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REVIEW

Antibody Therapies for Large B-Cell Lymphoma

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Abstract: Large B-cell lymphomas (LBCLs) constitute a subgroup of aggressive but highly curable lymphoproliferative diseases. Treatment of relapsed/refractory (R/R) patients still represents an unmet clinical need, and novel drugs and combinations are in continuous development. The pan–B cell panel of surface antigens that characterizes LBCL leads to a large umbrella of druggable targets. Monoclonal antibodies (mAbs) express their activity against lymphoma by targeting multiple tumor-specific antigens. This category consists of a number of molecules with different mechanisms of action, including naked mAbs, radioimmunoconjugates, antibody-drug conjugates, checkpoint inhibitors, and bispecific antibodies. In the last decade, apart from the well-known role of the anti-CD20 mAb rituximab, novel mAbs have led to remarkable steps forward in the treatment of R/R LBCL in monotherapy and combined with chemotherapy. Multiple studies are in development trying to bring these novel compounds into the frontline setting to empower the RCHOP effect or as alternative chemotherapy-free options for elderly/unfit patients. This review provides insight into antilymphoma mAbs, focused on the efficacy and safety of the main molecules approved or in development for LBCL andperspectives on the treatment of this disease.

Keywords: diffuse large B-cell lymphoma, immunotherapy, targeted therapy, monoclonal antibodies, checkpoint inhibitors, bispecific antibodies

Introduction

Diffuse large B-cell lymphoma (DLBCL) represents the most frequent histological subtype of B-cell non-Hodgkin lymphoma (B-NHL) in adults, affecting particularly males and older people.[1–3] DLBCL is a clinically and biologically heterogeneous disease typically characterized by pan–B-cell surface antigens, such as CD19, CD22, CD22, and CD79A/B, which can be considered potentially druggable targets.[1] A major milestone in DLBCL treatment has been the introduction of the anti-CD20 monoclonal antibody (mAb) rituximab, and its frontline addition to the standard chemotherapy combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) led to a cure rate around 60%–70% of cases.[4–6] Nevertheless, 30%–40% of DLBCL patients relapse and 10% are refractory to R-CHOP, and the prognosis of this subgroup is usually unfavorable.[7,8]

A less frequent B-NHL belonging to the LBCL category is primary mediastinal B-cell lymphoma (PMBCL), which is now recognized as a unique clinical and biological entity.[1] It occurs mainly in young adults, with a female predominance, and typically presents as a bulky mediastinal mass.[9] Despite its particular biological features, overlapping between B-NHL and classical HL, PMBCL expresses the same pan–B-cell targetable antigens of DLBCL (CD19, CD22, CD22, and CD79A/

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B). The frontline approach for PMBCL has not been standardized yet, but generally consists of rituximab plus an anthracycline-based regimen with or without radiotherapy consolidation.[10,11] PMBCL has a high cure rate, with long-term progression-free survival (PFS) of 70%–93% with different regimens. Nevertheless, 10%–30% of cases are refractory or eventually relapse within 12–18 months after first-line therapy, with consequent unfavorable outcomes.[8,12–20]

Effective treatment for R/R LBCL represents an unmet clinical need. Several biological compounds have been developed to ameliorate outcomes for untreated and R/R LBCL, and mAbs are protagonists in this field. This review focuses on mAbs approved or under investigation for treatment of LBCL. A literature search was performed for papers up to February 2021 on PubMed, National Comprehensive Cancer Network and European Society of Medical Oncology guidelines and abstracts from main international conference proceedings, such as American Society of Hematology, American Society of Clinical Oncology, and European Hematology Association meetings. Safety and efficacy data of mAbs derived from the studies on LBCL cited in the manuscript are detailed in Tables 1–3.

Naked Monoclonal Antibodies

mAbs bind to a specific cell target, inducing tumor-cell death by direct effects on tumor-cell signaling, complement-dependent cytotoxicity, Ab-dependent cytotoxicity, and indirect modulation of the tumor microenvironment. This antineoplastic effect is mediated both by the connection of mAbs with complement, which induces phagocytosis, cytotoxicity, and direct activation of the membrane attack complex, and by interaction with immunoeffector cells, which increases proinflammatory cytokines and cell killing.[21]

Rituximab was the first and is the most commonly used Ab in the treatment of lymphoproliferative diseases, due to its dramatic results in improving survival.[22] Since its approval, many combinations with other drugs have been studied, and nowadays biosimilar rituximab compounds and subcutaneous fixed-dose formulations have been approved, with lowering of costs and simplified and shortened drug preparation and administration, respectively.[23] However, in the last 10 years other similar Abs have been developed in an effort to improve treatment response and outcomes in lymphoproliferative malignancies (Figure 1, Table 1).

Obinutuzumab

Another anti-CD20 moAb, widely used in lymphoproliferative disorders is obinutuzumab (GA101), a glycol-engineered, humanized anti-CD20 Ab with higher antitumor activity than rituximab. Due to the encouraging results demonstrated in follicular lymphoma (FL), GA101 has also been tested for DLBCL. The GAUGUIN trial analyzed the efficacy and safety of single-agent GA101 at different doses for R/R DLBCL, and mantle-cell lymphoma. GA101 showed an overall response rate (ORR) of 32% in DLBCL., and the most common adverse events (AEs) were infusion-related reactions (IRRs) and neutropenia, which were all manageable.[24] Led by these data, a large phase III trial (GOYA) on 1,418 untreated DLBCL patients compared GA101 plus CHOP (G-CHOP) to the standard R-CHOP. After a median observation of 29 months, response rates were similar for the rituximab and GA101 groups, with ORR 77.9% (59.5% of complete responses [CR]) and 77.4% (CR 56.7%), respectively, as well as 3-year PFS rates (67% and 70%, respectively). No major unexpected events were reported, although GA101 was associated with a higher rate of neutropenia (48.3%) and IRRs (36.1%) than rituximab (40.7% and 23.5%, respectively).[25] The final analysis with 5-year follow-up confirmed the data of the primary analysis, demonstrating the good tolerability of G-CHOP, but without any superiority in terms of efficacy compared to R-CHOP. However, a trend toward a benefit of G-CHOP over R-CHOP was apparent in the germinal-center B-cell (GCB) subgroup, though more data are required.[26] Similar data of efficacy and safety were reported in a phase II trial of Fondazione Italiana Linfomi (FIL) in elderly unfit patients treated with GA101 plus dose-reduced CHOP.[27]

Tafasitamab

Tafasitamab (MOR208) is an anti-CD19 humanized Ab enhanced by the modification of two amino acids in the Fc region, which increases its affinity for Fcγ receptors. It mediates Ab-dependent cellular phagocytosis, Ab-dependent cellular cytotoxicity via NK cells, and direct cytotoxicity. In vitro and in vivo studies have demonstrated the efficacy of tafasitamab in lymphoproliferative diseases and in rituximab-refractory patients.[28] A phase II study tested tafasitamab as a single agent at 12 mg/kg weekly in R/R NHL for 8 weeks, followed by another four doses in patients with at least stable disease (SD) and monthly until progression in partial response (PR)

Table 1 Efficacy and safety profiles of naked monoclonal antibodies, antibody-drug conjugates and radioimmunoconjugates in LBCL

Therapy regimen	Target	Study	Line	Patients, n	Efficacy	PFS	OS	Toxicity	Other specific-drug toxicities of any grade AEs (%)
					ORR/CR (%)			Grade ≥3 AEs (%)	
Naked monoclonal antibodies									
GA101	CD20	Morschhauser et al[24]	>1	40 NHL, 25 DLBCL	32/16 in DLBCL	Median 2.6 months at FU of 14.2 mo[#]	—	Lymphopenia (15), anemia (10), IRRs (8)[#]	—
GA101–CHOP	CD20	Vitolo et al[25]	1	706 DLBCL	77/57	3 years PFS 81.2%	—	Neutropenia (46), FN (17), leukopenia (14), anemia (7), pneumonia (6)	IRRs (36), nausea (29), constipation (23)
GA101–mini-CHOP	CD20	Merli et al[27]	1	33 DLBCL	66/42	2 years PFS 49%	2 years OS 68%	Neutropenia (26), metabolic disorders (9), cardiac disorders (6), hepatobiliary disorders (6), connective-tissue disorders (6), neoplastic disorders (6)	Gastrointestinal disorders (33), thrombocytopenia (30), anemia (18), infections (18), nervous system, psychiatric disorders (18)
Tafasitamab	CD19	Jurczak et al[29]	>1*	92 NHL, 35 DLBCL	26/6 in DLBCL	Median 2.7 months	—	Neutropenia (17), anemia (9), thrombocytopenia (6), pneumonia (9), dyspnea (6)	IRRs (11%, all grade 1–2)
Tafasitamab–lenalidomide	CD19	Salles et al[31]	2–4*	80 DLBCL	60/43	Median 12 months	Median NR at FU of 19.6 months	Neutropenia (48), thrombocytopenia (17), FN (12), rash (9), anemia (7), hypokalemia (6), pneumonia (6)	≥Grade 3 thrombotic events: pulmonary embolism (2), deep-vein thrombosis (1), cerebrovascular accident (1), myocardial ischemia (1)
Antibody-drug conjugates									
Polatuzumab-BR	CD79B	Sehn et al[38]	>1	40 DLBCL	45/40	Median 9.5 months at median FU of 22.3	Median 12.4 months at median FU of 22.3 mo	Neutropenia (46), thrombocytopenia (41), anemia (28), lymphopenia (13), FN (10)	Peripheral neuropathy (44), diarrhea (38)
Polatuzumab–R-CHP or GA101–CHP	CD79B	Tilly et al[39]	1	66 DLBCL	89/77	—	—	Neutropenia (30), FN (19), leukocytosis (11), thrombocytopenia (10), leukopenia (8), pneumonia (7), hyperglycemia (7)	Peripheral neuropathy (42%, only 2% grade 3)

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Table 1 (Continued).

Therapy regimen	Target	Study	Line	Patients, n	Efficacy	PFS	OS	Toxicity	Other specific-drug toxicities of any grade AEs (%)
					ORR/CR (%)			Grade ≥3 AEs (%)	
Pinatuzumab± rituximab	CD22	Advani et al [36]	>1	75 NHL, 47 DLBCL	15 patients, with 7 CR in DLBCL°	—	—	Total of 69%, including neutropenia, fatigue, peripheral sensory neuropathy, hyperglycemia, and anemia[#]	—
Pinatuzumab–rituximab	CD22	Morschhauser et al[32]	>1	63 NHL, 42 DLBCL	60/26 in DLBCL	5.4 months in DLBCL	16.5 months in DLBCL	Neutropenia (29), hyperglycemia (10), 21% events grade 5, 55% infection-related[#]	Diarrhea (33), peripheral neuropathy (29)[#]
Loncastuximab	CD19	Hamadani et al[44]	>1	183 B-NHL	42.3 in DLBCL	5.4 months in all NHL	—	—	Most common AEs: hematological, fatigue, nausea, edema, liver-enzyme abnormalities
Coltuximab	CD19	Trněny et al[47]	>1	61 DLBCL	43.9 on 41 evaluable patients	Median 4.4 months on 41 evaluable patients	Median 9.2 months on 41 evaluable patients	Hepatotoxicity (3%) and abdominal pain (3%)	Eye disorders (25%, all grade 1–2)
Coltuximab–rituximab	CD19	Coiffier et al[48]	>1	52 DLBCL	31.1/8.9	Median 3.9 months	Median 9 months	—	Gastrointestinal disorders (52), asthenia (25)
Brentuximab	CD30	Jacobsen et al[51]	>1	68 NHL, 49 DLBCL	44/17 in DLBCL	Median 4 months in DLBCL	—	Neutropenia (37), fatigue (12), nausea (12), decreased appetite (8), diarrhea (6)	Peripheral neuropathy (24% all grades, 2% grade 3/4)
Brentuximab–R-CHP	CD30	Svodoba et al[52]	1	31 aNHL, 6 DLBCL	100/86 on 29 evaluable patients[#]	2 years PFS 85% on 29 evaluable patients[#]	2 years OS 100% on 29 evaluable patients[#]	Lymphopenia (46), neutropenia (42), leukopenia (32), FN (23), infection (15), thrombotic events (6)[#]	Neuropathy (71%, all grade 1–2)[#]
Naratuximab–emtansine	CD37	Stathis et al[56]	>1^	49 NHL, 24 DLBCL	22/6 in DLBCL	—	—	Neutropenia (33), thrombocytopenia (14), febrile neutropenia (14), pneumonia (4)[#]	Fatigue (49), neutropenia (37), pyrexia (37), thrombocytopenia (37)
BI836826	CD37	Kroschinsky et al[58]	>1^	48 NHL, 20 DLBCL	6/2[#]	—	—	Neutropenia (57), leukopenia (57), thrombocytopenia (41), commonly grade 3–4[#]	IRRs in 38%, mostly grade 1–2[#]

Radioimmunoconjugates									
Zevalin–BEAM	CD20	Shimoni et al[33]	≥1	43 aNHL, 14 DLBCL	—	2 years PFS 59%[#]	2 years OS 91%[#]	Mucositis (68), infection (28), cardiovascular diseases (14)[#]	
Zevalin	CD20	Morschhauser et al[29]	>1	102 DLBCL	Post-CT 52/24 in Ref, 53/40 in Rel; post R-CT: 19/12	Media PFS: post-CT in Ref 5.9 months, in Rel 3.5 mo, post–R-CT 1.6 months	Media OS: post-CT in Ref 21.4 months, in Rel 22.4 mo, post–R-CT 4.6 months	Hematological toxicity (43)	—
Zevalin–BEAM + ASCT	CD20	Ciochetto et al[34]	>1	37 NHL, 18 PML + DLBCL	86/59[#]	3 years PFS 61%[#]	3 years OS 61%[#]	Mucositis (10 patients), uninfectious enteritis (2 patients), one death due to aspergillosis + HINI pneumonia[#]	Fever of unexplained origin (8 patients), sepsis in aplasia (4 patients)[#]

Notes: *Prior treatments had to include rituximab; ^prior treatments had to include anti-CD20–based therapeutic regimen; °best overall response. [#]The trial included other lymphomas, and data reported are based on all enrolled patients. Polatuzumab-R-CHP, polatuzumab-R-GemOx, polatuzumab-R-ICE, and brentuximab-R-lenalidomide are under investigation.

Abbreviations: AEs, adverse events; aNHL, aggressive non-Hodgkin lymphoma; ASCT, autologous stem-cell transplantation; BEAM, carmustine + etoposide + cytarabine + melphalan; BR, bendamustine + rituximab; CHP, cyclophosphamide, doxorubicin, and prednisone; CHOP, vincristine + cyclophosphamide, doxorubicin, and prednisone; CR, complete response; CT, chemotherapy; DLBCL, diffuse large B-cell lymphoma; FN, febrile neutropenia; FU, follow-up; GA101, obinutuzumab; IRRs, infusion-related reactions; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PML, primary mediastinal B-cell lymphoma; R, rituximab; Ref, refractory; Rel, relapsed.

andCR cases. Tafasitamab reached a 26% ORR in DLBCL, with five of nine cases with durable response (>12 months). Median duration of response (DOR) was 20.1 months, with median PFS of 2.7 months. Refractoriness to rituximab did not impact response or survival. Major AEs included IRRs and neutropenia.[29] In vitro findings of enhanced NK cell–mediated cytotoxicity of tafasitamab through the addition of lenalidomide encouraged further investigations on the efficacy of this combination in a clinical setting, eg, the L-MIND trial.[30,31] In this study, R/R DLBCL patients ineligible for autologous stem-cell transplantation (ASCT) received tafasitamab 12 mg/kg per day on days 1, 8, 15 and 22 in cycles 1–3 and for cycle 4 twice a month for up to 12 cycles in association with lenalidomide 25 mg/day on day 1–21 of a 28-day cycle, followed by monthly monotherapy with tafasitamab (in SD cases) until progression. Among 80 treated patients, ORR was 60%, with 43% CR and 18% PR. At a median follow-up of 17.3 months, median PFS was 12.1 months, while at a median follow-up of 19.6 months, median overall survival (OS) was not reached. The most common AE was hematological toxicity, with grade 3 or worse neutropenia in 48%, thrombocytopenia in 17%. and febrile neutropenia in 12%, whereas other non-hematological severe events were rash in 9% and pneumonia in 9%.[31] These good results in a heavily pretreated cohort of DLBCL patients highlighted the possibility of treating these patients with a chemotherapy-free approach, and on this basis the FDA recently approved tafasitamab combined with lenalidomide (R^2) for treatment of R/R DLBCL noncandidates for transplant. Moreover, this prompted a new phase 3 randomized study for first-line high-risk DLBCL testing the addition of tafasitamab with lenalidomide to R-CHOP vs R-CHOP alone (EudractCT 2020-002990-84).

Radioimmunoconjugates

Radioimmunoconjugates, particularly ibritumomab tiuxetan (Zevalin), have been investigated in B-NHLs. This construct combines an antiCD20 mAb with the radionucleotide yttrium90, making it possible to target radiation to CD20-positive lymphoma B-cells, sparing irradiation to other normal cells (Figure 1). Zevalin has demonstrated acceptable toxicity and moderate activity as a single agent in transplant-ineligible elderly R/R DLBCL patients.[32] A phase III trial compared the pre–ASCT conditioning regimen carmustine, etoposide, cytarabine, and melphalan (BEAM) with BEAM plus Zevalin (Z-BEAM) in R/R

Table 2 Efficacy and safety profile of checkpoint inhibitors in LBCL

Therapy regimen	Target	Study	Line	Patients, n	Efficacy	PFS	OS	Toxicity	Other specific-drug toxicities of any grade (%)
					ORR/CR (%)			Grade ≥3 AEs (%)	
Checkpoint inhibitors									
Nivolumab	PD1	Lesokhin[62]	>1	81 NHL + MM (11 DLBCL)	34/18 in DLBCL	Median 7 weeks in DLBCL	—	Pneumonitis (4)	Fatigue (17), pneumonitis (11), decreased appetite (9), pruritus (9), rash (9), diarrhea (7), pyrexia (6), anemia (6)
Nivolumab	PD1	Ansell[63]	>1*	121 DLBCL	13/3	Median PFS 1.4 months (not eligible for ACST); 1.9 months (failed ASCT)	Median OS 5.8 months (not eligible for ACST); 12.2 months (failed ASCT)	Neutropenia (4), thrombocytopenia (3), increased lipase (3)	—
Nivolumab–CART	PD1–CD19	Cao[64]	>1	11 DLBCL	82/45	Median PFS 6 months	—	Cytopenia (anemia, neutropenia, and thrombocytopenia)	CRS (82%, of which 9% of grade 3), fever (72), fatigue (54), nausea (27), and one episode of neurotoxicity
Pembrolizumab	PD1	Zinzani[72]	>1	18 PMBCL	41/12	—	—	Neutropenia (6), veno-occlusive liver disease (6)	Hypothyroidism (11), diarrhea (11), nausea (11), fatigue (11), pyrexia (11), decreased appetite (11)
Pembrolizumab–vorinostat	PD1–HDAC	Herrera[78]	>1	30 NHL + HL, 9 DLBCL	56/33 in DLBCL	Median at 6 months 67%	Median at 6 months 71%	Thyroiditis (18), neutropenia (7), Stevens–Johnson syndrome (4), pulmonary embolism (4)[#]	Most common AEs of any grade: nausea (61), fatigue (57), hypertension (54), anemia (50), leukopenia (50), hyponatremia (43), diarrhea (43), neutropenia (39), thrombocytopenia (39)[#]
Pembrolizumab–CHOP	PD1	Smith[79]	1	30 DLBCL	90/77	2 years PFS 83%	2 years OS 84%	FN (23), syncope (10), infection (10), pneumonitis (3), gastrointestinal bleeding (3), pulmonary embolism (3)	Four IRAEs: hyperthyroidism (grade 1), colitis (grade 2), rash (grade 3), pneumonitis (grade 3)

Pembrolizumab–CART	PD1–CD22+CD19	Osborne[83]	>1	28 DLBCL	64/64	—	—	Neutropenia (89), thrombocytopenia (58), anemia (47), FN (16), hypophosphatemia (16), neurotoxicity (5)	—
Atezolizumab–CART	PDL1	Jacobson[89]	>1	28 DLBCL	75/46	Median NR	Median NR	Neurotoxicity (29), CRS (4)	
Atezolizumab–venetoclax–GA101	PDL1–BCL2–CD20	Herbaux[88]	>1	58 DLBCL	24 OMRR/18 CMR	—	—	Lymphopenia (35), neutropenia (33)	One episode of autoimmune colitis (grade 3) and hypothyroidism (grade 1)
Atezolizumab–RCHOP	PDL1	Younes[87]	1	42 DLBCL	87/77 (31 evaluable patients)	2 years PFS 75%	2 years OS 86%	Neutropenia (62), lipase increase (18), FN (17), syncope (9), anemia (7), considering induction and consolidation	—
Avelumab–RCHOP	PDL1	Hawkes[91]	1	22 DLBCL, 6 PMBCL	89/21 CMR	1-year FFP 76%	1-year OS 89%	One grade 3/4 episode of hepatitis and two of rash	Rash (53), hyper/hypothyroidism (29), FN/infection (28), liver dysfunction (26), diarrhea (21)
Durvalumab–RCHOP or R^2CHOP	PDL1	Nowakowski[94]	1	46 DLBCL	54 RCHOP and 67 R^2CHOP	1-year PFS: 68% RCHOP, 67% R^2CHOP	—		Neutropenia (52), peripheral sensory neuropathy (50)
Durvalumab–Ibrutinib	PDL1	Herrera[96]	>1	34 DLBCL	25[#]	Median 4.6 months	Median 18.1 months		Diarrhea (47), peripheral edema (38), IRAEs (20), neutropenia (20)
Durvalumab–CART	PDL1	Hirayama[97]	>1	15 aNHL	50/42	—	—		CRS (38, one event of grade 4), neurotoxicity (8)
Ipilimumab	*CTLA4*	Ansell[102]	>1	18 NHL	11 (1 FL, 1 DLBCL)/1 CR	—	—	Diarrhea (28)[#]	Diarrhea (56), fatigue (56), thrombocytopenia (28), abdominal pain (28), headache (22), anorexia (22), neutropenia (17)[#]

(*Continued*)

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Table 2 (Continued).

Therapy regimen	Target	Study	Line	Patients, n	Efficacy ORR/CR (%)	PFS	OS	Toxicity Grade ≥3 AEs (%)	Other specific-drug toxicities of any grade (%)
Ipilimumab-R	*CTLA4*	Tuscano[103]	>1, <4	33 NHL, 7 DLBCL, and 1 PMBCL	24/6[#]	Median PFS 2.6 months[#]	—	Diarrhea (4 events of grade 3)	
Ipilimumab–nivolumab after ASCT	*CTLA4–PD1*	Skarbnik[104]	≥1	35 NHL		Primary Ref DLBCL, 18 months PFS 86%, Rel DLBCL 29%	Primary Ref DLBCL, 18 months OS 100%, Rel DLBCL 57%		94% of patients had IRAEs of any grade
HUSF9G4-R	*CD47*	Advani[107,108]	>1	100 NHL, 63 DLBCL	39/20 in DLBCL	—	—	Anemia (15)	Infusion reactions (38), headache (34), chills (30), fatigue (30), anemia (27), nausea (24), pyrexia (23), vomiting (13), back pain (11)
TTI-621± R	*CD47*	Ansell[109]	>1	61 NHL, 35 DLBCL	23/7 in DLBCL	—	—	Thrombocytopenia (20), nausea (9), neutropenia (9)	Infusion reactions (43), thrombocytopenia (26), chills (18), fatigue (15), anemia (13), nausea (12), vomiting (9), neutropenia (9), diarrhea (10), pyrexia (10), headache (8), hypotension (5)

Notes: *In patients with DLBCL who failed autologous stem-cell transplantation (ASCT) or who were ineligible for ASCT; [#]included other lymphomas, reported data based on all enrolled patients. Pembrolizumab–blinatumomab or mogamulizumab or nivolumab associated with other immunochemoterapies or biological drugs and ipilimumab–nivolumab under investigation.

Abbreviations: AEs, adverse events; aNHL, aggressive non-Hodgkin lymphoma; ASCT, autologous stem-cell transplantation; CART, chimeric antigen receptor T-cell; CMR, complete metabolic response; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FFP, failure free survival; FL, follicular lymphoma; FN, febrile neutropenia; FU, follow-up; IRRs, infusion-related reactions; HDAC, histone deacetylase; IRAEs, immunorelated adverse events; MM, multiple myeloma; NR, not reached; OMRR, overall metabolic response rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; R^2CHOP, rituximab, lenalidomide, vincristine, doxorubicin, cyclophosphamide, and prednisone; Ref, refractory; Rel, relapsed.

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Table 3 Efficacy and safety profile of bispecific antibodies in LBCL

Therapy regimen	Target	Study	Line	Patients, n	Efficacy	PFS	OS	Toxicity	Other specific-drug toxicities of any grade (%)
					ORR/ CR (%)			Grade ≥3 AEs (%)	
Bispecific antibodies									
Blinatumomab	CD19–CD3	Goebeler[110]	>1	76 NHL, 14 DLBCL	69/37[#]; 55/36 in 11 patients with DLBCL	—	—	Lymphopenia (79), leukopenia (20), neutropenia (17), hyperglycemia (12), thrombocytopenia (12), γ-glutamyltransferase increase (9), fibrin D-dimer increase (8), anemia (7), hypokalemia (7)[#]	Neurotoxicity 71%, of which 22% were grade 3 (encephalopathy 8%, aphasia 4%, headache 3%)[#]
Blinatumomab	CD19–CD3	Viardot[111]	>1	25 DLBCL	43/19	Median 3.7 months	Median 5 months	Thrombocytopenia (17), leukopenia (17), device-related infection (13), pneumonia (13), hyperglycemia (9)	Most common AEs of any grade: tremor (48), pyrexia (44), fatigue, and edema (26). Neurological events ≥3: encephalopathy (9), aphasia (9)
Glofitamab	CD20–CD3	Hutchings[113]	>1	64 NHL, with 47 aNHL	33/21[#]	—	—	Neutropenia (14)[#]	Pyrexia (22) and CRS (22), all grade 1–2[#]
Glofitamab–GA101	CD20–CD3	Morschhauser[116]	>1	28 NHL, with 22 aNHL	38/31 in aNHL	—	—	Anemia (11), thrombocytopenia (11), neutropenia (11), CRS (8)[#]	All CRS events (57) (8% ≥grade 3), pyrexia (14), and hypokalemia (14), all grade 1–2[#]
Glofitamab–atezolizumab	CD20–CD3 + PDL1	Hutchings[118]	>1	38 NHL, with 33 aNHL	29/10 in aNHL	—	—	Neutropenia (18), anemia (13), three transient events of neurotoxicity[#]	CRS (42%, all grade 1–2), pyrexia (37), fatigue (24), decreased appetite (21), diarrhea (21)[#]
Mosunetuzumab	CD20–CD3	Schuster[121]	>1	218 NHL, with 141 aNHL	64/42 in aNHL	—	—	—	CRS 28% (1% grade 3), neurological AEs 44 (3% grade 3)[#]
Mosunetuzumab–CHOP	CD20–CD3	Phillips[122]	≥1	36 new DLBCL + 7 R/R NHL	89/71 in R/R, 96/85 in 1° line	—	—	Neutropenia (58), FN of any grade (19), grade 5 pneumonia (5)	CRS 49%, all grade 1–2

(*Continued*)

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Table 3 (Continued).

Therapy regimen	Target	Study	Line	Patients, n	Efficacy	PFS	OS	Toxicity	Other specific-drug toxicities of any grade (%)
					ORR/ CR (%)			Grade ≥3 AEs (%)	
Epcoritamab	CD20–CD3	Hutchings[125,126]	>1	45 DLBCL	66/33	—	—	Neurotoxicity (6), 3% grade 3	Pyrexia (70), CRS (58), all grade 1–2, injection-site reactions (48), fatigue (45)
Odronextamab	CD20–CD3	Bannerji[129]	>1	127 NHL, 71 DLBCL	60/60	—	—	CRS (7), neurological AEs (2)[#]	Pyrexia (76), CRS (6), and chills (43) of any grade[#]
Plamotamab	CD20–CD3	Patel[131]	>1	36 NHL + 8 CLL		—	—	Neutropenia (14), thrombocytopenia (8), pyrexia (6), CRS (3)[#]	Pyrexia (50), CRS (42), chills (22), hypotension (19), anemia (17), diarrhea (14), hypertension (14), constipation (11), vomiting (11), tachycardia (11)[#]

Notes: [#]The trial included other lymphomas, and reported data are based on all enrolled patients. Glofitamab–polatuzumab, glofitamab– + GA101 or R-CHOP or glofitamab-R-GemOx and several immunochemotherapy regimens with epcoritamab are under investigation.

Abbreviations: AEs, adverse events; aNHL, aggressive non-Hodgkin lymphoma; CHOP, vincristine + cyclophosphamide, doxorubicin, and prednisone, CLL, chronic lymphocytic leukemia; CR, complete response; CRS, cytokine-release syndrome; DLBCL, diffuse large B-cell lymphoma; FN, febrile neutropenia; GA101, obinutuzumab; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

DLBCL. Despite the safe toxicity profile of Z-BEAM, the primary endpoint (12-year PFS) was not met, though a trend of better OS using BEAM was observed.[33] Similarly, a nonsignificant trend of better PFS with the Z-BEAM–conditioning regimen compared with BEAM alone in R/R DLBCL transplantcandidates has been reported by a single-center retrospective analysis.[34] Due to a lack of clear evidence of effectiveness on DLBCL, interest in further investigations and clinical use of Zevalin for this disease is relatively sparse nowadays.

Antibody–Drug Conjugates

Ab–drug conjugates (ADCs) are compounds consisting of an mAb directed against a specific tumor-surface antigen linked with a cytotoxic drug that is delivered into malignant cells. Stable linkage between the mAb and the cytotoxic drug ensures that the drug does not detach from the Ab, giving a highly tumor-specific effect with elevated safety and efficacy (Figure 1).

Pinatuzumab Vedotin and Polatuzumab Vedotin

Polatuzumab vedotin is an ADC comprised of an anti-CD79B mAb conjugated with a protease-cleavable link with monomethyl auristatin E (MMAE), a microtubule-disrupting agent. Polatuzumab vedotin demonstrates modest activity as a single agent for B-NHL, including DLBCL.[35] The most frequent side effect is neutropenia, and neurotoxicity is a common treatment-emergent AE. Pinatuzumab vedotin is an anti-CD22 ADC loaded with MMAE. It has been demonstrated to be safe and active in R/R NHLs, including DLBCL, both as a single agent and combined with rituximab in a phase I study.[36]

More recently, a phase II, multicenter, open-label, randomized trial compared rituximab plus pinatuzumab or polatuzumab in R/R DLBCL and FL.[37] For the R/R DLBCL cohort, the combination rituximab + pinatuzumab demonstrated superimposable activity in respect of rituximab + polatuzumab in terms of response rates and PFS — ORR 60% and 54%, CR 26% and 21%, and median PFS 5.4 months and 5.6 months, respectively — but in the rituximab + pinatuzumab group, grade 5 AEs were more frequent (21.4% vs none).[37] Therefore, polatuzumab was selected for further development instead of pinatuzumab because of a better overall benefit–risk balance.

The combination polatuzumab vedotin plus bendamustine and rituximab (pola-BR) has been approved by the

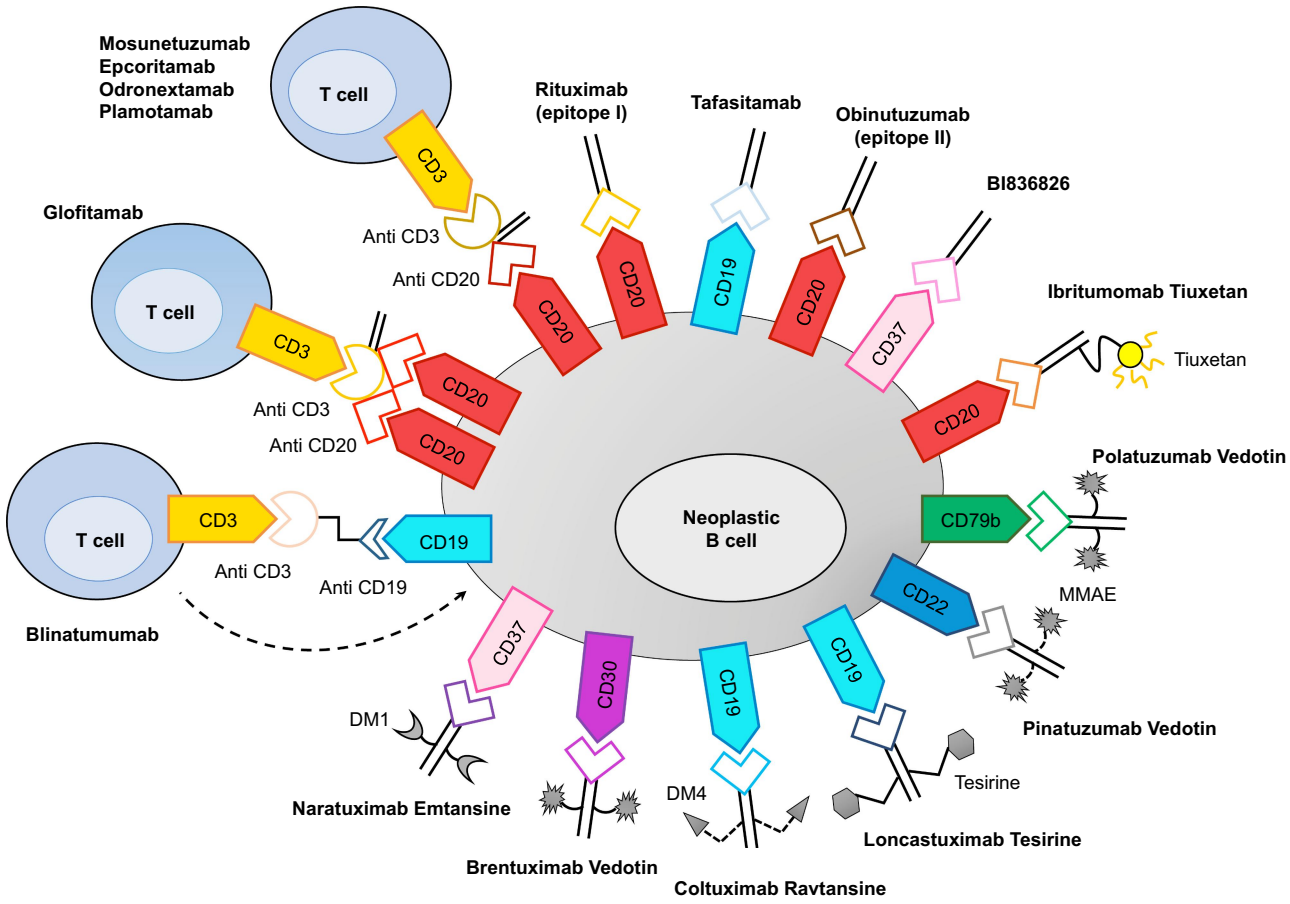

Figure 1 Monoclonal antibodies, including naked antibodies, antibody–drug conjugates, radioimmunoconjugates, and bispecific antibodies, are able to target Bcells on different surface antigens and with a number of cytotoxic mechanisms of action.

FDA and EMA for treatment of transplant-ineligible R/R DLBCL, led by the results from the phase II randomized trial by Sehn et al.[38] In that study, the experimental arm pola-BR compared to standard BR met the primary end point of CR improvement >20% (40% and 17.3% for pola-BR and BR, respectively) and increased survival in terms of both PFS and OS. Polatuzumab showed a safe toxicity profile when combined with an anti-CD20 mAb (rituximab or obinutuzumab) plus cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP or pola-G-CHP), omitting vincristine to avoid overlapping neurotoxicity, and a phase III trial (POLARIX) that compared the combination pola-R-CHP vs the standard R-CHOP in frontline therapy for DLBCL is ongoing.[39,40] Polatuzumab vedotin is also under investigation for the treatment of R/R transplant-eligible DLBCL in combination with ifosfamide, carboplatin, and etoposide (polaR-ICE) and in the phase III trial POLARGO, which is comparing polatuzumab plus rituximab, gemcitabine, and oxaliplatin (pola-R-GemOx) vs R-GemOx alone for R/R DLBCL.[41,42]

Loncastuximab Tesirine

Loncastuximab tesirine (ADCT402) is an ADC comprising a humanized anti-CD19 mAb conjugated through a cathepsin-cleavable linker to a pyrrolobenzodiazepine dimer toxin known as tesirine (SG3199). It has demonstrated high cytotoxic activity in vitro on CD19-expressing human cells.[43] The final results from a phase I study testing ADCT-402 for multirefractory NHLs, including DLBCL, FL, and mantle-cell lymphoma histology have recently been published.[44] ADCT showed an acceptable toxicity profile and a certain efficacy on R/R DLBCL, with ORR of 42.3% and median duration of response of 5.4 months, encouraging further investigation.[44]

Coltuximab Ravtansine

Coltuximab ravtansine (SAR3419) is a further compound constituted by an anti-CD19 mAb linked with a potent cytotoxic maytansinoid, DM4, via a cleavable disulfide bond. The optimal dosage of 55 mg/m^2 weekly for four

doses followed by four biweekly doses for R/R B-NHLs has been defined through the phase I dose-escalation study by Ribrag et al,[45] with a safer toxicity profile, and especially reduction in ocular toxicities in respect of what was seen in a previous trial.[46] Two phase II trials have tested SAR3419 as a single agent or combined with rituximab in R/R DLBCL patients, with moderate efficacy (ORR 31.9%–43.9%).[47,48]

Brentuximab Vedotin

Brentuximab vedotin (BV) is composed of an anti-CD30 mAb conjugated with MMAE. Following the high efficacy demonstrated for HL, typically characterized by CD30-expressing cells, BV has been tested on R/R PMBCL in a phase II study, with unsatisfactory results (ORR 13%) and early closure of the trial.[49] On the other hand, promising results have been observed with the combination BV plus nivolumab for pretreated PMBCL patients, with 70% ORR, 43% CR, and median PFS and OS not reached after a median follow-up of 11.1 months.[50] BV was also tested for CD30-positive R/R DLBCL patients, showing moderate activity (ORR 44%, CR 17%), irrespective of the grade of expression of CD30, and a safe profile.[51] In the same phase I/II trial, the combination with rituximab was also evaluated, with no additional benefit.[51] Moreover, in a phase I/II trial, BV has been combined with R-CHP (BV+R-CHP) as frontline treatment for CD30-positive B-NHL, including 22 PMBCL, 5 DLBCL, and two gray--zone lymphomas, with promising toxicity profile and efficacy (ORR 100%, CR 86%).[52] A phase III trial investigating the efficacy of rituximab and lenalidomide with or without BV for R/R transplant-ineligible patients is ongoing.[53]

Anti-CD37 Compounds

CD37 is a tetraspanin expressed on both healthy and malignant B-cell surfaces that plays a crucial role in cell survival and response of immune system.[54] Lower expression of CD37 in DLBCL cells has been associated with worse survival after immunochemotherapy, suggesting that CD37 may optimize rituximab activity.[55] These data encouraged the development of several anti-CD37 drugs for hematological neoplasms. Naratuximab emtansine, an anti-CD37 mAb conjugated with the potent antimitotic maytansine-derived microtubule disruptor (DM1), has been tested on 49 patients with R/R NHLs, resulting in 13% ORR (one CR and four PR), and a phase II trial in combination with rituximab on R/R NHL including DLBCL is ongoing.[56,57] BI836826, an anti-CD37 chimeric Ab, was tested on NHL in a phase I trial and demonstrated modest results, with response in three of 48 patients (one CR), despite a safe profile, with major AEs represented by hematological toxicities and manageable IRRs.[58] Other mAbs targeting CD37 include otlertuzumab, which has been studied in combination with bendamustine for CLL, AGS67E, an ADC conjugated with MMAE tested in AML and lymphoproliferative diseases, and betalutin, a murine radioimmunoconjugate, linked with the β-emitting isotope lutetium177, studied in preclinical models of NHL in association with rituximab, showing an improvement in anti-CD20 activity.[59–61]

Checkpoint Inhibitors

The promising therapeutic effects of checkpoint inhibitors have attracted great interest in the past decade and have undoubtedly revolutionized cancer treatment. Several mAbs capable of targeting cellular immunocheckpoints have been developed and investigated in the treatment of patients with LBCL. Checkpoint inhibitors work by disrupting the interaction between inhibitory receptors and their ligands and thus activating antitumor immunity. The compounds most actively studied for the treatment of LBCL are molecules that target PD1/PDL1, CTLA4), and CD47 (Figure 2, Table 2).

Anti-PD1/PDL1 Compounds

A member of the CD28 family, is a receptor expressed on the surface of T cells that is able to regulate its activation by interacting with two ligands (PDL1 and PDL2). PDL1 is expressed in a number of different cell types, as well as tumor cells. The interaction of PD1 with PDL1 or PDL2 results in the inhibition of T cell–receptor signaling and downregulates T-cell proliferation. Cancer cells exploit PD1 signaling to escape T cell–mediated eradication. Highly selective mAbs directed to PD1 (eg, pembrolizumab and nivolumab) or PDL1 (eg, atezolizumab, avelumab, and durvalumab) can disrupt receptor–antigen interaction and reverse T-cell inactivation, restoring the immune-system antitumor response.

Nivolumab

Nivolumab is another anti-PD1 mAb, nowadays approved for the treatment of HL patients that resulted R/R to ASCT. In the setting of R/R DLBCL, nivolumab as monotherapy was tested on eleven patients in a phase I trial with modest results. ORR was 36% (CR 18%) andmedian PFS

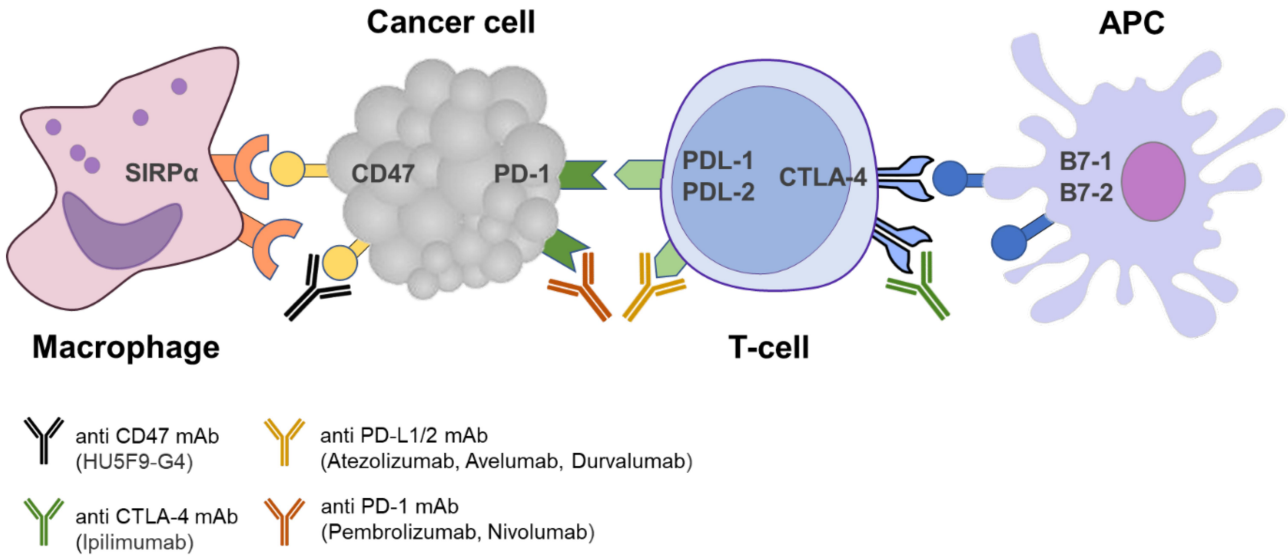

Figure 2 Checkpoint inhibitors (anti-CD47, anti-PDL1/2, antiCTLA4, and anti-PD1) disrupt interaction between inhibitory receptors and their ligands and thus activate antitumor immunity.

7 weeks: one of four patients in this group has had an ongoing response, and two continue to be followed.[62] Nivolumab has been reevaluated in terms of efficacy and safety in patients ineligible for ASCT. However, the results of a phase II study showed a low incidence of objective response (benefiting only a small subset of patients: ORR 10% among subjects treated following relapse following ASCT, and only 3% in ASCT-ineligible patients) despite a favourable safety profile.[63]

Nivolumab in combination with other anticancer therapies has been investigated in R/R DLBCL. A single-center study evaluated safety and efficacy of the combination anti-CD19 CART plus nivolumab for R/R B-NHL, showing manageable toxicity and opening up opportunities for further clinical trials. In this study oneleven R/R LBCL subjects, ORR and CR were 81.8% and 45.4%, respectively. With median follow-up of 6 months,median PFS was 6 months.[64] A number of further phase I/II studies are currently being carried out to investigate the therapeutic value of nivolumab with other antilymphoma treatments, such as rituximab and chemotherapy regimens, ipilimumab, varlilumab (anti-CD27 mAb), lenalidomide, rituximab + lenalidomide (R^2), and epacadostat (an IDO1-selective inhibitor) in LBCL patients.[65–71]

Pembrolizumab

Pembrolizumab has been the first humanized anti-PD1 mAb to receive accelerated FDA clearance for the treatment of R/R PMBCL. This approval was based on results of the phase IB KEYNOTE-013 and phase II KEYNOTE-170 trials, which demonstrated a high response rate, durable activity, and favorable safety profile in a subset of PMBCL patients.[72,73] A number of studies are currently evaluating the efficacy of pembrolizumab in DLBCL patients, either as single therapy or in combination with other drugs.[74–77]Of note, PD1 ligands appear to be poorly expressed in DLBCL, with 27% of tumor specimens being PDL1-positive onimmunohistochemistry, leading to low CR rates or no response to anti-PD1. However, the presence of *PDL1* gene alterations has been associated with objective response to pembrolizumab in R/R DLBCL patients. An ongoing phase II study has been designed to fully evaluate the possibility of using *PDL1* genetic alterations in R/R DLBCL to predict response to PD1 blockade.

The efficacy of pembrolizumab as monotherapy in DLBCL is still a matter of scientific debate. More success seems to have been achieved using pembrolizumab combined with other therapies. A combination of pembrolizumab and the oral histone-deacetylase inhibitor vorinostat has been tested by Herrera et al,[78] showing preliminary promising results on nine R/R transplant-ineligible DLBCL patients (ORR 56%, CR 33%).

Combination of pembrolizumab and R-CHOP in untreated patients with DLBCL has also been evaluated,[79] demonstrating a safe toxicity profile. Among 30 patients treated, ORR and CR were 90% and 77%, respectively. After a median follow-up of 25.5 months, 2-year PFS of 83% was reached.

The use of pembrolizumab after anti-CD19 chimeric antigen-receptor T-cell (CAR-T) therapy has been investigated. The PD1 blockade demonstrated interesting activity in this setting, enhancing the efficacy of CAR-T in R/R LBCL.[80] Based on these findings, multiple clinical trials looking at different aspects of the synergy between pembrolizumab and CAR-T have been initiated.[81,82] Promising results came from the phase I/II ALEXANDER trial, where combination of the bispecific anti-CD19/22 CAR-T (AUTO3) and pembrolizumab induced high response rates without causing some of the key severe side effects (ie, cytokine-release syndrome [CRS] and neurotoxicity). Across four cohorts treated with different doses of AUTO3 alone or in combination with pembrolizumab, ORR was 68% and CR 54%.[83] Contrarily, the consolidative use of pembrolizumab after ASCT for patients with R/R DLBCL has been investigated through a phase II multicenter study, but with no improvement in terms of PFS.[84] Other studies are currently looking into the combination of pembrolizumab with other drugs, such as the CD3xCD19 bispecific mAb blinatumomab and the anti-CCR4 mogamulizumab for R/R DLBCL.[85,86]

Atezolizumab

Atezolizumab is a fully humanized IgG_1 mAb targeting PDL1. Atezolizumab has been tested in combination with R-CHOP followed by consolidation with single-agent atezolizumab in previously untreated DLBCL patients. Preliminary data from this open-label phase I/II study are promising: among 40 patients who received at least one dose of atezolizumab, ORR of 87.5% and 77.5% CR have been obtained, with 2-year PFS and OS of 74.9% and 86.4%, respectively. However, nonnegligible toxicity has been observed, with AEs causing a high number of discontinuations (36% of patients), even if they appeared to be overall manageable and reversible.[87]

More recently, the combination atezolizumab plus obinutuzumab and venetoclax has been tested through a multicenter phase II trial in DLBCL patients who had failed at least one line of therapy. Preliminary analysis demonstrated durable response (ORR 23.6%) with a manageable safety profile.[88] The safety and efficacy of atezolizumab in combination with the anti-CD19 CAR-T cell axicabtagene ciloleucel (axi-cel) for R/R LBCL is under investigation in a phase I/II trial. The interim analysis demonstrated that PDL1 blockade with atezolizumab after axi-cel was well tolerated, and the study did not reveal increased incidence of AEs. However, efficacy and CAR-T cell levels reported in the study were comparable to those of patients treated with axi-cel alone.[89]

Avelumab

Similarly to atezolizumab, avelumab acts by targeting the PD1 pathway at the ligand level. In R/R DLBCL, a two-component phase IB/III study tested avelumab in combination with rituximab, utomilumab (a 41BB agonist) and chemotherapy drugs (ie, azacitidine, bendamustine, gemcitabine, and oxaliplatin). However, the phase III part of the study was never conducted, due to early closure of phase IB enrolment.[90] Another phase II multicenter single-arm trial is investigating the feasibility of adding induction and maintenance with avelumab to standard R-CHOP therapy in patients with stage II–IV DLBCL. At the time of the interim analysis, the trial had enrolled 28 patients and reported ORR and CR after R-CHOP of 89%. The ORR to two cycles of induction avelumab + rituximab (AvR) was 60%. Six patients (21%) progressed during AvR induction (with one completing only one AvR cycle), and all subsequently responded to R-CHOP. With a median follow-up of 16 months, 1-year failure-free survival was 76% and OS 89%.[91] The side effects and optimal dosing of avelumab, utomilumab, rituximab, ibrutinib, and combination chemotherapy are also being evaluated in a phase I clinical trial for R/R aggressive B-NHL (aNHL), including DLBCL.[92]

Durvalumab

The anti-PDL1 molecule durvalumab has been studied for the treatment of DLBCL as both a single-agent and in the context of combined immunochemotherapy regimens. FUSION NHL-001 is a phase I/II study assessing the safety and efficacy of durvalumab as monotherapy or in combination. Among a total of 38 patients with R/R DLBCL enrolled, aside acceptable toxicity, the therapy had limited benefit.[93]

The safety and efficacy of durvalumab plus R-CHOP or R^2CHOP in untreated high/high–intermediate risk DLBCL patients were assessed in a phase II open-label study. Patients received durvalumab + R-CHOP if considered GCB-DLBCL (arm A) or R^2CHOP if activated B-cellDLBCL (arm B), based on cell of origin defined by gene-expression profiling. CR at end of induction was 54% in arm A and 67% in arm B out of a total of 46 patients treated. Fatigue, neutropenia, peripheral sensory neuropathy, and nausea were the most common AEs.[94]

A phase IB study evaluated the combination durvalumab plus tremelimumab (an anti-CTLA4 mAb) or danvatirsen (an antisense oligonucleotide anti-STAT3) for R/R DLBCL. These regimens were generally well tolerated, but had limited therapeutic effectiveness (ORR 6.3%).[95]

In another phase IB/II multicenter open-label study that included GCB and non-GCB DLBCL subjects, the combination ibrutinib plus durvalumab had modest efficacy. ORR was 13% and 38% in GCB and non-GCB DLBCL patients, respectively, with AEs reported in 20%. It was concluded that ibrutinib and durvalumab had similar activity to ibrutinib alone, but with added toxicity typical of PDL1 blockade.[96] Durvalumab has also been used in combination with the anti-CD19 CAR-T JCAR014 in a phase I dose-finding study, showing a good safety profile. Of note, CRs were observed at both initial restaging after JCAR014 infusion and in patients continuing durvalumab therapy after initially failing to achieve CR.[97]

Other clinical trials have been initiated to assess the activity of durvalumab after ASCT or combined with other mAbs or lenalidomide, but these have either been terminated or withdrawn for different reasons.[98–100]

CTLA4 Blockade

CTLA4, also known as CD152, is a receptor that belongs to the Ig superfamily and is expressed on activated $CD4^+$ and $CD8^+$ lymphocytes. Activation of T lymphocytes results in upregulation of CTLA4 and its interaction with the B7 ligand, which is expressed on antigen-presenting cells and transduces an inhibitory signal to lymphocytes, thus maintaining immunoresponse homeostasis.[101]

Ipilimumab is a humanized $IgG_1\kappa$ mAb directed against the CTLA4 immunocheckpoint.

The first phaseI/II trial evaluating ipilimumab in a relapse setting was conducted in 2004 on 18 B-NHL patients. Only two were able to be evaluated, both showing clinical responses (CR of 31+ months for one DLBCL patient and PR up to 19 months for an FL patient).[102] The combination of ipilimumab and rituximab has been assessed through a phase I trial on R/R B-NHL, including DLBCL (n=7). Manageable toxicity and limited efficacy were observed for the entire cohort (ORR 24% and CR 6%), with only FL patients showing promising responses.[103] A phase IB trial has been conducted investigating combined checkpoint inhibition with ipilimumab and nivolumab after ASCT in hematological malignancies, including DLBCL. PFS and OS at 18 months post-ASCT were 85.7% and 100%, respectively, for primary refractory DLBCL and 28.6% and 57.1% for relapsed DLBCL. A manageable safety profile was also seen, indicating the combination's potential to improve outcomes following ASCT and response in patients with high-risk disease.[104] Another open-label phase I/II multicenter trial evaluating dual checkpoint–blocking Ab therapy with ipilimumab and nivolumab for R/R transplant-ineligible DLBCL is ongoing.[67]

Anti-CD47 Compounds

CD47 is a membrane receptor belonging to the Ig superfamily and involved in a number of physiological processes, including cellular migration and T lymphocyte/dendritic cell activation. In addition, it can inhibit phagocytosis by interacting with expressed on phagocytes.[105] By doing so, CD47 mediates the "do not eat me" signal, preventing the phagocytes from eliminating damaged and senescent cells. CD47 is ubiquitously expressed on normal cells; however, it has been demonstrated that malignant hematological cells, including DLBCL ones, overexpress this receptor, leading to tumor immunoevasion by preventing phagocytosis.[106] As such, CD47 blockade inhibits the CD47–SIRPα signaling pathway and prevents tumor progression by promoting phagocytosis of tumor cells.

Hu5F9-G4 (magrolimab, 5F9) is a humanized IgG_4 Ab macrophage immunocheckpoint inhibitor blocking CD47. Combination of 5F9 with rituximab was investigated for the first time in a phase IB/II study on 110 multirefractory B-NHL patients (63 DLBCL, 35 FL, two marginal-zone lymphomas). 5F9 plus rituximab was well tolerated, with most AEs being grade 1–2. Among 46 evaluable DLBCL patients, ORR was 39% and CR 20%.[107,108] Based on this encouraging safety/efficacy profile, a phase IB/II study investigating a combination of 5F9-rituximab plus GemOx for R/R indolent lymphomas and DLBCL has been designed.[108]

TTI-621 is a novel immunocheckpoint inhibitor that has received attention for the treatment of DLBCL. It is a recombinant fusion protein of the CD47-binding domain of SIRPα linked to the Fc region of human IgG_1 that (similarly to 5F9) enhances phagocytosis and antitumor activity. A phase I trial is evaluating the safety and activity of TTI-621 as monotherapy and in combination with rituximab in hematological malignancies (including DLBCL), with encouraging results. AEs have included IRRs, thrombocytopenia, chills, and fatigue. In DLBCL subjects, ORR was 29% with TTI-621 monotherapy and 21% with TTI-621 plus rituximab.[109]

Bispecific Antibodies

The term "bispecific Ab" (bsAb) defines a family of compounds designed to recognize two specific antigens or epitopes. The therapeutic activity of these molecules is led by the redirection of autologous T cells against tumor cells. bsAbs come in many formats, ranging from small molecules constituted by two antigen-binding fragments to entireIgG-like compounds enriched by an additional domain, engineered to target different antigens or epitopes on tumor cells. Several bsAbs are in development for treatment of B-NHLs and show promising activity, even in heavily pretreated patients (Figure 1, Table 3).

Blinatumomab

Blinatumomab is one of the first bsAbs tested on hematological malignancies, and is approved for treatment of R/R and MRD-positive B-cell acute lymphoblastic leukemia. This construct consists of two single-chain variable fragments that bind CD3 on T cells and CD19 on B cells, leading cytotoxic T-cell activity on B-lymphoma and normal cells. It has been tested on 76 R/R B-NHLs (including 14 DLBCL) in a phase I dose-escalation trial, demonstrating good tolerability and promising antilymphoma activity (ORR 69%).[110] In a phase II trial on R/R DLBCL, blinatumomab monotherapy showed moderate effectiveness, with ORR 43% and 19% CR, and main grade 3 toxicities (neurological events, including aphasia [9%] and encephalopathy [9%]), mostly resolved.[111] A phase II/III trial investigating the efficacy of blinatumomab in DLBCL not achieving complete metabolic response after a platinum-based salvage regimen is ongoing.[112]

Glofitamab

Glofitamab is a bsAb with a 2:1 molecular structure consisting of two CD20-binding fragments and a single CD3-binding fragment, which can potentially increase tumor-antigen avidity.[113] Glofitamab has been tested in a phase I trial in R/R B-NHLs, preceded by a 1,000 mg dose of obinutuzumab administered 7 days before the start of treatment, in order to debulk peripheral B cells and reduce systemic cytokine release.[113,114] Preliminary data of the first-in-human phase I trial on 64 R/R B-NHLs (47 aNHLs, including DLBCL and PMBCL) showed promising antitumor activity and manageable safety: among the subgroup of aNHLs treated with 300 µg or above, 33% ORR and 21% CR were observed, with the most frequent toxicity being transient CRS (22%, all grade 1 or 2).[113] Durable response and good tolerability have been confirmed in the updated analysis of the expansion cohort.[115] The promising results of single-agent glofitamab prompted further investigations with several treatment combinations. Interesting antilymphoma activity and an adequate safety profile have been reported from the preliminary data of the combination of glofitamab and obinutuzumab in a phase IB trial.[116] Another phase IB study combining glofitamab with atezolizumab or polatuzumab vedotin for R/R B-NHLs is recruiting.[117,118] Glofitamab plus immunochemotherapy (R-CHOP or G-CHOP) for R/R B-NHL and untreated DLBCL is under investigation, as well as a comparison of R-GemOx vs glofitamab + R-GemOx in a randomized phase III trial dedicated to R/R transplant-ineligible or refractory DLBCL.[119,120]

Mosunetuzumab

Mosunetuzumab is a full-length fully humanized IgG_1 CD3xCD20 bsAb. It has been investigated by Schuster et al[121] in a setting of 218 R/R B-NHL patients. Data from the dose-escalation part of the phase I/IB study showed a positive toxicity profile and high efficacy in the subset of aNHLs, mainly represented by DLBCL (n=87) and transformed FL (n=29), with 64.1% and 42.2% ORR and CR, respectively.[121] The study population was heavily pretreated with a median of three lines of therapy (range 1–14), including CAR-T in 23 of 218 cases. ORR and CR for patients R/R to CAR-T were 43.8% and 25%, respectively. Interestingly, after mosunetuzumab infusion, in vivo expansion of previously administered CAR-T cells was detected.[121] Moreover, preliminary data suggest possible efficacy of retreatment with mosunetuzumab for nonresponders.[121] Recently, an interim analysis of the GO40515 study, which investigated mosunetuzumab + CHOP in R/R B NHL and untreated DLBCL at high risk, has been presented.[122] Manageable toxicity has been described, with CRS not exceeding grade 2 and no neurotoxicity observed.[122] Among 27 DLBCL patients with evaluable response, an ORR of 96% was obtained with 85% CR.[122] The safety and efficacy of mosunetuzumab as consolidation for patients affected by DLBCL with SD or PR after one line of therapy or mosunetuzumab ± polatuzumab as frontline treatment for elderly/unfit DLBCL not considered candidates for immunochemotherapy are under investigation in a phase I/II trial. Preliminary data from the trial demonstrate acceptable toxicity and good rates of response of mosunetuzumab monotherapy in untreated unfit patients

(cohort B): 58% ORR and 42% CR among different doses tested, with no grade 3 CRS or neurotoxicity observed.[123,124]

Epcoritamab

Epcoritamab (GEN3013) is another molecule belonging to the group of CD3xCD20 bsAbs. It represents the first subcutaneous compound of this category and is characterized by binding the CD20 antigen on a different epitope to typical antiCD20 mAbs (ie, rituximab and GA101). Preliminary data of an ongoing phase I/II trial on R/R B-NHLs have been presented, confirming manageable toxicity of this category of molecules, with 58% CRS not exceeding grade 2 and 6% neurologic events (3% grade 3), all transient.[125,126] Epcoritamab demonstrated high activity on heavily pretreated B-NHL: in the dose-escalation part of the ongoing phase I/II study, among 45 R/R DLBCLs, including cases previously treated with CAR-T, an ORR of 66.7% (CR 33.3%) for patients receiving epcoritamab ≥12 mg and 100% (CR 28.6%) for those receiving ≥48 mg have been observed.[126] Due to the promising antilymphoma activity of single-agent epcoritamab, a number of combinations with immunochemotherapy regimens, such as R-CHOP, R-GemOx, BR, R^2, rituximab + dexamethasone, cytarabine, and cisplatin/oxaliplatin (R-DHAP/X), are under investigation in phase I/II and III trials for both untreated and R/R FL and DLBCL.[127,128]

Other Compounds

Odronextamab and plamotamab represent two further CD3xCD20 mAbs tested on B-cell malignancies.

Odronextamab is a fully human IgG_4-based bsAb, investigated in a phase I trial on R/R B-NHL, including FL and aNHL (mostly DLBCL).[129129129129130] It showed acceptable toxicity and relevant antitumor activity, even at low doses (≥5 mg) on FL (ORR 92.9%, CR 75%), and when administered at higher doses (≥80 mg) on DLBCLs (ORR and CR 60%). A global phase II study for R/R B-NHLs is ongoing.

Plamotamab is under investigation in a first-in-human trial for R/R B-NHLs and chronic lymphocytic leukemia (CLL). The trial is ongoing, and preliminary safety and antitumor-activity data on 44 subjects (36 B-NHLs, 8 CLL) are promising.[131]

Conclusion

MoAbs represent a major step forward in treatment of B-NHL, including LBCL, and are continuously improving survival for patients affected by these disorders, both as monotherapy and in combination with multiple chemotherapy regimens. Among naked mAbs, the novel anti-CD19 tafasitamab is the most promising agent, thanks to its synergic effect when combined with lenalidomide for R/R patients and the advantage of acting on an alternative target in respect of CD20. It received accelerated approval from the FDA in August 2020, and European approval is expected shortly, making tafasitamab in combination with lenalidomide already available in the US for the treatment of R/R DLBCL.

In the field of ADCs, polatuzumab vedotin is gaining importance for R/R DLBCL. The immunochemotherapy regimen pola-BR recently obtained approval for treatment of R/R patients ineligible for or relapsed after ASCT or CAR-T, and it is now in clinical practice in many countries. Many other combinations of polatuzumab + chemotherapy are under investigation for LBCL, and we are particularly eager to learn of the results from the POLARIX trial to know if polatuzumab + R-CHOP can give an advantage over R-CHOP in frontline treatment.

Among LBCLs, anti-PD1/PDL1 checkpoint inhibitors have demonstrated effectiveness most mostly PMBCL. Nevertheless, emerging data on their capacity to enhance CAR-T efficacy is increasing interest in these compounds in the field of LBCL treatment.

The relatively recent discovery of the "do not eat me" tumor-immunoescape signal and its antagonism with anti-CD47 compounds are surely of high interest. These drugs combined with rituximab and other agents could potentially have a role in the treatment of multirefractory patients, but further investigations are needed.

bsAbs represent a new frontier in therapeutic options for R/R LBCL, showing promising results in phase I/II trials both in terms of ORR and CR. Nowadays, they cannot be considered an alternative to CAR-T, due to a lack of consolidated long-term follow-up data. However, these compounds have the advantage of being an off-the-shelf option, more manageable (especially with subcutaneous administration), and with a safe toxicity profile when combined with chemotherapy, and they have now been moved to an earlier phase of treatment in LBCL. Based on results of combination studies, their characteristics may allow wider use of bsAbs in elderly and unfit patients, patients who have failed CART, or (in the not-too-distant future) first line in combination with standard immunochemotherapy in high-risk DLBCL patients.

In future, the integration of multiple novel agents, including mAbs and other molecules, with RCHOP could increase the curable rate of frontline therapy for LBCL and increase the options of salvage regimens for R/R patients.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, agreed to submit to the current journal, gave final approval to the version to be published, and agree to be accountable for all aspects of the work.

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