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Antibody–drug conjugates for previously treated aggressive lymphomas: focus on polatuzumab vedotin

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ABSTRACT

Introduction: Antibody-drug conjugates (ADCs) are immunoconjugates and comprise a monoclonal antibody that is chemically attached to a cytotoxic drug (or payload) via a stable chemical linker. Since the approval of the first ADC in 2000, there are now nine different approved agents and over 100 ADCs in the drug-development pipeline.

Areas covered: This review briefly describes the ADCs approved for treatment of lymphoma and their distinguishing factors in terms of target, linker and payload. The clinical implications of the use of ADCs are also considered. Here, we focus on polatuzumab vedotin, an ADC targeted to CD79b, which is approved for the treatment of patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) who have received at least one (EU approval) or two (US approval) prior therapies and are not eligible for bone marrow transplantation. The characteristics of polatuzumab vedotin are discussed and clinical data are presented. The future of polatuzumab vedotin clinical development, and ADCs in general, are also considered.

Expert opinion: ADCs represent a significant advance in the treatment of lymphoma. Polatuzumab vedotin has shown clinical efficacy and a tolerable safety profile in both first-line and R/R DLBCL; future studies are planned to further investigate this ADC.

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Antibody-drug conjugate; polatuzumab vedotin; DLBCL; NHL; monoclonal antibody

1. Introduction

Antibody-drug conjugates (ADCs) represent a significant advance in oncology therapy, particularly in hematologic malignancies [1,2]. ADCs are immunoconjugates comprised of an engineered monoclonal antibody (mAb) that is chemically attached to a cytotoxic drug (or payload) via a stable chemical linker [1,3–5]. The antibody targets of ADCs are carefully selected for specific cells of interest, such as tumor cells of a particular lineage [6]. The major therapeutic advantage of ADCs is their ability to selectively deliver a potent cytotoxic agent to target cancer cells, thereby minimizing off-target effects [3,4,7,8]. The cytotoxic payload is released into target cancer cells only after internalization of the intact ADC, for example, via receptor-mediated endocytosis and trafficking to the lysosome, where the linker is subsequently cleaved by protein degradation [2,6]. The combination of drug specificity through the mAb component and the stability of the ADC in circulation prior to engagement with the target cell reduces the likelihood of systemic exposure, thus minimizing unwanted toxicity [7–10].

Since the approval of the first ADC in 2000, the field has expanded considerably. There are now five different approved ADCs for malignant diseases, four for the treatment of solid tumors (ado-trastuzumab emtansine, enfortumab vedotin, famtrastuzumab deruxtecan-nxki, and sacituzumab govitecan-hziy), and more than 100 ADCs in the drug-development pipeline [3,9]. In this review, we compare ADCs approved for the treatment of hematologic malignancies, in terms of their primary components (antibody target, linker, and payload) and their clinical utility. We focus primarily on the differentiating characteristics of polatuzumab vedotin, recently approved for relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL), compared with other approved ADCs.

2. ADCs approved for the treatment of hematologic malignancies

Five ADCs have received approval for the treatment of lymphomas or leukemias: gemtuzumab ozogamicin, brentuximab vedotin, inotuzumab ozogamicin, moxetumomab pasudotox, and polatuzumab vedotin [1,11].

2.1. Gemtuzumab ozogamicin

Gemtuzumab ozogamicin is a recombinant, humanized immunoglobulin (Ig)G4 mAb with a high affinity to the CD33 receptor. The antibody is attached via a hydrolysable, bifunctional, and acid-labile linker to a cytotoxic derivative of calicheamicin [3,12,13]. Gemtuzumab ozogamicin was first approved in 2000 for CD33-positive acute myeloid leukemia (AML) but was

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Article highlights

- Antibody-drug conjugates (ADCs) represent a significant advance in oncology therapy, particularly for hematologic malignancies.
- Five ADCs are approved for hematologic malignancies, including polatuzumab vedotin, which is approved for treatment of relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL).
- The ADCs approved for hematologic malignancies differ in terms of their target antigen, antibody structure, linker, and/or payload.
- Polatuzumab vedotin has shown clinical activity and a tolerable safety profile in both the frontline and R/R DLBCL settings, with future studies planned to further investigate this ADC in these and other B-cell NHL subtypes.

withdrawn from the market in 2010, due to increased early deaths seen in newly diagnosed AML patients receiving this agent in combination with intensive chemotherapy. However, in 2017, new data based on a fractionated dosing schedule supported its re-approval for patients with newly diagnosed and R/R AML [12,14].

2.2. Brentuximab vedotin

Brentuximab vedotin is an ADC comprising an anti-CD30 chimeric IgG1 mAb conjugated to monomethyl auristatin E (MMAE) via a protease-cleavable linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (vc) [1,15]. Brentuximab vedotin received its first approval in 2011, and in the USA is currently indicated for patients with previously untreated Stage III or IV classical Hodgkin lymphoma, previously untreated systemic anaplastic large cell lymphoma (ALCL) or other CD30-expressing peripheral T-cell lymphomas, and relapsed systemic and primary cutaneous ALCL or CD30-expressing mycosis fungoides [15].

2.3. Inotuzumab ozogamicin

Inotuzumab ozogamicin is an ADC composed of a humanized anti-CD22 IgG4 mAb conjugated to a semisynthetic derivative of calicheamicin via an acid-labile linker [1–3]. Inotuzumab ozogamicin was approved in 2017 for the treatment of adults with R/R CD22-positive B-cell-precursor acute lymphoblastic leukemia (ALL) [16,17].

2.4. Moxetumomab pasudotox

Moxetumomab pasudotox is an anti-CD22 ADC containing the fragment variable of a recombinant murine mAb (with higher affinity for CD22 than the parent compound) genetically fused to *Pseudomonas aeruginosa* exotoxin (PE38) [1,2]. Moxetumomab pasudotox was approved in 2018 for patients with R/R hairy cell leukemia (HCL) who have received at least two prior systemic therapies, including a purine nucleoside analog [18].

2.5. Polatuzumab vedotin

Polatuzumab vedotin comprises a humanized IgG1 anti-CD79b mAb conjugated to MMAE via the protease-cleavable linker, vc (Figure 1) [19]. Polatuzumab vedotin was approved in 2019 for the treatment of R/R DLBCL after at least two prior therapies (US approval) or at least one prior therapy (EU approval) and who are ineligible for autologous stem cell transplantation (ASCT), in combination with bendamustine and rituximab (pola-BR) [20].

3. Differences between approved ADCs

Multiple components of the ADC influence the potency, efficacy, and safety of the drug, including the antibody (and biologic properties of the cell-surface target antigen), linker chemistry and the cytotoxic payload (Figure 2) [2,5,7,9,10,21–23]. The ADCs approved for hematologic malignancies differ in terms of their target antigen, antibody structure, linker, and/or payload (Table 1).

3.1. Target cell antigen and mAb structure

Selection of the target antigen for the mAb is an important component of an effective ADC – the target antigen should be highly expressed on malignant cells, and intracellular internalization should be triggered by mAb binding [1]. Hematologic malignancies have many surface antigens that are potential targets for ADCs [24]. Normal hematologic cells may also

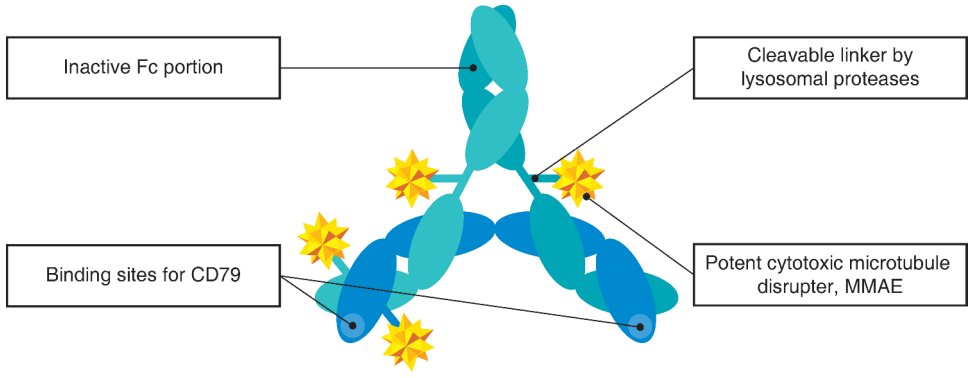
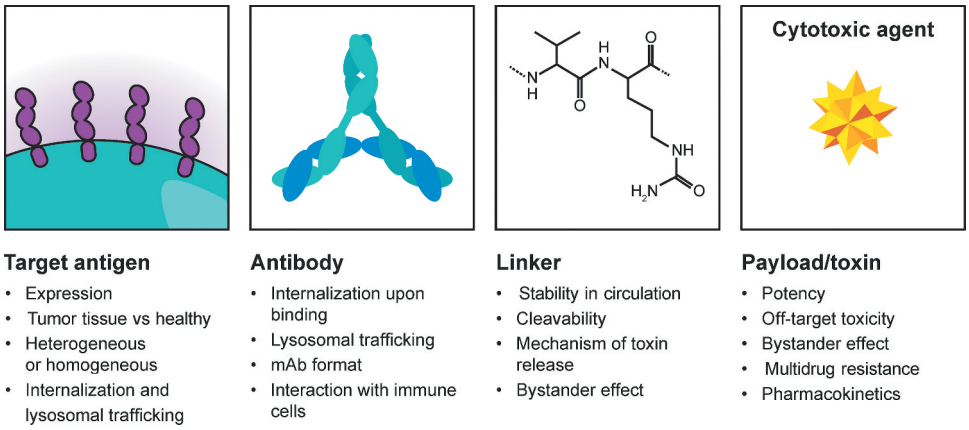


Figure 1. Structure of polatuzumab vedotin [36,43,46].
MMAE: monomethyl auristatin E; vc: maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl



ADC: antibody-drug conjugate; Ab: monoclonal antibody.

Figure 2. Factors affecting the potency, efficacy and safety of ADCs [2,5,7,9,10,21–23].

Table 1. Structural and mechanistic differences between ADCs approved for the treatment of hematologic malignancies.

ADC	Target antigen	mAb	Linker	Payload	Mechanism(s) of action
Gemtuzumab ozogamicin	CD33	Humanized IgG4	Cleavable, hydrolysable (acid labile)	Calicheamicin	Double-strand DNA breaks, cell-cycle arrest and apoptosis
Brentuximab vedotin	CD30	Chimeric IgG1	Protease-cleavable (vc)	MMAE	Microtubule disruption, cell-cycle arrest and apoptosis, plus ADCP
Inotuzumab ozogamicin	CD22	Humanized IgG4	Cleavable, hydrolysable (acid labile)	Calicheamicin	Double-strand DNA breaks, cell-cycle arrest and apoptosis
Moxetumomab pasudotox	CD22	Recombinant murine mAb (Fv fragment)	Recombinant fusion protein with furin cleavage site	*Pseudomonas aeruginosa* exotoxin (PE38)	Adenosine diphosphate-ribosylation of elongation factor 2, inhibition of protein synthesis, and apoptotic cell death
Polatuzumab vedotin	CD79b	Humanized IgG1	Protease-cleavable (vc)	MMAE	Microtubule disruption, cell-cycle arrest and apoptosis, plus antibody-mediated opsonization and ADCC

ADC: antibody-drug conjugate; ADCC: antibody-dependent cellular cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; Fv: fragment variable; Ig: immunoglobulin; mAb: monoclonal antibody; MMAE: monomethyl auristatin E; vc: maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl

express these targets, but in some cases, such as with normal B-cells and rituximab, the depletion of normal cells may be manageable in the setting of cancer treatment [19,25]. It is worth noting that hematologic targets are lineage-specific antigens, rather than targets associated with tumor growth as often described for solid tumors (e.g., HER2 overexpression in HER2-positive breast cancer) [26].

The effectiveness of an ADC is dependent not only on the characteristics of the target antigen, but also on the characteristics of the mAb. Ideally, the mAb component of an ADC should have minimal immunogenicity. This may be achieved by selecting a humanized or fully human antibody [3]. The mAb should also exhibit antigen (target) specificity and affinity, efficient internalization and have a long half-life in circulation. Factors that affect the mAb affinity for antigen and the ability to elicit immune effector functions (e.g., antibody-dependent cellular cytotoxicity [ADCC] and antibody-dependent cellular phagocytosis [ADCP]) include the IgG subclass and engineering of the Fc domain of the antibody. IgG1 antibodies, such as brentuximab vedotin and polatuzumab vedotin and IgG4 antibodies, such as gemtuzumab ozogamicin and inotuzumab ozogamicin are often used in ADCs. The chosen IgG subclass, as well as engineering of the Fc domain, has an impact on the antigen affinity and immune effector functions (e.g., ADCC and ADCP) of the drug. For example, IgG4 antibodies have reduced effector functions, including ADCC, compared with IgG1 antibodies [27].

Gemtuzumab ozogamicin targets CD33, which is expressed on hematopoietic cells of the myeloid lineage and myeloblasts in >80% of patients with AML [12]. Brentuximab vedotin targets CD30, a member of the tumor necrosis factor receptor family, expressed on the Reed–Sternberg cells in Hodgkin lymphoma and ALCL cells. *In vitro* data suggest that signaling through CD30-CD30L binding may affect cell survival and proliferation [15]. Inotuzumab ozogamicin and moxetumomab pasudotox bind to CD22, a B-cell-specific transmembrane protein responsible for the activation and regulation of B cells, with expression restricted to the B-cell lineage in most B-cell leukemia and lymphomas [3,16]. CD22 is expressed on leukemic blasts in >90% of ALL patients [28] and is highly expressed in HCL [29].

Polatuzumab vedotin binds to CD79b, a transmembrane protein and signaling component of the B-cell receptor that is expressed exclusively on the surface of normal and malignant B cells, but not on plasma cells and other hematologic cells [19,30,31]. This B-cell-restricted expression profile [32,33,34,35] makes CD79b a highly specific and appropriate target antigen for an ADC in patients with B-cell non-Hodgkin lymphoma (NHL). Unlike CD20, which is targeted by several currently available agents for the treatment of B-cell malignancies (such as rituximab), CD79b is rapidly internalized to the lysosomal compartment of the B cell upon antibody binding [30,36]. This provides an efficient means of delivering a cytotoxic agent to its required site of action within the cell.

This efficient internalization relates to the function of CD79b in class II antigen presentation [30,36]. It is worth noting that for polatuzumab vedotin, the engineering of Fc domain renders the ADCC/ADCP function of the mAb relatively inert, therefore the mechanism of action is driven primarily through the payload. In preclinical studies, administration of anti-CD79b ADC in cynomolgus monkeys (with surrogate anti-CD79b monkey antibody) resulted in an initial depletion of total B-cells by antibody-mediated opsonization followed by preferential, sustained depletion of proliferating B-cells (versus non-proliferating B-cells) by MMAE [37].

3.2. Linker

The chemistry of the linker and the sites of conjugation determine how and when the payload is released from the mAb, the pharmacokinetics and pharmacodynamics of the ADC, and its therapeutic index [3,5]. To avoid off-target toxicity, the linker should be stable in circulation and only be released following mAb binding and subsequent internalization into the malignant cell [3,38]. The vast majority of ADCs incorporate release mechanisms that enable controlled linker cleavage at the target site (i.e. they are 'cleavable'), though some have 'non-cleavable' linkers [11,22,39].

Cleavable linkers can release their payload in response to certain environmental conditions, such as low pH within the endosome/lysosome, as for the acid-sensitive hydrazone linkers used in gemtuzumab ozogamicin and inotuzumab ozogamicin, or in response to cellular processes such as proteolysis, as for brentuximab vedotin/polatuzumab vedotin [3]. Protease-cleavable linkers include dipeptide sequences like vc (used in brentuximab vedotin/polatuzumab vedotin) and valine-alanine (va).

The cathepsin-B-sensitive vc linker used in brentuximab vedotin and polatuzumab vedotin is degraded after internalization, not in the systemic circulation, because of the higher pH and absence of cathepsin B outside the cell. This feature of the vc linker offers an advantage over the hydrazone linker present in gemtuzumab ozogamicin (or inotuzumab ozogamicin), which has been associated with nonspecific breakdown outside of the target cell [9,22].

Non-cleavable linkers are more stable than cleavable linkers, but they depend on degradation of the entire antibody by the lysosome to release the payload. Examples of non-cleavable linkers include the thioether linkers N-succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate and maleimidocaproyl [1]. There is little potential for a 'bystander killing' effect with non-cleavable linkers because of the lack of cell permeability of the released payload that remains conjugated to a hydrophilic amino acid via a non-cleavable linker. Non-cleavable linkers are therefore most effective in the treatment of hematologic cancers/tumors with high antigen expression [39]. An example of an ADC with a non-cleavable linker is adotrastuzumab emtansine, used in breast cancer [26].

3.3. Payload

The payload of ADCs most often comprises either tubulin- or DNA-binding agents. As ADCs deliver a limited number of drug molecules to the target cell, the chosen payload must be highly cytotoxic [6]. The chemistry of the ADC also affects whether the cytotoxic payload can diffuse into surrounding cells, and lead to 'bystander killing' [40].

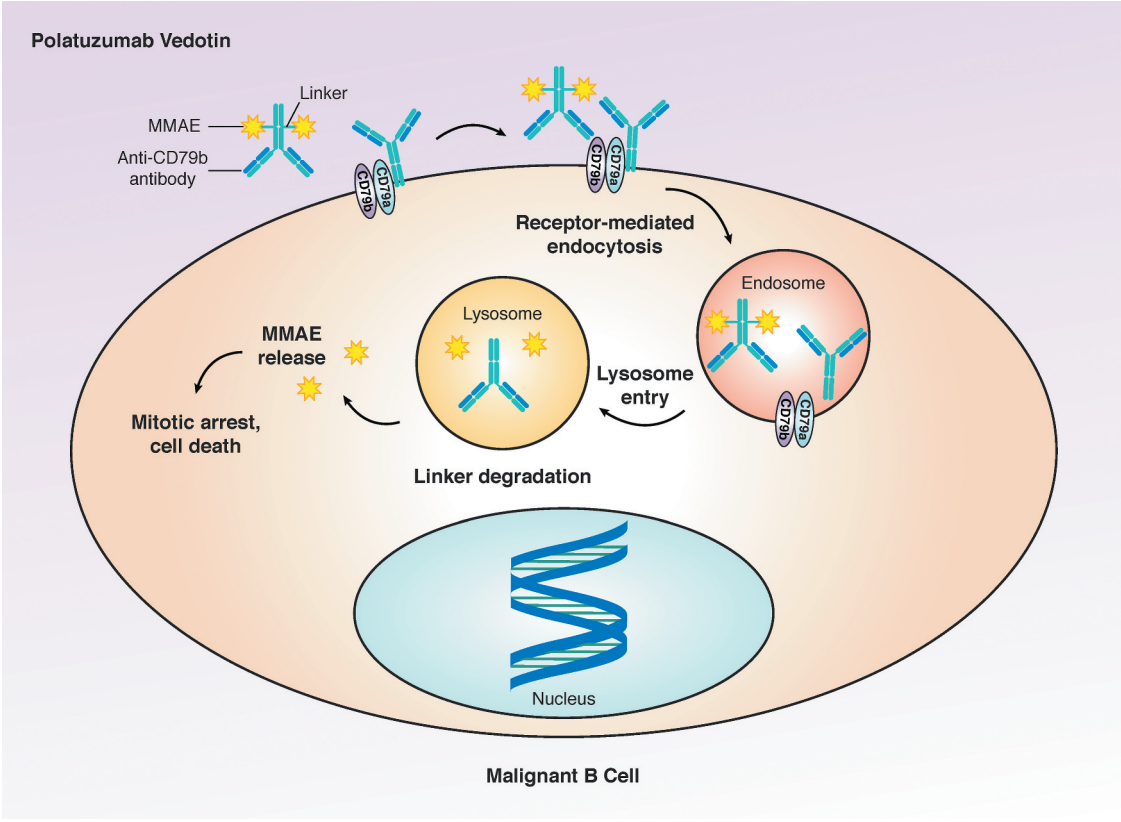
MMAE, the payload used in brentuximab vedotin and polatuzumab vedotin, is an auristatin derivative, a potent, synthetic small molecule that promotes cell death by binding to tubulin and disrupting the microtubule network in dividing cells, causing G2/M phase cell cycle arrest [3,41,42,44]. MMAE is 100–1000 times more potent that vincristine [45,46] and is toxic to neighboring cells through the bystander effect [1]. As cells undergoing mitosis are susceptible to MMAE, many non-malignant B-cells remain unaffected [6]. Another example of an auristatin derivative being used in ADCs in development is monomethyl auristatin F (mafodotin).

DNA-damaging agents being used as payloads (in approved or investigational ADCs) include calicheamicin, pyrrolobenzodiazepines, indolinobenzodiazepines, duocarmycins, and doxorubicin. Derivatives of calicheamicin are utilized in gemtuzumab ozogamicin and inotuzumab ozogamicin [1]. Moxetumomab pasudotox incorporates a truncated form (38 kDa fragment) of Pseudomonas exotoxin, known as PE38 [47]. This belongs to the A-B toxin class, which becomes active on cellular update via receptor-mediated endocytosis [38,48], and inhibits protein synthesis, but is not classed as a DNA-damaging agent.

ADC efficacy depends on both its intracellular trafficking and the mechanism(s) by which tumor cell death is triggered (by the payload, but also via the mAb) [5]. The inherent sensitivity of tumor cells to the payload is another variable that affects ADC efficacy, although this is difficult to quantify. When gemtuzumab ozogamicin is bound to CD33, the ADC is internalized and linker cleavage occurs in the lysosome or endosome. The free calicheamicin derivative causes breaks in double-strand DNA, cell cycle arrest and apoptosis [3,12]. Preclinical data suggest that the anticancer activity of brentuximab vedotin follows rapid internalization of the ADC-CD30 complex and the release of MMAE via proteolytic cleavage. In addition to MMAE-mediated cell cycle arrest and apoptosis, *in-vitro* data suggest that ADCP occurs [3,15]. Following internalization of the ADC-CD22 complex of inotuzumab ozogamicin, calicheamicin is released in the cell via hydrolytic cleavage of the linker. Intracellular glutathione reduces the calicheamicin to its active form, thus inducing double-strand DNA breaks and inducing cell cycle arrest and apoptotic cell death [3,16]. Internalization of moxetumomab pasudotox via CD22 binding results in adenosine diphosphate-ribosylation of elongation factor 2, inhibition of protein synthesis, and apoptotic cell death [18]. The mechanism of action of polatuzumab vedotin is mostly MMAE-mediated target-cell death (Figure 3). However, antibody-mediated opsonization and ADCC also play a role, in contrast with the minimized ADCC/ADCP function due to the Fc engineering [6,37]. Because of its selectivity, polatuzumab vedotin does not cause hematopoietic stem-cell toxicity [6].

3.4. Ratio of mAb to payload and payload/mAb conjugation

The ratio of mAb to payload (or drug–antibody ratio [DAR]) is the average number of payload molecules attached to a single



MMAE: monomethyl auristatin E.
Figure 3. Mechanism of action of polatuzumab vedotin. Adapted with permission from [6].

mAb. The DAR affects drug stability in the circulation, as well as the potency, antitumor efficacy, and toxicity of the ADC. The DAR can range from 0 to 8. An optimal DAR has not yet been fully established [3], although a ratio of 2–4 cytotoxic drugs per mAb may allow the best balance between potency and slow clearance. The higher the DAR, the higher the clearance [2]. Most ADCs have a DAR of 3.5–4, which, if the number of antigens on the tumor cell surface is low, can lead to a small amount of drug being delivered to malignant cells [2]. The DAR of polatuzumab vedotin and brentuximab vedotin are 3.5 and 4 MMAE molecules per antibody molecule, respectively [49,50]. The DAR of gemtuzumab ozogamicin is 2–3 calicheamicin molecules per antibody molecule [51]. If DAR values are too high, the risk of unwanted off-target (*in-vitro*) effects may increase [3].

Multiple conjugation strategies are used to attach linkers to a specific amino acid residue on the mAb e.g., lysine (gemtuzumab ozogamicin and inotuzumab ozogamicin) or cysteine (brentuximab vedotin and polatuzumab vedotin) [6,9,39]. Nonspecific linker binding can be disadvantageous to the performance of ADCs, as it can lead to variations in DARs, as well as cytotoxicity or pharmacokinetics [6]. THIOMAB® technology is a site-specific antibody conjugation that was developed to reduce ADC heterogeneity. Reactive cysteine residues are engineered into specific sites on the antibody, allowing drug conjugation with defined stoichiometry, but without disrupting interchain disulfide bonds [52]. The THIOMAB® ADC (TDC) DCDS0780A is comprised of MMAE conjugated with an anti-CD79b mAb via a protease labile linker [53]. A phase I dose escalation study of this TDC in patients with R/R B-cell NHL was conducted; however, further development was discontinued due to the observed ocular toxicity and the clinical efficacy of polatuzumab vedotin [53].

4. Polatuzumab vedotin clinical data in DLBCL

Several trials have been conducted to assess the efficacy and safety of polatuzumab vedotin in patients with NHL, including DLBCL (Table 2). The results have demonstrated clinical benefit, with promising response rates, durability of responses, survival outcomes, and a favorable safety profile.

4.1. Polatuzumab vedotin in R/R NHL

The greatest unmet need in DLBCL is an effective management of patients with R/R disease, particularly those who are not eligible for high-dose therapy plus ASCT or salvage chemotherapy, or those who relapse after ASCT, where the survival prognosis is very poor [54–56]. There have been several studies of polatuzumab vedotin in this setting.

4.1.1. Phase II randomized study of polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with R/R NHL (ROMULUS)

Single-agent polatuzumab vedotin (2.4 mg/kg every 21 days) had encouraging clinical activity in a phase I trial of patients with R/R B-cell NHL [19]. Pinatuzumab vedotin, another ADC

Table 2. Summary of polatuzumab vedotin clinical trials in NHL indications.

Trial name (NCT number)	Phase	Patient population(s)	Polatuzumab vedotin (pola) regimen(s)	Status	Primary results publication
GO01294 (NCT01290549)	I	R/R NHL, CLL	Pola, Pola-R	Complete	[19]
GO29044 (NCT01992653)	I/II	1L NHL	Pola plus R-CHP or G-CHP	Complete	[63]
ROMULUS (NCT01691898)	I/II	R/R DLBCL	Pola-R or Pola-G	Complete	[59]
GO29365 (NCT02257567)	I/II	R/R DLBCL, FL	Pola-BR or Pola-BG	Active, not recruiting	[60,61]
POLARIX (NCT03274492)	III	R/R DLBCL	Pola plus R-CHP (versus R-CHOP)	Recruiting	-
POLARGO (NCT04182204)	III	R/R DLBCL	Pola plus R-GemOx (versus R-GemOx)	Recruiting	-
GO29833 (NCT02611323)	I	R/R FL or DLBCL	Pola-R or Pola-G plus venetoclax	Recruiting	-
GO29834 (NCT02600897)	I	R/R FL or DLBCL	Pola-R or Pola-G plus lenalidomide	Recruiting	-
GO40516 (NCT03671018)	I	R/R FL or DLBCL	Pola plus mosunetuzumab	Recruiting	-
GO40515 (NCT03677141)	I/II	R/R B-cell NHL 1L DLBCL	Pola-CHP plus mosunetuzumab	Recruiting	-
BO29561 (NCT02729896)	I/II	R/R FL, R/R DLBCL	Pola-G or Pola-R plus atezolizumab	Complete	-
NP39488 (NCT03533283)	I	R/R B-cell NHL	Pola plus RO7082859	Recruiting	-

1L: first line; CHP: cyclophosphamide, doxorubicin, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; G: obinutuzumab; GemOx: gemcitabine and oxaliplatin; NHL: non-Hodgkin lymphoma, R: rituximab; R/R: relapsed/refractory

using MMAE as the cytotoxic payload but targeting CD22, was also evaluated in a separate phase I trial in this patient population. Pinatuzumab vedotin as monotherapy and in combination with rituximab, demonstrated objective responses with acceptable safety at a dose of 2.4 mg/kg every 21 days [57]. The results of these phase I trials, together with evidence of an add-on effect of rituximab on the clinical activity of the anti-CD22 ADC inotuzumab ozogamicin in patients with NHL [58], were the drivers for the development of the phase II ROMULUS study (NCT01691898) [59].

In the ROMULUS study, patients with DLBCL or follicular lymphoma (FL) were randomized to treatment with either polatuzumab vedotin or pinatuzumab vedotin (2.4 mg/kg, the recommended phase II dose [RP2D] determined from the phase I trials) in combination with rituximab (pola-R; pina-R), every 21 days [59]. For the 39 patients with R/R DLBCL who received pola-R, the objective response rate (ORR) was 54% with a complete response (CR) rate of 21%. The median progression-free survival (PFS) was 5.6 months (95% confidence interval [CI] 4.3–12.8) and median duration of response [DOR] was 13.4 months (95% CI 6.5–21.2). As of 10 April 2017, median overall survival (OS) was 20.1 months (95% CI 10.4–38.6). For the 42 patients with R/R DLBCL who received pina-R, the ORR was 60% and 26% achieved CR. Median PFS was 5.4 months (95% CI 3.9–10.6), median DOR was 6.2 months (95% CI 3.6–12.4) and median OS was 16.5 months (95% CI 7.5–32.5). In the R/R DLBCL cohort of ROMULUS, grade 3–5 adverse events (AEs) occurred in 77% of 39 patients receiving pola-R (most common were neutropenia [23%], anemia [8%] and diarrhea [8%]; no grade 5 AEs) and 79% of 42 patients receiving pina-R (most commonly neutropenia [29%] and hyperglycemia [10%]; nine [21%] grade 5 AEs, five of which were infection-related). Based on the longer DOR and favorable benefit-risk profile for pola-R versus pina-R in ROMULUS, pola-R was selected for further clinical development in NHL.

4.1.2. Phase Ib/II trial of polatuzumab vedotin combined with bendamustine and obinutuzumab and with bendamustine plus rituximab (BR) versus BR alone (GO29365)

The US-approved indication for polatuzumab vedotin is for the treatment of patients with transplant-ineligible R/R DLBCL after at least two prior therapies (or after at least one prior therapy in the EU), when given in combination with BR [20]. This was based on the data obtained from a randomized phase II cohort of the phase Ib/II GO29365 (NCT02257567) trial. Pola-BR resulted in a significantly higher CR rate and a 58% reduction in the risk of death compared with BR alone in patients with transplantation-ineligible R/R DLBCL [60].

Eighty patients with R/R DLBCL were randomized to polatuzumab vedotin (1.8 mg/kg) plus BR, or BR alone, every 21 days for 6 cycles. Transplant-eligible patients were excluded but patients could have experienced treatment failure with prior ASCT. Forty patients were randomized to each arm and 39 in each arm received ≥1 treatment dose. The primary endpoint was independent review committee (IRC)-assessed CR rate measured by positron emission tomography-computed tomography (PET-CT) at end of treatment (EOT) by modified Lugano response criteria 6–8 weeks after Cycle 6 Day 1 or last dose of study treatment. Pola-BR patients completed more treatment cycles versus BR patients, with median of 5 versus 3 completed cycles, and 6 cycles completed by 46.2% versus 23.1% patients, respectively. Early treatment discontinuation due to progressive disease occurred in 15.4% of patients receiving pola-BR, compared with 53.8% for BR.

Efficacy outcomes at a median follow-up of 22.3 months in the phase II randomized cohort (N = 80) are shown in Table 3. IRC-assessed CR rates at EOT were significantly higher with pola-BR versus BR, with a stratified hazard ratio (HR) of 0.36 (95% CI 0.21–0.63; $p < 0.001$). Median IRC-assessed DOR was longer with pola-BR versus BR (stratified HR 0.47 [95% CI 0.19–1.14]), although this was not statistically significant. Investigator (INV)-assessed response and PFS outcomes were highly concordant with the IRC results. Although the study was not statistically powered for survival analyses, a significant benefit was seen in OS for pola-BR versus BR (stratified HR 0.42 [95% CI 0.24–0.75; $p = 0.002$]). Multiple Cox regression analyses showed that after adjusting for potential prognostic factors and baseline characteristics, the treatment effects on survival of pola-BR were consistent with the primary analysis.

Although rates of grade 3–4 anemia and thrombocytopenia were higher with pola-BR versus BR (28.2% versus 17.9%, and 41.0% and 23.1%, respectively), transfusion rates were similar

Table 3. Efficacy outcomes of polatuzumab vedotin.

	Pola-BR (n = 40)	BR (n = 40)
EOT, n (%)		
IRC ORR	18 (45.0)	7 (17.5)
CR	16 (40.0)	7 (17.5)
INV ORR	19 (47.5)	6 (15.0)
CR	23 (57.5)	8 (20.0)
IRC median DOR, months (95% CI)	12.6 (7.2–NE)	7.7 (4.0–18.9)
INV median DOR, months (95% CI)	10.3 (5.6–NE)	4.1 (2.6–12.7)
Median OS, months (95% CI)	12.4 (9.0–NE)	4.7 (3.7–8.3)
IRC median PFS, months (95% CI)	9.5 (6.2–13.9)	3.7 (2.1–4.5)
INV median PFS, months (95% CI)	7.6 (6.0–17.0)	2.0 (1.5–3.7)

CI: confidence interval; CR: complete response; DOR: duration of response; EOT: end of treatment, IRC: independent review committee; INV: investigator; NE: not estimable; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; Pola-BR: polatuzumab vedotin plus bendamustine-rituximab

between arms (erythrocytes: 25.6% versus 20.5%; platelets: 15.4% versus 15.4%, respectively). Grade 3–4 neutropenia was higher with pola-BR than BR (46.2% versus 33.3%, respectively), but grade 3–4 infections and infestations were similar (23.1% pola-BR and 20.5% BR). The overall incidence of peripheral neuropathy (PN) was 43.6% in the pola-BR arm (11 grade 1, 6 grade 2), with resolution in 10 patients and improvement in 1 patient at clinical cutoff. PN was the only reason for dose reduction of polatuzumab vedotin, which occurred in 2 patients (5.1%; grade 2), and both cases resolved. Fatal AEs occurred in 9 patients receiving pola-BR and 11 patients receiving BR, with infection being the most common cause (4 pola-BR, 4 BR); some within the setting of progressive disease.

Extended follow-up data (data cutoff 15 March 2019, median 30 months) have shown the sustained clinical benefits of pola-BR versus BR [57]. The median INV-assessed PFS with pola-BR versus BR was 7.5 months (95% CI 4.9–17.0) versus 2.0 months (95% CI 1.5–3.7), respectively; HR 0.33 (95% CI 0.20–0.56; p < 0.0001). Median OS was 12.4 (95% CI 9.0–32.0) versus 4.7 (3.7–8.3) months (HR 0.41; 95% CI 0.24–0.71; p = 0.0011). Median DOR for all responding patients in the pola-BR (n = 28) versus BR (n = 13) arms was 12.7 (95% CI 5.8–27.9) versus 4.1 (95% CI 2.6–12.7) months (HR 0.42; 95% CI 0.19–0.91). Median DOR for confirmed responders in the pola-BR (n = 19) versus BR (n = 7) arms was 27.9 (95% CI 10.3–not estimable [NE]) versus 12.7 (95% CI 7.7–NE) months (HR 0.44; 95% CI 0.14–1.32). Nearly half (47%, 9/19) of patients with confirmed responses to pola-BR remained event free (Figure 4). Of these 9 patients, 8 had DOR ranging from 22+ to 34 + months (1 patient consolidated with allogeneic transplant) and 1 patient withdrew early from the study after 14.5 months of response. No new safety signals were observed with long-term follow-up.

The GO29365 trial also evaluated the combination of polatuzumab vedotin plus bendamustine and obinutuzumab (pola-BG). In the phase Ib safety run-in and a phase II expansion cohort of GO29365, 27 patients with R/R DLBCL received pola-BG. The ORR was 40.7% and the CR rate was 29.6%; median IRC-assessed PFS was 6.3 months (95% CI 3.5–30.4) and median OS was 5.8 months (95% CI 5.8–33.8). There was no indication of benefit of obinutuzumab over rituximab in this setting [60].

4.2. Future directions for polatuzumab vedotin

4.2.1. Polatuzumab vedotin in previously-untreated DLBCL

Many patients with previously-untreated DLBCL, particularly those with high-risk disease, are not cured by the standard treatment of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) [55,62]. Given the clinical benefit of polatuzumab vedotin observed in patients with R/R DLBCL, a trial evaluating polatuzumab vedotin in previously untreated patients with DLBCL was performed [63].

In a phase Ib/II study (GO29044; NCT01992653) promising response rates and survival outcomes were observed with polatuzumab vedotin administered with rituximab or obinutuzumab plus cyclophosphamide, doxorubicin and prednisone (R-CHP/G-CHP) in a previously untreated, high-risk DLBCL population, irrespective of molecular subtype. MMAE, the cytotoxic payload of polatuzumab vedotin, is a rational substitution for vincristine in a CHOP-based regimen given their overlapping side effect profile and anti-tubulin mechanism of action [63].

The phase Ib dose escalation of GO29044 established the RP2D for polatuzumab vedotin when combined with

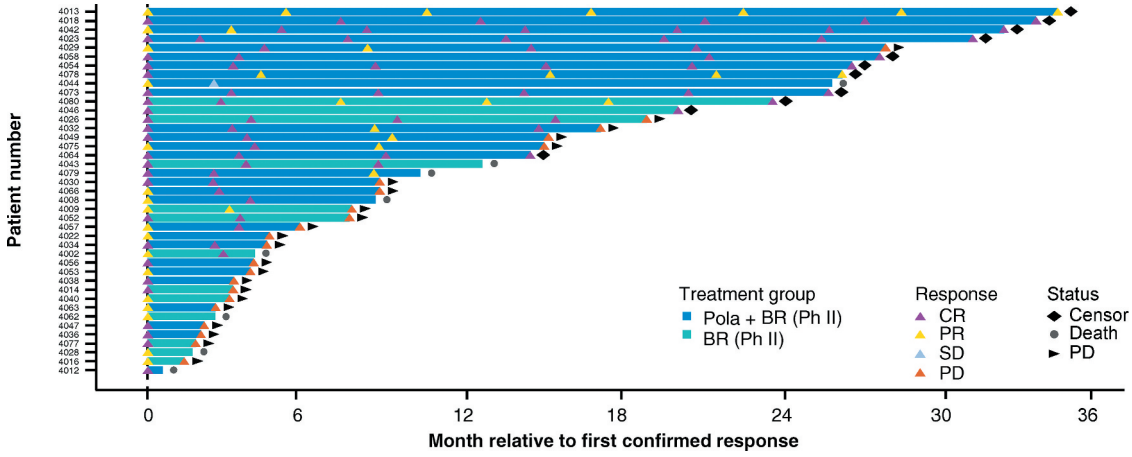


Figure 4. Duration of response by INV of polatuzumab vedotin [61].
BR: bendamustine-rituximab; CR: complete response; INV: investigator; PD: progressive disease; Ph: phase; Pola: polatuzumab vedotin; PR: partial response; SD: stable disease

immunochemotherapy as 1.8 mg/kg every 21 days. In total, 66 patients with previously untreated DLBCL received the RP2D of polatuzumab vedotin (1.8 mg/kg) plus R-CHP (n = 45) or G-CHP (n = 21) with a median study duration of 21.5 months. The median age of this combined cohort was 67.5 years; 65% of patients had an International Prognostic Index (IPI) score of 3–5. The ORR with polatuzumab vedotin plus R-CHP or G-CHP was 89%, including CR by PET-CT in 77% of patients. The 12- and 24-month PFS rates were 91% (95% CI 84–98) and 83% (95% CI 73–93), respectively. Post-hoc analyses showed no difference in PFS by number of treatment cycles planned (6 or 8), anti-CD20 antibody (R or G), and IPI category (0–2, 3 or 4–5). PFS was also similar irrespective of double expressor (MYC/BCL2) status and cell-of-origin (germinal center B-cell [GCB] and activated B-cell [ABC]). The 12-month OS rate was 94% (95% CI 88–100) and median OS was NE. The 12-month event-free survival (EFS) rate was 80% (95% CI 71–90). The proportion of patients with an ongoing response at 12 months was 95% (95% CI 89–100) and median DOR was not reached at the time of cutoff. Of 51/66 (77%) patients with previously untreated DLBCL who were evaluable for cell of origin, 25/28 patients (89%) with the GCB-like subtype and 13/16 (81%) patients with the ABC-like subtype achieved a CR by EOT. The ORR in the GCB group was 100%, compared with 88% for ABC DLBCL.

Polatuzumab vedotin plus R-CHP/G-CHP had an acceptable safety profile [58]. The most common grade ≥3 AEs were neutropenia (30%), febrile neutropenia (19%), infections (15%) and thrombocytopenia (9%), and the most common serious AEs were febrile neutropenia (14%), neutropenia (6%), and pneumonia (6%). Seven patients (11%) discontinued study treatment because of AEs after 1–5 cycles, including 4 (6%) who received G-CHP (pneumonia, myocardial infarction, prolonged thrombocytopenia, and fatal septic shock) and 3 (5%) who received R-CHP (complicated urinary tract infection, worsening of tremors, and syncope). Twenty-five patients (38%) experienced grade 1–2 PN and 7 (11%) continued to have PN at the data cutoff. Median time to resolution of all grades of PN from initial onset was 2.4 months (4.9 months for grade 2–3 PN).

Supported by the findings of the GO29044 study, the ongoing phase III POLARIX study (NCT03274492) is investigating the efficacy and safety of polatuzumab vedotin (1.8 mg/kg) plus R-CHP compared with R-CHOP in previously untreated DLBCL [64]. This international, randomized, double-blind, active-placebo-controlled study enrolled patients aged 18–80 years with DLBCL, Eastern Cooperative Oncology Group performance status 0–2, and an IPI score of 2–5. Patients are stratified by IPI score (2 versus 3–5), presence or absence of bulky disease and geographical region and randomized (1:1) to receive 6 cycles of either polatuzumab vedotin 1.8 mg/kg plus R-CHP and vincristine placebo, or polatuzumab vedotin placebo plus R-CHOP. Rituximab monotherapy is administered in Cycles 7 and 8 (both arms). The primary endpoint is INV-assessed PFS and secondary endpoints include IRC-assessed CR rate at EOT, EFS, 2-year PFS rate, and OS. POLARIX has completed accrual and is awaiting results. As all DLBCL subtypes were permitted to be enrolled, this study will also be able to show the effect of polatuzumab vedotin plus R-CHP versus R-CHOP in various molecularly and histologically defined subtypes in a prospective randomized trial setting.

4.2.2. Other areas of investigation with polatuzumab vedotin

In addition to the phase III POLARIX trial in previously treated DLBCL, additional evaluations of polatuzumab vedotin in combination with chemotherapy, chemoimmunotherapy, or single-agent mAbs are ongoing in trials of patients with B-cell NHLs, including DLBCL and FL (Table 2). Clinical data from ROMULUS and GO29365 have demonstrated that pola-R, pola-G, pola-BR and pola-BG provide clinical responses and are well tolerated in patients with R/R FL [59,60,65]. Areas of further research to fill data gaps for polatuzumab vedotin in DLBCL include: combination with other chemotherapy regimens; gemcitabine plus oxaliplatin; rituximab plus ifosfamide, carboplatin, and etoposide; combination with bispecific antibodies (e.g., mosunetuzumab); combination with immune checkpoint inhibitors; potential to bridge to chimeric antigen receptor T-cell therapy in R/R DLBCL; and further studies in the first-line setting and in elderly patients. Polatuzumab vedotin may also be considered in combination with novel and targeted agents that are effective in other B-cell NHL subtypes, such as FL and mantle cell lymphoma.

5. Discussion

ADCs combine the high target specificity of a mAb with the strong antitumor effects of an attached cytotoxic agent, while limiting effects on normal cells [23]. ADCs can be combined safely with chemotherapy and mAbs and are now leading to improved clinical outcomes for patients with both Hodgkin and NHL. Several ongoing trials of ADCs in combination with chemoimmunotherapy and bispecific antibodies in B-cell NHL have the potential to change clinical practice even further.

Polatuzumab vedotin combines a highly cytotoxic payload with antibody-mediated antitumor effects, and the cleavable linker provides efficient drug delivery. The design advantages of this ADC are demonstrated by its clinical efficacy and favorable safety profile in patients with previously-untreated first-line and R/R DLBCL and in R/R FL. In the phase II randomized study of pola-BR versus BR in patients with transplant-ineligible R/R DLBCL (GO29365; NCT02257567), pola-BR was associated with a significantly higher CR rate, and improved PFS and OS compared with BR alone [60]. The CR rate supported the US FDA approval of pola-BR for patients with R/R DLBCL after at least two prior therapies [20]. It also supported the European Commission conditional marketing authorization of pola-BR in patients with transplant-ineligible R/R DLBCL [66]. The phase Ib/II study (GO29044; NCT01992653) of pola plus R-/G-CHP showed promising efficacy outcomes and an acceptable profile, which informed the phase III POLARIX study (NCT03274492) of polatuzumab vedotin plus R-CHP versus R-CHOP.

The clinical success of newer ADCs in clinical development will continue to be determined by all aspects of their design (e.g., choice of antibody, linker, and payload) [67]. Modern ADCs are being developed with more potent payloads than

previously employed [2]. In recent years, advanced conjugation technologies have helped to optimize the stability, potency and homogeneity of ADCs, resulting in improved preclinical activity and toxicology compared with first generation agents [68].

The limited clinical success of some ADCs may be expected given that multiple criteria must be met to ensure their potency, efficacy, and safety, such as adequate and selective expression of the target antigen, the rate of internalization of the payload, linker stability, and the minimization of off-target toxicities [67]. In addition, the choice of regimen that an ADC is combined with can be a limiting factor due to the compounded safety profile. The therapeutic potential of many of the latest ADCs remains to be established [68]. Another factor associated with the efficacy of ADCs is the development of therapeutic resistance. The mechanisms for this are not fully understood and strategies to overcome resistance are being devised [23].

6. Conclusions

ADCs represent a significant advancement in the treatment of aggressive lymphomas. Polatuzumab vedotin has demonstrated clinical efficacy and a tolerable safety profile in both R/R and first-line DLBCL, with future studies planned to further investigate this ADC in these and other B-cell NHL subtypes.

7. Expert opinion

Using innovative designs and novel mechanisms of action, the ADCs discussed in this article have improved clinical outcomes for patients with various hematologic malignancies, including AML, Hodgkin lymphoma, T-cell lymphomas, ALL, hairy cell leukemia, and DLBCL. ADCs now have an established role in the modern treatment armamentarium and represent a readily available 'off-the-shelf' and efficient class of therapies, with acceptable safety profiles. As with the development of most novel agents, initial indications for use have been in patients with relapsed and refractory disease, where there is a great unmet medical need. Subsequent studies have investigated ADCs in combination with chemotherapy for patients with newly diagnosed hematologic malignancies, such as gemtuzumab ozogamicin in combination with daunorubicin and cytarabine in AML and brentuximab vedotin in Hodgkin lymphoma.

In the case of polatuzumab vedotin, the initial demonstration of clinical benefit and FDA approval were for R/R DLBCL. However, polatuzumab vedotin should not be used for all such patients. For example, at the present time a relatively young, fit patient who suffers a first relapse of DLBCL should generally be treated with a salvage chemotherapy regimen that does not contain polatuzumab vedotin, followed by high-dose chemotherapy plus ASCT. Polatuzumab vedotin is reserved for patients with a relapse after ASCT or after one or two lines of chemotherapy in patients who are not candidates for ASCT. An ongoing clinical trial is investigating whether polatuzumab vedotin improves clinical outcomes when given with chemoimmunotherapy as initial therapy for DLBCL. Another area for potential future development of polatuzumab vedotin is in patients with follicular lymphoma, where early studies suggest efficacy with manageable toxicity.

The field of ADCs will undoubtedly continue to evolve in the future. Novel ADCs not reviewed in this article that are in late stage development or are recently approved include: enfortumab vedotin, targeting Nectin-4, approved in December 2019 for bladder cancer; sacituzumab govitecan, targeting TROP-2, approved in April 2020 for breast cancer and other solid tumors; belantamab mafodotin, targeting the B-cell maturation antigen, under investigation in multiple myeloma; and loncastuximab tesirine, targeting CD19, under investigation in B-cell non-Hodgkin lymphoma. As these and other ADCs assume more of a role in patients with R/R malignancies, ADCs will continue to be tested in earlier lines of therapy, including front line. We anticipate that, perhaps 10 years from now, ADCs will be incorporated, along with other chemotherapy drugs, mABs, and targeted agents, into standard clinical practice for a variety of hematologic malignancies and other cancers. As more ADCs with different targets become available, there is the possibility of combination therapies with multiple ADCs, which may present challenges in terms of safety profiles, but should be further investigated. It is worth noting that economic cost could delay uptake of ADCs into clinical practice, i.e. if insurers or regulatory authorities fail to approve or cover the drugs due to cost, as is the case with all new oncology drugs.

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