMA-1 trial, only glucocorticoids have been allowed for bridging to CAR T-cells. Overall, 83% of patients treated with axicabtagene ciloleucel and 50% of patients receiving HDT/ASCT showed a response with CR rates of 65% and 32%, respectively.[16] The primary end point of event-free survival (EFS) significantly differed between treatment groups with a 2-year EFS of 41% in the CAR T-cell arm *versus* 16% in the HDT/ASCT group (hazard ratio for event or death 0.4, $p < 0.001$). Two-year OS was 61% *versus* 52%, respectively. The reported rates of toxicity corresponded to previous reports: severe CRS (⩾grade 3) occurred in 6% and neurologic toxicity (⩾grade 3) in 21% of cases.[16]

The TRANSFORM trial was a global phase III trial randomizing 184 patients with primary refractory large B-cell lymphoma or early relapse within 12 months after front-line therapy to either standard care comprising salvage therapy and HDT/ASCT or CAR T-cell therapy with lisocabtagene maraleucel.[18] Baseline characteristics were well comparable between treatment groups. Patients receiving lisocabtagene maraleucel showed an ORR of 86% compared with 48% for patients receiving HDT/ASCT. In line with the data of the ZUMA-7 trial, the median EFS was significantly improved for patients of the CAR T-cell group with 10.1 months compared with 2.3 months in the standard care group (hazard ratio 0.349, $p < 0.0001$).[18] Median OS was not reached *versus* 16.4 months, respectively.

Finally, the BELINDA trial investigated the role of tisagenlecleucel in second-line therapy.[17] In this international phase III trial, 322 patients with R/R aggressive B-cell lymphoma were randomized between salvage therapy followed by HDT/ASCT and tisagenlecleucel including optional prior bridging therapy. As in the ZUMA-7 and TRANSFORM trials, eligible patients were primary refractory or showed early relapse within 12 months after front-line therapy. In total, 32.5% of patients in the standard care group responded to salvage therapy and received subsequently HDT/ASCT. In total, 95.7% of patients randomized to the CAR T-cell group received tisagenlecleucel. In contrast to the JULIET trial, patients were not excluded from CAR T-cell infusion in case of progressive disease following bridging therapy. Overall, 46.3% of patients treated with tisagenlecleucel showed a response compared with 42.5% of patients belonging to the HDT/ASCT group. The primary end point EFS reached a median of 3 months in both treatment groups (hazard ratio for event or death in the tisagenlecleucel group 1.07, $p = 0.61$).[17] Severe CRS and neurotoxicity (⩾grade 3) occurred in 5.2% and 1.9% after tisagenlecleucel infusion, respectively.

The encouraging results of the ZUMA-7 and TRANSFORM trials show that CAR T-cell therapy might evolve as the new standard for the treatment of patients with R/R DLBCL relapsing early after chemoimmunotherapy. However, the results of the BELINDA trial also underscore that selection of suitable patients is of major importance for the success of CAR T-cell therapies.[59] When further analyzing and comparing these trials, it has to be considered that different populations of patients have been included in these studies. Based on the yet available data, it is premature to conclude that one CAR T-cell product is superior to the other, although this also cannot be excluded at this stage. In the ZUMA-7 trial, only glucocorticoids were allowed as bridging therapy before CAR T-cell infusion and patients with impending organ-compromising disease were excluded leading – at least to a certain degree – to a selection bias toward patients with less aggressive disease.[16] In the ZUMA-7 trial, time from leukapheresis to final product release took only 13 days.[16] In contrast,

multiple rounds of bridging therapy were allowed and patients with impending organ-compromising disease were not excluded from the BELINDA trial.[17] Despite bridging therapy, 26% of patients showed progressive disease before CAR T-cell therapy. Median time from leukapheresis to CAR T-cell infusion was significantly longer with 52 days.[17] Moreover, baseline characteristics of patients show that significantly more patients with DLBCL of the ABC subtype, that are characterized by adverse prognosis, have been included in the BELINDA compared with the ZUMA-7 trial (32% *versus* 9%).[16,17]

Allogeneic stem cell transplantation

Allogeneic stem cell transplantation has been used in the treatment of patients with R/R DLBCL especially after failure of HDT and ASCT.[60,61] However, with a plethora of novel alternative treatment options emerging, the role of allogeneic stem cell transplantation remains to be defined.

The curative potential of allogeneic stem cell transplantation is in part caused by the immune effect exerted by donor T cells termed graft *versus* lymphoma (GvL) effect. However, in DLBCL, the GvL effect seems less prominent compared with other lymphoma entities reflected by relatively high relapse rates.[62] In addition, graft *versus* host disease (GvHD) of various severities can occur in any allografted patient despite successful recipient/donor matching resulting in significant morbidity and mortality.[63] Registry data of R/R DLBCL patients who underwent allogeneic stem cell transplantation reported 3-year OS rates ranging from 30 to 50%.[61,64,65] The only prospective trial evaluating the role of allogeneic stem cell transplantation for R/R DLBCL patients was the DSHNHL 2004-R3 trial in which 84 lymphoma and 42 DLBCL patients were included.[66] In total, 55% of enrolled patients showed refractory disease. For the whole study population, the 3-year PFS and OS (post transplant) were 39% and 42%, respectively. The non-relapse mortality (NRM) rate at 1 year was 35%. Lower NRM and better OS were reported for patients with a 10/10 human leukocyte antigen (HLA)-matched donor and patients receiving anti-thymocyte globulin (ATG) for GvHD prophylaxis. Retrospective comparison evaluating the efficacy and safety of allogeneic stem cell transplantation and CAR T-cells suggests similar efficacy but substantially less toxicity after CAR T-cell therapies.[67]

In summary, the exact role of allogeneic stem cell transplantation in the treatment algorithm of DLBCL patients needs to be defined and it may remain a valid option for fit patients relapsing after CAR T-cell therapy.

Novel therapeutic approaches

Bispecific antibodies

Bispecific T-cell engagers (BITEs) are antibodies comprising two antigen-binding sites, one directed against a tumor antigen and one directed against a T-cell antigen bringing T cells and tumor cells into direct proximity (Figure 2).[68] In early clinical trials, BITEs have shown very promising anti-lymphoma activity also in heavily pretreated patients.[34–36]

Blinatumomab was the first BITE approved for the treatment of patients with R/R and minimal residual disease (MRD)-positive acute lymphoblastic leukemia.[69,70] Blinatumomab consists of two single-chain variable fragments directed against CD19 and CD3 but lacks its own Fc domain leading to a shorter halftime and therefore necessitating prolonged periods of continuous infusion. In a phase I/II trial, blinatumomab led to encouraging anti-lymphoma activity in intensively pretreated R/R DLBCL patients with ORR ranging from 43 to 55% with some long-term remissions (Table 1).[33,71,72] However, the disadvantageous pharmacokinetics and the occurrence of serious neurological side effects in some patients led to the development of alternate BITEs.

Mosunetuzumab is a full-length humanized IgG bispecific antibody targeting CD20 and CD3.[73] In a multicenter phase I/Ib trial, 124 patients with R/R aggressive lymphomas including DLBCL and transformed follicular lymphoma were treated (Table 1).[34] Patients were heavily pretreated with a median of three prior lines of therapy including ASCT and CAR T-cell therapies. The response rate in the overall cohort was 37.1% while 22.2% of patients who were previously treated with CAR T-cells responded. In the overall cohort, roughly 20% of patients achieved a CR. Overall tolerability was good and only 1.1% of patients developed a severe CRS of grade 3 or higher.

Glofitamab is a novel bispecific, bivalent antibody containing two domains targeting CD20 and one domain directed against CD3.[74] In a phase I trial, 171 R/R lymphoma patients including 73 DLBCL patients were treated with glofitamab (Table 1).[35] Overall, the median age of patients included in the study was 64 years. Patients had received a median of three prior lines of therapy with 90.6% of patients being refractory to any prior treatment. In patients with R/R DLBCL, an ORR of 41.1% with a CR in 28.8% of cases was observed. Among patients with aggressive lymphoma, median PFS was short with 2.9 months. However, of patients in CR, 72.8% sustained a CR after 12 months. Again, the tolerability was good as a severe CRS (⩾grade 3) occurred in only 3.5% of patients.

Finally, epcoritamab that can be applied subcutaneously is a bispecific antibody targeting CD20 and CD3.[75] In an early clinical dose escalation study, epcoritamab showed high activity suggesting further evaluation in a phase I/III trial (Table 1).[36] In 22 evaluable R/R DLBCL patients, the ORR was 68% with 45% of patients achieving a CR. No dose-limiting effects were observed. Most frequent adverse events were pyrexia and local reactions at the injection site. Severe CRS did not occur.

In summary, bispecific antibodies have shown impressive efficacy in heavily pretreated patients with R/R DLBCL. However, these findings need to be confirmed in larger studies and longer follow-up is required to be able to fully appreciate if the observed responses represent indeed long-term remissions.

Immune checkpoint inhibitors

Drugs targeting immune checkpoints modulate immune responses and re-establish anti-lymphoma activity of the immune system. A well-explored axis is the interaction of programmed cell death proteins 1/2 (PD-1/2) and their respective ligands (PD-L1/2).[76,77] By expression of PD-L1/2, cells are able to bind to PD-1/2 receptors expressed on B and T cells and to exert inhibitory effects.[78] Despite promising results observed in other lymphoma entities such as Hodgkin lymphoma, targeting PD-1 has not been successful in the treatment of DLBCL patients.[79] In a phase II trial, R/R DLBCL patients who were transplant-ineligible or who failed HDT/ASCT were treated with the anti-PD-1 monoclonal antibody nivolumab (Table 1).[37] Overall, in only 10% of patients following HDT and ASCT and in 3% of the transplant-ineligible patients, respectively, an objective response was observable. Median duration of response was 11 and 8 months, respectively. Potentially, the combination with conventional chemoimmunotherapy might improve results of checkpoint inhibitors in DLBCL. To this end, a large international phase III trial currently investigates the combination of rituximab, gemcitabine, oxaliplatin, and nivolumab in patients with R/R aggressive B- and T-cell lymphomas (NCT03366272).

Encouraging results were achieved in an early clinical trial for patients with R/R lymphoma including 15 DLBCL patients who were treated with the macrophage immune checkpoint inhibitor magrolimab (Hu5 F9-G4) in combination with rituximab (Table 1).[38] Magrolimab blocks CD47 signaling that induces an antiphagocytic signal. CD47 is highly expressed by a variety of tumor cells including lymphoma cells. Notably, 40% of R/R DLBCL patients showed an objective response with 33% achieving a CR. At a median follow-up of 6 months, more than 90% of responses were ongoing.

Targeted small-molecule inhibitors

A profound understanding of the molecular pathogenesis of DLBCL is required to incorporate specific pathway inhibitors into the treatment of affected patients. DLBCL is a heterogeneous diagnostic category comprising several distinct molecular subtypes. Based on gene expression profiling, at least two distinct subtypes termed activated B-cell-like (ABC) and germinal center B-cell-like (GCB) DLBCL have been identified.[2,3,80] Follow-up work detected subtypes within and beyond ABC and GCB DLBCL based on recurrent mutations, copy number alterations, and structural variants.[4–6] However, these subtypes are not just characterized by differences in genetic abnormalities and their gene expression profile but also by their dependencies to oncogenic pathways which can be targeted by specific inhibitors.

Over the last years, multiple agents have been developed to target specific genetic aberrations. Chronic active BCR signaling represents a hallmark of ABC DLBCL biology leading to constitutive activation of the oncogenic nuclear factor-kappa B (NF-κB) pathway (Figure 2).[81]

The oral small-molecule ibrutinib is an irreversible inhibitor of the Bruton's tyrosine kinase (BTK) which is centrally involved in BCR signaling.[82] In a phase I/II trial, 80 patients with R/R DLBCL were treated with ibrutinib monotherapy (Table 1).[39] Among patients with ABC DLBCL, 37% had an objective response compared with only 5% of subjects with GCB DLBCL. In particular, patients with concomitant mutations of *CD79B* and *MYD88* showed high response rates following BTK inhibition.[39,83]

The phase III trial PHOENIX investigated whether the standard of R-CHOP chemoimmunotherapy in front line could be further improved by the addition of ibrutinib for non-GCB DLBCL patients.[7] Although this study did not meet its primary end point, a subgroup analysis revealed that younger patients (age $<$ 60 years) showed a survival benefit following R-CHOP in combination with ibrutinib.[7] Moreover, in a recent analysis, patients with DLBCL of the MCD or N1 subtypes showed 3-year EFS of 100% following R-CHOP and ibrutinib.[84] In contrast, patients with DLBCLs belonging to the MCD or N1 subgroups who had received R-CHOP alone showed a significantly worse 3-year EFS of 42.9% and 50%, respectively.[84]

The immunomodulatory drug lenalidomide exerts multiple different effects on the malignant B cells as well as on bystander cells.[85–88] A preclinical study investigating the molecular mechanisms of lenalidomide efficacy in DLBCL cell lines suggested predominant activity of lenalidomide in ABC DLBCL compared with other molecular DLBCL subtypes.[89] In a clinical phase II/III trial including 102 R/R DLBCL patients treated with lenalidomide or investigator's choice, the ORR was 27.5% following lenalidomide monotherapy.[40] In the lenalidomide arm, median PFS reached 15.1 weeks for patients with non-GCB DLBCL compared with 10.1 weeks for GCB DLBCL patients. Different lenalidomide combinations yielded encouraging results (see also 'New monoclonal antibodies'). In a small clinical study, lenalidomide was used in combination with rituximab (four cycles for induction followed by lenalidomide maintenance for 8 months) for the treatment of elderly transplant-ineligible patients.[90] Complete response rate (CRR) at the end of maintenance was 35% with some patients responding long time to this combination.[90] Based on these encouraging data, the addition of lenalidomide to standard R-CHOP therapy was investigated in untreated DLBCL patients. A randomized phase II trial showed a PFS benefit for R-CHOP plus lenalidomide (R2-CHOP),[91] while the ROBUST phase III trial failed to show a significant difference between R2-CHOP and R-CHOP plus placebo for patients with ABC DLBCL.[8] The exact reasons for these discrepant results remain unclear, but might be related to patient selection (including all molecular DLBCL subtypes *versus* ABC DLBCL only) and lenalidomide dosing.

Another important downstream signaling cascade of the BCR and downstream target of CD19 signaling is the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway (Figure 2). Especially, DLBCLs of the ABC subtype are addicted to signaling via the alpha- and delta-isoforms of PI3K.[92] In a single-arm phase II study, 67 patients with R/R DLBCL were treated with single-agent copanlisib, a pan PI3K inhibitor with potent activity against the PI3K-α and PI3K-δ isoforms (Table 1).[41] The ORR was 19.4%, 31.6% in ABC, and 13.3% in GCB DLBCL patients. Median PFS and duration of response were 1.8 and 4.3 months, respectively. Studies investigating the efficacy of copanlisib in combination with R-CHOP are currently running (NCT04263584).

BCL2 is an important regulator of apoptosis (Figure 2). In roughly 35% of all GCB DLBCLs, *BCL2* translocations are detectable, while roughly 38% of primary ABC DLBCL samples show *BCL2* gains or amplifications.[93,94] In a phase I trial enrolling 34 DLBCL patients, monotherapy with the orally bioavailable BCL2 inhibitor venetoclax led to an ORR of only 18% with a short median PFS of 1 month (Table 1).[42] Clinically relevant tumor lysis syndrome as particularly seen in the treatment of patients with chronic lymphocytic leukemia (CLL) did not occur. In the phase II CAVALLI trial, R-CHOP combined with venetoclax in first-line therapy showed a trend for improved PFS and OS compared with patients with similar characteristics treated on the GOYA study with R-CHOP alone.[95]

Mutations of *enhancer of zeste homolog 2* (*EZH2*) are a frequent genetic event in GCB DLBCLs. EZH2 represents a histone methyltransferase and recurrent activating mutations in the encoding gene were reported to enhance proliferation and

to block further differentiation of germinal center B-cells.[96] In a multicenter phase II trial, 157 R/R DLBCL patients were treated with a monotherapy of the oral EZH2 inhibitor tazemetostat (Table 1).[43] The ORR was 17% of all patients regardless of the mutational status of *EZH2*. However, the median duration of response was significantly longer in patients with DLBCL harboring *EZH2* mutation (11 months *versus* 7 months).

Another target for the treatment of DLBCL patients that has recently been described is the protein exportin 1 (XPO1) being involved in the transport of various proteins from the nucleus to the cytoplasm (Figure 2). The oral selective XPO1 inhibitor selinexor induces the accumulation of different tumor suppressor proteins in the nucleus re-establishing and enhancing their tumor-suppressive effects.[97] In a multicenter phase II trial, 127 patients with R/R DLBCL received a monotherapy with selinexor (Table 1). ORR was 28% with 12% of patients achieving a CR.[44] Median duration of response was 9.3 months. Based on these data, in June 2020, the FDA approved selinexor for the treatment of adult R/R DLBCL patients after two prior lines of systemic treatment.

In summary, different specific targeted agents have shown efficacy to a different degree. However, these responses were generally short term. Therefore, several trials aimed to reach higher efficiency by combining different agents and by exploiting synergistic effects. In a phase Ib trial, 45 patients were treated with the combination of rituximab, ibrutinib, and lenalidomide. The ORR was 44% and the CR was 28%.[98] In patients with non-GCB DLBCL, the ORR was 65% and the median duration of response was 15.9 months. The overall toxicity was manageable. In another phase Ib/II trial, patients with R/R B-cell lymphoma were treated with 2–6 cycles of venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide every 21 days.[99] In 27 patients with aggressive lymphoma, the ORR was 56% and the CR 37%. Overall, with a median follow-up of 13 months, 69% of responses were ongoing. Median PFS was 9 months and median OS was not reached.[99]

As outlined above, distinct biological parameters such as gene expression profiles or specific genetic alterations emerge as biomarkers to predict the success of targeted therapeutic approaches. So far, most parameters do not belong to the routine diagnostic workup of patients with lymphoma. To select the most appropriate targeted agent for the treatment of patients with DLBCL, fast and cost-effective diagnostic assays applicable in clinical routine will be needed.

Conclusion and outlook

The therapeutic armamentarium for patients with R/R DLBCL has significantly improved in the last couple of years. Various novel antibodies, ADCs, specific small-molecule inhibitors, as well as CAR T-cells have been approved for the treatment of affected patients. However, the ideal sequence and combination of these and other new approaches remain to be elucidated in future clinical trials. In addition, our understanding why some patients respond to specific therapies while others are resistant is still very limited. In the same lines, it is still unclear which patients will benefit from which therapeutic approach. To this end, a significantly better understanding of the biology of DLBCL and how these novel agents and approaches influence DLBCL biology is critically warranted. Clarifying these crucial questions might pave the way for novel combinations and optimal sequencing of our therapies to cure more patients with R/R DLBCL.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Fabian Frontzek: Conceptualization; Data curation; Investigation; Methodology; Project administration; Visualization; Writing – original draft.

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Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Fabian Frontzek and Imke Karsten have no conflicts of interest to declare. Norbert Schmitz received financial support by BeiGene, research support by Janssen, travel grants and honoraria by Takeda, honoraria by Riemser/Esteve, and owns stock by BMS. Georg Lenz received research grants from AGIOS, AQUINOX, AstraZeneca, Bayer, Celgene, Gilead, Janssen, Morphosys, Novartis, Roche, and Verastem. GL received honoraria from Abbvie, Amgen, AstraZeneca, Bayer, BMS, Celgene, Constellation, Genmab, Gilead, Incyte, Janssen, Karyopharm, Morphosys, NanoString, Novartis, and Roche.

Availability of data and materials

Not applicable.

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