



# New drugs for the management of relapsed or refractory diffuse large B-cell lymphoma

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**Abstract:** Approximately 65% of patients with diffuse large B-cell lymphoma (DLBCL) can be cured with standard front-line therapy and achieve an overall survival comparable to the general population. Of the 35% of patients who fail front-line therapy, less than a quarter can be salvaged and cured by intensive chemotherapy followed by an autologous stem cell transplant. Patients who are transplant-ineligible (including elderly patients with co-morbidities, patients who are chemotherapy-refractory or those who have failed transplant) represent an unmet medical need population with a very poor outcome. While chimeric antigen receptor T-cell (CAR-T) therapy has shown promise in this setting, many patients will be unsuitable or relapse after CAR-T therapy. These patients are ideal candidates for less toxic novel therapies and a more tailored personalized approach, recognizing the biological heterogeneity of DLBCL. In this review, we will briefly summarize the standard management options for relapsed/refractory DLBCL and then focus on the novel therapies currently in development. We aim to discuss the biological rationale and available clinical data for the most promising agents, including monoclonal antibodies, antibody-drug conjugates (ADC), pathway inhibitors, immunomodulatory agents and epigenetic modifiers.

**Keywords:** Diffuse large B-cell lymphoma (DLBCL); relapse; targeted therapies

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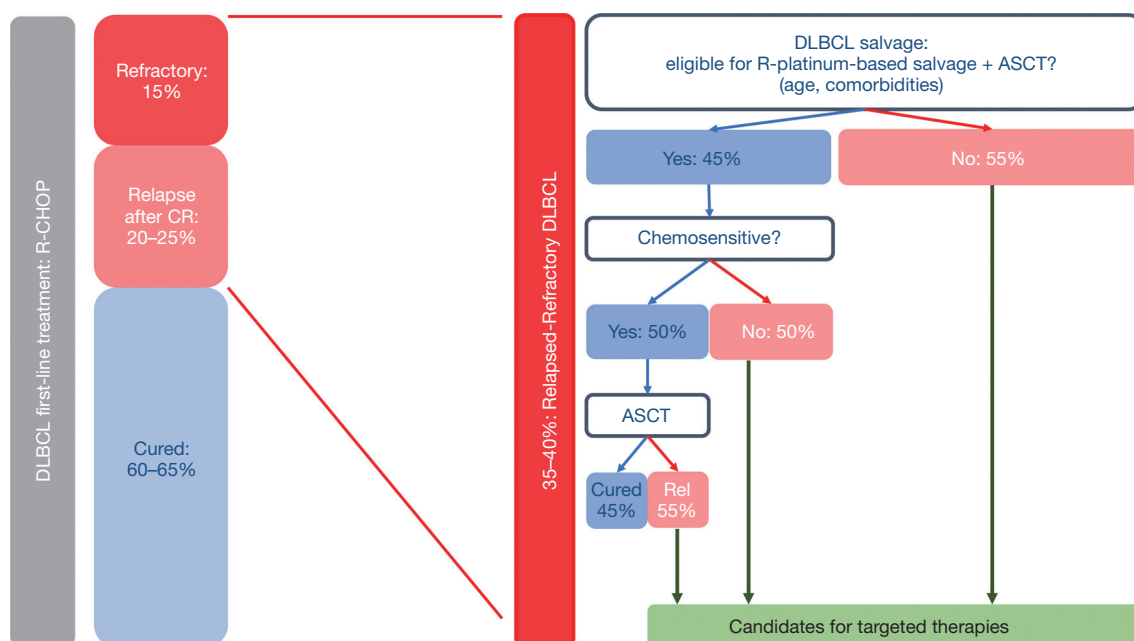
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## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL). Approximately 60–65% of patients can be cured with standard front-line therapy, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). Patients who remain event-free within the first 2 years from diagnosis, have an overall survival (OS) in the range of an age and sex matched general population (1-3). The remaining 35–40% of patients will exhibit primary refractory disease or relapse following an initial response to therapy and will have a very poor outcome. Intensive salvage strategies including

autologous stem cell transplantation (ASCT) provide the best chance for cure in the second-line setting. However, less than half of the patients with relapsed/refractory (rel/refr) DLBCL will be transplant-eligible based on age and co-morbidities. Of these patients, less than half will be chemotherapy-sensitive and proceed to transplant, and less than half who proceed to transplant will achieve long-term disease-free survival. All in all, 75–80% of the rel/refr population represents an unmet medical need (*Figure 1*). While chimeric antigen receptor T-cell (CAR-T) therapy has shown promise in this setting, many patients will be unsuitable or relapse after CAR-T therapy and require



**Figure 1** The unmet medical need for the relapse-refractory DLBCL patients. As represented on the left part of the diagram, 60–65% of patients can be cured with R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone) and 35–40% will exhibit primary refractory disease or relapse following an initial response. For these relapsed-refractory patients (represented on the right part of the diagram), intensive salvage strategies including ASCT provide the best chance for cure in the second-line setting, however, less than half will be transplant-eligible based on age and co-morbidities. Of these patients, less than half will be chemotherapy-sensitive and proceed to transplant, and less than half who proceed to transplant will achieve long-term disease-free survival (DFS). Therefore, candidates for new targeted therapies represent around 30% of the initial DLBCL population. DLBCL, diffuse large B-cell lymphoma.

alternative options (4,5).

In the past 15 years, impressive progress on the “bench-side”, has led to improved characterization of the biologic heterogeneity of DLBCL leading to a refined classification (6). On the “bed-side”, these biological advances have led to the development of novel targeted drugs that are now being evaluated in clinical trials. In this article, we will briefly summarize the standard management of rel/refr DLBCL and explore the promise of novel therapies that are most advanced in development.

### Relapsed and refractory DLBCL: standard approaches

The majority of relapses occur within 2 to 3 years from completion of initial treatment, although a low incidence of late relapse exists (7). Patients with R-CHOP-refractory disease (1,2,8) have a particularly poor prognosis with a median OS of less than a year (9-13).

### Chemotherapy-based salvage regimens

Intensive strategies including ASCT (14) offer the best chance for cure for patients with rel/refr DLBCL and is the standard in the rituximab era (15). The most frequently used salvage regimens are platinum-based chemotherapy combinations, including DHAP (dexamethasone, cytarabine and cisplatin), ICE (ifosfamide, carboplatin and etoposide), and GDP (gemcitabine, dexamethasone and cisplatin) (16,17). Approximately 40–50% of these patients will exhibit chemosensitive disease and proceed to transplant (16) with a PFS at 3 years that can reach 50–60% (18-21). Patients failing to achieve a response to second-line salvage have a median OS of less than 6 months (22). For elderly and/or transplant ineligible patients, alternative chemotherapy-based regimens such as R-bendamustine, R-GEMOX (gemcitabine and oxaliplatin), R-GEM-P (gemcitabine, cisplatin and methylprednisone) or R-DHAOX (Dexamethasone, high-dose cytarabine, and oxaliplatin) can achieve an ORR ranging from 50% to 75%, with a median

OS of 1 or 2 years in the majority of the studies (23-25). While CAR-T therapy may be considered for some patients who have failed 2 prior lines of therapy, cellular therapy will not be discussed within this article.

In conclusion, with a rituximab-platinum salvage regimen followed by ASCT, 20–30% of transplant-eligible patients may achieve prolonged survival. However, chemo-insensitive, as well as transplant-ineligible patients have a very poor outcome and represent a significant unmet medical need that must be addressed through alternative strategies. Recent biological insights have translated into the development on novel targeted agents that offer promise for this challenging subset of patients.

### Biological heterogeneity of DLBCL

Molecular analyses have revealed DLBCL to be a complex and heterogeneous disease (26-30) which can be classified based on gene expression profiling (GEP) as germinal center B-cell (GCB) or activated B-cell (ABC), reflecting a different cell-of-origin (COO) and oncogenic pathway activation (31-33). In addition, patients with a dual rearrangement of *MYC* and *BCL2* and/or *BCL6*, “double-hit” lymphoma, have been reclassified within the World Health Organization (WHO) Classification into a high-grade category with poor prognosis (6,34,35). Interestingly, a recent Nanostring-based classification has been proposed, identifying within GCB-DLBCL a subgroup of patients with a double-hit signature and a poorer outcome (36).

ABC and GCB-DLBCL subtypes are driven by different oncogenic mechanisms, and therefore may require selective therapeutic approaches. GCB-DLBCL may be preferentially sensitive to strategies targeting apoptosis, PI3K/AKT/mTOR pathway or *EZH2*, whereas strategies targeting the BCR, NF- $\kappa$ B or JAK/STAT pathways may be preferred in ABC-DLBCL. However, relying on COO classification alone may be insufficient to identify optimal treatment, as response to targeted agents may depend on the tumor’s mutational profile (30,37,38). Indeed, response to BTK inhibition has been shown to be dependent on select genetic abnormalities (such as *CD79a/b*, *MYD88* or *CARD11*) (37). Based on mutational profiling, DLBCL has been further segregated into genetic subsets with distinct genotypic, epigenetic and clinical characteristics, which may become the platform upon which future targeted approaches rely (30,39,40).

While numerous studies have explored the biology of

DLBCL at the time of diagnosis, fewer have focused on rel/refr disease. Importantly, a different pattern of mutations between diagnostic and relapsed samples has been shown (41). Indeed, by analyzing the exome of rel/refr DLBCL, Morin *et al.* (42) identified genes implicated in therapeutic resistance and reported mutations that may affect sensitivity to novel therapeutics such as *MYD88* and *CD79B* mutations in ABC-DLBCL, and *STAT6* in GCB-DLBCL. Other studies have looked at clonal evolution and suggest that oncogenic events occurring under chemotherapy selection pressure may be the main driving force at relapse (43), with a mild increase in overall mutations compared to diagnostic samples (44). In the era of precision medicine, it will become increasingly important to perform a biopsy at time of relapse in order to guide therapeutic strategies utilizing novel targeted agents.

### Novel drugs and targeted strategies (Table 1)

#### *Monoclonal antibodies and Antibody-drug conjugates (Figure 2)*

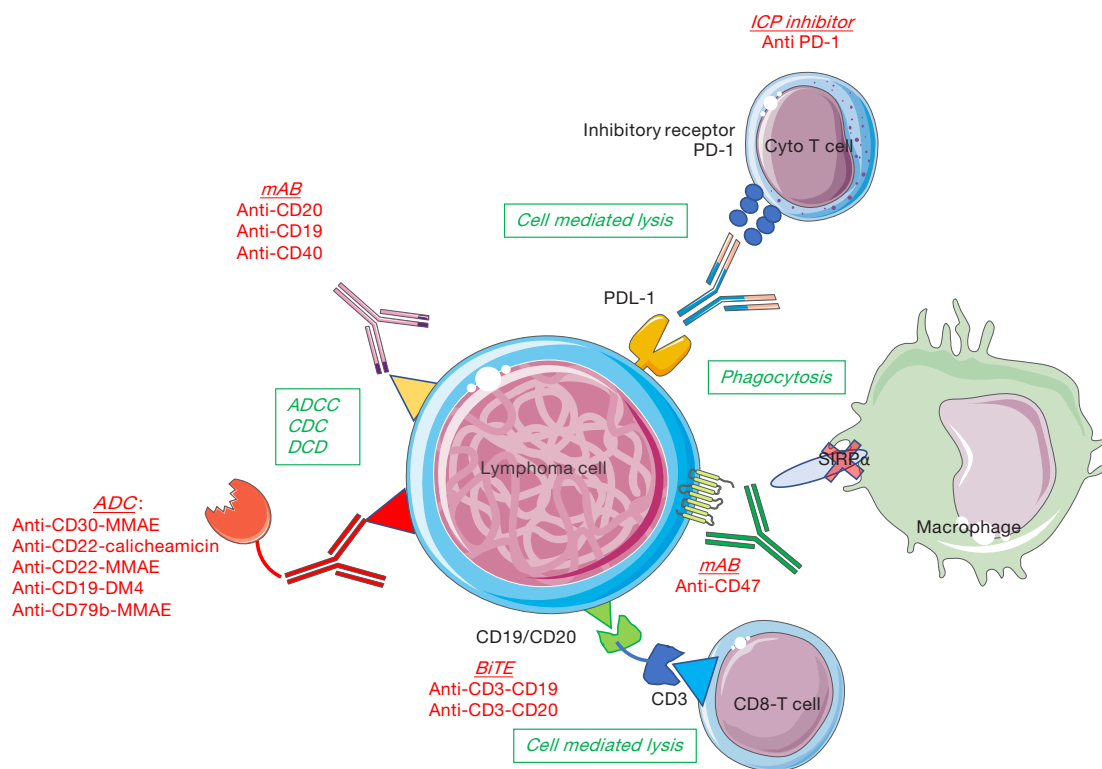
##### Monoclonal antibodies (mAbs)

To improve the efficiency of targeting CD20 and to overcome rituximab resistance, novel anti-CD20 mAbs have been engineered. Obinutuzumab, a type II IgG1 glycoengineered Fc-optimized mAb, has been designed to augment antibody-dependant cellular cytotoxicity compared with rituximab. The results in DLBCL have been disappointing, with an ORR of only 20% in rituximab pre-treated patients (45). Furthermore, the randomized study of obinutuzumab-CHOP *vs.* R-CHOP in the first-line setting (GOYA trial) did not show any difference in ORR or PFS between the 2 arms (83). Ofatumumab is a novel anti-CD20 mAb targeting a different epitope than rituximab, but in a randomized phase II trial, no difference in efficacy was found between ofatumumab-DHAP and R-DHAP in rel/refr DLBCL (18). MOR208 is an Fc-engineered, humanized, anti-CD19 antibody that demonstrated an ORR of 26% as a single agent in patients with rel/refr DLBCL in a phase 2 trial (duration of response (DoR) >12 months in 5/9 cases) (46). The favorable safety profile permits combination therapy (discussed below). Dacetuzumab (SGN-40) is a non-blocking, partial agonist, humanized IgG1 anti-CD40 mAb (48) that showed a low (9%) ORR as a single agent, and failed to show benefit when combined with R-ICE in a phase III trial that was prematurely stopped when a futility analysis failed to demonstrate higher CR

**Table 1** New drugs in development in RR DLBCL

Class	Target	Agent	Reference	Phase	ORR	CR
Antibody	CD20	Obinutuzumab	Morschhauser (45)	2	20%	–
		Ofatumumab-DHAP	van Imhoff (18)	2	38%	15%
	CD19	MOR208	Jurczak (46)	2	26%	–
		MOR208 + LEN	Salles (47)	2	58%	33%
	CD40	Dacetuzumab	De Vos (48)	2	9%	–
Dacetuzumab/R-ICE		Fayad (49)	2b	36%	–	
Ab drug conjugate	CD30	Brentuximab Vedotin	Jacobsen (50)	2	44%	17%
	CD22	Inotuzumab ozogamicin (IO)+R	Dang (51)	3	41%	–
		IO + R-CVP/IO + R + R-GDP	Ogura (52)/Sangha (53)	1	57%/33%	–
	CD79b	Polatuzumab vedotin	Palanca (54)	1	56%	–
		Pola V + R-Benda	Sehn (55)	1/2	70%	58%
	CD19	Coltuximab ravtansine/CR + R	Trneny (56)/Coiffier (57)	2	44%/31%	–
		Denintuzumab mafodotin	Moskowitz (58)	1	33%	22%
		Loncastumab tesirine	Radford (59)	1	40%	22%
NF-κB and BcR	Proteasome inhibitor	Bortezomib/Bort + DA-EPOCHR	Dunleavy (60)	2	4%/34%*	–
	BTK inhibitor	Ibrutinib	Wilson (37)	1/2	37% (ABC)	–
	SYK Inhibitor	Fostamatinib	Flinn (61)	2	3%	–
PI3K/AKT/mTOR	PI3K Inhibitor	Copanlisib (all/ABC)	Lenz (62)	2	25%/37%	13%/25%
		Buparlisib	Younes (63)	2	11.5%	–
	mTOR	Everolimus + R	Barnes (64)	2	38%	11%
		Temsirolimus	Smith (65)	2	28%	12%
	Pan-PI3K/mTOR	Voxtalisib	Brown (66)	2	5%	–
Other target	XPO1	Selinexor	Kuruvilla (67)	1	31%	–
	BCL2	Venetoclax	Davids (68)	1	18%	–
		Venetoclax R-ICE	Caimi (69)	1	85%	69%
Immunomodulation	IMiD	Lenalidomide	Witzig (70)	2	28%	13%
		Len + R-Benda	Cheson (71)	1	20%	–
		Len + R-ESHAP + ASCT*	Martin (72)	1b	78.9%	47%
		Len + R-ICE + ASCT*	Feldman (73)	1/2	73%	60%
		Ibru + Len + R	Ramchandren (74)	2	55%	30%
	Checkpoint, PD-1	Nivolumab	Ansell (75)	2	10%	–
	CD47	Hu5F9-G4	Advani (76)	1	40%	33%
	BiTE	Blinatumomab	Viardot (77)	2	43%	19%
		RG6026	Hutchings (78)	1	33%	–
		Mosunetuzumab	Budde (79)	1	33%	21%
Epigenetic	EZH2	Tazemetostat	Morschhauser (80)	2	29%**	–
	HDAC	Panabinstat +/- R	Assouline (81)	2	28%	–
	HDAC-PI3K	CDUC-907	Oki (82)	1	37%	17%

\*, bortezomib single agent/bortezomib + DA-EPOCH; \*\*, ORR among EZH2 mutated patients. DLBCL, diffuse large B-cell lymphoma.



**Figure 2** Antibodies and antibodies-drug conjugates. Monoclonal antibodies are directed against cell surface antigens on the surface of the tumor cell. These antibodies can mediate complement-dependent cytotoxicity (CDC) and membrane attack complex, antibody-dependent cell-mediated cytotoxicity (ADCC) or direct cell-death (DCD). Antibodies-drug conjugates (ADC) consist of a mAb covalently linked to a small-molecule (drug) that combine a targeted strategy to cytotoxicity in order to increase the efficacy with the minimum of off-target effect. Therapeutic immuno-modulation of the T-cell response can be obtained by different mechanisms, including inhibition of the PD-1/PD-L1/2 receptor/ligand axis, or with Bi-specific T-cell (BiTE) engaging antibody construct that allows T-cell activation through transient ligation of CD3-positive T-cells to CD19/CD20-positive lymphoma cells leading to T-cell mediated lysis. Lenalidomide (not shown here) can also provide immunomodulation thanks to cytotoxic T-cell activation.

rates (36% *vs.* 42% with placebo) (49).

### **Antibody-drug conjugates (ADCs)**

ADCs consist of a mAb covalently linked to a small-molecule drug allowing the targeted delivery of a cytotoxic agent with aim to increase efficacy and minimize off-target effects. Brentuximab vedotin (BV) is an FDA-approved ADC, targeting CD30 and delivering the antimicrotubule agent monomethyl auristatin E (MMAE). In a phase II trial, Jacobsen *et al.* (50) reported an ORR of 44% (CR rate 17%) in rel/refr DLBCL, with a median DoR of 5.6 months (16.6 months in CR patients). Neutropenia and peripheral sensory neuropathy were the most frequent adverse events (AEs). The combination of BV with rituximab showed

similar results (84). Inotuzumab ozogamicin (IO) is an ADC targeting CD22 linked to calicheamicin and FDA approved for the treatment of acute lymphocytic leukemia (ALL). In a phase III trial including 338 patients with rel/refr aggressive B-cell lymphoma (51), randomized between IO + rituximab versus chemotherapy + rituximab, there was no difference in ORR, PFS and OS between the 2 arms (ORR 41%, median PFS 3.7 months and median OS 9.5 months with IO + R) with more AEs leading to treatment discontinuation in the IO + R arm. Combinations of IO with R-CVP (cyclophosphamide, vincristine, and prednisone) and R-GDP have also been evaluated, with ORRs of 57% (52) and 33% (53), respectively. Polatuzumab vedotin (pola) is an ADC combining an anti-CD79b MAb with MMAE that has shown promising activity in a phase



1 trial, yielding an ORR of 56% in patients with rel/refr DLBCL (54). The most common grade 3–4 AEs were neutropenia (40%), anemia (11%), and peripheral sensory neuropathy (9%). In a phase II randomized study, the combination of polatuzumab plus bendamustine (B) and rituximab was compared to BR alone in transplant-ineligible patients with rel/refr DLBCL. With 40 patients included in each arm, the PET-CR rate was significantly higher with polatuzumab-BR *vs.* BR alone, 40% *vs.* 18%, respectively. Similarly, the median OS was significantly improved with polatuzumab-BR (12.4 *vs.* 4.7 months) (55). Coltuximab ravtansine, an anti-CD19 mAb conjugated to maytansinoid DM4, was evaluated in two phase II studies, demonstrating only moderate clinical benefit. As a single agent, Trneny *et al.* (56) reported an ORR of 44% with a modest DoR of 4.7 months. In combination with rituximab in patients with rel/refr DLBCL, Coiffier *et al.* (57) reported an ORR of 31% (that did not meet the primary objective of the study) with a DoR of 8.6 months. SGN-CD19A or denintuzumab mafodotin is another ADC targeting CD19, conjugated with MMAF that showed similar responses in a phase I trial (ORR 33%, CR 22%) (58). A particular AE, microcystic keratopathy leading to visual disturbances, occurred in 84% of patients. A combination study with R-ICE is ongoing (NCT02592876). Finally, a large phase I trial including 183 patients with rel/refr DLBCL evaluated the safety and efficacy of loncastuximab tesirine, an ADC also targeting CD19 and conjugated to a pyrrolobenzodiazepine dimer toxin. The majority (73%) of patients experienced a grade 3 AE requiring a dose reduction. The ORR was 40.2% (22% CR) and median DoR was 4.2 months (59).

Overall, among the recently developed monoclonal antibodies and ADCs, polatuzumab vedotin has been the only drugs evaluated in a comparative trial, and has shown the most encouraging safety and efficacy profile.

### Pathway Inhibitors (Figure 3)

#### NF- $\kappa$ B and BCR pathway

B cells have the capacity to respond to a variety of stimuli due to the combined expression of an antigen-specific B-cell receptor (BCR) and germline-encoded receptors of the innate immune system, Toll-like receptors (TLR) (85). These stimuli activate downstream transcription factors, such as NF- $\kappa$ B, that controls numerous cellular processes involved in lymphoma development. In ABC-DLBCL, mutations in *CARD11* (86), *CD79A/B* (87), and *MYD88* (38),

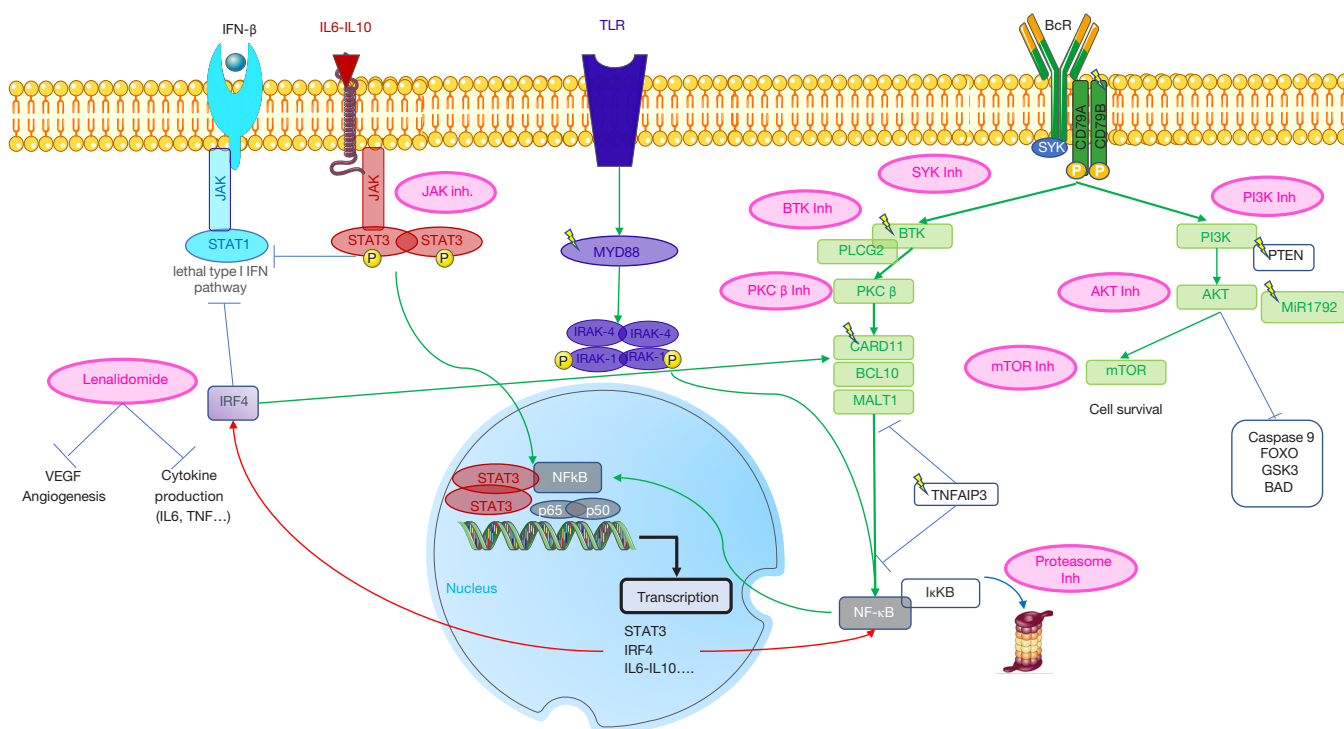
or loss of the regulating agent A20 (*TNFAIP3*) (88) are some of the mechanisms that can induce a constitutive activation of the BCR pathway and ultimately of NF- $\kappa$ B (89) with IRF-4 (interferon regulatory factor 4) upregulation. Importantly, it has been shown that cases presenting with CBM (*CARD11*, *BCL10*, *MYD88*) signaling mutations or *MYD88* mutation without *CD79A/B* mutations will require inhibition downstream of this complex to kill tumor cells (such as proteasome inhibitors), compared to cases without *CARD11/MYD88* mutations or with both *MYD88* and *CD79A/B* mutations that will be sensitive to inhibition of kinases upstream of the NF- $\kappa$ B complex (such as BTK inhibitors) (37).

#### Proteasome inhibitors

Based on the biological rationale of NF- $\kappa$ B constitutive activation in ABC-DLBCL (89), it was hypothesized that proteasome inhibition could be beneficial in this subtype. In a phase I/II study evaluating bortezomib alone or in combination with DA-EPOCH in 49 patients with rel/refr DLBCL, bortezomib alone had no activity (ORR 4%) (60). Whereas, when combined with DA-EPOCH, a higher ORR was observed in patients with ABC-DLBCL compared with GCB-DLBCL (83% *vs.* 13%) leading to a higher median OS (10.8 *vs.* 3.4 months). Based on this promising signal of activity, bortezomib was evaluated in 2 randomized trials in combination with R-CHOP in untreated patients with non-GCB or ABC DLBCL, but no benefit was observed (90,91). The utility of bortezomib in DLBCL seems questionable, although a phase II randomized study with R-DHAP is ongoing (NCT01805557). Promising preclinical data with the novel proteasome inhibitor carfilzomib (92) in combination with a pan-HDAC inhibitor vorinostat (93,94) has led to an ongoing phase I study (NCT 01276717).

#### BCR pathway inhibition

The Bruton tyrosine kinase (BTK) is a member of the Tec kinase family with an early positioning within the BCR cascade. Ibrutinib is a selective and irreversible BTK inhibitor, via specific active-site occupancy (87). *In vitro* data showed a selective activity of ibrutinib in ABC-DLBCL cell lines with chronic active BCR signaling (87). In a phase 1/2 clinical trial including 80 patients with rel/refr DLBCL, ibrutinib resulted in an ORR of 37% in ABC-DLBCL, but only 5% in GCB-DLBCL. Furthermore, the authors showed that patients with concomitant *MYD88* and *CD79A/B* mutations had high response to ibrutinib (37), as well as those with both wild-type (WT) BCR and *MYD88*, whereas those with *MYD88* mutations and WT *CD79A/B*



**Figure 3** Pathway inhibitors. The BCR/NF-κB pathway controls proliferation and survival of the tumor cell. This pathway can be targeted with BTK (Bruton's tyrosine kinase) inhibitors, SYK inhibitors (spleen tyrosine kinase), or with the downstream PI3K/AKT/mTOR effector inhibitors. NF-κB can also be indirectly targeted by proteasome inhibitors that will inhibit IKKβ degradation and NF-κB nucleus translocation. Beside its immunomodulation function, lenalidomide can induce the lethal type I IFN pathway activation via the inhibition of IRF-4 production.

*B* were resistant. The main AEs associated with ibrutinib are thrombocytopenia and bleeding risk, neutropenia, atrial fibrillation and aspergillosis infections (95). The combination of Ibrutinib, bendamustine and rituximab in a phase Ib trial led to an ORR of 37% in rel/refr DLBCL (96). Grade 3/4 toxicities included lymphopenia (77%), neutropenia (33%), thrombocytopenia (19%), and rash (25%). Recently, a randomized phase III trial evaluated the addition of ibrutinib to R-CHOP in previously untreated patients with non-GCB-DLBCL (97). The study did not meet its primary endpoint in the intention-to-treat population due to a significant interaction between treatment and age. Interestingly, in patients younger than 60 years of age, ibrutinib plus R-CHOP improved EFS, PFS and OS (HR 0.579, 0.556, 0.330 respectively). However, in patients older than 60 years of age, the increased toxicity profile of the combination compromised treatment delivery and likely reduced efficacy. The encouraging signal observed with the addition of ibrutinib in younger patients in this up-

front trial justifies further exploration of BTK inhibition in patients with rel/refr disease. Acquired Ibrutinib resistance due to *BTK*<sup>Cys481</sup> mutations occurs in B-cell NHL, with a subclonal presentation (98), emphasizing the need for novel inhibitors. The next-generation BTK inhibitors acalabrutinib (ACP-196), tirabrutinib (ONO, GS-4059), GDC-0853 (99) and BGB-3111 (100,101) are currently being evaluated in DLBCL. Interestingly, 3 patients with *BTK*<sup>Cys481</sup> mutation had a response to GDC-0853 (99).

The kinase SYK, important for tonic BCR signaling (102), is another potential target in ABC-DLBCL. SYK is activated following Iga and Igβ ITAM phosphorylation, engaging additional adaptor proteins and initiating downstream signaling. Chemical SYK blockade decreases cell proliferation and induces apoptosis in DLBCL cell lines dependent on BCR signaling (103). Fostamatinib is an oral SYK kinase inhibitor recently evaluated in a phase II trial with very disappointing results (3% ORR) and many off-target effects (61). Entospletinib is an adenosine

triphosphate competitive inhibitor that disrupts SYK kinase activity with a more selective action than fostamatinib. In a phase II trial including patients with CLL and NHL, the most common serious AEs were dyspnea, pneumonia, febrile neutropenia, dehydration, and pyrexia (104). ORR was reported for CLL patients only (61%). A phase Ib trial in combination with R-CHOP in first-line DLBCL is ongoing (NCT03225924).

### PI3K/AKT/mTOR pathway

PI3K signals downstream of the BCR and leads to AKT activation which phosphorylates and inhibits pro-apoptotic molecules. AKT also promotes cell cycle progression and mTOR activation (mammalian target of rapamycin), a kinase that favors tumor cell survival via protein synthesis and cell proliferation. In GCB-DLBCL, deletion of the tumor suppressor *PTEN* and amplification of the oncogenic microRNA cluster, *mir-17-92* (which inhibits *PTEN* translation), leads to loss of control of this pathway (33,105). Multiple forms of PI3K inhibitors exist, with differing specificities. Idelalisib (a PI3K $\delta$  inhibitor) has been approved in rel/refr FL (106) and is currently being evaluated in a phase II trial in patients with rel/refr DLBCL (NCT03576443). Based on biological rationale (107), combination studies with the BTK inhibitor tirabrutinib are ongoing. Importantly, a phase 2 study of idelalisib with entospletinib was stopped due to serious AEs including pneumonitis in 18% of patients (with 2 fatal cases) (108). Similarly, two combination trials of idelalisib, lenalidomide and rituximab were stopped due to an excess of unexpected serious toxicities (109,110). Copanlisib (PI3K  $\alpha/\delta$  inhibitor) also has limited efficacy as a single agent in rel/refr DLBCL, with an ORR of 25%, but appeared slightly higher in ABC-DLBCL [ORR 37.5%, CR rate 25%, in a non-intention to treat analysis (ITT)] (62). Buparlisib is a pan-PI3K inhibitor that has been evaluated in a phase 2 trial (63) including 26 patients with DLBCL resulting in an ORR of only 11.5% and a short duration of response of 2.2 months, with a similar toxicity profile to other PI3K inhibitors. Umbralisib (TGR-1202) is a PI3K $\delta$  inhibitor (111) recently evaluated in a phase I study enrolling 90 patients with rel/refr CLL and NHL. The most common grade 3–4 AEs were neutropenia (13%), anemia (9%), thrombocytopenia (7%), pneumonia (3%), and colitis (2%). A phase I combination study of umbralisib, ublituximab (UTX, a novel glycoengineered anti-CD20) and bendamustine was performed, enrolling 15 patients with rel/refr DLBCL. The only grade 3–4 AE reported in more than 10% of patients

was neutropenia (22%). Among 11 patients evaluable for response, the ORR was 73%, with a CR rate of 45% (112). Everolimus (RAD001) is an orally bioavailable rapamycin analog and inhibitor of mTOR inducing inhibition of cell cycle progression *in vitro* by decreasing phosphorylation of mTOR targets (113). In a phase II trial including 26 patients with rel/refr DLBCL, the combination of rituximab and everolimus (64) resulted in an ORR of 38% with 3 patients achieving a CR and a median DoR of 8 months. The most common grade 3–4 toxicities were neutropenia, anemia, and thrombocytopenia. A phase I trial in 24 patients with untreated DLBCL showed that the combination of everolimus/R-CHOP was safe and promising. Indeed, after a FU of 37 months, only one relapse with low grade follicular lymphoma has occurred and no patients have relapsed with DLBCL within the 24 months from treatment initiation (EFS24) (114). These results are even more impressive since the median time from diagnosis to treatment was rather short (14 days) in this trial, with an expected EFS24 failure rate of 44% (115). Another rapamycin analog and mTOR inhibitor, temsirolimus, administered intravenously, has been evaluated in a phase II trial including 32 patients with rel/refr DLBCL and transformed FL. The ORR was 28%, with a CR rate of 12%, but the median DoR was only 2.4 months (65). A phase II combination study of temsirolimus with R-DHAP (116) has been conducted in patients with rel/refr DLBCL who had received a maximum of 2 prior regimens, resulting in an ORR of 78% (CR rate 22%) (117). Voxelisib, a pan-PI3K/mTOR inhibitor, has been investigated in a large series of 167 patients with rel/refr NHL exhibiting a similar safety profile but a very disappointing ORR of 5% in the 42 patients with rel/refr DLBCL (66).

### JAK/STAT pathway

The signal transducer and activator of transcription (STAT) proteins is a family of transcription factors that regulate many cellular events [differentiation, proliferation, and cell survival (118)] and can be activated by cytokines and growth factors through cell surface receptor binding, leading to the activity of receptor-associated Janus kinase (JAK) family members. JAKs then phosphorylate STATs, leading to their dimerization and transit to the nucleus. Some of the transcriptional targets of STAT proteins play a role in cell-cycle progression, survival and regulation of the lethal type I IFN signaling pathway. The constitutive activation of NF- $\kappa$ B signaling in ABC-DLBCL leads to



a positive loop regulating the production of target genes such as IL6 and IL10 leading to JAK activation, STAT3 phosphorylation (119) and intracellular signaling resulting in NF- $\kappa$ B nucleus transfer and synergistic activation of several genes (120). Lam *et al.* (121) characterized a subset of ABC-DLBCL with high *STAT3*, *IL-6* and/or *IL-10* and showed that ABC-DLBCL cell lines secreting IL-6 and/or IL-10 were selectively killed by an inhibitor of STAT3 signaling, a small JAK inhibitor, in synergy with NF- $\kappa$ B pathway inhibition. More recently, Lu *et al.* (122) showed that STAT3 also negatively regulates the lethal type I IFN signaling pathway (by inhibiting expression of *IRF7*, *IRF9*, *STAT1*, and *STAT2*) leading to an *in vitro* and *in vivo* synergistic effect of the inhibition of STAT3 by ruxolitinib with the type I IFN inducer lenalidomide on ABC-DLBCL models. Despite this biological rationale, little data on the clinical utility of JAK inhibitors is available in DLBCL. Clinical trials with ruxolitinib are ongoing (NCT 01431209, in combination with bortezomib NCT 02613598) as well as with cerdulatinib, a new SYK/JAK inhibitor showing activity in an *in vitro* model of DLBCL (123). Younes *et al.* reported a phase I trial of pacritinib, an oral JAK1/2 inhibitor, in DLBCL demonstrating a favorable safety profile but modest activity (10% ORR) (124).

## Others agents

### XPO1 inhibitors

Exportin 1 (XPO1/CRM1) is a protein responsible for the export from the nucleus of various tumor suppressors (p53, p73, p21, p27, Rb, BRCA1/2 and I $\kappa$ B) leading to their inactivation (125) and is also involved in the regulation of the cytoplasmic levels of mRNA transcripts of several oncoproteins (*MYC*, *BCL2*, *BCL6*). Increased expression of XPO1 has been associated with disease aggressiveness (126) and mutations have been reported in different types of lymphoma, although not in DLBCL (127). Selinexor is a first-in-class oral XPO1 inhibitor. In a phase I trial, the most common grade 3/4 AEs were thrombocytopenia (47%), neutropenia (32%), anemia (27%), leukopenia (16%), fatigue (11%), and hyponatremia (10%) and the ORR was 31% (22/70) across various NHL histologies, with similar ORRs seen in ABC and GCB-DLBCL, as well as in double-hit lymphoma (3 responses/6). Interestingly, the 4 patients that achieved a CR were still alive and 3 remained on treatment with follow-up ranging from 16–35 months (67).

### Apoptosis and BCL2 inhibition

The t(14;18)(q32;q21) translocation has been reported in

more than 30% of GCB-DLBCL, and is associated with higher expression of the anti-apoptotic protein BCL2 compared to t(14;18) negative cases (128). Other molecular abnormalities involving the *BCL2* locus, such as copy number variations (CNV), have also been reported in ABC-DLBCL (129). Venetoclax is a selective, oral small molecule inhibitor of BCL2. Davids *et al.* (68) recently reported the results of a phase I trial in 106 patients with R/R NHL. Venetoclax was well tolerated with only 3 cases of laboratory tumor lysis syndrome occurring. Grade 3/4 events were reported in 56% of patients, with the most common being anemia (15%), neutropenia (11%), and thrombocytopenia (9%). The ORR was 44% for the overall cohort, but was only 18% in the DLBCL population with an estimated PFS of only 1 month. Safety results of a phase I combination study of venetoclax plus R-ICE including 18 patients with R/R DLBCL were recently reported (69). The ORR of 85% was impressive, including a metabolic CR rate of 69%. Hematologic toxicities (primarily neutropenia) were common and one patient died from TLS.

In conclusion, these novel targeted therapies have shown limited efficacy as single agents and none are FDA-approved. Combination studies appear promising, but have raised concern regarding tolerability. Results from numerous ongoing combination trials are eagerly awaited.

## Immunomodulation (Figure 2)

### IMiDs

In ABC-DLBCL, activation of both the NF- $\kappa$ B and TLR pathways result in constitutive expression of IRF4, leading to the downregulation of IFN- $\beta$  production and amplification of NF- $\kappa$ B signaling due to *CARD11* transactivation (130). The immunomodulatory agent lenalidomide downregulates IRF4 and its cofactor SPIB (Spi-B Transcription Factor, a member of the ETS-family proteins) leading to IFN- $\beta$  production and downregulation of BCR-dependant NF- $\kappa$ B signaling, resulting in death of ABC-DLBCL cell lines (130,131). Blockade of BCR signaling with ibrutinib also downregulates IRF4 and consequently synergizes with lenalidomide, suggesting an attractive therapeutic combination (NCT01955499). Lenalidomide (LEN) also acts as an antiangiogenic agent, which is another rationale for its utility in DLBCL where high VEGF levels have been associated with poorer outcome (132). In a large phase II trial including 217 patients with R/R aggressive B-cell NHL, the ORR of LEN as a single agent was 35% (28% for DLBCL) with a CR

rate of 13% and a DoR of 10.6 months. The most common AE was myelosuppression, with grade 4 neutropenia and thrombocytopenia observed in 17% and 6% of patients, respectively (70). As expected, ABC-DLBCL had a higher ORR and PFS than GCB-DLBCL (ORR 53% *vs.* 8% and median PFS 6.2 *vs.* 1.7 months) (133). These results led to a planned randomized phase II/III trial investigating LEN 25 mg daily versus investigators' choice (IC: gemcitabine, rituximab, etoposide, or oxaliplatin) in R/R DLBCL (134). In the stage I part of the study, LEN-treated patients had an ORR of 27.5% versus 11.8% in the IC arm and median PFS was increased (13.6 weeks versus 7.9 weeks; in IC arm,  $P=0.041$ ), with greater improvements in non-GCB patients (15.1 *vs.* 7.1 weeks, respectively;  $P=0.021$ ) compared with GCB patients (10.1 *vs.* 9.0 weeks, respectively;  $P=0.550$ ). However, the stage 1 results did not meet the protocol-specified threshold and therefore the study did not proceed to stage 2.

In a retrospective analysis, Ivanovo *et al.* reported a noteworthy ORR of 41.2%, with a CR rate of 35.3% with the combination of LEN and rituximab, with a median DoR of 26.5 months (135). However, in a phase I trial, the combination of LEN with R-Bendamustine showed limited activity in R/R DLBCL with an ORR of 20%, similar to what had been reported with LEN alone (71). In another phase Ib combination study with R-ESHAP, including transplant eligible patients, the maximum tolerated dose was 10 mg due to grade 3 angioedema at 15 mg. The ORR was 78.9% and CR rate of 47.4% (72), but different inclusion criteria preclude comparison between these studies. In a similar phase I/II trial, the combination of LEN and R-ICE showed a better tolerability profile (recommended phase 2 dose 25 mg daily), exhibiting a 73% ORR and 60% CR rate (73). Responding patients underwent ASCT followed by LEN maintenance, with neutropenia being the most frequent AE during this period, without significant infections. In rel/refr DLBCL patients responsive to salvage R-chemotherapy but not eligible for ASCT, LEN maintenance (25 mg, until lymphoma progression) was evaluated in a phase II trial: again, neutropenia was the most frequent AE leading to 4 cases of febrile neutropenia and one treatment-related death (intestinal infarction) (136). At 1 year from trial registration, 28/46 (61%) patients were progression-free, which was higher than the predetermined efficacy threshold, suggesting a possible role for LEN maintenance in this population (136). The IR<sup>2</sup> regimen, Ibrutinib (560 mg), LEN (20 mg) and R was evaluated in a phase I/II trial with 85% of the patients experiencing a

grade 3 or more AE. Among the 44 evaluable patients, the ORR was 55% and the CR rate was 30%, with median DoR of 9 months (74). The association of LEN with the anti-CD19 MOR208 has been evaluated in a phase I/II trial (81 patients, with a maximum of 3 prior therapies, and excluding patients with primary refractory disease). The main reported AEs were hematological and 42% of the patients required LEN dose reduction. CR was observed in 33% and PR in 25% of patients, with 15% of patients experiencing stable disease. The median PFS was 16.2 months and median DoR not reached (47). While these results are encouraging, the trial included better-risk patients due to strict selection criteria, making these results difficult to compare. Finally, the results of a large phase III trial comparing R-CHOP plus lenalidomide (R<sup>2</sup>-CHOP) with placebo/R-CHOP in patients with previously untreated ABC-type DLBCL were recently presented (137). The trial did not meet its PFS primary endpoint with a HR of 0.85 (2 years OS was 79% for R<sup>2</sup>-CHOP and 80% for placebo/R-CHOP). Discordant results were reported in a randomized phase II study showing an improved outcome with the R<sup>2</sup>-CHOP regimen with a 33% reduction in risk of progression or death compared to R-CHOP [HR 0.67 (95% CI: 0.44–1.03,  $P$  (one-sided) 0.03)] (138). Differences in trial design, as well as population differences as highlighted by a shorter time-to-treatment from diagnosis might, in part, explain these discrepant results.

In conclusion, in the relapsed setting, LEN combined with chemotherapy and/or targeted strategies appears promising, although the tolerability profile may be an issue for elderly and/or heavily pre-treated patients. However, in previously untreated patients, a large phase III trial failed to show a better outcome with R<sup>2</sup>-CHOP compared to R-CHOP.

### Checkpoint inhibitors

The program death 1 immune checkpoint (PD-1) pathway is used by lymphoma cells to avoid T cell immune surveillance. In a phase II trial, rel/refr DLBCL patients achieving at least a PR after salvage therapy prior to ASCT received the PD-1 inhibitor pidilizumab every 42 days at 1.5 mg/kg IV for 3 doses, beginning 1 to 3 months after ASCT. The most frequently reported grade 3/4 AEs were neutropenia (19%) and thrombocytopenia (8%). The PFS at 16-months was 72% and the study met its primary endpoint (139). Interestingly, the PFS of patients who were PET-positive before ASCT was comparable to those who were PET-negative. Another PD-1 inhibitor, nivolumab,

has shown impressive activity in classical HL but efficacy in DLBCL as a single agent was less remarkable. In a recent phase II single arm study including 121 patients with rel/refr DLBCL, the ORR was 10% and 3% in patients who had failed ASCT and transplant-ineligible patients, respectively (median DoR, 11 and 8 months, respectively) (75). This lack of efficacy might be related to the low incidence of 9p24.1 gain/amplification (including the *PD-L1* locus) in patients with rel/refr DLBCL. Indeed, only 16% of the evaluable cases had copy number gains and 3% had amplification.

### Macrophage and CD47 blockade

Recently, Advani *et al.* (76) reported the first trial of a macrophage immune checkpoint inhibitor. Hu5F9-G4 is an Ab targeting CD47, which is expressed on lymphoma cells, inhibiting tumor-cell phagocytosis. Hu5F9-G4 may help to overcome rituximab resistance, creating a synergistic effect when both drugs are combined. In this phase I trial, 22 patients were treated (including 15 with RR DLBCL), 95% of which were rituximab-refractory. In the DLBCL population, the ORR was 40%, with 33% of patients achieving a CR and 91% exhibiting ongoing response after 6 months of follow-up. AEs were predominantly grade 1-2, the most common being anemia (an expected-on target effect) and infusion-related reactions.

### Bi-specific antibodies

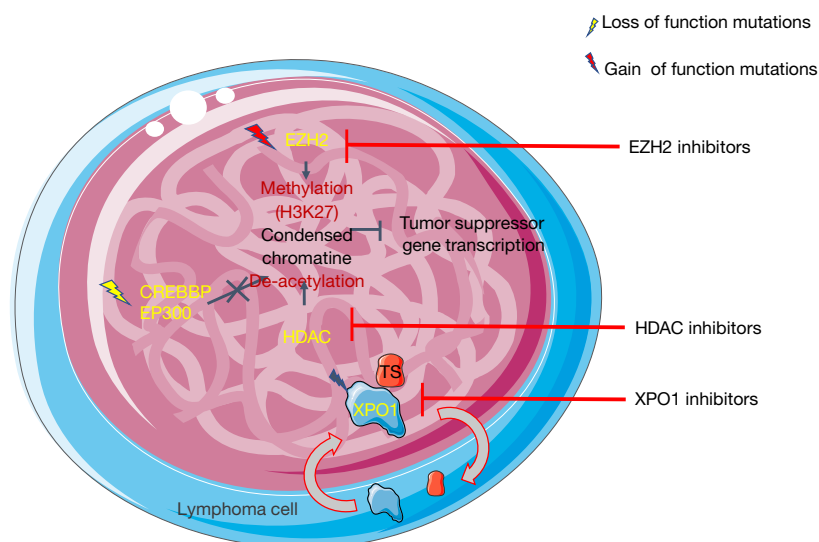
CD3-CD19 bi-specific T-cell engaging antibody (BiTE) constructs allow T-cell activation through transient ligation of CD3-positive T-cells to CD19-positive lymphoma cells leading to T-cell mediated lysis. Blinatumomab is a first-in-class BiTE approved by the FDA for the treatment of Philadelphia chromosome-negative rel/refr B-cell acute lymphoblastic leukemia (ALL). In a Phase I (140) trial including patients with rel/refr NHL, the major DLTs were neurological events and cytokine release syndrome (CRS). The MTD was 60  $\mu\text{g}/\text{m}^2/\text{day}$  as a continuous infusion over 4 to 8 weeks. In the subgroup of patients with DLBCL, the ORR of 55% was very promising, with 36% of patients achieving a CR and a median DoR of 404 days. A phase 2 study evaluated stepwise dosing (9/28/112  $\mu\text{g}/\text{d}$  with weekly dose increases; n=23) or flat dosing (112  $\mu\text{g}/\text{d}$ ; n=2) by continuous infusion for up to 8 weeks, with dexamethasone prophylaxis, in heavily pretreated rel/refr DLBCL. The flat dose cohort was stopped prematurely due to neurologic AEs. Among 21 evaluable patients, the ORR after 1 cycle was 43%, including CR in 19%, and the median DoR was

11.6 months. The most common AEs were tremor (48%), pyrexia (44%), fatigue (26%), and edema (26%). Grade 3 encephalopathy and aphasia occurred in 9% and tremor, speech disorder, dizziness, somnolence, and disorientation in 4% (77). In another phase II study including patients not in CR after platinum-based salvage therapy, blinatumomab was given for a single cycle of 70 days, followed by an optional 28 days cycle. The ORR was 37% (22% CR) with grade 3 toxicities reported in 59% of the 41 patients (141). Mosunetuzumab is a full-length CD20/CD3 bi-specific antibody being evaluated in a phase I trial with 2 different schedules: every 21 days at a fixed dose and step-up dosing during cycle 1. CRS was the most frequently reported AE (21%, all grade 1–2). Grade 3 AEs occurred in 52% of patients, including 2 deaths. ORR in the DLBCL population was 33% (13/39), with 21% (8/39) achieving a CR (79). The bi-specific antibody RG6026, with a 2:1 format (two CD20 binders in addition to a CD3 binder) and an administration schedule of every 2 weeks has demonstrated a similar ORR in RR DLBCL (33%), without CNS toxicity or significant CRS (78).

In conclusion, the response rates and DoR of novel bi-specific antibodies under evaluation are very promising with a favorable tolerability profile.

### Epigenome (Figure 4)

Large scale genomic studies have revealed frequent mutations in histone modifying genes in DLBCL (29,142). For instance, heterozygous mutations of the histone methyl transferase and catalytic subunit of the PRC2 chromatin remodeling complex, *EZH2*, have been observed in ~10% of NHL (143). These gain of function mutations are exclusively found in lymphomas of GC origin and act in concert with wild-type *EZH2* to generate abnormally high levels of H3K27Me3, leading to abnormal repression of PRC2 targets, driving lymphomagenesis (144). Furthermore, *EZH2* plays an essential role in GC formation in normal B-cells via a PRC2-mediated repression of target genes, allowing B-cells to undergo clonal expansion and somatic hypermutation (145). Tazemetostat is a first-in-class oral selective inhibitor of *EZH2* (146). Phase I and II trials of tazemetostat as a single agent have shown a very good safety profile, with only 5% of AEs leading to dose reduction or treatment discontinuation (147). In the phase I trial, including a highly pre-treated population, the ORR was 38% among DLBCL patients (147). In the phase II trial, the ORR among *EZH2* mutated DLBCL patients was



**Figure 4** epigenetic targeting and transcription regulation. Dysfunction of epigenetic regulation, mainly characterized by DNA methylation and histone acetylation, has been found as an important feature of DLBCL. Indeed, epigenetic associated gene mutations have been reported in the DNA methyl-transferase *EZH2* (gain of function), but also in the histone acetyltransferases *CREBBP* and *EP300* (loss of function). To target these abnormalities, new agents such as *EZH2* inhibitors or histone deacetylase inhibitors (HDAC) are currently in development in DLBCL. DLBCL, diffuse large B-cell lymphoma.

29% versus 15% among patients with WT *EZH2* (median of 3 to 4 lines of prior therapy) (80). Panabinstat is a histone deacetylase inhibitor recently evaluated in a phase II study in rel/refr DLBCL (30 mg orally 3 times a week), with and without rituximab. The ORR was 28% (11/40) and the median DoR was 14.5 months, without apparent benefit of rituximab. Interestingly, early responses could be predicted by mutations in *MEF2B* (81). Other HDAC inhibitors have shown modest activity as single agents in phase II trials [mocetinostat (148), ORR 18.9% and belinostat (149), ORR 10.5%]. CUDC-907 is a dual PI3K/HDAC inhibitor recently evaluated in phase I trial (150). The most frequent AEs were thrombocytopenia, neutropenia and hyperglycemia. At the recommended phase 2 dose of 60 mg/day 5 days a week, the promising ORR was 37% in the expanded DLBCL cohort. The ORR in the evaluable *MYC*-altered DLBCL patients (defined by *MYC* rearrangement assessed by FISH or *MYC* overexpression by IHC) was 64% (7/11; 4 CR and 3 PR), while it was 29% (2/7) in *MYC*-unaltered, and 17% (2/12) in those with unknown *MYC* status (82). The median duration of response was 11.2 months in the global cohort; 13.6 months in *MYC*-altered patients versus 6.0 and 7.8 months in *MYC*-unaltered and unknown status, respectively.

The favorable safety profile of these epigenome-targeting agents suggests that combination therapy with other targeted agents may be a feasible strategy.

## Conclusions

Recent progress in molecular biology has led to a better understanding of the oncogenic drivers of DLBCL, resulting in the development of a large number of targeted therapies undergoing evaluation in phase I and II trials. However, these agents have yet to earn regulatory approval, emphasizing the need for more efficient development strategies. Clinically available biomarkers to prioritize these options are also greatly needed. Importantly, as these agents emerge within the CAR-T cell era, optimal combinations and sequencing will need to be determined.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest



to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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