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Review Article

Multifunctional CD38 in the pathogenesis and treatment of B-cell lymphomas

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Abstract: B-cell lymphoma is a group of non-Hodgkin lymphomas with high heterogeneity. Despite advancement in therapeutics, the clinical outcomes of B-cell lymphomas need to be improved. CD38, a transmembrane multifunctional protein, is widely expressed across various B-cell lymphoma subtypes. Research indicates that CD38 plays multiple pathogenic roles in B-cell lymphomas, including regulation of proliferation, apoptosis, immune modulation, primarily through its enzymatic activity and its influence on signaling pathways in malignant lymphoma cells and immunosuppressive cells, making it a valuable therapeutic target. In recent years, CD38-targeted therapies, such as anti-CD38 antibodies and CD38-directed CAR-T cell therapies, have been explored for B-cell lymphomas. This review summarizes the knowledge on CD38 molecular functions, data of CD38 heterogeneous expression and prognostic role in B-cell lymphomas (from indolent to aggressive subtypes), anti-CD38 antibody efficacy and mechanisms of action, current understanding of the treatment resistance mechanisms, frontier advances in CD38-targeted therapies, and the challenges of novel targeted and immunotherapies in clinical applications, thereby seeking to provide a deep understanding of the role of CD38 in the pathogenesis and treatment of B-cell lymphomas. CD38-targed therapy is especially promising as a novel and optional treatment for CD20-negative lymphomas, for which standard treatment has not been established. Although the efficacy of anti-CD38 antibodies in most other B-cell lymphomas is low in previous clinical trials, in contrast to the remarkable efficacy of daratumumab in multiple myeloma, novel therapeutic strategies and combination therapies in ongoing clinical trials have the potential to overcome the counteracting actions and to improve the clinical outcomes of patients with relapsed/refractory B-cell lymphoma.

Keywords: CD38, B-cell lymphoma, biomarker, prognosis, antibody, daratumumab, isatuximab, CAR-T immunotherapy, targeted therapy, CD20-negative large B-cell lymphomas

Introduction

Non-Hodgkin lymphoma (NHL) is the most prevalent group of hematologic malignancy, and approximately 85-90% of NHL cases are B-cell lymphomas, which encompass a heterogeneous collection of lymphoproliferative disorders that vary considerably in clinical presentation and outcomes, largely driven by the underlying genetic heterogeneity and diverse etiopathological mechanisms. Over the past two decades, therapeutic advancements have significantly enhanced the survival rates of patients with B-cell lymphomas [1]. Immunochemotherapy, exemplified by the R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) regimen, has been the foundational first-line treatment for many B-cell lymphoma types. Furthermore, targeted therapies, such as Bruton's tyrosine kinase (BTK) inhibitors and phosphatidylinositol 3-kinase (PI3K) inhibitors, and cellular immunotherapies [2, 3] have markedly improved clinical outcomes of specific lymphoma subtypes. However, the prognosis of patients with relapsed or refractory disease remains notably poor, and most indolent B-cell lymphomas are generally regarded as incurable.

Studies have shown that CD38 is often highly expressed in most B-cell lymphomas [4]; cross-linking of CD38 has been observed to elicit distinct cellular effects, such as activation, proliferation, rescue from apoptosis, calcium ion (Ca^{2+}) mobilization, metabolism, immunomodulation, and immune evasion [5, 6], suggesting that CD38 is a viable therapeutic target in B-cell lymphomas. Data suggest potential efficacy of CD38-targeting in treating patients with B-cell lymphomas for whom standard therapies are

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limited or ineffective. For example, in some patients with relapsed/refractory B-cell lymphoma, CD20 expression decreased following rituximab treatment and retreatment, limiting rituximab efficacy.

Beyond B-cell lymphomas focused in this review article, CD38 is also expressed in some T-cell lymphoma subtypes, and showed potential values in diagnosis [7] and therapeutics [8]. In refractory extranodal natural killer cell-T-cell lymphoma, anti-CD38 therapy with daratumumab showed efficacy in a case report [9] but the duration of response was short in a phase 2 clinical trial [10]; however, combined anti-CD38 and anti-PD-1 therapies with isatuximab and cemiplimab demonstrated sustained efficacy in a phase 2 clinical trial [11].

Materials and methods

Relevant literature in the PubMed database was searched using keywords, including CD38, B-cell lymphoma, each B-cell lymphoma subtype name, prognosis, CD38 antibody, daratumumab, isatuximab, targeted therapy, CAR-T, immunotherapy, conjugate, bispecific, and inhibitor. Valuable data were organized under the sections below. Other more specified searching keywords, such as BCR, CD19, calcium mobilization, saporin, immunotoxin, radioimmunotherapy, Tet-on and Tet-off were also used for various topics in the review, as well as reverse searching method and Google search of Tet-on® 3G inducible expression systems user manuals. The date of last literature search was March 20, 2026.

Results

Structure and function of CD38

CD38 is an ecto-enzyme, a receptor, and adhesion molecule first identified as a T lymphocyte cell surface receptor by Reinherz *et al* in the 1980s (initially called OKT10) [12]. It was subsequently established as a surface marker widely expressed ins various hematologic cells, including B cells [13], T cells [14], natural killer (NK) cells [15], macrophages, monocytes [16], and neutrophils [17], as well as in numerous non-hematologic cell types, with higher levels in plasma cells and NK cells [13, 18].

CD38 is a type II transmembrane glycoprotein of 300 amino acids that is structurally characterized by three distinct domains: a large C-terminal extracellular domain, a single-chain transmembrane region, and a short N-terminal cytoplasmic tail [19]. CD38, primarily through its extracellular domain of 42-kilodalton, catalyzes the conversion of nicotinamide adenine dinucleotide (NAD) into cyclic adenosine diphosphate ribose (cADPR), and subsequently hydrolyzes cADPR into adenosine diphosphoribose (ADPR) [20]. Under specific conditions, CD38 catalyzes the transformation of nicotinamide adenine dinucleotide phosphate (NADP) into nicotinic acid adenine dinucleotide phosphate (NAADP) [21]. The reaction products, cADPR, ADPR, and NAADP, act as potent secondary messengers in cellular Ca^{2+} mobilization, a crucial step in the regulation of intracellular signaling pathways that influence lymphocyte proliferation and activation (**Figure 1**). The crystallographic structural model of the soluble extracellular domain of CD38 with three ecto-enzymatic functions contains two CD38 molecules, each consisting of 252 amino acids [22].

CD38 is traditionally viewed as an “activation marker” [14]. In B cells, CD38 plays a role in signal transduction. CD38 is expressed in B cells from their earliest developmental stages, with its expression levels increasing as B cells mature and being highest in terminally differentiated plasma cells. Stimulation with anti-CD38 antibody led to robust ERK phosphorylation and induced apoptosis in a CD38-transfected murine pro-B Ba/F3 cell line [5]. In immature B cells, CD38 ligation and dimerization by specific antibodies (T16, IB4, and THB7) induces rapid and transient tyrosine phosphorylation of several intracellular proteins, including protein tyrosine kinase Syk, phospholipase C-gamma (PLC-γ), and the p85 subunit of phosphatidylinositol 3-kinase (PI3K), as well as inhibition of cell growth and induction of apoptosis [5, 23, 24]. Notably, most CD38-induced phosphorylation events are transient, detectable only within minutes of treatment, and disappear within 30 min, suggesting the presence of other natural ligands [5, 23, 24].

The precise molecular mechanisms by which CD38 regulates the signaling cascades remain unclear. Although many transmembrane proteins directly activate signaling cascades via their cytoplasmic domains, the short cytoplasmic tail of CD38 lacks the tyrosine residues

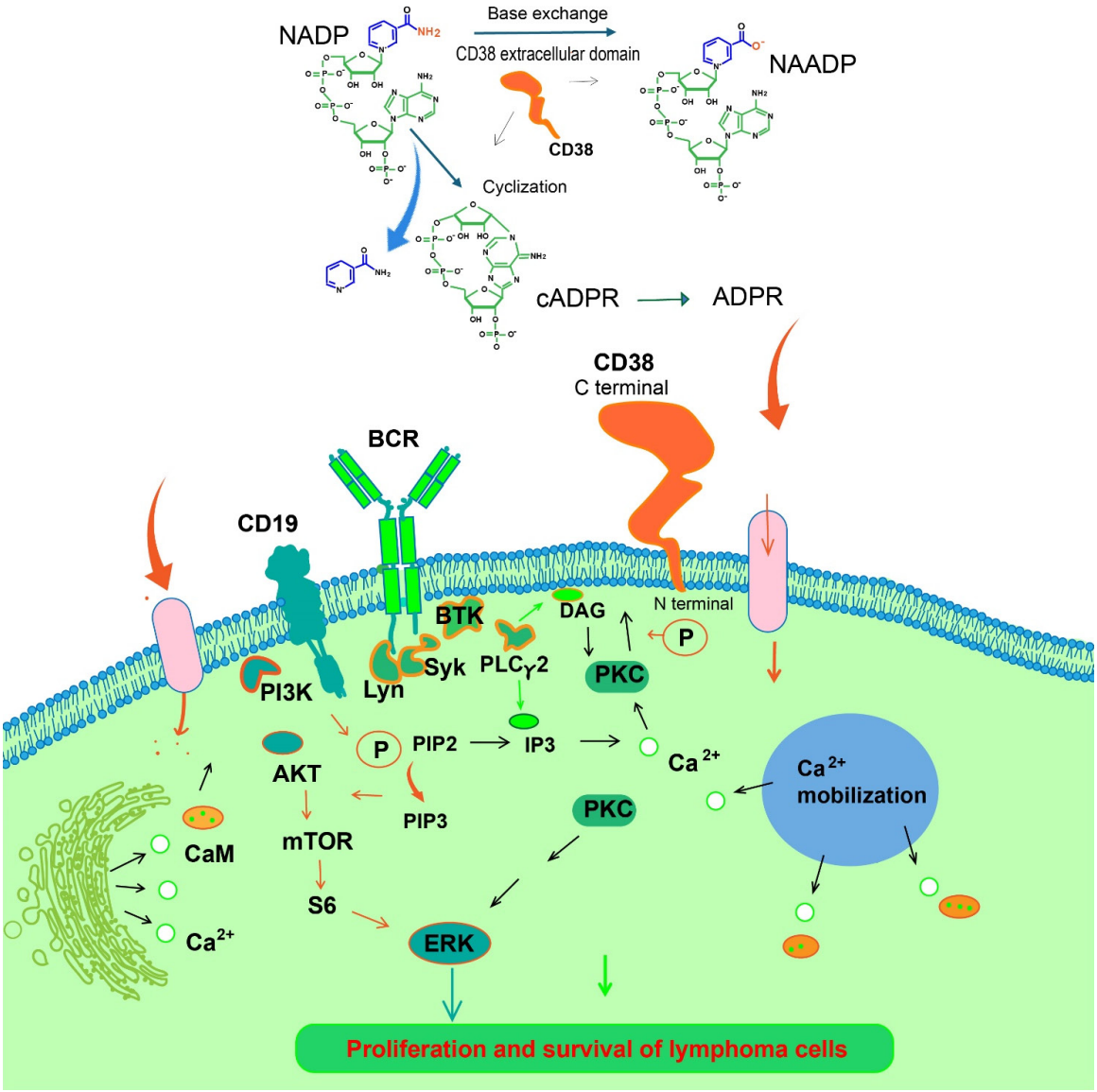

Figure 1. CD38 enzymatic function and role in B cell signaling. CD38 catalyzes the conversion of NAD+ into cADPR, which can then be further hydrolyzed into ADPR. In addition, CD38 catalyzes the conversion of NADP into NAADP. cADPR, ADPR, and NAADP serve as potent Ca^{2+}-mobilizing second messengers, to release calcium from endoplasmic reticulum and lysosomal stores. Intracellular Ca^{2+} mobilization triggers activation signaling cascades and enhances the cell cycle. In addition, CD38 acts as a scaffold protein or co-receptor of the BCR and CD19 complex, and promotes phosphorylation and activation of the BCR signaling pathway, relaying signals through associated proteins, including Lyn, Syk, BTK, PLCγ2, PKC, and ERK1/2. CD19 plays a critical role in the CD38 signaling cascade, as CD38 facilitates the activation and transduction of CD19-associated molecules, such as PI3K, AKT, mTOR, and S6. Through the enzymatic and signaling function, CD38 promotes proliferation and survival of lymphoma cells. Abbreviations: NAD, nicotinamide adenine dinucleotide; cADPR, cyclic adenosine diphosphate ribose; ADPR, adenosine diphosphoribose; NADP, nicotinamide adenine dinucleotide phosphate; NAADP, nicotinic acid-adenine dinucleotide phosphate; BCR, B-cell receptor; DAG, diacylglycerol; PKC, protein kinase C; CaM, calmodulin.

and tyrosine kinase domains. Thus, CD38-mediated signal modulation is thought to operate via secondary messengers or through interactions with other transmembrane molecules [25]. In murine pro-B cells, CD38 mutants lacking cytoplasmic regions are still capable of inducing signaling cascades [26]. In chronic lymphocytic leukemia (CLL) cells, CD38 regulate signaling cascades through its enzymatic function in Ca^{2+} mobilization (different from

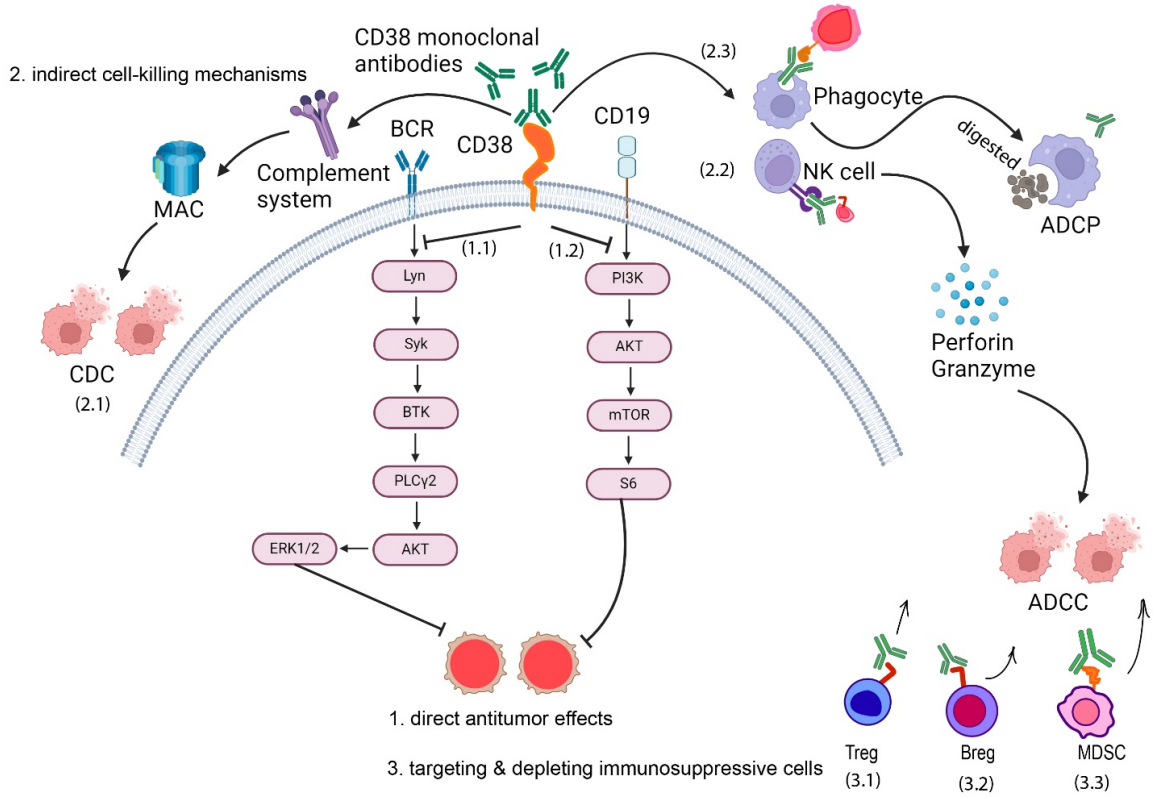

Figure 2. Illustration of the antitumor activities of CD38 antibodies. CD38 antibodies can directly inhibit the proliferation and survival of B-cell lymphoma cells by antagonizing the phosphorylation of the BCR and CD19 signaling pathway proteins (1.1 and 1.2 in the figure) and indirectly eliminate B-cell lymphoma cells through CDC, ADCC, and ADCP (2.1 to 2.3 in the figure) in the figure. Additionally, CD38 antibodies deplete immunosuppressive cells, including Tregs, Bregs, and MDSCs, which express high levels of CD38 (3.1 to 3.2 in the figure), thereby enhancing the antitumor immunity of the patients. Abbreviations: CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; MAC, membrane attack complex; Treg, regulatory T cell; Breg, regulatory B cell; MDSC, myeloid-derived suppressor cell.

another study in tonsillar B cells [27]), and elevated intracellular Ca^{2+} levels enhance signaling pathways such as ERK1/2 and p38/JNK [28]. Upon treatment of CLL cells with the CD38 antibody daratumumab, the phosphorylation of key signaling molecules, including Syk, BTK, PLCγ2, ERK1/2, AKT, and p38/JNK, was significantly reduced [28, 29].

Additionally, several studies have demonstrated that CD38 mediates signal transduction in B cell precursors, mature B cells, and various B cell lymphoma cell lines through interactions with CD19 [24, 25, 27]. Targeting CD38 with an antibody disrupts the connection between CD19 and the IgM class B-cell receptor (BCR), thereby impairing BCR signaling in both normal and malignant B cells [13]. Complete inhibition of the CD38 signaling pathway following CD19-specific elimination further substantiates the critical role of CD19 in the CD38 signaling cascade [27]. In Waldenström's macroglobulinemia (WM) cells, daratumumab treatment downregulated canonical BCR signaling pathways, specifically affecting LYN, SYK, BTK, PLCγ2, and ERK1/2. This was accompanied by the concurrent downregulation of the CD19-associated signaling proteins AKT, mTOR, and S6 [30].

Therapeutic anti-CD38 antibodies

Anti-CD38 antibodies have been developed for the immunotherapy of multiple myeloma since 1995 [31]. Dual mechanisms are involved in the antitumor effects of the CD38 antibodies (**Figure 2**). First, CD38 antibodies can induce death of $CD38^+$ cells via both direct and indirect mechanisms. The direct cytotoxic effects primarily depend on modulation of CD38's enzymatic activity, regulation of signal transduc-

tion pathways, and direct induction of apoptosis in tumor cells. Indirect cell-killing mechanisms of action involve classic Fc-dependent immune-effector pathways, such as complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) [32]. Second, CD38 antibodies enhance host antitumor immunity by targeting and depleting immunosuppressive cells with high CD38 expression and reducing immunosuppressive adenosine in the tumor microenvironment (TME) [33]. In multiple myeloma, in addition to targeting CD38-expressing myeloma cells, daratumumab depletes inhibitory $CD38^+$ regulatory T cells and myeloid-derived suppressor cells, increases effector T cells and TCR clonality [34], and targets $CD38^+$ NK cells enhancing phagocytosis [15].

Daratumumab was the first developed CD38 antibody and approved for treating multiple myeloma by the U.S. Food and Drug Administration (FDA) in November 2015 [19]. It is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that targets a unique epitope on the CD38 molecule and shows exceptional CDC and extensive ADCC activity in B-cell lymphomas and multiple myeloma [19]. Isatuximab (former name: SAR650984) is another chimeric mouse/human CD38 antibody that has been approved for the treatment of relapsed/refractory multiple myeloma in 2020 [35]. In contrast to daratumumab, isatuximab was selected from antibody screening because of its ability to directly induce apoptosis in lymphoma cells in the absence of cross-linking agents and effector cells [36]. Isatuximab targets a distinct epitope that binds specifically to a 23-amino-acid region on human CD38, and compared with daratumumab [37], isatuximab shares mechanisms of action of immune cell-mediated ADCC (more dependent on CD38 receptor density [38]) and ADCP, but rarely acts through CDC [37, 38], and the apoptosis induction requires less cross-linking, especially in lymphoma cells. Moreover, isatuximab effectively inhibits CD38's enzymatic function [36, 37]. Other anti-CD38 antibodies being developed include MOR202 and SAR442085 which have shown promising efficacy in clinical trials for multiple myeloma [39, 40]. More recent studies have included a novel humanized anti-CD38 antibody, FTL004, with negligible binding to red blood cells, which exhibited enhanced pro-apoptotic ability and ADCC *in vitro* and an effective antitumor effect in xenograft models of multiple myeloma and NHL [41].

According to the Human Protein Atlas (proteinatlas.org), lymphoma cell lines have higher mean and median *CD38* and CD38 expression levels than myeloma and leukemia cell lines, although normal plasma cells have higher *CD38*/CD38 expression levels than normal B cells. Hence, targeting CD38 is a compelling treatment strategy for B-cell lymphomas as for multiple myeloma [29, 30, 42]. The mechanisms of action of the first-in-class daratumumab against CLL, follicular lymphoma (FL), mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL) cells *in vitro* mainly include ADCC and ADCP, but not CDC (different from in multiple myeloma) [42, 43], whereas also include potent CDC in Burkitt lymphoma (BL) cells [44] and primary effusion lymphoma (PEL) cells [45] (however, no CDC in another study [46]), and directly induce apoptosis in PEL, CLL, and WM cells with attenuated BCR and CD19-related signaling pathways [29, 30]. Isatuximab, which rarely induces CDC, also acts differently in lymphoma cells compared with in myeloma cells, showing increased apoptosis induction but ADCP-resistance in DLBCL cell lines [38]. The lack of CDC induction was likely due in part to complement-inhibitory proteins (such as CD46, CD55, and CD59) as well as the low density of CD38 molecules in B-cell lymphomas [38, 43, 46].

In recent years, bispecific antibodies employing anti-CD38 Fab' fragment from daratumumab and istuximab and additional Fab fragment of other antibodies, such as anti-CD20 rituximab and obinutuzumab or anti-CD22, induced "heteroreceptor crosslinking" that directly initiates apoptosis, and demonstrated enhanced efficacy compared with single-targeting antibodies in BL models [47]. An innovative CD38 × ICAM-1 tumor-targeting bispecific antibody also demonstrated potent tumor inhibition activity in myeloma and BL *in vivo* [48].

CD38 expression and antibody efficacy in indolent and aggressive B-cell lymphoma subtypes

CLL: CLL is the most prevalent form of leukemia among adults in Western countries. This disease exhibits significant heterogeneity in

clinical behavior: while some patients experience an indolent disease course and may live for many years without symptoms, others face rapid disease progression despite intensive therapy [49]. Although new therapies, including BTK inhibitors and rituximab, have improved survival outcomes in CLL, these treatments are limited by several factors including low rates of complete remission, development of resistance, and occasional severe toxicities, and drugs with less off-target toxicities are being developed.

The degree of CD38 expression (**Figure 3A**) varies significantly across CLL patients. With a positivity cutoff of expression in 20% or more of leukemic cells, the CD38 expression frequency was approximately 43% in a study of 218 patients and another study of 133 patients with CLL, associated with significantly poorer overall survival (OS) [50, 51]. In another two studies using a cutoff of ≥30% CLL cells, the frequency of high CD38 expression was 37.3 and 47%, respectively [52, 53]. Similarly, unfavorable prognostic effects of high CD38 expression have been reported in studies that simultaneously analyzed the prognostic effect of immunoglobulin variable region mutation status [53-56], as well as in a study of 227 young adult patients with CLL, associated with shorter median time to first treatment, shorter time to developing Richter transformation, and poorer OS [57]. High CD38 expression in CLL is associated with unfavorable clinical characteristics varied in some studies, such as incidence of lymph node involvement, lower hemoglobin level, splenomegaly, atypical morphology, higher Rai stage, elevated lactate dehydrogenase, higher β2-microglobulin levels, higher lymphocyte counts, and enhanced homing to lymphoid tissues, which reflect an increased tumor burden and more extensive disease involvement [50, 58, 59]. However, when untreated CLL patients were excluded and the analysis was limited to a symptomatic group receiving fludarabine, CD38 expression levels were not associated with therapeutic response to fludarabine-based chemotherapy or progression-free survival (PFS) [60].

The unfavorable prognostic role of high CD38 expression in CLL underscores its importance as a potential therapeutic target. Inhibiting CD38 activity may not only disrupt key signaling pathways that promote CLL cell survival and proliferation but also potentially modulate the TME to counteract immune evasion. Proof-of-concept *in vitro* and *in vivo* studies have demonstrated the efficacy of daratumumab in prolonging the OS of mouse models and reducing CLL cell dissemination [29, 42]. However, no clinical trial data are currently available regarding the efficacy of CD38 antibodies in CLL. In a patient reported, daratumumab combination therapy successfully controlled multiple myeloma but failed to eliminate residual CLL in that patient [61].

Lymphoplasmacytic lymphoma (LPL) and WM: LPL/WM is a subtype of indolent B-cell lymphoma characterized by cells that exhibit features intermediate between those of small lymphocytes and plasma cells. The frequency of CD38 expression in WM cells is 40-70% [62-64]. While there is limited evidence directly correlating CD38 expression levels with disease aggressiveness, resistance, or OS in LPL/WM, the high prevalence of CD38 positivity (**Figure 3B**) suggests the potential of CD38 targeted therapies in WM. Daratumumab elicits direct apoptosis of WM cells *in vitro*, delays tumor growth in WM xenografted mice and attenuates BCR signaling, irrespective of acquired resistance to ibrutinib [30]. A multicenter phase 2 clinical trial in previously treated WM demonstrated a lower than expected overall response rate (ORR) of 23% (and a major response rate of 15%) to daratumumab monotherapy in previously treated patients with WM [65], whereas the synergy of daratumumab and ibrutinib in WM remains unknown.

Marginal zone lymphoma (MZL): MZL (**Figure 3C**) is an indolent yet incurable B-cell lymphoma characterized by a high frequency of relapses following therapy. It encompasses three distinct subtypes, each with unique clinical and pathological features: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), splenic marginal zone lymphoma (SMZL), and nodal marginal zone lymphoma (NMZL) [66]. Understanding CD38's potential role in MZL may provide new insights into the biology of this lymphoma subtype and aid in the development of tailored therapeutic strategies. However, owing to the relative rarity and heterogeneity of MZL, data on CD38 expression frequency in this lympho-

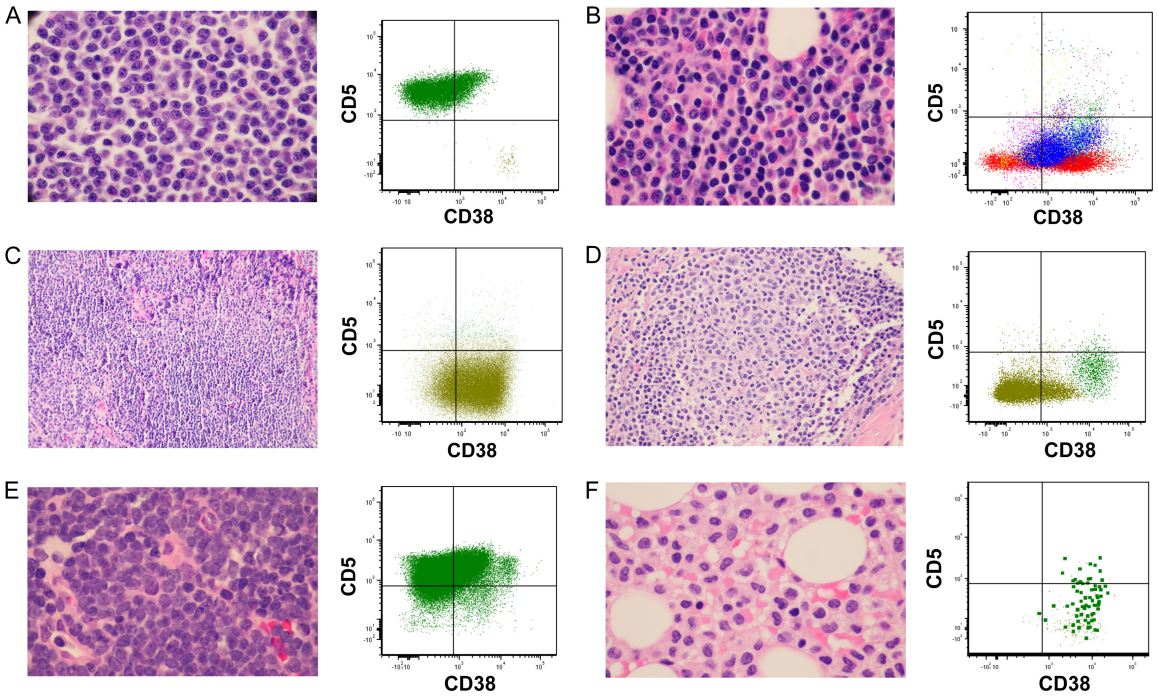

Figure 3. Representative H&E staining images and immunophenotyping by flow cytometry analysis for low-grade B cell lymphoma cases with CD38 expression. A. H&E image of a lymph node with chronic lymphocytic leukemia/small lymphocytic lymphoma (magnification, 100×) and flow cytometry plot showing CD5 and partial CD38 expression. B. H&E image of a bone marrow biopsy with lymphoplasmacytic lymphoma (magnification, 100×), and flow cytometry plot showing high CD38 expression. C. H&E image of a lymph node biopsy with marginal zone lymphoma (magnification, 40×) and flow cytometry plot showing strong CD38 expression. D. H&E image of a lymph node biopsy with follicular lymphoma (magnification, 40×) and flow cytometry plot showing partial CD38 expression. E. H&E image of a lymph node biopsy with mantle cell lymphoma (magnification, 100×) and flow cytometry plot showing CD5 and partial CD38 expression. F. Histomorphology and flow cytometry analysis for a bone marrow biopsy with hairy cell leukemia which showed abnormal CD38 expression (CD38 expression is generally considered to be low or negative in classical hairy cell leukemia cases). 100× magnification.

ma subtype are limited and vary from 9.1% of 27 SMZL cases [67] to 42% of 27 NMZL cases [68], warranting further large-scale subtype-specific studies. In a mixed cohort of various MZL subtypes, CD38 expression was observed in 32% of cases [69]. Regarding prognostic effects, CD38 expression did not correlate with PFS or OS in patients with NMZL [68] or in a mixed cohort of indolent lymphoplasmacytic and MZL patients [70].

FL: FL is the second most common subtype of NHL, representing 20-30% of all lymphoma cases. While most patients with FL achieve prolonged survival with immunochemotherapy, those with advanced-stage or relapsed/refractory FL continue to have poor prognosis with limited effective treatment options. CD38 is expressed (**Figure 3D**) in a high proportion of FL patients (66.7% [71] to 100% [72]). Despite the high $CD38^+$ frequency, CD38 expression levels in neoplastic B cells in FL (measured by flow cytometry median fluorescence intensity) are significantly lower than CD38 expression in reactive germinal center B cells in follicular hyperplasia, but not significantly different from those in normal B and T cells in FL and non-germinal center B cells in follicular hyperplasia [71]. No correlation was observed between CD38 expression levels and the pathological grade of FL [71], clinical features, or prognosis of FL, in contrast to the correlations of high CD38 expression with poor prognosis and more aggressive clinical behavior in other B-cell lymphomas.

In a preclinical study evaluating daratumumab in B-cell lymphomas, daratumumab inhibited FL tumors *in vitro* and *in vivo* and improved the OS of a mouse model with dim CD20 expression requiring treatment alternatives to rituximab [43]. However, a clinical trial for daratu-

mumab included 16 patients with refractory/relapsed FL with a median CD38 expression of 67.5%, and the ORR was only 12.5% [73], which may be consistent with the role of CD38 reflected from decreased CD38 levels in FL cells and lack of prognostic role of CD38 in FL.

MCL: MCL is an aggressive B-cell lymphoma accounting for approximately 2-6% of all NHL cases. The standard treatment for MCL typically involves intensive chemotherapy, followed by autologous hematopoietic stem cell transplantation. However, despite aggressive treatment, many patients with MCL continue to have a poor prognosis and limited survival [74]. In relapsed or refractory MCL cases, even with the introduction of novel agents such as BTK inhibitors, the outcomes remain suboptimal, highlighting the need to improve therapeutic strategies [75]. In contrast, a subset of MCL patients have a more indolent clinical course, who can survive for extended periods (7-10 years or more), known as indolent or smoldering MCL [76].

Studies have reported that CD38 positivity in conventional MCL (**Figure 3E**) varies between 48% and 94%, depending on the cohort and methodology used [77-80]. Indolent MCL is typically characterized by low CD38 expression and a Ki-67 proliferation index of less than 30%, in contrast to conventional MCL, which generally displays high CD38 expression and an elevated Ki-67 index [76, 79]. Furthermore, increased CD38 expression has been associated with bortezomib resistance and poorer OS in patients with MCL [77, 81].

In a preclinical study evaluating daratumumab in B-cell lymphomas, daratumumab inhibited MCL tumor growth *in vitro* and *in vivo*, showed efficacy comparable to rituximab in a disseminated *in vivo* model of blastic MCL (an aggressive subtype), and potentiated the antitumor activity of R-CHOP in MCL xenograft [43]. However, in a clinical trial of daratumumab that recruited five relapsed/refractory MCL patients with a median CD38 expression of 60% (the trial screened NHL patients for $CD38^+$ expression ≥50%), no patients responded and four patients (80%) had disease progression and died (median OS of five patients: 4.8 months) [73]. Also noteworthy, hairy cell leukemia is another indolent type of NHL with abnormal CD38 expression (**Figure 3F**) in approximately 14-36% of patients. However, currently no clinical studies on anti-CD38 antibodies are available in hairy cell leukemia.

DLBCL: DLBCL is the most common subtype of B-cell lymphoma, accounting for 30-40% of all NHL cases. Standard treatment with R-CHOP regimen achieves complete remission rates of 70-90%. However, 30-40% of DLBCL patients will experience refractory or relapsed disease despite initial responses, significantly lowering their life expectancy. CD38 expression (**Figure 4A-F**) has emerged as a significant prognostic marker in DLBCL. A retrospective study of 137 DLBCL patients reported that CD38 was highly expressed in 37 (27%) patients, and high expression correlated with significantly poorer PFS and OS [82]. A study of 36 patients with relapsed/refractory DLBCL *de novo* or transformed from FL found that high CD38 expression in 25% of the cohort was associated with significantly poor clinical outcomes [83]. A higher frequency of immunohistochemical CD38 expression, 83.3%, was observed in 142 patients with Richter transformation DLBCL [84].

In DLBCL, *MYC* gene translocation is an important prognostic indicator of poor outcomes, and the majority of cases with *MYC* rearrangements show bright CD38 expression on flow cytometry [85]. Double-hit or triple-hit (DH/TH) DLBCL cases, molecularly harboring concurrent *MYC* and *BCL2* and/or *BCL6* translocations, have been identified to be associated with an aggressive clinical course and inferior survival and have been re-classified as high-grade B-cell lymphoma with *MYC/BCL2* (HGBL-DH-*BCL2)* and/or *BCL6* rearrangements (DLBCL/HGBL-DH-*BCL6*), separated from DLBCL-not otherwise specified [86]. Notably, bright CD38 expression was observed in 82% of DLBCL cases with a single *MYC* rearrangement and in 56% of DH/TH DLBCL/HGBL cases, whereas only 17% of *MYC*-negative DLBCL cases exhibited strong CD38 expression [87]. Other studies have further confirmed this association, and combined biomarkers have been proposed to identify DH/TH DLBCL cases [85, 88, 89]. However, a flow cytometry study demonstrated that there were no significant differences in CD38 percentage expression and median fluorescence intensity between DH, DLBCL with single *MYC* rearrangement, DLBCL-not otherwise specified, and BL (patient numbers: 10, 8, 19, and 14, respectively) [90]. The

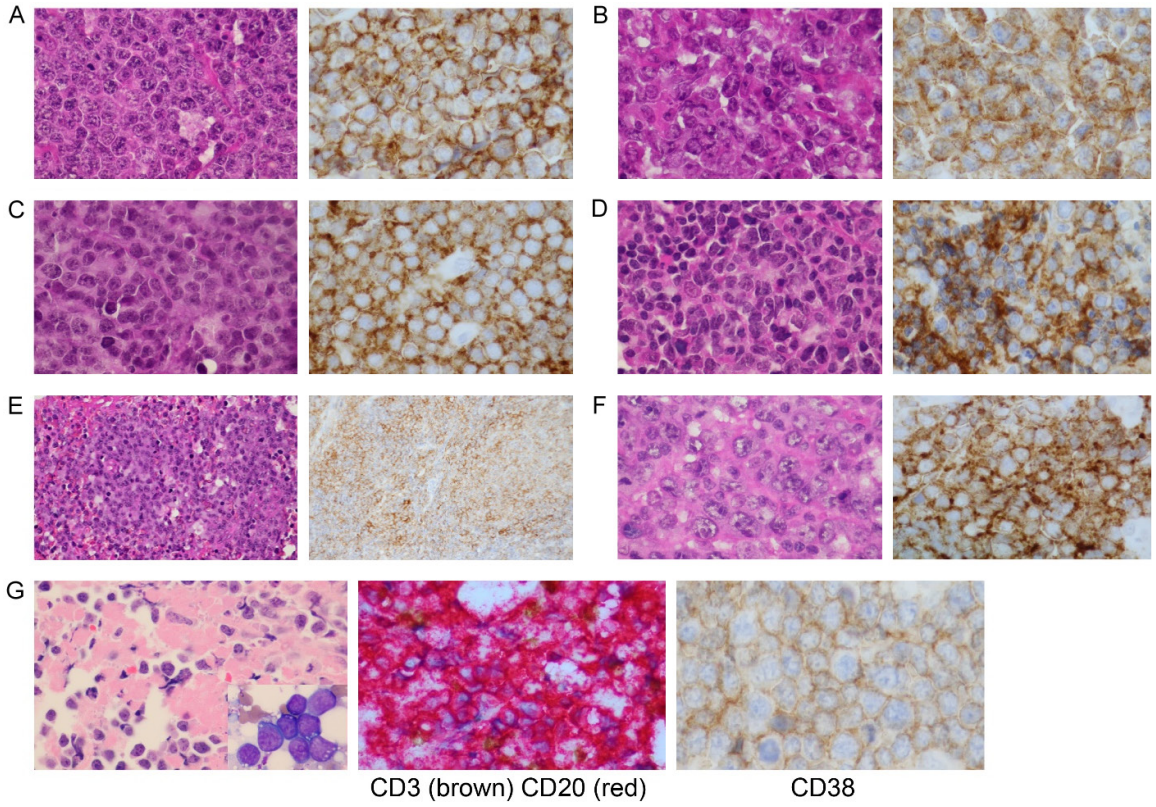

Figure 4. Histomorphology and CD38 immunohistochemistry of representative high-grade B cell lymphoma cases. A. A representative case with DLBCL, germinal center B cell-like subtype, showing uniform membrane CD38 expression. Magnification, 100×. B. A representative case with DLBCL, activated B cell-like subtype, showing granular membrane and cytoplasmic CD38 expression. Magnification, 100×. C. A representative double-hit lymphoma case with high-grade B cell lymphoma with *MYC* and *BCL2* rearrangements, showing uniform membrane CD38 expression. Magnification, 100×. D. A representative Richter transformation case with DLBCL transformed from previous chronic lymphocytic leukemia/small lymphocytic lymphoma, showing membrane CD38 expression. Magnification, 100×. E. A representative case with DLBCL transformed from previous follicular lymphoma, showing uniform membrane CD38 expression. Magnification, 40×. F. A representative case with EBV+ DLBCL, showing granular membrane and cytoplasmic CD38 expression. Magnification, 100×. G. A representative case with Burkitt lymphoma and extensive necrosis that shows membrane CD38 expression. Double CD3/CD20 immunohistochemistry shows CD20 stains in both necrotic and viable lymphoma cells. Magnification, 100×.

molecular pathways connecting CD38 with *MYC* rearrangement and DH have not been revealed. Also notably, peripheral (circulating) T cells of DLBCL (including DH) patients were CD38$^+$, and T cells of DH DLBCL/HGBL patients were more exhausted [91].

In a patient-derived DLBCL xenograft model, daratumumab monotherapy was comparable to R-CHOP and the combined therapy led to complete tumor regression [43]. A previous study reported that daratumumab was temporarily effective in a patient with post-transplant lymphoproliferative disease after rituximab treatment failure [92]. The efficacy of daratumumab was enhanced by the addition of venetoclax in BCL-2$^+$ DLBCL/HGBL-DH-*BCL2* cell lines owing to enhanced phagocytosis by macrophages [93]. A recent report demonstrated clinical efficacy of daratumumab in combination with chemotherapy in three of four CD38$^+$ DLBCL patients with CD20 loss or mutation after multiple lines of treatments, which helped two patients to successfully bridge chimeric antigen receptor (CAR) T cell therapy [94].

However, in a clinical trial of daratumumab in selected NHL patients with ≥50% CD38$^+$ expression, 15 DLBCL patients with a median 80% expression were recruited, but the response rate was only 6.7%, and 12 (80%) pa-

tients showed disease progression [73]. In a phase I/II study of isatuximab in combination with cemiplimab (anti-PD-1), the overall response in DLBCL patients was also disappointingly low, 5.9% [95]. Whether the efficacy of daratumumab/isatuximab correlates with CD38 expression, *MYC* rearrangement or DH (in which conventional treatments fall short), and whether $CD38^+$ T cells are off-targets of anti-CD38 therapy are unknown.

BL: BL is a highly aggressive B-cell lymphoma characterized by a single *MYC* translocation that drives rapid proliferation and malignancy. BL can be divided into three distinct clinical variants: endemic, sporadic, and immunodeficiency-associated variants. Endemic BL primarily affects children in equatorial Africa and is closely associated with Epstein-Barr virus (EBV) infection. In contrast, sporadic BL accounts for the majority of cases in the U.S and represents approximately 1% of adult NHL cases [96]. Intensive multi-agent chemotherapy regimens are commonly used to treat BL, achieving cure rates of >90% in many patients. As discussed in the DLBCL section, CD38 expression is strongly correlated with MYC-positive lymphomas [89, 97], including BL (**Figure 4G**), with a 51.5%-91% frequency [98, 99]. However, unlike other B-cell lymphomas, CD38 expression in BL is not associated with prognosis.

In the study that discovered daratumumab, xenograft models used to test daratumumab included BL (Daudi cells) and multiple myeloma; daratumumab demonstrated potent efficacy in both early and late treatment settings [44]. Targeting CD38 in BL cells *in vitro* disrupted BCR and PI3K signaling, suppressed cell proliferation, and induced apoptosis; isatuximab showed higher efficacy than daratumumab in BL cells [100]. Further studies are warranted to investigate the CD38's role in BL and determine the efficacy of CD38 targeted therapy in BL cases as well as personalized therapeutic strategies for patients resistant to standard treatments.

CD20-negative large B-cell lymphomas: CD20-negative large B-cell lymphomas include four rare subtypes of lymphoproliferative disorders: plasmablastic lymphoma (PBL), PEL, large B-cell lymphoma arising from human herpesvirus 8 (HHV8)-associated multicentric Castleman disease ($HHV8^+$ LBCL), and anaplastic lymphoma kinase-positive LBCL (ALK^+ LBCL). These CD20-negative LBCLs typically present with extranodal involvement and are associated with a relatively poor prognosis, likely due to their aggressive behavior and lack of response to CD20-targeted therapies [101]. CD20-negative LBCLs are characterized by a reduction in B-cell differentiation markers, such as CD20 and PAX5, and overexpression of CD38 (expressed in more than 90% of PEL and PBL cases [102]) and key transcription factors involved in plasma cell differentiation. Given that CD20-negative LBCLs lack CD20 expression, therapies based on CD20 antibodies such as rituximab are generally ineffective. This makes CD38 a particularly appealing target in these cases, as it is one of the few highly expressed markers that can be used for therapy [103]. Daratumumab has shown both *in vitro* and *in vivo* efficacy in PEL models [45, 46]. Despite the rarity of PEL, several case reports have demonstrated the successful use of daratumumab [46, 103].

In a single-center retrospective analysis of patients with advanced-stage PBL, daratumumab monotherapy or combined therapy was found to be safe and well tolerated, producing complete response in all six evaluated patients with PBL after treatment, among whom four patients maintained durable responses (12-31 months and ongoing) [104]. To treat relapsed PBL, combining daratumumab with ifosfamide, carboplatin, and etoposide [ICE] in four patients was safe and effective, achieving a complete response after 3-4 cycles of therapy. However, the response and myelosuppression were transient in one patient, and neutropenia was observed in three patients [105]. A phase 2 trial is evaluating the efficacy of subcutaneous daratumumab in relapsed/refractory PEL, PBL, and multicentric Castleman disease (NCT05907759).

Combination therapies with anti-CD38 antibodies in B-cell lymphomas: **Table 1** summarizes the clinical data of daratumumab in relapsed/refractory B-cell lymphomas. Daratumumab efficacy was low in DLBCL, FL, and MCL patients (ORR, only 6.7%, 12.5%, and 0%, respectively) [73], intermediate in WM, promising in PEL and PBL, and unknown in CLL and BL despite of their potential. Although the sample sizes in these studies were small, the disappointingly

Table 1. CD38 expression and prognostic significance in B-cell lymphomas

Lymphoma subtype	CD38 positivity rate	Prognostic effect	References
CLL	33%-47%	Unfavorable	PMID 11418478 [50], PMID 31122288 [52], PMID 35975791 [148], PMID 11840260 [51], PMID 10477712 [53], PMID 11807008 [54], PMID 11843819 [55], PMID 12149225 [56], PMID 10477712 [53], PMID 33973230 [57]
LPL/WM	40%-70%	Undefined	PMID 19287458 [62], PMID 16191510 [63], PMID 25853860 [64]
MZL	9.1%-42%	Not significant	PMID 12766579 [68], PMID 18500740 [69], PMID 23928529 [67]
FL	67%-100%	Not significant	PMID 19382196 [71], PMID 30066366 [72]
MCL	48%-80%	Unfavorable	PMID 12511405 [77], PMID 12609845 [80], PMID 24352646 [79], PMID 29246179 [76], PMID 20956803 [81]
DLBCL	25-44.4%, 83% in RT DLBCL	Unfavorable	PMID 34327725 [82], PMID 35045767 [83], PMID 36933995 [84]
BL	51.5%-91%	Not significant	PMID 29327714 [98], PMID 20003543 [99]
$CD20^-$ LBCL (PBL, PEL, $HHV8^+$ LBCL, ALK^+ LBCL)	≥90% in PEL and PBL	Undefined	PMID 26459310 [102]

Abbreviations: CLL, chronic lymphocytic leukemia; LPL, lymphoplasma cell lymphoma; WM, Waldenström's macroglobulinemia; MZL, marginal zone lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; RT, Richter transformation; BL, Burkitt lymphoma; LBCL, large B-cell lymphoma; PBL, plasmablastic lymphoma; PEL, primary effusion lymphoma; $HHV8^+$ LBCL, large B-cell lymphoma arising in the context of human herpesvirus 8 (HHV8)-associated multicentric Castleman disease; ALK^+ LBCL, anaplastic lymphoma kinase-positive LBCL.

low efficacy of daratumumab in B-cell lymphomas could be caused by resistance mechanisms counteracting CDC, ADCC, and ADCP (for example, complement-inhibitory proteins, PD-1/L1 pathway, TGF-β) [38], lower and heterogeneous CD38 intensity than that in myeloma [38, 73], and non-tumor on-target effects on immune cells in B-cell lymphomas. To enhance the efficacy of daratumumab, all-trans retinoic acid (ATRA) and a pan-histone deacetylase inhibitor panobinostat can be used to increase CD38 expression and the susceptibility of low-CD38-expressing cells to daratumumab-induced lysis, including ADCC [18, 46, 106].

Although anti-CD38 antibodies as monotherapy have shown low efficacy in most B-cell lymphomas, they may be valuable in combination therapies to overcome the resistance mechanisms. A patient with relapsed/refractory p53-mutated DLBCL (transformed from FL) was successfully treated with daratumumab, venetoclax, GEMOX followed by anti-CD19 CAR-T cells [107]. Daratumumab has demonstrated synergistic antitumor activity when combined with ibrutinib and (R)-CHOP in *in vitro* and *in vivo* models of PBL, WM, MCL, FL, and DLBCL [29, 30, 43]. The efficacy of daratumumab combined with ibrutinib is being evaluated in clinical trials for various B-cell malignancies, including treatment-naïve CLL (NCT03447808), relapsed/refractory CLL (NCT04230304), and WM (NCT03679624), and daratumumab combined with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH) is currently being tested for newly diagnosed PBL (NCT04139304) (**Table 2**). Combined treatment with daratumumab and a SUMOylation inhibitor TAK-981, which promotes IFN1-dependent macrophage and NK cell activation in a mouse syngeneic model bearing mouse A20 B-cell lymphoma tumor cells, significantly extended mouse survival, although daratumumab or TAK-981 monotherapy had a minimal effect on survival [108].

Novel therapeutic strategies

Anti-CD38 drug conjugates, immunotoxins, radioimmunotherapy, and bispecific T cell engager antibodies: Monoclonal antibodies exhibit excellent tumor cell-targeting capabilities; however, their cytotoxicity is often limited. To en-

Table 2. Clinical trials of CD38-targeted treatment for B-cell lymphomas

Clinical trial identifier	Status	Phase	Treatment	Patients	ORR	References
NCT02413489	Terminated	2	Daratumumab	R/R FL (n=16), DLBCL (n=15) and MCL (n=5)	12.5% in FL; 6.7% in DLBCL; 0% in MCL	PMID 30795996 [73]
NCT03187262	Completed	2	Daratumumab	R/R WM (n=13)	23%	PMID 33085756 [65]
NCT03769181	Terminated	1/2	Isatuximab + Cemiplimab	R/R cHL (anti-PD-1/L1 naive, n=18; anti-PD-1/L1 progressors, n=12), DLBCL (n=17), PTCL (n=11)	cHL: 55.6% in anti-PD-1/L1 naive and 33.3% in anti-PD-1/L1 progressors; DLBCL: 5.9%; PTCL: 9.1%	PMID 36251503 [95]
NCT04230304	Active, not recruiting	2	Daratumumab + Ibrutinib	R/R CLL		
NCT03447808	Active, not recruiting	1	Daratumumab + Ibrutinib	Symptomatic CLL		
NCT03734198	Recruiting	2	Daratumumab + Ibrutinib	R/R CLL with p53 dysfunction		
NCT04139304	Recruiting	2	Daratumumab + dose-adjusted EPOCH	PBL		
NCT03679624	Terminated	2	Daratumumab + Ibrutinib	WM		
NCT05907759	Recruiting	2	Daratumumab administered subcutaneously	PEL, PBL, MCD		
NCT04824794	Completed	1/2	GEN3014	R/R MM, DLBCL, AML		
NCT03125577	Unknown	1/2	Combination CAR-T therapy	B-cell malignancies		
NCT03754764	Unknown	1/2	CD38 CAR-T Cells	Relapsed B-cell ALL after CD19 CAR-T therapy		

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; cHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; FL, follicular lymphoma; MCD, multicentric Castleman disease; MCL, mantle cell lymphoma; MM, multiple myeloma; ORR, overall response rate; PBL, plasmablastic lymphoma; PEL, primary effusion lymphoma; PTCL, peripheral T-cell lymphoma; R/R, refractory or relapsed; WM, Waldenström's macroglobulinemia.

hance antitumor efficacy, antibody-drug-conjugates (ADCs) couple monoclonal antibodies with cytotoxic drugs by a linker. Currently, three ADCs, brentuximab vedotin (BV, anti-CD30), polatuzumab vedotin (Pola, anti-CD79), and loncastuximab tesirine-lpyl (Lonca, ZYNLONTA™, anti-CD19), have been approved by the FDA for the treatment of various types of lymphomas [109]. In contrast, CD38-directed ADCs are still under development. In a preclinical proof-of-concept study, anti-CD38 daratumumab-polymer-conjugated doxorubicin demonstrated significantly better anti-lymphoma efficacy than anti-CD20 rituximab and anti-CD19 conjugated doxorubicin in CD20-negative NHL xenograft models, whereas three types of ADCs showed similar efficacy in an untreated $CD20^+$ MCL xenograft model [110]. The *in vivo* anti-lymphoma efficacy of anti-CD38 ADCs was mainly mediated by targeted drug delivery to the tumor rather than immunologic mechanisms of action [110]. The same study group also developed another anti-CD38 conjugate with a different payload, the microtubule inhibitor monomethylauristatin E (MMAE, a component of vedotin), showing enhanced anti-lymphoma efficacy compared to standard ADCs in a BL xenograft model [111].

Saporin and other ribosome inactivating proteins, which are potent toxins after entering the cell, have also been coupled to anti-CD38 monoclonal or bispecific antibodies, referred to as immunotoxins, and have shown great efficacy in myeloma and lymphoma cells *in vitro* and *in vivo* [112, 113]. Their efficacy could be further augmented by the small-molecule triterpenoid saponin [114]. Anti-CD38-saporin immunotoxins prolonged the survival of the BL mouse model (but eventually all mice succumbed to disease) and showed synergy with anti-CD19 immunotoxins [115]. However, no clinical trials were for anti-CD38-saporin. In a phase 1 clinical trial, anti-B4-blocked ricin (to reduce the toxicity of normal hematopoietic progenitors in the bone marrow) showed an 8.8% of ORR with tolerable reversible toxicity [116], and rendered no sustained clinical response in 16 patients with relapsed NHL in a phase 2 clinical trial [117].

Radioimmunotherapy (RIT) with radioisotope-labeled monoclonal antibody conjugates to metal chelators selectively delivers radiation to tumor cells, as exemplified by anti-CD20 RIT (Zevalin and Bexxar) approved for relapse/refractory NHL [118, 119]. CD38-specific RIT has been investigated at the preclinical stage in B-cell lymphoma models. $^{89}Zr/^{177}Lu$-labeled daratumumab facilitated immunoPET imaging (by ^{89}Zr, as did ^{64}Cu-labeling [120]) and RIT (by ^{177}Lu) of lymphoma in preclinical $CD38^+$ BL and DLBCL models, and significantly enhanced tumor growth inhibition compared with daratumumab [121]. Addressing the immunogenicity and endogenous biotin blocking issues associated with RIT, bispecific anti-CD38 × anti-^{90}Y-labeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid [Y-DOTA] antibody-mediated RIT induced 100% complete remission in lymphoma xenograft models of multiple myeloma and BL and ultimately cured 80% of the mice [122].

Bispecific T cell engagers (BiTEs) are bispecific antibody conjugates that recognize certain tumor-associated antigens and recruit $CD3^+$ T cells to kill tumor cells. For example, Blinatumomab, a CD19 BiTE approved for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) [123], and Epcoritamab, a CD20 BiTE approved for B-cell NHL, including DLBCL [124]. Currently, anti-CD38 × CD3 bispecific antibodies have only been investigated in multiple myeloma models *in vitro* and *in vivo* [125].

Like CD3 antibodies, antibodies targeting macrophages can also be conjugated with anti-CD38 antibody. A CD38/CD47 bispecific antibody demonstrated high antitumor efficacy in BL *in vitro* [126]. A bispecific antibody comprising a SIRPα decoy domain and a CD38-targeting arm stimulated robust anti-tumor responses in multiple xenograft models of aggressive B-cell lymphomas [127].

CD38-directed CAR-T cell therapy: CAR-T cell therapy uses CAR expressed by genetically modified T cells to target antigens via antibody specificity and to kill tumor cells via T cell cytotoxicity. Among all CAR-T cell therapies developed to treat hematologic malignancies, anti-CD19 CAR-T cell therapies have shown high efficacy in heavily treated B-cell malignancies [2, 3]. Despite the high clinical response to anti-CD19 CAR-T cell therapies, long-term PFS remains limited to 30-40% in relapsed/refractory patients with aggressive B-cell lympho-

mas following CD19-targeted CAR-T cell therapy. The causes of relapse in the rest of (approximately 60%) patients include loss or downregulation of CD19 antigens by trogocytosis [128], tumor cell escape [129], diminished persistence of CAR-T cells, and immunosuppression [130].

CD38 can be an alternative target to overcome the resistance due to loss of CD19 expression. An *in vitro* study by Mihara et al showed that both anti-CD38 CAR-T cells and anti-CD19 CAR-T cells (generated from peripheral blood mononuclear cells of donors) effectively eradicated primary DLBCL/HGBL-DH cells at an effector:target ratio of 1:2 for three days, and that these two types of CAR-T cells exerted synergistic cytotoxicity at lower effector:target ratios [131]. In the early development stage of CAR-T cell therapy, inspired by the clinical promise shown in NHL [132], this Japanese group initiated a preclinical anti-CD38 CAR-T cell study in $CD38^+$ B-cell lymphoma models. They first transduced a $CD38^{-/low}$ T cell line with an anti-CD38 (patented single-chain variable fragment) CAR-containing vector, which demonstrated powerful cytotoxicity and eliminated over 95% of $CD38^+$ B-cell lymphoma cell lines and primary cells *in vitro*. However, the generation of anti-CD38-CAR-T cells using human peripheral T cells was successful only when they simultaneously added anit-CD38 antibodies to block T cell autolysis (because activated T cells strongly express CD38), facilitating T cell expansion and the ability to eradicate lymphoma cells *in vitro* and *in vivo* [133].

In contrast, a recent USA study [134] showed that $CD38^+$-expressing anti-CD38-CAR T cells were protected from self-lysis, and that their expansion and antigen-specific effector functions were not impaired by CD38 expression. However, this study indeed found that anti-CD38 CAR-T therapy resulted in a reduction in $CD34^+CD38^+$ progenitors in a xenograft model of normal human hematopoiesis, and suggested caution and monitoring of on-target, off-tumor toxicity in the clinic [134]. In another USA study, a rapid expansion protocol was adopted to achieve 80-100 fold expansion, and the resultant anti-CD38-CAR T cells acquired a $CD38^{low}$ phenotype [18].

Similar self-lysis protection by CAR was also observed in another USA study on anti-CD38-CAR NK cells and $CD38^{KO}$/CD38-CAR NK cells using isatuximab-derived anti-CD38 single-chain variable fragments, which were fratricide-resistant regardless of their surface CD38 expression, and showed potent cytotoxicity toward $CD38^+$ lymphoma, including BL, leukemia, and myeloma [135]. Steric hindrance through cis interactions masking CD38 epitopes has been proposed to explain protection from self-targeting [135], and variations in CAR designs have been proposed to explain the discrepancy in different studies [134]. In contrast, a Chinese study group used blocking antibodies and proteins that block CD38 and the CAR single-chain variable fragment domain on activated $CD38^+$ T cells, respectively, during anti-CD38 CAR-T cell manufacturing, to inhibit fratricide while promoting CAR-T cell expansion and enrichment [136]. In one patient with relapsed B-ALL after the failure of bispecific CD19/CD22 CAR-T cell therapy, anti-CD38 CAR-T cell therapy demonstrated potent antitumor efficacy; however, the toxicity of CAR-T cells (fever and cytokine release syndrome) could not be ameliorated by medications [137]. Moreover, although anti-CD38 CAR-T cells significantly decreased $CD38^+$ B-ALL cells, the number of CAR-T cells in the peripheral blood declined to close to the baseline within 10 days [137], suggesting that the safety and persistence of anti-CD38 CAR-T cells need to be improved.

Such tumor non-specificity, toxicity, and limited expansion/persistence of anti-CD38-CAR-T cells may have hindered the application of anti-CD38 CAR-T cell therapy, although it is at least as effective *in vitro* and *in vivo* as current immunotherapies for AML, ALL, multiple myeloma, and NK/T-cell lymphoma [134, 138]. To overcome the non-tumor targeting issues of anti-CD38 CAR-T cells for safe clinical application, Drent *et al* developed multiple strategies and tested them in multiple myeloma models, including (i) incorporating a tetracycline-controlled Tet-on/off "switch" regulated by the administration or withdrawal of low doses of tetracycline derivative doxycycline (**Figure 5**) [139], (ii) reducing anti-CD38 affinity to generate anti-CD38-CAR-T cells that can effectively lyse CD38-high tumor cells but spare CD38-low healthy cells [140], and (iii) introducing an inducible caspase-9-based suicide gene as a safety switch to control anti-CD38-CAR-T cells [141, 142]. Moreover, CD38 expression heterogeneity in B-cell lymphoma tumors (compared

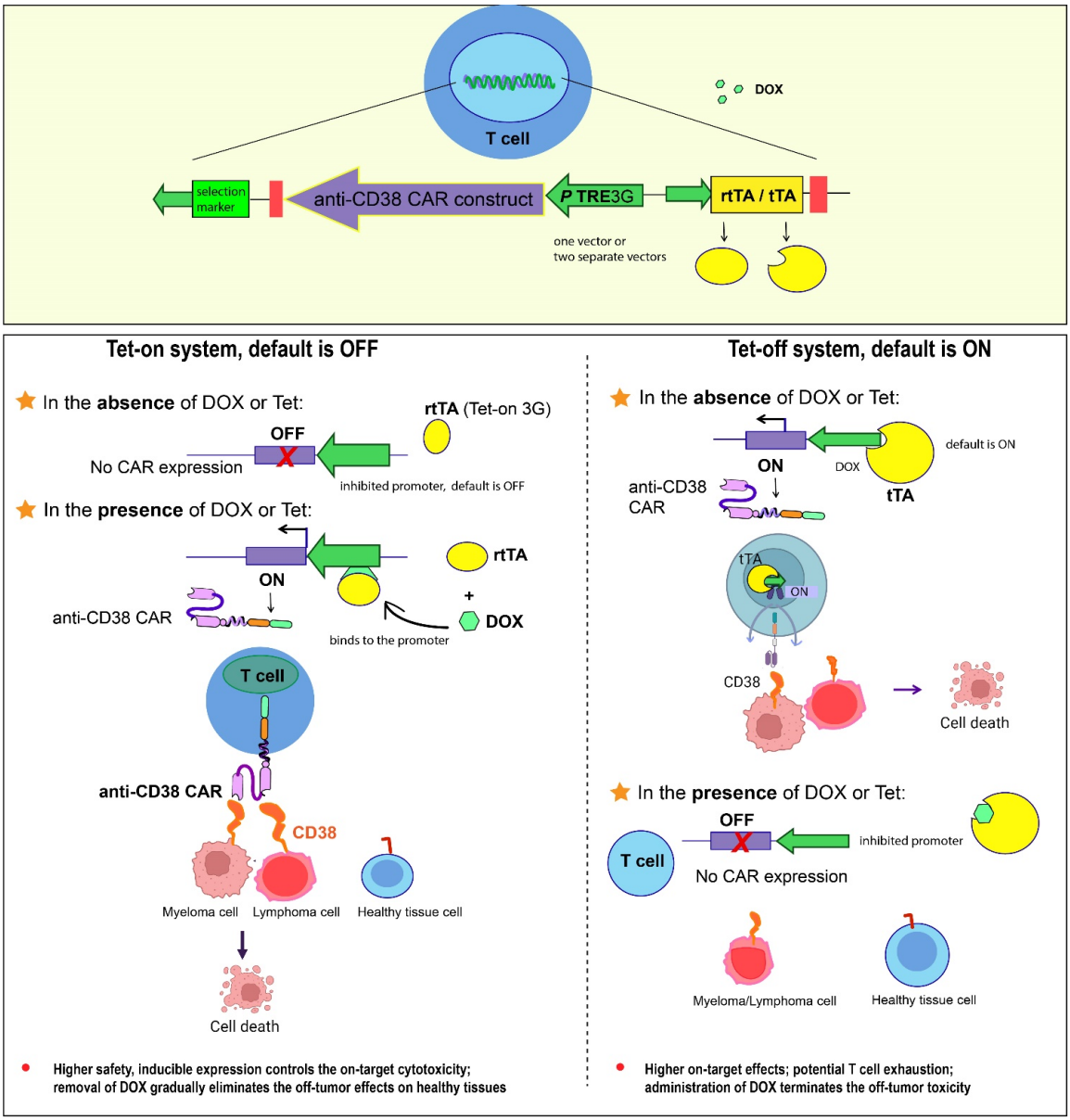

Figure 5. Illustration of tetracycline-controlled Tet-on/off switch for controlling the expression and activity of CAR-T cells. The expression of anti-CD38-CAR construct after retroviral transduction is put under the regulation of a third generation tetracycline (Tet)-response element promoter (*P*TRE3G) containing an array of Tet-operator sequences, inducible by binding of a transactivator protein. In the Tet-on system, the default mode is OFF and the reverse Tet transactivator protein (rtTA) is inactive, unable to bind to the *P*TRE3G promoter in the absence of tetracycline or derivatives like doxycycline, thus no CAR expression is detectable. Upon doxycycline administration, the binding of doxycycline activates the rtTA. Subsequently, the doxycycline-bound transactivitor binds to the *P*TRE3G promoter and transactivates the expression of CD38-CAR construct; high levels of CAR expression are detected. In contrast, in the Tet-off system with a Tet-controlled transcriptional activator (tTA), the default mode is ON in the absence of doxycycline. Binding of Tet or doxycycline at high dose induces a conformation change of tTA which prevents its binding to the *P*TRE3G promoter. Abbreviations: CAR, chimeric antigen receptor; DOX, doxycycline; *P*TRE3G, third-generation Tet response element promoter; rtTA, reverse Tet transcription activator fusion protein.

to the expression uniformity in multiple myeloma) is an additional cause of low anti-CD38-CAR-T therapy. ATRA can increase CD38 expression and enhance the antitumor activity of anti-CD38-CAR-T cells as shown in a MCL xenograft model [18].

Data on anti-CD38 CAR-T trials in B-cell lymphomas are currently unavailable. To date, reported clinical trials of CD38-directed CAR-T therapy include only one phase I/II clinical trial in AML [143] and two phase 1 trials of bispecific BCMA/CD38 CAR-T cells in relapsed/refractory multiple myeloma [144, 145].

Small-molecule inhibitors: The enzymatic activities of CD38 implicated in tumor cell proliferation and signaling can be directly targeted by small-molecule inhibitors. Many compounds have been reported to have CD38 inhibitory activity, which can be categorized into covalent (all NAD analogs) and non-covalent or reversible (mostly heterocyclic compounds and flavonoids) inhibitors [146]. Kuromanin is a natural flavonoid (anthocyanin) inhibitor that reversibly binds to CD38 and forms hydrophobic interactions with Trp125 and Trp189 as well as Trp125, Lys129, Asp155, Asp156, and Glu226 residues to inhibit its enzymatic function [147]. Targeting the enzymatic activity of CD38 with kuromanin results in CLL cell apoptosis and downregulation of BCR-associated proteins, mimicking the attenuation of BCR signaling by daratumumab [29], and disrupts CLL cell chemotaxis, adhesion, and homing to the bone marrow and spleen *in vivo*, thereby increasing the efficacy of chemotherapy against CLL cells trapped in the blood of a xenograft mouse model [28]. Combined kuromanin and ibrutinib treatment induces significantly higher apoptosis in CLL cells than either agent alone [29]. In addition, small-molecule CD38 inhibitors generally exhibit non-CD38 functions and off-target effects. Consequently, no clinical trial data on small-molecule inhibitors of CD38 have been reported yet.

Conclusions

CD38 is expressed in various subtypes of B-cell lymphoma and implicated in the pathogenesis and progression of lymphoma. Through its enzymatic activity, receptor roles, and regulation of signaling pathways, CD38 plays crucial roles in cellular proliferation and immune evasion in B-cell lymphomas, underscoring its importance as a therapeutic target. However, clinical trials of CD38 antibody-based immunotherapies have only shown limited efficacy in most B-cell lymphoma types, which could be attributed to the low cellular levels and heterogeneous CD38 expression among lymphoma and non-tumor cells, CD38's diverse functional roles, and resistance mechanisms counteracting antibody actions. Nonetheless, CD38 has the potential to become a therapeutic target alternative to CD19/CD20 when conventional treatments fall short, and combination therapy strategies and innovative strategies to optimize CD38-directed CAR-T cell therapies (regarding both toxicity and therapeutic effectiveness) may improve the clinical outcomes of relapsed/refractory patients. Particularly, for CD20-negative lymphomas without established regimens, CD38-targeted therapy is promising as an optimal treatment option.

Disclosure of conflict of interest

None.

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