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Advancing the Frontier of Immunotherapy in Diffuse Large B-Cell Lymphoma: A Comprehensive Review of Emerging Targets and Multi-Target Strategies

Haolan Ji

Health Science Center, Peking University, Beijing, 100191, China

2210122713@stu.pku.edu.cn

Abstract

Despite advances with R-CHOP and CD19 CAR-T, many patients develop resistance through antigen escape and immunosuppression. Promising novel targets include CD37, ROR1, CD79b, CD70-CD27, and BAFF-BAFFR axes. Bispecific antibodies, antibody-drug conjugates, and multi-target CAR-T therapies demonstrate enhanced efficacy by overcoming tumor heterogeneity. Future DLBCL management will likely integrate these multi-target approaches with conventional therapies, tailored to molecular profiles for improved outcomes in refractory disease.

Keywords

Diffuse large B-cell lymphoma (DLBCL); Immunotherapy; CAR-T cell therapy; Bispecific antibodies; Antibody-drug conjugates (ADCs); CD37; ROR1; CD79b; CD70-CD27 axis; BAFF-BAFFR axis; Multi-target therapy; Tumor microenvironment.

1. DLBCL

1.1. Introduction

B-cell lymphomas represent a heterogeneous group of malignancies originating from B lymphocytes. Based on the WHO classification system, B-cell neoplasms are categorized into distinct entities: B-cell-derived tumor-like lesions, precursor B-cell neoplasms (B-lymphoblastic leukemia/lymphoma), mature B-cell neoplasms, plasma cell disorders, and paraproteinemia-associated conditions. Among mature B-cell neoplasms, the spectrum encompasses both preneoplastic conditions and neoplastic proliferations, including chronic lymphocytic leukemia (CLL), various subtypes of non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma [1].

diffuse large B-cell lymphoma (DLBCL) represents the most prevalent subtype of NHL, comprising approximately 25-30% of NHL cases. Clinically, patients typically present with rapidly enlarging nodal or extranodal masses, often accompanied by systemic symptoms that may progress with disease dissemination. DLBCL exhibits both nodal and extranodal involvement, with extranodal disease observed in up to 40% of cases. The gastrointestinal tract (particularly stomach and ileum) constitutes the most frequent extranodal site, though DLBCL may manifest in virtually any extranodal location, including the skin, central nervous system, bone, testes, soft tissues, parotid glands, lungs, female genital tract, liver, kidneys, spleen, and Waldeyer's ring. Notably, primary bone marrow involvement and/or leukemic presentation are uncommon in DLBCL.

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1.2. Classification

The latest World Health Organization (WHO) classification refines large B-cell lymphoma categories, with DLBCL, not otherwise specified (DLBCL, NOS) being the most common but highly diverse type. Gene expression profiling identifies two main DLBCL subtypes: germinal center B-cell-like (GCB) and activated B-cell-like (ABC), with about 10–15% of cases unclassifiable. Clinically, ABC-DLBCL has worse outcomes, with a 3-year progression-free survival (PFS) of 40–50% compared to 75% in GCB-DLBCL. Molecularly, ABC-DLBCL is defined by continuous B-cell receptor (BCR) signaling and NF-κB pathway activation, while GCB-DLBCL expresses germinal center markers like BCL6 and EZH2. Although immunohistochemical methods (e.g., Hans classifier) are used in practice to group cases into GCB and non-GCB categories, they only approximate gene expression results and have high misclassification risk. New molecular analyses, including mutational and copy number variation profiling, allow for classifications beyond cell-of-origin, which may better capture DLBCL diversity and support precision medicine [2].

2. CURRENT IMMUNOTHERAPY OF DLBCL

2.1. Rituximab

Rituximab, a chimeric anti-CD20 monoclonal antibody FDA-approved in 1997, remains a cornerstone of lymphoma immunotherapy by targeting CD20 on mature and malignant B cells, inducing cell death through complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and direct apoptosis. It enhances chemotherapy sensitivity in NHL by modulating immune responses, such as reducing IL-10 and increasing Raf-1 kinase inhibitory protein expression. The R-CHOP regimen has been the standard first-line therapy for DLBCL for over two decades, improving survival, though optimizations like R-miniCHOP for elderly patients and pola-R-CHP (replacing vincristine with polatuzumab vedotin) have shown efficacy, with the latter significantly reducing disease progression in untreated intermediate- and high-risk patients [3]. Despite this, 30–40% of DLBCL patients develop primary resistance or refractory disease, with the SCHOLAR-1 study reporting only a 26% ORR and median overall survival of 6.3 months for R/R cases. Resistance mechanisms include reduced CD20 expression via epigenetic silencing or post-translational changes, downregulation of MHC class II and costimulatory molecules, upregulation of PD-L1, intrinsic apoptosis resistance from Bcl-2 overexpression, and immunosuppressive tumor microenvironment factors like regulatory T cells and cytokines (IL-6, IL-17, TGF-β).

2.2. CD19 CAR-T

CAR T-cell therapy is a groundbreaking cancer treatment that uses genetically engineered T-cells to target tumor antigens. It involves modifying a patient's T-cells to express chimeric antigen receptors (CARs) that recognize CD19 on malignant B-cells, leading to T-cell activation and tumor cell destruction. Three anti-CD19 CAR T-cell therapies are approved for R/R DLBCL: axicabtagene ciloleucel (from the ZUMA-1 trial), tisagenlecleucel (from the JULIET study), and lisocabtagene maraleucel (from TRANSCEND-NHL-001). These therapies have shown durable responses and are now used earlier in treatment, supported by trials like ZUMA-7 and TRANSFORM/PILOT.

Despite success, about 60% of patients relapse. Resistance can occur due to CD19 loss on tumor cells, effects of the tumor microenvironment (e.g., TAMs, Tregs, MDSCs), or CAR T-cell exhaustion. CAR T-cell therapy can cause serious side effects, including cytokine release syndrome (CRS) and neurotoxicity (ICANS). CRS involves fever, low blood pressure, and organ problems due to cytokine release, managed with drugs like tocilizumab. ICANS can cause confusion, seizures, or other neurological issues. Early monitoring and care are crucial. Other

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challenges include limited access to specialized centers, T-cell dysfunction in patients, long production times (3–6 weeks), and the need for bridging therapy, which can affect outcomes [4].

2.3. Immune Checkpoint Inhibitors

Cancer cells use multiple strategies to evade immune detection and create an immunosuppressive tumor microenvironment (TME). Key mechanisms include: recruiting immunosuppressive cells like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs); reducing or losing tumor antigens; causing T-cell death or exhaustion; and secreting molecules that activate inhibitory immune checkpoints. The PD-1/PD-L1 pathway is particularly important: tumor cells with high PD-L1 can bind to PD-1 on T cells, inhibiting their activation, proliferation, and cytokine production. Similarly, CTLA-4 suppresses immunity by removing co-stimulatory molecules (CD80/CD86) from antigen-presenting cells, and LAG-3 blocks T-cell activation by competing with CD4 for MHC II binding. These pathways together create an immunosuppressive environment that promotes tumor growth and limits immunotherapy effectiveness [5].

The role of immune checkpoints in immune evasion has led to immune checkpoint inhibitors (ICIs) as a cancer treatment. Six antibodies targeting PD-1 (nivolumab, pembrolizumab, cemiplimab) or PD-L1 (durvalumab, atezolizumab, avelumab) are FDA/EMA-approved and under study in various cancers. However, PD-1 blockade with nivolumab showed limited benefit in R/R DLBCL. This resistance may be due to high PD-L1 expression in lymphoma cells, which varies by DLBCL subtype and correlates with disease progression. PD-L1 patterns could serve as prognostic and predictive biomarkers for ICI response, requiring more research to optimize patient selection.

3. INNOVATIVE TARGETS FOR DLBCL IMMUNOTHERAPY

3.1. CD37

(1) Structure, expression and physiological role

CD37 is a tetraspanin protein with four transmembrane domains, two extracellular loops, and a short cytoplasmic tail. It is highly expressed during B-cell development but absent in plasma cells, and present at low levels on T cells, NK cells, and monocytes. CD37 is found on the cell surface and in intracellular vesicles, suggesting a role in trafficking and antigen presentation [6]. CD37 interacts with other tetraspanins (e.g., CD53, CD81, CD82) and MHC class II molecules to form tetraspanin-enriched microdomains (TEMs). These networks act as scaffolds and may influence ion channels. CD37 binds to signaling proteins (e.g., PI3Kγ/δ, Lyn kinase, SHP-1), B-cell coreceptors (e.g., CD19, CD22), immune regulators, and structural proteins, regulating processes like antigen presentation, cell proliferation, and antibody production. It can also affect immune synapse organization by competing with other tetraspanins for MHC class II binding.

CD37 regulates key signaling pathways: it activates pro-survival pathways (e.g., PI3Kδ/p-Akt/p-GSK3β/β-catenin) and inhibits others (e.g., SHP-1/p-Akt/Foxo3 and SOCS3/Jak), balancing cell survival and death. In neutrophils, it controls adhesion and migration; in macrophages, it reduces IL-6 production. In T cells, CD37 modulates TCR signaling and migration. In B cells, it is crucial for survival, and its deficiency increases apoptosis in plasma cells and reduces IgG production. Tetraspanins like CD82 show varied roles, highlighting their complex immune regulation.

(2) Role in DLBCL

Emerging evidence positions CD37 as a critical negative regulator of B NHL tumorigenesis [7]. CD37-deficient mice demonstrate spontaneous development of germinal center-derived B-

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cell lymphomas in lymphoid organs, exhibiting significantly higher tumor incidence compared to Bcl2-transgenic models (50% vs 20%). This lymphomagenesis is mediated through constitutive activation of IL-6 signaling pathways [8]. Clinically, loss of CD37 expression in DLBCL patients correlates with IL-6 pathway activation and serves as an independent prognostic marker for inferior progression-free and overall survival. Interestingly, CD37 exhibits context-dependent tumorigenic functions, as evidenced by its elevated mRNA expression in acute myeloid leukemia (AML). The immunosuppressive BR1 cell subset (IL-10-secreting regulatory B cells) shows specific CD37 downregulation, suggesting a mechanism by which these tumor-promoting immune cells evade immune surveillance. CD37 may enhance rituximab's therapeutic efficacy through multiple mechanisms including ADCC potentiation, lipid raft-mediated signaling modulation, and promotion of sustained T-cell responses. Furthermore, as key organizers of extracellular vesicle biology, tetraspanins including CD37 are enriched on exosomal surfaces in metastatic cancers, where they participate in immune evasion through targeted vesicle trafficking - with the specific tetraspanin composition determining exosomal homing to recipient cells.

(3) Progress in CD37-based research

CD37 has re-emerged as a promising therapeutic target in B-cell malignancies, particularly for patients refractory to CD20-directed therapies, due to its role in the PI3K-Akt survival pathway [9]. Monoclonal antibodies like BI 836826, which enhances ADCC and induces apoptosis, demonstrated a 38% ORR in DLBCL when combined with gemcitabine/oxaliplatin in clinical trials (NCT01403948, NCT02624492), including one complete remission. Otlertuzumab (TRU-016) induces caspase-independent apoptosis and synergizes with anti-CD20 antibodies, achieving responses in 23% of CLL and NHL patients in a trial (NCT00614042). DuoHexaBody-CD37, a bispecific antibody improving avidity and hexamer formation for enhanced ADCC/ADCP, was evaluated in a phase 1/2 trial (NCT04358458) but discontinued. Antibody-drug conjugates such as AGS67E (with MMAE) induced CRs in 2 DLBCL patients in an early-phase trial (NCT02175433), while naratuximab emtansine (with DM1) achieved objective responses in 13% of NHL patients, including DLBCL subgroups (NCT01534715). Debio 1562 combined with rituximab showed a 44.7% ORR in R/R DLBCL, with 31.6% complete remissions (NCT02564744). Radioimmunoconjugates like 177Lu-tetulomab faced resistance in DLBCL trials but achieved a 61% remission rate in indolent NHL (NCT01796171). CD37-directed CAR-T therapies demonstrated superior cytotoxicity in DLBCL models, with a clinical trial (NCT04136275) reporting objective response in 4 of 5 patients (3 complete and 1 partial remission), though pancytopenia occurred in 3 cases, highlighting both efficacy and safety considerations. These advances position CD37 as a viable target for overcoming resistance in aggressive B-cell malignancies.

(4) Limitations

The current development of CD37-directed immunotherapies has primarily focused on CAR-T cell approaches and multi-targeting strategies, particularly combinations with CD19 and CD20. However, several critical considerations emerge when targeting CD37 for cancer immunotherapy. As CD37 has been identified as a negative regulator of B-cell lymphoma tumorigenesis, a key concern is whether anti-CD37 therapies might inadvertently select for CD37-deficient tumor clones with enhanced proliferative or metastatic potential. This potential for immune evasion warrants careful investigation in clinical applications. CD37 holds a unique position as the only tetraspanin currently being explored for therapeutic applications in humans, primarily due to its restricted expression pattern. Its expression is largely confined to mature B- and T-lymphocytes, with notably higher levels observed in malignancies derived from these cell types. However, CD37 cannot be considered a universal target for all B-cell malignancies. Its utility is limited by its absence during early B-cell differentiation stages and

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significantly reduced expression in plasma cells, rendering it ineffective for targeting ALL and multiple myeloma. This expression pattern underscores the importance of careful patient selection and diagnostic evaluation when considering CD37-targeted therapies. The current therapeutic landscape suggests that while CD37 shows promise for specific B-cell malignancies, particularly certain subtypes of NHL, its application requires careful consideration of tumor biology, potential resistance mechanisms, and precise patient stratification to maximize clinical benefit while minimizing the risk of adverse selection pressures on tumor populations.

Table 1. Clinical trials of immunotherapeutic agents targeting CD37 for the treatment of DLBCL

Drugs	Class	Mechanism	Study	Phase	Number	population	Results
BI 836826	mAb	IgG1, apoptosis induction, validated in the Ramos mouse model of human B-cell lymphoma	NCT01403948	Phase I	48	NHL	3 patients responded, 1 patient with DLBCL CR
			NCT02624492	Phase I	17	R/R DLBCL	In combination with gemcitabine and oxaliplatin, the ORR was 38%, including 2 (10%) CRs and 6 (29%) PRs.
Otlertuzumab	mAb	Targeting homodimers triggers caspase-independent cell death, ADCC	NCT00614042	Phase 1/1b	57 dose-escalation phase 26 Dose Extension Phase Receiving Treatment	CLL and NHL patients and did not include patients with DLBCL	19 cases (23%) PR
AGS67E	mAb	Complete human anti-IgG2 antibody, cell death, cell cycle alterations	NCT02175433	Phase I	50 (with 19 DLBCL pts)	Subjects with R/R lymphoid malignancies	7 CR (with 4 DLBCL) and 4 PR
Naratuximab emtansine (IMGN 529)	ADC	Microtubule disruptor DM 1-coupled humanized anti-CD 37 antibody	NCT01534715	Phase I	49-	R/R NHL	13% ORR and 22%ORR in DLBCL (1CR 3PR)
Debio 1562M	ADC	Coupling of naratuximab and DM1 derivatives	NCT02564744	Phase II	100	Patients with R/R DLBCL and other forms of NHL	In combination with rituximab, 44.7% ORR for 76 EE DLBCL pts with 31.6% CR and 13.2% PR. part 2, ORR was 50%
177Lu-tetulomab	ADC	Radiolabeled 177 Lu linked to anti-CD 37 antibody tetulomab	NCT02658968	Phase I	18--	Patients with R/R DLBCL	MTD, safety and tolerability, pharmacokinetics, biodistribution
			NCT01796171	Phase I/IIa	74	Patients with R/R inert NHL	The ORR was 61%, including 30% CR, and for patients with rituximab-refractory FL ≥2 prior therapy, the ORR was 67%, with a CR rate of 24%.
CD37 CAR- T	CAR-T	Production of Th1-type cytokines, cytotoxicity	NCT04136275	Phase I	5	Recurrent or refractory CD37+ hematologic malignancies	Antitumor response was observed in 4 cases, of which 3 cases were CR and 1 PR

3.2. ROR1

(1) Structure, Expression and Physiological Role

Receptor tyrosine kinase-like orphan receptor 1 (ROR1), a member of the receptor tyrosine kinase (RTK) family, is highly expressed during embryonic development, where it regulates cellular differentiation and organogenesis through precisely controlled activity. Structurally, human ROR1 contains an extracellular region with an immunoglobulin-like domain, two Frizzled-homologous cysteine-rich domains, and a Kringle domain, along with an intracellular

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region featuring a tyrosine kinase domain, a proline-rich domain, and two serine/threonine-rich domains. Its primary ligand, Wnt5a, engages ROR1 upon binding, with STAT3 serving as a key transcription factor for both ROR1 and Wnt5a expression. Similar to other RTKs, ROR1 dimerizes and autophosphorylates upon ligand interaction, activating non-canonical Wnt signaling pathways that promote cell survival via NF-κB, WNT/PCP, MAPK/ERK, and PI3K/AKT, while inhibiting apoptosis through p38-mediated FoxO downregulation. Functionally, ROR1 coordinates cell migration, intercellular communication, and intracellular signaling. The ROR family includes ROR1 and ROR2, which share 58% amino acid homology; ROR2 is constitutively expressed in most adult tissues, whereas ROR1 exhibits restricted expression in mature individuals. During B-cell development, ROR1 peaks at intermediate stages, such as large/small pre-BII and immature B cells, but becomes undetectable in mature B lymphocytes, underscoring its distinct roles in developmental versus mature contexts.

(2) Role in DLBCL

ROR1 demonstrates significant overexpression across various malignancies, encompassing both solid tumors (including lung and colorectal carcinomas) and hematologic neoplasms such as CLL, MCL, DLBCL and AML. This aberrant expression pattern correlates with unfavorable clinical outcomes and diminished therapeutic responses in multiple cancer types. Notably, ROR1 is frequently detected in primary refractory DLBCL, Richter transformation, and transformed follicular lymphoma, while showing reduced expression in relapsed DLBCL cases [10]. Experimental evidence confirms that ROR1 knockdown effectively suppresses DLBCL cell proliferation both in vitro and in vivo, establishing its potential as a therapeutic target. Elevated ROR1 expression at either mRNA or protein level has been consistently observed in substantial subsets of primary MCL, marginal zone lymphoma (MZL), DLBCL, and follicular lymphoma specimens.

ROR1 orchestrates multiple pro-tumorigenic processes through complex signaling networks, including maintenance of tumor cell survival, induction of cytoskeletal reorganization, promotion of cellular migration, stimulation of proliferation, and facilitation of epithelial-mesenchymal transition (EMT). The receptor's activity is mediated through several key pathways: Wnt5a-induced NF-κB activation via the Frizzled (FZD) receptor domain contributes to therapeutic resistance; PI3K/AKT signaling modulates EMT-related gene expression; and the Wnt5a/ROR1 axis engages with both BMI-1 and YAP/TAZ pathways to enhance proliferative capacity, drive tumor progression, and confer drug resistance. Notably, NF-κB activation leads to nuclear translocation of phosphorylated p65, which transcriptionally upregulates Wnt5a expression, establishing a positive feedback loop [11]. This autocrine signaling mechanism is further amplified by YAP/TAZ-mediated transcriptional activation, which concomitantly elevates ROR1 expression, thereby reinforcing the oncogenic signaling cascade.

(3) Research progress based on ROR1

The restricted expression profile of ROR1 makes it an ideal therapeutic target. Small molecule inhibitors KAN0441571C, which binds the intracellular tyrosine kinase domain, demonstrate promising efficacy in MCL and ibrutinib-resistant CLL models. The anti-ROR1 monoclonal antibody zilovertamab has shown clinical activity across multiple trials, with phase 1 studies (NCT02860676, NCT02222688) establishing its safety and mechanism of action in CLL, and in solid tumors (NCT02776917), where 38% of breast cancer patients achieved PR and another 38% maintained SD. Most notably, the combination with ibrutinib (NCT03088878) yielded impressive responses: MCL patients showed an 83% ORR comprising 33% complete remission (CR) and 50% PR, while CLL cohorts demonstrated an 88% ORR (92% in treatment-naïve and 86% in relapsed settings) with 3% CR and 85% PR rates, validating ROR1 as a viable target and highlighting the potential of combination approaches. The therapeutic landscape has expanded with ADCs such as zilovertamab vedotin (ZV), which combines an anti-ROR1 monoclonal

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antibody with monomethyl auristatin E (MMAE). Initial phase 1 trials (NCT03833180) in refractory hematologic malignancies showed promising activity, with ORRs of 47% in MCL (7 of 15 patients, including 3 CRs) and 60% in diffuse large B-cell lymphoma (DLBCL) (3 of 5 patients, including 2 CRs), and a favorable safety profile. Subsequent phase 2 trials further validated efficacy, with CR rates of 97.2% in treatment-naïve DLBCL patients receiving ZV plus R-CHP (NCT05406401), and an ORR of 30% in R/R DLBCL (NCT05144841) with durable responses. Ongoing trials include combinations with R-GemOx in R/R DLBCL (NCT05139017, phase 2/3), where the recommended phase 2 dose was 1.75 mg/kg, and ORRs were 27% (3 CR, 1 PR), 56% (8 CR, 1 PR), and 57% (3 CR, 1 PR) across cohorts, with median overall survival of 11.5 months, not reached, and 7.4 months, respectively, and 6-month overall survival rates of 70.0%, 78.8%, and 68.6%; with R-CHP/R-CHOP in frontline DLBCL (NCT06717347, phase 3, recruiting); and in pediatric/young adult patients (NCT06395103, phase 1/2, recruiting). Beyond ZV, other ROR1-targeted ADCs like LCB-71 (CS5001), featuring a PBD-based warhead, demonstrated a 50% ORR in DLBCL patients (1 CR and 2 PR among 6 evaluable patients) in its phase 1 trial (NCT05279300), with overall 2 CRs (1 Hodgkin lymphoma and 1 DLBCL) and 3 PRs (2 Hodgkin lymphoma and 1 pancreatic cancer) among 34 patients with post-baseline assessment, while NBE-002 was discontinued (NCT04441099), highlighting ROR1 as a validated target with ZV advancing to phase 3 testing. ROR1-directed CAR-T cell therapies have also emerged as a promising approach, with preclinical studies showing that CAR-T cells incorporating the R12 single-chain variable fragment effectively lysed CLL and MCL progenitor cells and exhibited favorable safety profiles in non-human primate models, selectively accumulating in ROR1-expressing B-cell niches without off-target toxicity. Clinical trials include ONCT-808, an autologous ROR1 CAR-T therapy, which in a phase 1/2 trial for R/R aggressive B-cell lymphoma (NCT05588440) achieved complete metabolic responses in two of three patients and one partial response, though development was subsequently discontinued. Ongoing investigations include PRGN-3007 in phase 1/1b testing for ROR1-positive hematologic malignancies and triple-negative breast cancer (NCT05694364), LYL797 for ROR1-expressing solid tumors (NCT05274451), and RD14-01 for R/R NHL and solid tumors (NCT05444322, NCT05748938). Earlier trials provided proof-of-concept, such as a phase I trial in triple-negative breast cancer (NCT02706392) reporting stable disease in two patients lasting 15-19 weeks.

(4) Limitations

The therapeutic potential of ROR1-targeted immunotherapies must be carefully balanced against potential on-target, off-tumor toxicity, given its expression in select normal adult tissues, including the parathyroid gland, pancreatic islets, and gastrointestinal tract (duodenum, esophagus, and stomach). While ROR1-directed therapies—including CAR-T cells, antibody-drug conjugates, and monoclonal antibodies—have demonstrated promising activity in B-cell malignancies, their applicability extends to solid tumors, broadening their clinical relevance. However, this expanded therapeutic scope also introduces challenges in ensuring tumor-selective targeting, as ROR1 expression in healthy tissues may limit the therapeutic window. Current clinical studies are actively exploring strategies to enhance specificity, such as fine-tuning antibody affinity, optimizing CAR-T cell persistence, and developing conditional activation systems to mitigate off-tumor effects. Additionally, biomarker-driven patient selection may help maximize efficacy while minimizing toxicity. As the field advances, a deeper understanding of ROR1 biology in both malignant and normal tissues will be crucial to refine these therapies and unlock their full potential across hematologic and solid malignancies.

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Table 2. Clinical Trials of Immunotherapeutic Drugs Targeting ROR1 for the Treatment of DLBCL

Drugs	Class	Mechanism	Study	Phase	Number	population	Results
Zilovertamab (cirmtuzumab)	mAb	Effective inhibition of ROR signaling pathway, ADCC	NCT02860676 NCT02222688	Phase I	--	CLL	--
			NCT02776917	Phase I	16	breast tumor	In combination with paclitaxel, 6 (38%) had a PR and 6/16 (38%) patients were stable.
			NCT03088878	I b/II	46 (with 12 MCL)	CLL/SLL, MCL and MZL	Combination with ibrutinib, MCL Efficacy: 83% ORR, 33% CR, 50% PR
LCB-71 (CS5001)	ADC	Coupling of huXBR1-402 and pyrrolobenzodiazepine pretoxin loads	NCT05279300	Phase I	49 (17 with lymphomas)	solid tumors and lymphomas	In pts with DLBCL, 1/6 patients achieved CR and 2 achieved PR, with an ORR of 50.0%.
Zilovertamab vedotin (ZV)	ADC	Targets the extracellular structural domain of ROR1 and couples with the anti-microtubule cytotoxin methyl eosin	NCT03833180	Phase I	32	Patients with MCL, CLL, DLBCL, Follicular Lymphoma, Marginal Zone Lymphoma, or Ricci Transformation Lymphoma	ORR was induced in 7 of 15 MCL (47%, 4 partial and 3 complete) and 3 of 5 DLBCL patients (60%; 1 partial and 2 complete).
			NCT05406401	Phase II	36	DLBCL not treated for disease	combination with R-CHP, 34 CR (94.4%)
			NCT05144841	Phase II	98	R/R DLBCL	ORR 29%, 10 CR, 13 PR, 10 SD
			NCT05139017	Phase II/III	40	R/R DLBCL	Combined R-GemOx, ORR was 27% (3 CR, 1 PR), 56% (8 CR, 1 PR), and 57% (3 CR, 1 PR), respectively.
			NCT06717347	Phase III	--	Untreated DLBCL	Combined R-CHP or R-CHOP, No results published
			NCT06395103	Stage I/II	--	Pediatrics/Young CLL, DLBCL	No results published
NBE-002	ADC	Anthracycline derivative PNU-159682 coupled to humanized recombinant IgG1 mAb	NCT04441099	Stage I/II	--	advanced solid tumor	Terminated
ROR1 CAR-T	CAR-T	Non-toxic to normal tissues, accumulates in sites with abundant ROR-1-positive B cells, such as bone marrow and lymph nodes.	NCT05588440	Stage I/II	3	R/R aggressive B-cell lymphoma	terminated, 2/3 patients complete metabolic response (CMR), 1/3 patient PR
			NCT02706392	Phase I	4	Triple-negative breast cancer (TNBC)	terminated, 2 patients were diagnosed as stabilized at 15 and 19 weeks.
			NCT02194374	Phase I	--	CLL	Withdrew
PRGN-3007 T cells	CAR-T		NCT05694364	Phase I / I b	--	ROR1-positive CLL, MCL, ALL, DLBCL, and TNBC with solid tumors	No results published
754 LYL797	CAR-T	Enhanced with genetic and epigenetic reprogramming techniques, strong proliferation, less depletion and stem cell-like properties	NCT05274451	Phase I	57	Advanced TNBC and Non-Small Cell Lung Cancer (NSCLC)	No results published
RD14-01	CAR-T		NCT05444322	Phase I	--	R/R B-cell NHL (MCL, DLBCL, FL)	No results published
			NCT05748938	Phase I	--	solid tumor	No results published

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3.3. CD79b

(1) Structure, Expression and Physiological Role

The B cell receptor (BCR) serves as the defining molecular complex of B lymphocytes, playing critical roles throughout B cell development and function. This transmembrane complex consists of membrane-bound immunoglobulin (mIg) non-covalently associated with the signaling heterodimer CD79a (Igα)/CD79b (Igβ). The BCR governs fundamental cellular processes including survival, activation, differentiation, and plasma cell transformation. The CD79a/CD79b heterodimer is structurally organized into three functional domains: an extracellular immunoglobulin-like domain, a transmembrane segment, and an intracellular signaling tail [12]. This essential signaling subunit undergoes phosphorylation by Src family kinases upon antigen engagement, initiating downstream BCR signaling cascades. The non-covalent association between the mIg antigen-recognition component and the CD79a/CD79b signaling module is crucial for both BCR surface expression and signal transduction capability.

The B cell receptor (BCR) coordinates a complex signaling network essential for B lymphocyte physiology. Antigen binding induces BCR aggregation, activating downstream cascades including PLC-γ2, PI3K/AKT, and MAPK pathways to mediate antigen capture, processing, and presentation, critical for B cell function as antigen-presenting cells. Beyond antigen-dependent activation, BCR generates constitutive tonic signals through sustained PI3K activity, vital for B cell development and survival. BCR signaling precisely regulates B cell fate decisions by suppressing plasma cell differentiation via Lyn-, PI3K-, BTK-, IKK2-, and JNK-dependent inhibition of Ets1 while controlling immunoglobulin class switch recombination through activation-induced cytidine deaminase (AID). Additionally, it modulates fundamental metabolic processes such as glycolysis, mitochondrial biogenesis, autophagy, and apoptosis. Central to these functions, the CD79a/CD79b heterodimer mediates survival signals through NF-κB and PI3K/AKT pathways and regulates BCR assembly and trafficking via glycosylation modifications. The signaling complex also interacts functionally with the BAFF receptor to coordinate antibody responses and participates in MHC class II-mediated signaling through Src family kinases and calcium mobilization, highlighting BCR's integral role in both innate and adaptive immune functions [13].

(2) Role in DLBCL

The B-cell receptor (BCR) is frequently retained on the surface of B-cell-derived tumors, where it contributes to malignant cell growth and survival across various lymphoma subtypes, including mantle cell lymphoma, follicular lymphoma, Burkitt lymphoma, and marginal zone lymphoma. In diffuse large B-cell lymphoma (DLBCL), pathogenic BCR signaling drives proliferation and sustains survival through constitutive or antigen-dependent activation, with genetic alterations and microenvironmental cues amplifying this signaling to reinforce lymphomagenesis and disease progression [14]. BCR signaling operates through two distinct modes: antigen-dependent and antigen-independent. In antigen-dependent signaling, BCR engagement with self-antigens such as apoptotic cell debris or glycans triggers chronic NF-κB activation, promoting tumor growth, particularly in activated B-cell-like (ABC) DLBCL, where most cases retain IgM expression due to impaired class switch recombination. In contrast, antigen-independent tonic BCR signaling supports malignant B-cell survival through constitutive PI3K/AKT/FOXO1 pathway activation, which is more common in germinal center B-cell-like (GCB) DLBCL. These divergent signaling patterns highlight the biological differences between ABC and GCB subtypes and rationalize tailored therapeutic interventions, such as BTK inhibitors for ABC-DLBCL and PI3K/AKT pathway inhibitors for GCB-DLBCL [14].

Genetic alterations further modulate BCR signaling, with CD79B mutations occurring in 4–23% of B-cell malignancies and being most prevalent in ABC-DLBCL (up to 30% of cases). These mutations, often affecting the immunoreceptor tyrosine-based activation motif (ITAM) domain,

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impair BCR endocytosis, increase surface BCR expression, and promote antigen-independent clustering, sustaining NF-κB activation while suppressing negative feedback. CD79B mutations frequently co-occur with MYD88 alterations, particularly the MYD88 L265P variant, which is common in primary central nervous system lymphoma and primary testicular lymphoma. This co-mutation facilitates the formation of the MYD88-TLR9-BCR supercomplex, driving constitutive NF-kB and mTOR signaling and representing a distinct molecular pathway in lymphomagenesis independent of high-grade translocations. Clinically, CD79B dysregulation is associated with therapeutic resistance, such as ibrutinib resistance in ABC-DLBCL, underscoring its role as a critical regulator and potential therapeutic target in B-cell malignancies [15].

(3) Advances in CD79b-based research

The development of CD79b-targeted ADCs marks a major advance in treating B-cell malignancies. Polatuzumab vedotin, the leading CD79b ADC, combines an IgG1 mAb with MMAE via a cleavable linker. After CD79b binding, the ADC is internalized and processed in lysosomes, releasing MMAE to disrupt microtubules and trigger apoptosis. Approved in 2019 for R/R DLBCL, it remains the only FDA-approved CD79b therapy [16]. Another candidate, DCDS0780A, uses a humanized anti-CD79b IgG1 (MCDS0593A) also linked to MMAE. A phase 1 trial (NCT02453087) in 60 NHL pts showed 47% ORR (17 CR, 11 PR), though 54 pts experienced TRAEs, underscoring the need for toxicity monitoring. These ADCs demonstrate successful translation of BCR pathway targeting, with polatuzumab establishing CD79b as a validated target in aggressive lymphomas. Current research focuses on optimizing ADC designs and combo strategies for R/R disease.

The breakthrough in ADC has spurred interest in developing next-generation CD79b-directed therapies, particularly chimeric antigen receptor (CAR) T-cell approaches. Unlike CD19-targeted CAR-T cells, CD79b-directed CAR-T therapies offer a potential solution to CD19 antigen escape—a common resistance mechanism in B-cell malignancies—since CD79b surface expression remains unaffected by CD19 downregulation. Preclinical studies have demonstrated that anti-CD79b CAR-T cells, whether as single-target agents or in combination with CD19-targeting scFvs, effectively recognize and eliminate CD19-negative lymphoma cells [17]. This dual-targeting strategy may provide broader antigen coverage and reduce relapse risks. Currently, several CD79b-specific CAR-T cell products are undergoing early-phase clinical evaluation, including a CD79b CAR-T trial for R/R NHL and ALL (NCT04609241) and JV-213 for R/R B-cell lymphomas (NCT05773040). While preliminary results from these studies remain pending, the therapeutic rationale builds upon the established role of CD79b in B-cell receptor signaling and its consistent expression across B-cell malignancies. The parallel development of CD79b-targeted ADCs and CAR-T cells reflects a multifaceted approach to overcoming treatment resistance in aggressive lymphomas. As clinical data mature, these therapies may offer new options for patients who have failed conventional CD19-directed immunotherapies, potentially reshaping the treatment landscape for R/R DLBCL [18].

The therapeutic landscape for CD79b/MYD88-mutant DLBCL is expanding with several tyrosine kinase inhibitors under clinical investigation. Zanubrutinib, a next-generation BTK inhibitor (NCT05068440), is being evaluated alongside studies of rituximab combinations (NCT04668365: 12 TN pts and 9 R/R pts had been evaluated for response. There were 10 CRs (83.3%) and 2 PRs (16.7%) in the TN cohort; 5 CRs (55.6%), 2 PRs (22.2%), and 2 PDs (22.2%) in the R/R cohort) and the SYK inhibitor mivavotinib (NCT05319028: 43 patients were enrolled, and there were 5 CR (4 with incomplete count recovery). The development reflects a growing precision medicine approach to disrupt the CD79b/MYD88-mediated survival signals that drive NF-κB activation and lymphoma progression. By specifically targeting these oncogenic

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pathways, these inhibitors may offer improved therapeutic options for patients whose tumors harbor these genetic alterations [19].

Table 3. Clinical Trials of Immunotherapeutic Drugs Targeting CD79b for the Treatment of DLBCL

Drugs	Class	Mechanism	Study	Phase	Number	population	Results
Polatuzumab	mAb	gg1, apoptosis induction, ADCC	NCT0327 4492 (pivotal)	FDA approval in 2019 Phase III	879	R/R DLBCL who have received at least 2 previous therapies	The risk of progression, relapse, or death was lower in the pola-R-CHP group than in the R-CHOP group (stratified hazard ratio, 0.73)
Polatuzumab vedotin	ADC	Coupling of the mitotic inhibitor monomethyl auristatin E (MMAE) with Polatuzumab	NCT0418 2204 (pivotal)	FDA approval in 2019 Phase III	270	Adult patients with R/R DLBCL	Overall survival was 19.5 months with polatuzumab vedotin plus R-GemOx
DCDS0780A	ADC	Humanized IgG1 anti-CD79B monoclonal antibody coupled to MMAE (MCDS0593A) Composition	NCT0245 3087	Phase I	60	NHL	The response rate was 47% (n = 28), including 17 complete and 11 PRs.
CD79b CAR-T	CAR-T	Aligns with CD19 scFv alone or in a dual-targeted format to recognize CD19-negative lymphoma B cells	NCT0460 9241	Phase I	--	R/R's NHL as well as ALL	No results published
JV-213	CAR-T		NCT0577 3040	Phase I	--	R/R B-cell lymphoma	No results published

3.4. CD70-CD27 Axis

(1) Structure, expression and physiological role

The CD27-CD70 axis is a critical component of the T cell co-stimulatory network, where CD70, a type II transmembrane glycoprotein of the TNFSF, interacts with its receptor CD27, a TNFRSF member with cysteine-rich domains forming disulfide-linked homodimers. CD27 mediates signaling through TRAF adaptor proteins (TRAF2, TRAF3, TRAF5), activating NF-κB and c-Jun kinase pathways. CD70 exhibits restricted expression in normal tissues but frequent dysregulation in malignancies, underpinning its appeal as a therapeutic target in hematologic and solid tumors [20]. CD70 is selectively expressed on immune cells including Tregs, B cells, T cells, DCs, and NK cells, while CD27 shows graded expression in lymphoid tissues and is constitutive on naïve and memory T and B cells, with downregulation in CD8+ T cells potentially contributing to T cell exhaustion. Membrane-bound CD70 activates CD27 via oligomerization, delivering co-stimulatory signals that drive T cell activation, survival, proliferation, and cytokine production (e.g., IL-2, IFNγ), promote Th1 differentiation, inhibit Th17 development, and modulate Treg-mediated immunosuppression. This axis also regulates T-dependent B cell responses, plasma cell differentiation, and germinal center formation [21], enhances NK cell proliferation, IFNγ production, and cytotoxicity [22], and facilitates CD70 reverse signaling through PI3K/Akt and MEK pathways to influence cell expansion and effector functions. Although CD27 can induce apoptosis via Siva, this mechanism remains poorly characterized [23].

(2) Role in DLBCL

CD70 demonstrates significant overexpression across diverse malignancies, including renal cell carcinoma, cervical squamous cell carcinoma, mesothelioma, and hematologic cancers such

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as DLBCL, where co-expression with CD27 on malignant B cells correlates with poorer treatment outcomes and higher Epstein-Barr virus infection rates [24, 25]. Paradoxically, somatic CD27 or CD70 mutations or deletions also increase susceptibility to lymphomas like DLBCL and Hodgkin lymphoma, underscoring the pathway's complex role in lymphomagenesis [26]. Tumor-derived CD70 engages CD27 on T cells, triggering cleavage into soluble CD27 (sCD27), which impairs costimulatory signaling and promotes immunosuppression by reducing membrane-bound CD27 and neutralizing CD70. Elevated sCD27 levels serve as a prognostic biomarker in acute myeloid leukemia and NHL. This axis drives oncogenic processes including proliferation via MEK/AP-1 and Wnt/β-catenin signaling, metastasis through epithelial-mesenchymal transition, and cancer stemness, while facilitating drug-tolerant persistent cells in non-small cell lung cancer and acute myeloid leukemia [27]. Reverse signaling through CD70 modulates malignant cell proliferation and apoptosis by regulating Bcl-2 family proteins, with context-dependent outcomes such as NF-κB-mediated pro-apoptotic effects. Immunologically, the CD70-CD27 axis promotes immunosuppression in tumor microenvironments by downregulating pro-apoptotic Noxa, upregulating anti-apoptotic Bcl-2, enhancing regulatory T cell proliferation, depleting NK cells, and inducing CD8+ T cell exhaustion characterized by PD-1 and TIM-3 upregulation. Therapeutic CD70 blockade can reverse these effects, restoring CD27 expression and rescuing T cell function, highlighting its potential in cancer immunotherapy.

(3) Research progress based on CD70-CD27 axis

CD70-targeted therapies encompass multiple modalities, including antibody-drug conjugates (ADCs), monoclonal antibodies, CAR-T cells, combination strategies, and vaccine adjuvants. In ADCs, SGN-75 (NCT01015911) demonstrated antitumor activity in CD70-positive NHL and metastatic RCC, with 1 CR and 3 PRs in 20 patients, though it was not advanced for NHL. MDX-1203 (NCT00944905) achieved disease stabilization in 69% (18/26) of RCC and NHL patients. SGN-CD70A (NCT02216890) induced 1 CR and 3 PRs in DLBCL and RCC, with two responses lasting ≥42.9 weeks, but severe thrombocytopenia limited development.

The anti-CD70 monoclonal antibody cusatuzumab reduces leukemic stem cells and promotes myeloid differentiation/apoptosis in AML, with Phase 1/2 trials (e.g., NCT03030612) exploring combinations like venetoclax ± azacitidine. SEA-CD70, a novel agent, is in Phase 1 evaluation for myeloid malignancies (NCT04227847).

CD70-directed CAR-T cells are under investigation in 29 Phase 1/1/2 trials. In solid tumors, one RCC trial (NCT04438083) reported durable responses, including a CR lasting >18 months and a 76.9% disease control rate. For hematologic malignancies, a T-cell lymphoma trial (NCT04502446) showed a 46% ORR (6 CRs, 10 PRs in 39 patients), but responses in B-cell malignancies like DLBCL remain limited. CD70 CAR-NK cells are entering Phase 1 trials for T-cell lymphoma, AML, and ALL (NCT06696846).

Combination approaches include imatinib, which epigenetically upregulates CD70 via SP1 induction and DNMT1 downregulation, enhancing CD70 expression and Wnt activation in CML. CD27 agonism independently promotes T-cell proliferation and expands tumor-infiltrating lymphocytes without MAPK/AKT/mTOR pathway involvement, enabling synergistic targeting. The CD27 agonist varlilumab was evaluated in Phase 1 monotherapy (NCT01460134) for CD27-positive B-cell lymphomas (including DLBCL), achieving 1 PR with 77% tumor reduction and 3 SD cases. In a Phase 2 trial with nivolumab (NCT03038672), R/R aggressive B-cell lymphoma patients had a 12.5% ORR (4 CRs in 48 evaluable patients) [28, 29].

As a vaccine adjuvant, CD27 costimulation enhances CTL responses. Varlilumab combined with DC vaccines (NCT03688178) or peptide vaccines (NCT03617328, NCT02924038) boosted peripheral T-cell immunity in glioblastoma and melanoma, though tumor microenvironment effects were limited [27, 30]. These findings underscore CD70's therapeutic potential while highlighting the need for optimized strategies to address efficacy and toxicity challenges.

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(4) Limitations

Table 4. Clinical Trials of Immunotherapeutic Drugs Targeting CD70 for the Treatment of DLBCL

Drugs	Class	Mechanism	Study	Phase	Number	population	Results
SGN-75	ADC	Humanized anti-CD70 IgG1 monoclonal antibody backbone chemically coupled with microtubule disrupting agent MMAF	NCT01015911	Phase I	58	Renal cell carcinoma and NHL	Demonstrated moderate efficacy CD70-positive NHL or patients with re-metastatic RCC, not recommended with NHL
MDX-1203	ADC	IgG1 monoclonal antibody (MDX-1115) conjugated to the alkylating small drug molecule MED-2460 or duocarmycin	NCT00944905	Phase I	26	Clear cell renal cell carcinoma (ccRCC) and NHL	18 (69%) had the best response to stabilization without any significant correlation to the dose administered
AMG 172	ADC	Improved development of conjugated SGN-70A, a pyrrolobenzodiazepine (PBD) dimer coupling targeting CD70	NCT02216890	Phase I	20	DLBCL, renal cell carcinoma	1 CR and 3 PRs, 2 of which lasted at least 42.9 weeks
Cusatuzumab	mAb	Enhanced ADCC activity reduces leukemic stem cells (LSC) and triggers gene signatures associated with myeloid differentiation and apoptosis apoptosis	NCT04241549 NCT04023526 NCT04150887 NCT03030612	Stage I/II	--	AML	--
			NCT04241549 NCT04264806 NCT03030612	Stage I/II	--	High-risk myelodysplastic syndromes (MDS)	--
			NCT04264806	Stage I/II	--	CMML	--
			NCT06384261	Phase II	--	AML	Recruiting
SEA-CD70	mAb	Humanized, non-fucosylated monoclonal antibody	NCT04227847	Phase I	--	medullary malignant tumor	Recruiting
CD70 CAR-T	CAR-T	Trans Recognition of CSRs on CAR-T Cells Enhances the Efficacy and Sustained Effectiveness of CAR-T Cells via the CD27-CD70 Axis	29 trials	--	--	CD70-positive advanced/metastatic solid tumors, multidrug-resistant nephrotic syndrome, glioblastoma multiforme, ovarian cancer, cervical cancer and other gynecologic malignancies	Recruiting
CTX130	CAR-T	CD70 targeting	NCT04502446	Phase I	39	T-cell lymphoma	18 ORR. At dose level 3 and higher, there were 16 ORRs, 6 CRs, and 10 PRs in 31 patients.
CD70 CAR-NK	CAR-NK		NCT06696846	Phase I	--	R/R T-cell lymphoma, AML & ALL	--

CD70-targeted therapy faces significant limitations due to its expression on activated immune cells and essential role in T cell homeostasis, with modulation risking immune disruption. Animal models show CD27/CD70 deficiency causes lethal GVHD, underscoring the pathway's regulatory importance. CD70 targeting broadly affects B cells, NK cells, and T cell subsets, reducing specificity. In solid tumors, challenges include poor CAR-T cell trafficking, limited penetration, and insufficient persistence, compounded by sparse clinical data on cytotoxic constructs and notable toxicities with cellular therapies [31]. CD27 agonism presents a balancing challenge: it enhances anti-tumor immunity but chronic stimulation drives T-cell

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depletion, necessitating patient-specific response analysis and optimized dosing [32]. CD27 attenuates Th17 polarization, which complicates therapy due to Th17 cells' anti-tumor role and involvement in adverse events. Combination with IL-15 may synergistically boost NK cell responses [33]. While CD27 agonism can disrupt PD-1/PD-L1 interactions and restore CD8+ T cell function, the narrow therapeutic window and exhaustion risk highlight the need for deeper mechanistic insights into T-cell differentiation and apoptosis, plus integrated strategies to balance immune activation and competence.

Table 5. Clinical Trials of Immunotherapeutic Drugs Targeting CD27 for the Treatment of DLBCL

Drugs	Class	Mechanism	Study	Phase	Number	population	Results
Varlilumab	Agonistic mAb	Based on the physiological function of co-stimulation, CD27 agonist antibody induces enhanced activity of tumor-infiltrating CD8+ T cells and NK cells and reduces Treg numbers	NCT04941287 NCT04081688 NCT02335918	Phase II Phase I Phase I/II	57 15 175	advanced biliary tract cancer Refractory NSCLC Squamous cell solid cancer, respectively	
			NCT02386111	Phase I	17	Metastatic renal cell carcinoma	Combined with ipilimumab
			NCT01460134	Phase I	13	In CD27-positive B-cell hematologic malignancies (including DLBCL)	1 patient with HL presented PR and measurable disease contraction of 77
			NCT03038672	Phase II	53	DLBCL in patients with R/R aggressive B-cell lymphoma	Combined with the anti-PD-1 monoclonal antibody Nivolumab, ORR was achieved in 6 patients (12.5%), with 4 CRs.
	adjuvant	Enhancement of CTL responses, with reports that CD27 stimulation significantly increased the size of T cell responses to peptide or protein antigens	NCT03688178	Phase II	--	glioblastoma	DC cell depletion after receiving CMV pp65-LAMP mRNA-pulsed autologous DCs under Varlilumab
			NCT03617328	Stage I/II	--	melanoma (type of skin cancer)	As an adjuvant in the Enhancement of immune responses to 6 related peptide-stimulated helper T-cell (6MHP) vaccines
			NCT02924038	Phase I	--	Grade II glioma	Enhancement of the rate and magnitude of CD4+ and CD8+ T cell responses after receiving the IMA950 peptide vaccine

3.5. BAFF-BAFFR Axis

(1) Structure, Expression and Physiological Role

BAFF (TNFSF13B), a TNF family cytokine essential for mature B cell survival, binds three receptors: BAFFR (TNFRSF13C), TACI (TNFRSF13B), and BCMA (TNFRSF17), with TACI and BCMA also interacting with APRIL (TNFSF13). BAFF-BAFFR signaling primarily activates the non-canonical NF-κB pathway through TRAF3 degradation, NIK stabilization, IKK1

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phosphorylation, and p100-to-p52 processing, enabling p52:RELB nuclear translocation. Concurrently, it engages canonical NF-κB, PI3K, and ERK pathways [34].

Genetic and pharmacological evidence confirms BAFF-BAFFR signaling is critical for mature B cell survival, particularly in splenic T2, follicular, and marginal zone B cells in murine models [35]. BAFFR synergizes with BCR signaling for immature-to-mature B cell transition, while TACI maintains innate immune tolerance in marginal zone B cells. Although germinal center B cells and plasma cells are BAFFR-independent, IgM+ and IgG1+ memory B cells require BAFF for long-term survival, with BAFF deficiency impairing T-dependent and T-independent humoral responses. Plasma cells depend on BCMA and TACI when BAFF and APRIL are absent. BAFF and APRIL also induce AP-1 and STAT3 phosphorylation in marginal zone and B1 cells, promoting IL-10-producing regulatory B cell (Breg) differentiation via TACI [36].

The BAFF/APRIL system influences diverse immune cells: activated CD4+ and CD8+ T cells upregulate BAFF-R and receive co-stimulatory signals, while Tregs constitutively express BAFF-R and respond with enhanced proliferation and TGF-β production. Myeloid cells, including monocytes (a major BAFF source), show BAFF-enhanced survival, M1 polarization, and pro-inflammatory cytokine production (IL-6, TNFα, IL-1β). Dendritic cells upregulate CD80/CD86 and produce cytokines/chemokines upon BAFF stimulation [37]. Non-hematopoietic cells like osteoblasts and astrocytes also produce BAFF, indicating broader immunological roles.

(2) Role in DLBCL

Emerging evidence highlights the critical involvement of BAFF/APRIL signaling in the pathogenesis and treatment resistance of B-cell malignancies. In DLBCL, tumor cells exhibit BAFFR expression levels comparable to normal B cells while additionally expressing TACI, BCMA, and HSPG. Clinically, elevated serum and tumor tissue levels of BAFF and APRIL consistently correlate with adverse prognosis across various lymphoma subtypes. At the molecular level, BAFF-BAFFR signaling promotes malignant B-cell survival through concurrent activation of both classical and alternative NF-κB pathways [38]. This signaling axis has been mechanistically linked to the development of resistance against targeted therapies including ibrutinib, idelalisib, and venetoclax, as well as conventional chemotherapeutic agents like fludarabine and bendamustine in CLL and other B-cell malignancies.

The oncogenic effects of BAFF signaling extend beyond canonical survival pathways through multiple mechanisms. BAFF treatment induces phosphorylation of Syk kinase, thereby amplifying BCR signaling in CLL cells, while in Burkitt's lymphoma models it upregulates BST2 (CD317) expression, a marker associated with tumorigenesis. Paradoxically, BAFF stimulation also enhances NLRP3 inflammasome activation and pro-IL1β production in malignant B cells, suggesting complex immunomodulatory roles [39]. Importantly, BAFF-mediated non-canonical NF-κB signaling persists despite ibrutinib treatment, providing a rationale for combination therapeutic strategies targeting both BAFF-R and BTK pathways. The tumor microenvironment further contributes to this signaling network through APRIL-expressing tumor-infiltrating neutrophils, although the precise pathogenic role of APRIL in DLBCL remains to be fully elucidated. These findings collectively position the BAFF/APRIL system as both a prognostic biomarker and a promising therapeutic target in B-cell malignancies, particularly for overcoming acquired treatment resistance.

(3) Research progress based on BAFF-BAFFR axis

The BAFF-BAFFR axis is a well-established therapeutic target in autoimmune diseases and multiple myeloma. FDA-approved therapies include telitacicept, a TACI-Fc fusion protein that blocks both BAFF and APRIL signaling for systemic lupus erythematosus (SLE), and belimumab, a BAFF-neutralizing monoclonal antibody for SLE with limited effects on memory B cells and long-lived plasma cells [40, 41].

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Novel agents in development include AMG-623 (a BAFF antagonist evaluated in SLE trials NCT02411136 and NCT02443506), AMG-570 (a bispecific ICOSL/BAFF inhibitor showing efficacy in collagen-induced arthritis models and in Phase 1/2 trials), atacicept (TACI-Ig in Phase 3 for lupus nephritis), ALPN-303 (an enhanced-affinity TACI variant in Phase 1/2 for lupus nephritis, NCT05732402), tibulizumab (a BAFF/IL-17A bispecific antibody discontinued for primary Sjögren's syndrome, NCT04563195), and tabalumab (a BAFF monoclonal antibody that failed Phase 3 SLE endpoints, NCT01196091).

Ianalumab (VAY736), an anti-BAFFR monoclonal antibody with ADCC-mediated B-cell depletion, has shown activity in autoimmune disorders and hematologic malignancies. Phase 1/2 trials in Sjögren's syndrome, SLE, and others are completed, with Phase 3 studies recruiting. In NHL, a Phase 1 trial (NCT04903197) is ongoing, and a CLL trial with ibrutinib (NCT03400176) reported 6 CRs (CRs), 4 stable disease (SD), and 4 progressive disease (PD) in 15 patients.

CAR-T therapies targeting BAFF/APRIL receptors include BCMA-directed approaches, with 228 clinical studies primarily in multiple myeloma and trials in NHL (e.g., NCT05836896 for R/R DLBCL). BAFFR CAR-T trials are active: NCT04690595 for R/R ALL (1 CR post-allogeneic HCT), NCT05370430 for R/R NHL (2 MCL CRs, 1 THRBCL partial response) , and NCT06191887 for CLL/NHL. No TACI CAR-T trials have been initiated.

(4) Limitations

Table 6. Clinical Trials of Immunotherapeutic Drugs Targeting BAFF for the Treatment of DLBCL

Drugs	Class	Mechanism	Study	Phase	Number	population	Results
Telitacicept	mAb	Novel fusion protein consisting of a human transmembrane activator, the extracellular domain of the TACI receptor, and a human IgG Fc domain	FDA Approval in 2021 NCT02885610 (pivotal)	--	--	primarily for autoimmune diseases (systemic lupus erythematosus, SLE)	--
belimumab	mAb	Blocked BAFF signaling and less affected by memory B cells or longer surviving plasma cells	FDA Approval in 2011 NCT01639339 (pivotal)	--	--	SLE	--
AMG-62	mAb	BAFF antagonist	NCT02411136 NCT02443506	--	--	SLE	Evaluations have been completed
Atacicept (TACI-Ig)	mAb	Recombinant fusion protein containing the extracellular ligand-binding portion of the TACI receptor and the Fc portion of human IgG	--	--	--	--	Phase 1 and 2 clinical trials have been conducted in a variety of autoimmune diseases
ALPN-303	mAb	Fusion of the TACI vTD structural domain with human IgG Fc to further enhance affinity for BAFF and APRIL	NCT05732402 NCT06564142 NCT05757570	Stage I/II Phase III Stage I/II	--	LN IgAN Membranous nephropathy, thrombocytopenia, autoimmune hemolytic anemia	Recruiting
Tabalumab (LY2127399)	mAb	Complete IgG4 BAFF monoclonal antibody	NCT01196091	Phase III	--	SLE	Key clinical efficacy endpoints did not reach statistical significance

Current therapeutic development targeting the BAFF-BAFFR signaling pathway in DLBCL has been primarily driven by CAR-T cell therapy, reflecting the successful paradigm established by BCMA-targeted approaches in multiple myeloma (MM). However, emerging evidence suggests that alternative immunotherapeutic modalities - including bispecific antibodies (e.g., AMG-420,

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202511_11(11).0010

Elranatamab, REGN-5458/5459, TNB-383B) and antibody-drug conjugates (e.g., Belantamab-Mafodotin, MEDI2228) - represent equally promising avenues for BAFF-BAFFR targeting in NHLs. These diversified approaches may offer complementary mechanisms of action to overcome the limitations of single-agent therapies.

Notably, while BCMA-directed CAR-T therapy has demonstrated remarkable efficacy in MM, several challenges have emerged that may similarly impact BAFF-BAFFR-targeted therapies. These include: antigen escape through loss of surface expression, expansion of antigen-negative tumor clones, T-cell exhaustion and dysfunction, and the development of an immunosuppressive tumor microenvironment. These obstacles highlight the critical need for next-generation strategies that incorporate combination therapies, sequential treatment approaches, and novel engineering solutions to enhance T-cell persistence and functionality.

Table 7. Clinical Trials of Immunotherapeutic Drugs Targeting BAFF-R for the Treatment of DLBCL

Drugs	Class	Mechanism	Study	Phase	Number	population	Results
Ianalumab (VAY736)	mAb	Anti-BAFFR whole human IgG1 monoclonal antibody, direct ADCC-mediated B cell depletion	--	--	--	--	Extensive phase 1 and 2 clinical trials completed in multiple autoimmune diseases, phase 3 trials recruiting
BCMA CAR-T	CAR-T	Blocked BAFF signaling and less affected by memory B cells or longer surviving plasma cells	175 trials	--	--	MM	--
			NCT02954445 NCT05513612 NCT05513612 NCT05528887 NCT03302403 NCT06758713 NCT04191941	--	--	NHL	No results published
MDC-CAR-BCMA00	CAR-T		NCT05836896	Phase I		R/R DLBCL	No results published

4. MULTI-TARGET THERAPY AND COMBINATION THERAPY

4.1. Multi-target Antibodies

(1) Advantages and mechanism of action

Single-target immunotherapies in DLBCL, such as monoclonal antibodies and CAR-T cells, face significant limitations due to antigen escape mechanisms—exemplified by CD19-negative relapse after CD19-CAR T therapy or CD20 downregulation post-rituximab—driven by target heterogeneity and clonal evolution. These approaches also contend with adaptive resistance from the immunosuppressive tumor microenvironment, immune exhaustion, and toxicities like cytokine release syndrome (CRS) and neurotoxicity.

Multi-targeted strategies overcome these issues by simultaneously engaging multiple molecules and pathways, broadening antigenic coverage, reducing clonal selection pressure, and enhancing anti-tumor specificity and potency while potentially mitigating toxicity. Bispecific antibodies (BsAbs) exemplify this approach, engineered to bind two distinct targets—such as CD3 on T cells and tumor antigens—to redirect immune cytotoxicity, improve tumor selectivity, and block multiple signaling pathways [42]. Structurally, BsAbs include IgG-like formats (>150 kDa) with Fc-mediated effector functions (ADCP, CDC, ADCC), as well as bispecific T-cell engager (BiTE) and dual-affinity retargeting (DART) platforms. By addressing

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antigen heterogeneity and enhancing immune recruitment, BsAbs offer a promising alternative to single-target therapies in DLBCL.

(2) Advances in Drug Research

The therapeutic landscape for R/R DLBCL has been significantly advanced by the recent regulatory approvals of two CD3-CD20 bispecific antibodies - epcoritamab and glofitamab - in the United States, Canada, and Europe [43]. Epcoritamab (Gen3013), a subcutaneously administered full-length IgG1 bispecific antibody featuring bivalent CD20 binding, represents a notable therapeutic innovation. Its clinical validation stems from the pivotal EPCORE NHL-1 study (41% (65/157) of pts had CR), which demonstrated sufficient efficacy to warrant FDA accelerated approval in May 2023 for R/R DLBCL and high-grade B-cell lymphomas following ≥2 prior lines of therapy. This bispecific antibody is currently undergoing further evaluation comparing its performance against physician's choice regimens in transplant-ineligible R/R DLBCL patients. Glofitamab (RG6026), another CD20×CD3 bispecific antibody, has shown compelling clinical activity in the NP30179 Phase I/II trial. The Phase I component (n=171) established an ORR of 53.8%, with 36.8% of patients achieving CR at the recommended Phase II dose. Subsequent Phase II evaluation (n=155) revealed durable responses, with 39% of patients maintaining CR at a median follow-up of 12.6 months with median PFS of 4.9 months and overall survival (OS) of 11.5 months, accompanied by a 12-month PFS rate of 37%. These robust clinical data supported the FDA's accelerated approval for R/R DLBCL and large B-cell lymphoma patients refractory to ≥2 systemic therapies.

The therapeutic landscape for R/R lymphomas continues to evolve with the development of novel bispecific antibodies targeting CD19 and CD20. Mosunetuzumab (BTCT4465A), a first-in-class fully humanized IgG1 CD20×CD3 bispecific antibody engineered using knob-in-hole technology, received FDA accelerated approval in December 2022 for R/R follicular lymphoma (FL) following two or more lines of systemic therapy. While demonstrating promising activity in indolent lymphomas, its efficacy in aggressive subtypes appears more modest, prompting ongoing investigations into combination strategies.

Odronextamab (REGN1979), another fully human IgG4-based CD20×CD3 bispecific antibody, has shown compelling clinical activity across multiple lymphoma subtypes. Phase I trial data (NCT02290951) involving 145 heavily pretreated patients revealed an ORR of 51%. Notably, follicular lymphoma patients achieved an impressive ORR of 91% (29/32 patients), with 72% achieving CRs (CR) at doses of 5mg or higher. In DLBCL cohorts, treatment-naive patients receiving ≥80mg doses demonstrated an ORR of 53% with all responders achieving CR (8/15 patients), while CAR-T experienced patients showed an ORR of 33% (10/30) with 27% CR rate [44]. These findings were further explored in the ELM-2 phase II trial (NCT03888105), with updated results presented at the 2022 ASH Annual Meeting, ORR and CR rate confirmed by ICR were 52% (66/127) and 31% (39/127), respectively,

The development pipeline also includes TNB-486, an innovative CD19×CD3 bispecific antibody currently in phase I evaluation for R/R DLBCL. Blinatumomab (MT103), the first FDA-approved CD19×CD3 bispecific T-cell engager for B-cell ALL, has demonstrated activity in NHL Phase I data (NCT04594642) showed 91% ORR in FL pts and durable responses with a median duration of response of 404 days, albeit with significant toxicity including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), observed in 22% of patients at grade 3 severity.

In addition, bispecific/multi-targeted antibodies to the emerging targets described above have likewise been extensively explored, with results and associated clinical trials tabulated below:

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Table 8. Bispecific Antibodies, Clinical Trials of Immunotherapeutic Drugs for the Treatment of DLBCL

Drugs	Target	Mechanism	Study	Phase	Number	population	Results
TNB-486	CD3-CD19		NCT04594642	Phase I	17--	R/R B-cell NHL	ORR and CR rate were 91%
PSB202	CD20-CD37	Anti-CD20 antibody (PSB102) and humanized anti-CD37 antibody (PSB107) are produced in a 1:1 molecular ratio.	NCT05003141	Ia/ Ib		Patients with inert, recurrent, CD20+ and CD37+ expressing B-cell malignancies (not included in DLBCL)	Recruiting
AMG-570	ICOSL-BAFF		NCT02618967 NCT03156023 NCT04058028	Stage I/II	--	SLE, rheumatoid arthritis	--
NVG-111	CD3-ROR1	Targeted T cell activity to induce effective killing of tumor cells in vitro and in vivo	NCT04763083	Phase I	53	Chronic Lymphocytic Leukemia (CLL), Small Lymphocytic Lymphoma (SLL), MCL, FL and DLBCL, etc.	Responses were observed in all 5 evaluable patients who completed efficacy evaluations after 3 NVG-111 cycles
PRV-3279	CD32B-CD79	DART, which triggers suppression of B-cell function and autoantibody production	NCT05087628	Phase IIa	--	SLE	--
MGD010	CD32B-CD79	DART	NCT02376036	Phase I		SLE	Safety and Tolerance Validation
CDX-527	PD-L1-CD27	Effectively inhibits PD-1 signaling and induces CD27-mediated T cell co-stimulation via PD-L1 cross-linking	NCT04440943	Phase I	73	Multiple recurrent, locally advanced or metastatic solid tumor cancers	8 patients received varying doses of CDX-527.3 are still on treatment

(4) multi-targets

Building upon the clinical success of bispecific antibodies, the field is now advancing toward more sophisticated tri-specific antibody platforms. PIT565 represents a pioneering example of this next-generation immunotherapy, engineered to simultaneously engage CD19 on malignant B-cells while co-targeting both CD3 and CD2 on T-cells. This innovative triple-targeting approach creates a more robust immunological synapse, potentially overcoming limitations observed with conventional CD3 bispecific antibodies [45].

Preclinical studies have demonstrated that PIT565's unique binding profile results in enhanced T-cell activation and more potent cytotoxic activity against CD19+ tumor cells compared to standard bispecific constructs. The molecule's ability to engage CD2 – a critical costimulatory molecule expressed on T-cells – appears particularly promising, as it may lead to both deeper and more durable clinical responses by preventing T-cell exhaustion and sustaining anti-tumor activity.

Currently under evaluation in an ongoing Phase I clinical trial (NCT05397496), PIT565 is being investigated for R/R NHL and ALL. This first-in-human study aims to characterize the safety profile, pharmacokinetics, and preliminary efficacy of this novel tri-specific engager. The trial's outcomes are eagerly anticipated, as they may validate the theoretical advantages of tri-specific platforms, including potentially improved response durability and reduced incidence of resistance mechanisms that frequently emerge with single-targeted therapies.

The development of PIT565 exemplifies the logical progression in immuno-oncology from mono-specific to multi-specific targeting strategies. By simultaneously engaging multiple immune checkpoints and tumor antigens, such tri-specific antibodies may offer solutions to key challenges in the field, including antigen escape, tumor heterogeneity, and the

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immunosuppressive tumor microenvironment. As clinical data mature, these next-generation molecules could redefine treatment paradigms for aggressive B-cell malignancies.

Table 9. Multi-target therapy, clinical trials of immunotherapeutic agents for the treatment of DLBCL

Drugs	Target	Mechanism	Study	Phase	Number	population	Results
GNC-035	d-l1-cd3-4-1bb-ror1	Further activates T cells by blocking inhibitory signaling at immune checkpoints.	NCT05944978 NCT06066203 NCT05104775	Phase I/II	--	R/R CLL and NHL	Recruiting
			NCT05160545	Phase I/II	--	lymphoma	Recruiting
JNJ-80948543	CD3ε-CD20-CD79b	Exhibits high affinity and stable binding in lymphoma cells expressing different endogenous CD79b and CD20 receptor densities	NCT05424822	Phase I	--	NHL and CLL	No results published
EO-246	CD20-CD22-CD37-BAFFR	Tetravalent peptide vaccine using non-self microbial derived peptides corresponding to epitope molecules such as CD8 HLA-A2 mimicry	NCT04669171	Phase II	9	FLMZL	alone and the co-administration of lenalidomide and lenalidomide, 7 (78%) achieved a CR

(5) Limitations

BsAbs demonstrate a generally favorable safety profile compared to CAR-T therapy, with lower incidence and severity of cytokine release syndrome (CRS) and neurotoxicity [46]. Mitigation strategies include step-dosing regimens, subcutaneous formulations to reduce cytokine storm potential, and pretreatment with cytotoxic anti-CD20 antibodies to decrease tumor burden. Resistance to BsAbs arises through multiple pathways: tumor cell-intrinsic adaptations involve CD20 deficiency due to truncating MS4A1 mutations in approximately 80% of progressive disease cases, alongside TP53 mutations and hyperactivated MYC signaling; T cell-intrinsic dysfunction results from chronic CD3 stimulation, leading to TCR downregulation and exhausted phenotypes; and extrinsic immunosuppression by tumor microenvironment components, such as myeloid-derived suppressor cells and tumor-associated macrophages, exhibits age-dependent prevalence, affecting 68% of pediatric ALL cases versus 13% of adult patients. These coexisting mechanisms highlight the necessity for combinatorial approaches targeting both malignant cells and the immunosuppressive microenvironment to achieve durable therapeutic responses.

4.2. Multi-target Cell Therapy

To address tumor cell escape, antigen downregulation, and T-cell exhaustion, multi-targeted CAR-T strategies have emerged as alternatives to conventional single-target approaches. In ALL, clinical studies have explored advanced engineering solutions such as tandem or dual-transposon CAR constructs, co-administration of multiple CAR-T products, and sequential targeting against combinations like CD19/CD22 or CD19/CD20. These approaches aim to enhance anti-tumor responses and reduce immune evasion by engaging multiple antigens, yet they remain vulnerable to secondary antigen loss. Current research focuses on developing CARs targeting more stable antigens and triple-specific approaches simultaneously engaging CD19, CD20, and CD22, representing an evolution toward comprehensive multi-antigen systems to overcome adaptive resistance in B-cell malignancies. Future directions may involve optimizing these strategies through combination with tumor microenvironment-modulating therapies to address T-cell dysfunction and improve long-term efficacy [47].

Recent clinical developments have demonstrated promising outcomes with novel bispecific CAR-T cell therapies targeting conventional immunotherapeutic antigens. MPT-314 (rondecabtagene autoleucel), an autologous CD19/CD20 bispecific CAR-T product, was

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designed to address key limitations of conventional CAR-T therapies by enhancing cellular persistence, reducing T-cell exhaustion, and mitigating single-antigen escape. In an ongoing Phase 1/2 multicenter trial (NCT05826535) involving heavily pretreated, CAR-T experienced patients with R/R large B-cell lymphoma (LBCL), early results showed remarkable efficacy. Among 12 treated patients, evaluable responses at day 28 demonstrated a 100% ORR (11/11), with 73% (8/11) achieving complete remission by 3 months. With a median follow-up of 5.6 months (range: 1.1-8.8), 73% of patients (8/11) maintained responses at last assessment. The safety profile appeared favorable, with 75% of patients (9/12) experiencing only low-grade (1-2) cytokine release syndrome (CRS) and no reported high-grade CRS events.

Parallel developments include pLTG1497, another tandem CD19/CD20 CAR-T construct that demonstrated enhanced anti-lymphoma activity in preclinical models. The first-in-human Phase I study of pLTG1497 (MB-CART2019.1) in R/R (NCT03870945) showed an ORR of 75% (9/12), including 5 complete remissions. Notably, dose-level dependent responses were observed, with 50% ORR (3/6) at DL1 and 100% ORR (6/6) at DL2. MB-CART2019.1 is currently challenging conventional immune-chemotherapy in a randomized Phase II trial for elderly, non-transplant eligible pts with first progression or relapse of aggressive B-NHL (NCT04844866).

Further expanding the bispecific CAR-T landscape, AUTO3 incorporates a dual cis-retroviral vector encoding anti-CD19 (with OX40 co-stimulation) and anti-CD22 (with 41BB co-stimulation) CARs. In a study (NCT03287817) involving 19 treated patients (89% with refractory disease, 74% with DLBCL NOS, and 26% with transformed DLBCL), evaluable patients (n=18) receiving doses >50×10^6 CAR-T cells achieved 64% ORR and 55% CR rate. These collective findings underscore the potential of bispecific CAR-T strategies to improve outcomes in challenging patient populations while maintaining manageable safety profiles. The differential response patterns across constructs highlight the importance of optimal target selection, costimulatory domain configuration, and dosing strategies in maximizing therapeutic efficacy.

5. CONCLUSION

Looking ahead, several critical challenges must be addressed to advance the field. Managing sequential and combination therapies will be essential to optimize efficacy while minimizing overlapping toxicities and resistance. Overcoming TME-mediated immunosuppression remains a major barrier, necessitating strategies to reprogram the TME through agents targeting metabolic pathways, cytokines, or immune checkpoints. Additionally, addressing antigen escape and tumor heterogeneity will require dual- or multi-targeting approaches to prevent relapse. Expanding the efficacy of CAR-T therapies to solid tumors and improving their scalability and access through "off-the-shelf" alternatives are also crucial to broaden their clinical impact.

Promising next-generation technologies are emerging to address these challenges. Allogeneic CAR-T cells, engineered to reduce graft-versus-host disease and host rejection, offer the potential for scalable, readily available cellular products. Armored CARs, designed to resist TME suppression by expressing cytokines or checkpoint blockers, aim to enhance T-cell persistence and function. Switchable CARs incorporating exogenous control mechanisms allow precise regulation of activity, improving safety profiles. Moreover, multi-targeting platforms such as tandem CARs and bispecific antibodies engaging both tumor antigens and T-cell costimulatory molecules are being developed to mitigate antigen escape and amplify immune responses. Beyond T-cell-focused therapies, CAR-NK and CAR-macrophage platforms present alternative strategies with favorable safety profiles and unique mechanistic advantages. Finally, advanced antibody-drug conjugates and radioimmunoconjugates with optimized linkers, novel payloads,

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and improved selectivity continue to evolve, offering enhanced tumor targeting and reduced off-tumor toxicity.

This review has comprehensively examined the current therapeutic landscape and emerging immunotherapeutic strategies for diffuse large B-cell lymphoma (DLBCL), a disease characterized by significant molecular and clinical heterogeneity. Despite advances with standard R-CHOP chemoimmunotherapy and the transformative success of CD19-directed CAR-T cell therapy in R/R settings, a substantial proportion of patients still experience primary resistance, relapse, or refractory disease. Key mechanisms underlying treatment failure include antigen escape, T-cell exhaustion, an immunosuppressive tumor microenvironment (TME), and the emergence of resistant tumor clones. The development of novel immunotherapies—such as bispecific antibodies, antibody-drug conjugates targeting antigens like CD79b and ROR1, and next-generation cellular therapies—has expanded the arsenal against DLBCL. However, these approaches are limited by on-target/off-tumor toxicities, modest efficacy in aggressive subtypes, and logistical challenges related to manufacturing and administration.

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