

Recent Advances in Antibody-Drug Conjugates for Lymphoma

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ABSTRACT: Antibody-drug conjugates (ADCs) comprise a unique class of chemoimmunotherapy agents, incorporating cytotoxic payloads covalently linked to a monoclonal antibody via specialized linkers. This strategy attempts to exploit antibody-antigen specificity to selectively deliver a potent ‘warhead’ payload to tumor cells (**Figure**), while sparing nontumor antigen-negative cells. Decades of development have culminated in the recent approvals of a handful of ADCs across multiple tumor types. ADCs for the treatment of lymphoma are particularly attractive due in part to the favorable spectrum of cell surface markers uniquely expressed on lymphocytes compared with other tissues. Here we discuss general principles of ADC design, including antigen/antibody, payload, and linker selection. We highlight the clinical successes of the 2 approved ADCs for treatment of lymphomas: brentuximab vedotin (Adcetris) and polatuzumab vedotin (Polivy). Finally, we describe several ADC agents currently under development for lymphoma, including emerging efficacy and toxicity data from early-stage clinical trials (**Table**).

Introduction

The mainstay of treatment for the majority of lymphomas has been systemic cytotoxic chemotherapy, either single-agent or multiagent, for many decades. Advances in biotechnology through the 1990s facilitated the development of the anti-CD20 monoclonal antibody (mAb) rituximab (Rituxan), which is now widely used both as a monotherapy and in combination with chemotherapy for the treatment of a wide range of B-cell malignancies (in addition to being used for several non-malignant conditions).¹ Oral and in-

travenous (IV) targeted small molecule therapies have demonstrated impressive efficacy in various frontline and relapsed settings for a range of lymphoid malignancies,² but balancing the effectiveness and toxicities of lymphoma treatments remains a key goal in this area. The lymphoma community has continued to seek novel therapies that specifically target tumor cells, as the lineage-specific agent rituximab does, which would allow for increasingly potent treatments to be offered to patients by selectively delivering cytotoxic agents to sites of disease while sparing healthy tissues

from drug exposure. Antibody-drug conjugates (ADCs) are one manifestation of this “magic bullet” that was historically imagined by Paul Ehrlich.³ Two ADCs have been approved for the treatment of lymphomas; several other agents are being actively explored and showing early clinical promise. Complex factors must be considered when constructing potential ADCs, as these multicomponent cancer therapies come with compounding levels of nuance in their design strategies.

Antigen Selection and Antibody Design

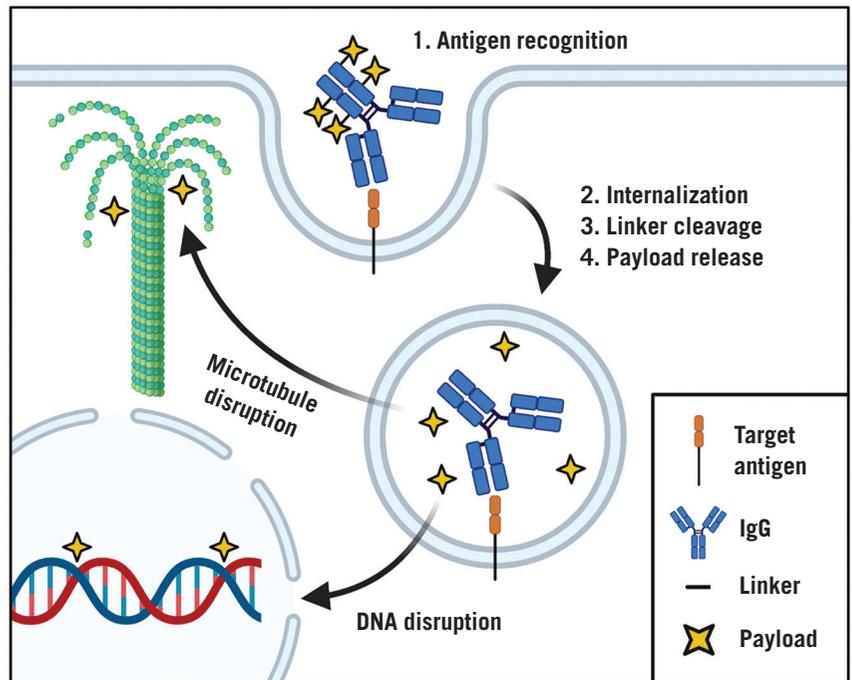
The fundamental goal of an ADC is the tumor-specific delivery of a cytotoxic drug, so it is vital to identify an appropriate antigenic target for an ADC’s mAb component. This first major hurdle has been overcome with varying degrees of ease or difficulty depending on tumor type. For epithelial malignancies, which can share considerable cell surface marker expression with other organs of endodermal origin, the identification of tumor-specific instead of tissue-specific antigens has been one key to successful ADC development.⁴ In contrast, multiple lymphoid lineage-specific markers are ripe for exploitation by ADCs for the treatment of lymphomas, as any nontumor B- and/or T-cell ablation can

often be tolerated, and minimal nonhematopoietic end-organ toxicities would be predicted. Later in this review, we outline many of the cell surface markers currently being utilized for lymphoma ADC development, including their spectrum of expression in different hematopoietic compartments plus other tissues. Not only does one strive for high tumor cell expression of an ADC target antigen compared with limited or no expression in other tissues, but this target antigen must also localize to the cell surface to be accessible to the circulating ADC. Upon binding, the ADC should then be transported intracellularly for release of its cytotoxic payload. Some cell surface antigens, however, are noninternalizing, creating additional challenges for drug development.

Due to the unique mechanism of action of ADCs, it is not required for their mAb component to possess any intrinsic non-ADC (“naked”) clinical activity. Furthermore, many ADCs are also the first agents to show clinical activity targeting a particular antigen. The anti-CD30 ADC brentuximab vedotin (Adcetris; BV), as described in more detail below, is an example of both principles, and there are also similar examples in diseases other than lymphoma. Additionally, whether the mAb used in an ADC exerts any antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) could complicate the potential adverse event (AE) profile of the ADC, separate from the expected toxicities that may be caused by off-target exposure to the actual cytotoxic payload of the ADC.

Lastly, while not specific to ADCs, mAb design in general must also address immunogenicity and isotype selection. Whether a mAb is chimeric, humanized, or fully human will influence the potential for antidrug antibodies (ADAs) to emerge. This phenomenon has been shown to be detrimental to ADC effectiveness in a variety of settings.⁵ Most ADCs utilize immunoglobulin (Ig) G

FIGURE. General Principles of ADCs.



IgG, immunoglobulin G.
Illustration created with BioRender.com.

mAbs, and the choice of specific isotype impacts production ease, payload linkage ease, and pharmacokinetics, as well as potential AEs when the ADC is administered clinically.⁶⁻⁸ IgG3 mAbs suffer from faster clearance, making them largely unsuited for use in ADCs. IgG1, IgG2, and IgG4 mAbs have differing numbers of disulfide bonds, which potentially impact where and how many payloads can be affixed. Further, the potential for ADCC and CDC varies among isotypes, with more for IgG1 and less for IgG2 or IgG4. Related to this, recent advances in mAb design have explored the introduction of mutations to modulate these mAb functions. One aim has been to abrogate off-target effects via silencing mutations of the Fc domain, thus minimizing FcγR binding and theoretically reducing subsequent thrombocytopenia, which has been observed with the anti-HER2 ADC trastu-

zumab emtansine (Kadcyla) for breast cancer.⁹ In other contexts, Fc domain mutations have been introduced to enhance ADCC by increasing the mAb affinity for FcγRIIIa, such as with an anti-BCMA ADC for multiple myeloma.¹⁰

Choice of Payload

The ADCs that are currently approved utilize a relatively narrow set of cytotoxic payloads as “warheads” due to a number of limitations, but extensive active research continues in this arena. Most ADCs achieve drug-to-antibody ratios between 3:1 and 5:1, and the absolute number of target antigens expressed on the tumor cell surface is in the range of 10^3 to 10^7 in most circumstances.¹¹ This results in relatively low absolute drug delivery to a tumor cell in terms of intracellular cytotoxic agent concentration compared with the concentrations commonly achieved

by systemic IV chemotherapy. In turn, most ADCs take advantage of payloads that are highly potent, often with a half maximal inhibitory concentration in the range of 10^{-10} to 10^{-12} molar. These drugs commonly target microtubules (and so are cytotoxic to proliferating cells) or DNA (and so are cytotoxic to both proliferating and nonproliferating cells). Most frequently used are auristatins, such as monomethyl auristatin E (MMAE) and F, which are microtubule disrupting agents.¹² These are synthetic analogues of dolastatin 10, a pentapeptide derived from the marine mollusk *Dolabella auricularia* but which is too toxic for use outside of the ADC context. Next most common are ADCs with payloads derived from maytansine, a natural product of the African shrub *Maytenus ovatus* that also disrupts microtubules; examples include drug maytansinoid (DM)1 and DM4.¹³ Also under investigation are tubulysins, which comprise a third, less common class of ADC payloads that targets microtubules.

Of the payloads that target DNA, common classes include calicheamicins, which bind the minor groove of DNA and induce site-specific double-strand cleavage, and duocarmycins, which are alkylating agents.¹⁴ Also under development are several ADCs with pyrrolone benzodiazepine (PBD) payloads, which are naturally occurring antitumor antibiotics that dimerize then bind and crosslink DNA.¹⁵ ADCs with camptothecin analogues, such as prodrugs of the established chemotherapeutic agent irinotecan, inhibit DNA topoisomerase I. They are already being advanced in nonlymphoma settings and have the benefits of particularly high potency and water solubility.¹⁶ Finally, several other classes of cytotoxic payloads are in preclinical development, including RNA polymerase II inhibitors, cryptophycin-based tubulin inhibitors, novel anthracyclines, and RNA spliceosome inhibitors.

Linker Optimization

In addition to mAb and cytotoxic payload selection, optimizing the linkage between these 2 components plays a vital role in the toxicity, efficaciousness, and manufacturing ease of an ADC. On one hand, an ADC must remain stable in circulation and tissues—for a period ranging from days to potentially weeks—without releasing its cytotoxic payload and harming areas without tumor. On the other, once internalized, an ADC must make the payload available to exert its cytotoxic effects, often by conditional release in specific subcellular compartments. Some linkers being explored are noncleavable, which would make ADCs dependent on proteolytic degradation of the mAb to release its payload.¹⁷ In contrast, cleavable linkers are also utilized, such as those sensitive to lysosomal proteases, acidic pH, or reduction by glutathione, which all trigger intracellular dissociation of the payload from the mAb.¹⁸ Despite generally aiming to avoid extracellular release of the toxic payload of ADCs, strategies to overcome heterogeneity of antigen expression in tumors have included tolerating and even intentionally exploiting a “bystander effect.”¹⁹ Released payloads (often with part of the linker attached) that are able to cross cellular membranes have the potential to reach nearby antigen-negative tumor cells, which could enhance an ADC’s therapeutic effect. Nonpolar agents have the greatest potential for exhibiting a beneficial bystander effect, but this can come with disadvantages beyond toxic exposure to the payload. Specifically, increasing linker-payload hydrophobicity can induce circulating ADC aggregation, accelerate ADC clearance, and lead to reduced ADC potency in tumors expressing MDR1.^{20,21} In the end, striking the perfect balance between excessive and ineffective local exposure to the toxic payload can be difficult. Overall, there is no single optimal strategy for ADC development as it

pertains to these aforementioned issues; instead, there are complex tradeoffs with each decision that impact efficacy and toxicity, often unique to each target antigen and tumor type.

Brentuximab Vedotin

CD30 is a member of the tumor necrosis factor (TNF) receptor superfamily and is traditionally expressed on the surface of subsets of T cells, B cells, and macrophages.²² However, its characteristic expression in a variety of lymphoid malignancies and its rapid endocytic internalization upon binding by a mAb made it an attractive target for the development of the ADC BV. BV consists of a chimeric anti-CD30 IgG1 mAb with the antitubulin agent MMAE attached via a protease-sensitive dipeptide valine–citrulline linker.²³ Pharmacokinetic analyses revealed that steady-state concentrations of BV are achieved with dosing every 3 weeks, such that minimal to no accumulation occurs with repeated dosing.²⁴

The multicenter, open-label, phase 1 dose-escalation study of BV explored doses between 0.1 and 3.6 mg/kg administered every 21 days.²⁵ It enrolled 45 patients with relapsed or refractory (R/R) CD30-positive hematologic malignancies, primarily Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (ALCL). The maximum tolerated dose (MTD) was 1.8 mg/kg and the most common AEs were fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy. Initial regulatory approval was derived from a subsequent multicenter, open-label, phase 2 study that carried forward the MTD of 1.8 mg/kg, treating 102 patients with HL relapsing after autologous stem cell transplantation (autoSCT).²⁶ The ORR was 75%, with complete remission (CR) in 34% of patients. The median progression-free survival (PFS) for all patients was only 5.6 months, but the median duration of response (DOR) for those achieving CR was a promising 20.5 months. The confirmatory trial,

Continued on page 530

Review Article: ADCs in Lymphoma

Continued from page 524

leading to an expanded label, came from the AETHERA study, which tested BV consolidation in patients undergoing autoSCT for relapsed high-risk HL.²⁷ A significant improvement in PFS was demonstrated in patients receiving BV (5-year PFS of 59% vs 41% in those receiving placebo), which has led to a new standard of care in this patient population. Peripheral neuropathy led 23% of patients to discontinue treatment prior to completing all planned 16 cycles, and another 31% required dose modifications or delays, revealing the difficulties with long-term use of this agent. BV is now also approved for use in frontline HL management. The multicenter, randomized, open-label, phase 3 ECHELON-1 study explored BV plus doxorubicin, vinblastine, and dacarbazine, compared with the standard-of-care of bleomycin plus the same latter 3 agents (ABVD) in the frontline HL setting.²⁸ Modified PFS at 3 years was superior in patients receiving BV plus chemotherapy (83%) compared with those who received ABVD (76%). How BV-containing regimens are integrated with modern PET-adapted treatment strategies is still evolving.

CD30 is also expressed in a portion of cases of peripheral T cell lymphoma (PTCL) not otherwise specified, angioimmunoblastic T-cell lymphoma, adult T-cell leukemia/lymphoma, and cutaneous T-cell lymphoma (CTCL) including Sezary syndrome and mycosis fungoides (MF).²² The landmark multicenter, randomized, double-blind, phase 2 ECHELON-2 study²⁹ in untreated patients with CD30-positive PTCL demonstrated a survival advantage with the addition of BV to frontline chemotherapy, improving median PFS from 20.8 to 48.2 months and reducing the risk of death by 34%. Similarly, the phase 3 ALCANZA trial³⁰ compared BV with physician's choice of therapy (methotrexate or bexarotene)

in the treatment of R/R CD30-positive CTCL, with an objective global response being seen in 56.3% of patients receiving BV compared with 12.5% of those on the physician's-choice arm. BV is now indicated for use in the settings of untreated HL, R/R HL, HL after autoSCT, R/R MF, untreated PTCL, untreated ALCL, and R/R ALCL. When used in combination with chemotherapy for untreated lymphomas, G-CSF prophylaxis is indicated.²⁴

Interestingly, there are provocative data regarding the correlation between CD30 expression and responses to BV. One analysis integrated data from 5 prospective clinical trials that included 275 patients with B- and T-cell lymphomas treated with BV.³¹ Of these, 143 had tumors with CD30 expression of <10%, including 58 of the 143 who had undetectable CD30 by this independent review. BV activity was observed at all levels of CD30 expression; the ORR was 34% (20/58) in cases with undetectable CD30. While hypothesis-generating at this point, these observations raise important questions regarding the methodology of assessing heterogeneous CD30 expression on lymphomas, as well as potential off-target consequences of BV such as bystander effects within tumors with low or undetectable CD30 expression.

Polatuzumab Vedotin

Polatuzumab vedotin (Polivy; PV) was the second ADC to receive approval for the treatment of lymphoma. It is composed of a humanized anti-CD79b IgG1 mAb, and it mimics BV in its use of the same protease-cleavable linker to affix the microtubule-targeting MMAE payload.³² Together, CD79a and CD79b form the heterodimeric signaling component of the B-cell receptor (BCR). Crosslinking of the BCR by antigens or antibodies triggers internalization and trafficking of the complex to the lysosomal-like major

histocompatibility complex (MHC) class II endocytic compartment. This internalization, combined with the restriction of CD79b expression to the B-cell lineage, makes CD79b an attractive candidate target for ADC development.

The multicenter, open-label, phase 1 study of PV enrolled patients with B-cell non-Hodgkin lymphoma (NHL) or chronic lymphocytic leukemia (CLL) who had R/R disease or no available curative treatment options.³³ PV was dosed between 0.1 and 2.4 mg/kg every 21 days, and the MTD in NHL was 2.4 mg/kg. The ORR in patients with NHL treated at the PV MTD was 51% (23/45), with median PFS and DOR of 5.7 and 6.2 months, respectively. There were also expansion cohorts for patients with NHL to combine rituximab with PV at the MTD. However, no expansion CLL cohort was pursued due to lack of activity in the PV monotherapy dose-escalation CLL cohort. On the whole, the most common grade 3 or higher AEs were neutropenia, anemia, and peripheral neuropathy, perhaps aligning in part with what was seen in trials of BV due to a common cytotoxic payload. Notably, 51% of patients (23/45) discontinued PV treatment due to an AE, including discontinuation due to peripheral neuropathy in 24% of patients (11/45). One part of the subsequent multicenter, open-label, phase 2 ROMULUS study explored the combination of rituximab with PV at the 2.4 mg/kg MTD in a larger cohort.³⁴ Promising ORRs of 54% and 70% were seen in both the R/R diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) settings, respectively. These findings motivated further PV combination studies. In contrast, the other arm of the ROMULUS study explored pinatuzumab vedotin, a similarly designed ADC targeting CD22, but due to shorter DOR, shorter PFS, and nine grade 5 AEs occurring in patients receiving pinatuzumab vedotin, this anti-CD22 ADC was not recommended for further study at that time.

TABLE. Notable Active/Recruiting Clinical Trials of ADCs in Development for Lymphoma

ADC Name (sponsor)	Target	Additional Agents	Phase	NCT Number	Eligible Histologies	Start Date	Completion Date
Loncastuximab tesirine (Lonca, ADCT-402; ADC Therapeutics)	CD19	None	2	NCT03589469	R/R DLBCL	August 2018	March 2021
		Durvalumab	1	NCT03685344	R/R DLBCL, MCL, FL	December 2018	January 2021
		Ibrutinib	1/2	NCT03684694	R/R DLBCL, MCL	December 2018	April 2023
		Rituximab, gemcitabine, oxaliplatin	3	NCT04384484	R/R DLBCL	September 2020	December 2024
MT-3724 (Molecular Templates)	CD20	None	1/2	NCT02361346	R/R B-cell NHL, CLL	February 2015	September 2021
		Gemcitabine, oxaliplatin	2	NCT03488251	R/R B-cell NHL	August 2018	February 2023
		Lenalidomide	2	NCT03645395	R/R B-cell NHL	April 2019	July 2022
TRPH-222 (Triphase)	CD22	None	1	NCT03682796	R/R DLBCL, MCL, FL, MZL	October 2018	August 2022
Camidanlumab tesirine (Cami, ADCT-301; ADC Therapeutics)	CD25	None	2	NCT04052997	R/R HL	September 2019	May 2024
Naratuximab emtansine (Debio1562, IMG592; Debiopharm)	CD37	Rituximab	2	NCT02564744	R/R DLBCL, MCL, FL, MZL	June 2016	January 2021
STRO-001 (Sutro Biopharma)	CD74	None	1	NCT03424603	R/R B-cell NHL, MM	February 2018	November 2023
VLS-101 (VelosBio)	ROR1	None	1	NCT03833180	R/R B cell NHL, CLL, Richter transformation, T-cell NHL, ALL, AML, Waldenström macroglobulinemia	February 2019	June 2021

ADC, antibody-drug conjugate; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed or refractory.

Recently, the results of an important phase 1b/2 study of PV have provided important insight into how and where in the lymphoma treatment algorithm this agent should be used. Prior studies as well as exposure-response and time-to-event analyses revealed the cumulative nature of peripheral neuropathy leading to PV discontinuations.³⁵ In turn, dosing of PV was limited to 1.8 mg/kg. This multiarm study³⁶ explored PV combined with the alkylating agent bendamustine plus the second-generation anti-CD20

mAb obinutuzumab (Gazyva). It also explored a randomized comparison of PV plus bendamustine and rituximab (BR) vs BR alone, in the autoSCT-ineligible R/R DLBCL setting. Impressively, in the randomly assigned cohort (40 patients per arm), patients receiving PV with BR had a significantly higher CR rate (40% vs 17%), as well as longer median PFS (9.5 vs 3.7 months) and median OS (12.4 vs 4.7 months) compared with patients receiving BR alone. Of the responses to PV with BR, 64% (16/25) lasted at least

6 months and 48% (12/25) lasted at least 12 months. Rates of neutropenia, anemia, and thrombocytopenia were higher in patients receiving PV in addition to BR, but grade 3 to 4 infection rates were similar between the 2 cohorts. Peripheral neuropathy associated with PV occurred in 43% of patients but was typically grade 1 to 2 and resolved in most patients. In turn, PV was approved for use with BR under the FDA's accelerated approval program for the R/R DLBCL setting. Of note, prophylaxis for both *Pneumocystis*

jiroveci pneumonia and herpes virus should be given throughout treatment with this regimen.³⁷

In parallel, PV was studied in a phase 1b/2 trial in combination with either rituximab or obinutuzumab, plus cyclophosphamide, doxorubicin, and prednisone (CHP) in patients with previously untreated DLBCL.³⁸ In 66 patients who received PV at 1.8 mg/kg, hematologic toxicities and peripheral neuropathy were common but occurred at expected rates. The ORR was 89% (59/66) with 77% of patients achieving CR. Ongoing exploration of PV includes the follow-up phase 3 POLARIX study of PV plus rituximab (R) and CHP vs traditional frontline R-CHOP (CHP plus vincristine) in untreated DLBCL, the phase 3 POLAR BEAR study of PV plus R-mini-CHP vs R-mini-CHOP in elderly and/or frail patients with untreated DLBCL, as well as studies of PV in combination with atezolizumab (Tecentriq; anti-PD-L1) or mosunetuzumab (an anti-CD3/CD20 bispecific antibody).

ADCs in Development for Lymphoma CD19

Loncastuximab tesirine (lonca or ADCT-402) is an ADC targeting CD19, an antigen expressed early in B-cell development starting at the pro-B-cell stage, making this an attractive target for both B-cell lymphoblastic leukemia as well as lymphomas derived from B-cells through the late plasmablast stage.³⁹ This agent incorporates a humanized anti-CD19 IgG1 mAb and a PBD dimer payload attached via a protease-cleavable valine-alanine linker.⁴⁰ A multicenter, open-label, phase 1 dose-escalation (15 to 200 µg/kg) and dose-expansion study of lonca enrolled 88 patients with R/R B-cell NHL.⁴¹ Common AEs included cytopenias, fatigue, edema, liver test abnormalities, nausea, rash, and dyspnea. The ORR at doses >120 µg/kg was 59% (41/69), with 40% CR and 19% PR rates. Median DOR, PFS, and OS were 4.8, 5.5, and 11.6 months, respectively.

There was moderate drug accumulation with higher doses, but no evidence of immunogenicity. The subsequent multicenter, open-label, phase 2 LOTIS-2 study treated 145 patients with R/R DLBCL, high-grade B-cell lymphoma, or primary mediastinal B-cell lymphoma with lonca monotherapy dosed at 150 µg/kg every 3 weeks for 2 cycles, then 75 µg/kg every 3 weeks for subsequent cycles for up to 1 year.⁴² Data from this study were presented in mid-2020, and they observed an ORR of 48% (70/145), with 24% CR and 24% PR; median DOR was 10.3 months. These promising results motivated a September 2020 submission of a biologics license application to the FDA for lonca for the treatment of patients with R/R DLBCL. Two additional ongoing phase 1 studies are exploring lonca in combination with either ibrutinib (Imbruvica; an oral Bruton tyrosine kinase inhibitor) or durvalumab (Darzalex; anti-PD-L1). Finally, a phase 3 study has been announced that will incorporate a safety run-in to explore combining lonca with rituximab; it will then randomize patients with R/R DLBCL to lonca plus rituximab vs chemotherapy (gemcitabine and oxaliplatin) with rituximab.

Less successful than lonca has been an alternative anti-CD19 ADC agent, coltuximab ravtansine (SAR3419). It incorporates a humanized anti-CD19 IgG1 mAb with DM4 (a microtubule-targeting maytansine derivative) payload, linked via an N-succinimidyl-4-(2-pyridylthio) butyrate glutathione-sensitive linker.⁴³ The initial phase 1 study of SAR3419 (administered weekly at doses between 5 and 70 mg/m²) observed episodes of grade 3 optic neuropathy and grade 3 paresthesia, which were reversible but led to treatment discontinuation.⁴⁴ Due to this and other clinical evidence of cumulative toxicities, the study transitioned to a dosing schedule of 4 weekly doses followed by 4 biweekly doses. The ORR was 30% in the total cohort, with dosing schema not significantly impacting response rate. Two phase 2 studies explored SAR3419 in

R/R DLBCL, either as a monotherapy or in combination with rituximab.^{45,46} In the monotherapy group, the ORR was 44% (18/41) with median DOR, PFS, and OS of 4.7, 4.4, and 9.2 months, respectively. Grade 3-4 AEs were reported in 38% of patients, and eye disorders (all grade 1-2) occurred in 25% of patients. The combination of rituximab and SAR3419 in the R/R DLBCL setting failed to meet its primary end point, observing an ORR of 31%. Likely due to the modest clinical activity of this agent and the various toxicities, there are no ongoing clinical trials for SAR3419.

Denintuzumab mafodotin (SGN-CD19A) is another ADC targeting CD19 and it incorporates an MMAE payload. It was studied in a phase 1 trial⁴⁷ in R/R B-cell NHL, and the MTD was not reached (0.5 to 6 mg/kg every 21 days). Only 1 DLT was observed (grade 3 keratopathy at 3 mg/kg), but the reported AEs included blurry vision (65%), dry eye (52%), fatigue (35%), keratopathy (35%), constipation (29%), photophobia (27%), and nausea (26%). Overall, 33% (20/60) of efficacy-evaluable patients achieved objective responses, including 22% (13/60) with CRs. Randomized phase 2 trials to evaluate rituximab plus ifosfamide, carboplatin, and etoposide salvage treatment with or without SGN-CD19A were opened but later terminated due to sponsor decision based on portfolio prioritization.

CD20

MT-3724 is an ADC specifically targeting CD20, which is expressed from the pre-B-cell stage through the plasmablast stage, and this agent possesses multiple unique design features. Specifically, in contrast to the common intact IgG mAb, MT-3724 utilizes a single-chain variable fragment (scFv), and it is connected via a peptide linker to an irreversible ribosome inhibitor derived from the Shiga-like toxin (SLT) A subunit. CD20 is a noninternalized surface antigen, thus MT-3724 exploits proprietary engineered toxin

bodies technology to achieve intracellular localization.⁴⁸ Specifically, SLTA is normally coupled to its cognate SLTB subunit to target the CD77 cell-surface marker, a noninternalizing glycosphingolipid. In MT-3724, a genetically engineered SLTA subunit with no cognate SLTB component is able to trigger spontaneous internalization, and it then goes on to inhibit protein translation. A multicenter, open-label, phase 1 dose-escalation and dose-expansion study of MT-3724 monotherapy in patients with R/R NHL is ongoing.⁴⁹ Preliminary analyses reported an ORR of 38%. Interestingly, the development of ADAs did not preclude benefit of MT-3724. Other ongoing studies of MT-3724 include phase 2 trials combining this agent with gemcitabine and oxaliplatin chemotherapy, or with lenalidomide, in the second-line, autoSCT-ineligible, R/R DLBCL setting. An unplanned interim analysis of the study of MT-3724 plus lenalidomide found grade 2 capillary leak syndrome was occurring at lower doses of MT-3724 than expected.⁵⁰ Thus, a modified MT-3724 dosing schedule (twice weekly rather than 3 times weekly) is under development. Preliminary response data revealed 2 CRs and 3 PRs in the 7 evaluable patients.

CD22

CD22 is a member of the sialic acid-binding immunoglobulin-like lectin receptor family, and it is expressed on the surface of immature and mature B-cells. It plays a critical role in baseline BCR signaling inhibition and is rapidly internalized upon antibody binding. Inotuzumab ozogamicin is an ADC that targets CD22 with a humanized IgG4 mAb that uses an acid-labile covalent linker to attach a semisynthetic calicheamicin derivative that binds DNA and triggers strand scission.⁵¹ Inotuzumab ozogamicin monotherapy is approved for R/R B-cell acute lymphoblastic leukemia, and it is also being increasingly incorporated off-label into lower-intensity frontline combination approaches for patients who

are less fit.⁵²⁻⁵⁴ Its study in lymphoma has shown mixed results. A phase 1 study⁵⁵ of inotuzumab ozogamicin in the R/R B-cell NHL setting tested doses between 0.4 and 2.4 mg/m², administered once every 3 or 4 weeks. The MTD was determined to be 1.8 mg/m², and common AEs included thrombocytopenia (90%), asthenia (67%), nausea (51%), and neutropenia (51%). The ORR was 39% (68% for FL; 15% for DLBCL) for the 79 enrolled patients. Among the follow-up studies, a phase 2 trial administered inotuzumab ozogamicin with rituximab every 3 weeks for 3 planned cycles (but up to 6 were permitted), followed by high-dose therapy and autoSCT in patients with high-risk R/R DLBCL.⁵⁶ Sixty-three patients enrolled, and the ORR after 3 cycles (the primary end point) was 28.6%. Eighteen patients underwent autoSCT, with serious infections and hepatic toxicity following autoSCT occurring in 33% and 22%, respectively. The 1-year PFS for all enrolled patients was 29% (median PFS, 3.0 months), thus showing lower-than-expected activity as a salvage regimen for transplant-eligible patients with DLBCL.

Another anti-CD22 ADC that is relatively early in development is TRPH-222. This agent incorporates a mAb containing formylglycine modifications to facilitate site-specific conjugation of a maytansinoid antimicrotubule payload via a noncleavable, protease-insensitive linker.⁵⁷ A multicenter, open-label, phase 1 study with dose escalation and dose expansion phases in R/R B-cell NHL is ongoing. TRPH-222 was dosed between 0.6 and 5.6 mg/kg every 21 days, and 26% (5/19) of evaluable patients achieved CR without reaching the MTD. In turn, a 10 mg/kg dosing cohort is being explored. Notably, peripheral neuropathy, which is common with antimicrotubule ADCs, has not been observed in the patients to date.

CD25

CD25, the interleukin-2 receptor alpha, is expressed on many tissues; these include

activated and regulatory T cells, activated B cells, a subset of thymocytes, myeloid precursors, and oligodendrocytes. It is overexpressed in a variety of malignant settings; therefore, camidanlumab tesirine (cami or ADCT-301) has been developed to combine a human anti-CD25 IgG1 that is conjugated via a dipeptide cleavable linker to a PBD dimer payload.⁵⁸ In vitro and in vivo studies found high potency of this agent, with significant bystander killing of CD25-negative cells. An initial multicenter, open-label, phase 1 study explored ADCT-301 in patients with R/R HL and NHL that express CD25.⁵⁹⁻⁶¹ Of a total of 77 treated patients, 65% had skin-related AEs; other AEs included liver function test abnormalities (39%), edema (25%), peripheral neuropathy (9%), and Guillain-Barre syndrome (GBS) and radiculopathy (6% each). In the 75 evaluable patients, ORR was 70.7% (53/75), with CR in 40 patients; in addition, the response rate was an impressive 93% in patients with R/R HL relapsing within 6 months of immune checkpoint inhibitor treatment. Based on this phase 1 study, the recommended phase 2 dose was 45 µg/kg every 3 weeks for 2 cycles followed by 30 µg/kg every 3 weeks. This phase 2 study was reopened for enrollment after being placed under a partial clinical hold to allow for exploration of the atypical toxicities, including GBS, from the phase 1 study.

CD37

CD37 is a member of the tetraspanin family and mediates aspects of immune response signal transduction.⁶² Its expression is restricted to hematopoietic cells, and it is most robustly found on mature B cells, with CD37 loss leading to spontaneous lymphomagenesis in a mouse model. Naratuximab emtansine (IMG529 or Debio1562) is an ADC that incorporates a humanized IgG1 anti-CD37 mAb, which on its own exhibits significant ADCC and CDC.⁶³ It uses a thioether linker that can undergo lysosomal cleavage to carry the

maytansinoid-derivative DM1 payload. IMGN529 was explored in a multicenter, open-label, phase 1 trial⁶⁴ in patients with R/R B-cell NHL. Of 49 patients receiving doses escalating from 0.1 to 1.8 mg/kg, DLTs included peripheral neuropathy, neutropenia, and thrombocytopenia. AEs led to treatment discontinuation in 20% of patients (10/50), with 16% (8/50) having serious treatment-related AEs, the most common being grade 3 febrile neutropenia. The MTD was determined to be 1.4 mg/kg every 3 weeks, with growth factor support being required. An objective response was achieved by 13% (5/39) of response-evaluable patients. After Debiopharm acquired IMGN529 from ImmunoGen, it was renamed Debio1562, and now a phase 2 study of this agent in combination with rituximab is underway.

CD70

CD70 is the ligand of the TNF receptor family member CD27, and it is expressed on a broad range of malignancies including lymphomas (about 50% to 60% of NHL).⁶⁵ SGN-CD70A is an ADC incorporating an anti-CD70 mAb with a protease-cleavable linker and a DNA-crosslinking PBD dimer payload. This agent has been studied only in a phase 1 trial including patients with relapsed renal cell carcinoma, mantle cell lymphoma (MCL), DLBCL, and FL grade 3.⁶⁶ It was administered at dose levels ranging from 8 to 200 µg/kg every 21 days, but because prolonged thrombocytopenia was observed, the study was amended to dose SGN-CD70A every 6 weeks. Overall, 20 patients with lymphoma were enrolled and treated, with an MTD of 30 µg/kg every 6 weeks being determined. Common AEs included

thrombocytopenia (75%), nausea (55%), anemia (50%), and fatigue (50%). Responses were seen only in 20% (4/20) of patients. Due to very modest single-agent activity and the frequency and severity of thrombocytopenia, no subsequent studies have been opened with this agent.

CD74

CD74 is a multifunctional protein that serves as an MHC class II chaperone; it partially localizes to the cell surface, where it is a receptor for macrophage migration inhibitory factor as well as a regulator of B-cell survival.⁶⁷ It is highly expressed on various B-cell malignancies, and STRO-001 is a novel ADC that incorporates an anti-CD74 mAb that uses a noncleavable linker to achieve site-specific attachment of 2 maytansinoid payloads.⁶⁸ An initial phase 1 trial that includes patients with R/R B cell NHL and multiple myeloma is underway. Preliminary results described common infusion reactions and 2 DLTs (one grade 3 and one grade 5 thromboembolic event, resulting in a protocol amendment requiring screening for thrombosis at baseline). No ocular toxicity signals had been observed and the MTD had not been reached. Both CRs and PRs have been observed in patients with DLBCL.

ROR1

ROR1, a transmembrane receptor, has been found to be expressed on multiple tumor types but not on normal adult tissues.⁶⁹ DLBCL, CLL, and MCL commonly express ROR1, motivating the development of VLS-101, an ADC that links an MMAE payload to the mAb cirmtuzumab. This agent incorporates a highly specific, humanized, IgG1 mAb that triggers rapid internalization and

trafficking to lysosomes. A phase 1 clinical trial of VLS-101 is ongoing in patients with R/R lymphomas and leukemias. One particularly promising feature of VLS-101 is its potential use in Richter syndrome (RS), as this agent has been effective in eliminating xenografts derived from RS patients in mice.

Conclusions

ADCs exploit the antigen specificity of mAbs to selectively deliver highly potent cytotoxic payloads to tumors while sparing normal tissues. Lymphomas present attractive clinical scenarios in which to utilize ADCs, in part due to their relatively unique surface antigen repertoires. The anti-CD30 agent brentuximab vedotin has been approved for use in untreated and R/R HL, as well as in several R/R T cell lymphomas. More recently, the anti-CD79b agent PV was approved for use in R/R DLBCL, and key clinical trials are underway to study the incorporation of this agent into frontline multiagent treatment regimens for DLBCL. Substantial advances in mAb optimization and linkage chemistry have facilitated significant progress in ADC design, leading to a number of novel agents recently entering clinical trials. Preliminary data suggest that several of these novel ADCs may possess attractive therapeutic windows, and subsequent studies will shed light on how to pair these therapies with other agents possessing complementary targets, mechanisms of action, and AE profiles. ■

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➤ For full reference list, visit cancernetwork.com/Lymphoma_ADC



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