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Antibody-drug conjugates: Resurgent anticancer agents with multi-targeted therapeutic potential

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ABSTRACT

Antibody–drug conjugates (ADCs) constitute a relatively new group of anticancer agents, whose first appearance took place about two decades ago, but a renewed interest occurred in recent years, following the success of anticancer immunotherapy with monoclonal antibodies. Indeed, an ADC combines the selectivity of a monoclonal antibody with the cell killing properties of a chemotherapeutic agent (payload), joined together through an appropriate linker. The antibody moiety targets a specific cell surface antigen expressed by tumor cells and/or cells of the tumor microenvironment and acts as a carrier that delivers the cytotoxic payload within the tumor mass. Despite advantages in terms of selectivity and potency, the development of ADCs is not devoid of challenges, due to: i) low tumor selectivity when the target antigens are not exclusively expressed by cancer cells; ii) premature release of the cytotoxic drug into the bloodstream as a consequence of linker instability; iii) development of tumor resistance mechanisms to the payload. All these factors may result in lack of efficacy and/or in no safety improvement compared to unconjugated cytotoxic agents. Nevertheless, the development of antibodies engineered to remain inert until activated in the tumor (e.g., antibodies activated proteolytically after internalization or by the acidic conditions of the tumor microenvironment) together with the discovery of innovative targets and cytotoxic or immunomodulatory payloads, have allowed the design of next-generation ADCs that are expected to possess improved therapeutic properties.
This review provides an overview of approved ADCs, with related advantages and limitations, and of novel targets exploited by ADCs that are presently under clinical investigation.

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Abbreviations: ADC, antibody drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Auto-HSCT, autologous-hematopoietic stem cell transplantation; B-ALL, B cell precursor acute lymphoblastic leukemia; BCMA, B cell maturation antigen; CAB, conditionally active biologic; CAM, cell adhesion molecule; CEACAM, carcinoembryonic antigen-related cell adhesion molecule; CI, confidence intervals; CLL, chronic lymphocytic leukemia; CSCs, cancer stem cells; cHL, classic Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; DLL3, delta-like ligand 3; EMA, European Medicine Agency; EMT, epithelial-mesenchymal transition; ENPP3, ectonucleotide pyrophosphatase/phosphodiesterase 3; ET_BR, endothelin B receptor; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; FRα, folate receptor α; GCC, guanylyl cyclase C; GPNMB, glycoprotein non-metastatic B; GPR20, G protein-coupled receptor 20; HER, human epidermal growth factor receptor; HGFR, hepatocyte growth factor receptor; HR, hazard ratio; Ig, immunoglobulin; IGF-1R, insulin-like growth factor type 1 receptor; ISAC, immunostimulatory antibody conjugate; KAAG1, kidney-associated antigen 1; LAMP-1, lysosomal-associated membrane protein 1; mAb, monoclonal antibody; MC-val-cit-PABC, maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl; MIF, migration inhibitory factor; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; MUC1, mucin-1; NLR, neutrophil-to-lymphocyte ratio; Non-HL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PBD, pyrrolobenzodiazepine dimers; PDC, probody-drug conjugate; PFS, progression free survival; PTK7, protein tyrosine kinase 7; PSMA, prostate-specific membrane antigen; ROR, receptor tyrosine kinase-like orphan receptor; sALCL, systemic anaplastic large cell lymphoma; SCLC, small cell lung cancer; SMCC, succinimidyl trans-4-(maleimidylmethyl)cyclohexane-1-carboxylate; $T_{1/2}$, half-life; TF, tissue factor; TLR7/8, toll-like receptor 7/8; TME, tumor microenvironment; TNBC, triple-negative breast cancer; TFR1, transferrin receptor 1; VEGFR, vascular endothelial growth factor receptor.

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1. Introduction

Immunotherapy represents a successful and rapidly evolving research area, which has led to the approval of a number of therapeutic agents for the treatment of cancer. The great potential of immunotherapy was first recognized in 1970s, when the development of the hybridoma technology allowed the reliable production of monoclonal antibodies (mAbs) (Schietinger et al., 2008). In the last decades, four sequential antibody prototypes have been developed: murine, chimeric, humanized, and human, in an effort of reducing mAb immunogenicity that may impair clinical efficacy and result in adverse effects. Antibody–drug conjugates (ADCs) represent a step forward in the recombinant mAb technology, combining the target specificity of mAbs with the antitumor properties of cytotoxic molecules to selectively deliver chemotherapy to the tumor tissue with consequent reduction of systemic toxicity (Chau et al., 2019; Ducry and Stump, 2010).

Typically, the mAb moiety binds to a target antigen expressed on the surface of tumor cell or of tumor microenvironment (TME) cellular components and, after internalization of the ADC complex, cell death is induced by the cytotoxic drug that is released within the cytoplasm. The linker (i.e., the ADC region that connects the drug to the antibody) plays a significant role in the proper ADC delivery. In fact, the ideal linker should confer stability to the ADC while in the bloodstream so that the immunoconjugate can reach the tumor mass intact, but it should be readily cleaved once internalized in cancer cells to allow the release of the cytotoxic drug (Shim, 2020).

In addition to the linker properties, several other factors contribute to the overall efficacy of ADCs, including their pharmacokinetic parameters that are mainly influenced by the antibody backbone. Thus, absorption, distribution, metabolism, and excretion properties of the ADC correspond to that of the unconjugated immunoglobulin G (IgG), usually represented by low distribution volume, slow clearance, long half-life ($T_{1/2}$), and proteolysis-mediated catabolism (Lin et al., 2013; Lobo et al., 2004).

However, ADCs are not devoid of toxicity, especially if the target antigen is expressed also on normal cells, or if an early cleavage of the linker occurs, thus leading to a premature systemic release of the cytotoxic drug in the blood. Additionally, ADCs may also be associated with risk of immunogenicity. Lastly, mechanisms of resistance have been demonstrated with ADCs, primarily due to *multidrug resistance 1* (*MDR1*) gene overexpression and consequent P-glycoprotein mediated drug efflux of the cytotoxic payload (Wolska-Washer and Robak, 2019).

Aim of this review is to provide a comprehensive overview of approved ADCs, with a special focus on advantages and limitations, and of currently ongoing phase 3 clinical trials testing them, as single agents or in combination with chemotherapy. In the second part of the manuscript, novel ADCs, under clinical development, are described according to their target antigens that in most cases are still therapeutically unexploited molecules expressed by solid tumors.

2. Approved ADCs: mechanism of action and registration clinical trials

Currently, several ADCs have been approved, by the Food and Drug Administration (FDA) and European Medicines Agency (EMA), for the treatment of solid and hematological malignancies, and many others are under evaluation in different stages of clinical trials. In particular, eight ADCs have been approved by both FDA and EMA: gemtuzumab ozogamicin, brentuximab vedotin, ado-trastuzumab emtansine, inotuzumab ozogamicin, polatuzumab vedotin-piiq, belantamab mafodotin-blmf, fam-trastuzumab deruxtecan-nxki, and sacituzumab govitecan-hziy. Other three ADCs so far have gained only FDA approval, i.e. enfortumab vedotin-ejfv, loncastuximab tesirine-lpyl and tisotumab vedotin-tftv, for a total of eleven approved ADCs in the US (Hafeez et al., 2020) (Fig. 1 and Table 1). In the following sections, these ADCs are listed and described in the chronological order of approval date.

2.1. Gemtuzumab ozogamicin

The first ADC to receive FDA approval in 2000, for the treatment of acute myeloid leukemia (AML), was gemtuzumab ozogamicin, consisting in a calicheamicin derivative bound to a humanized IgG4 mAb that targets the myeloid antigen CD33. In detail, calicheamicins are actinomycete-derived antibiotics that induce cell death as a consequence of DNA double-strand breaks, with ozogamicin being a semisynthetic derivative. The mAb and the payload are joined together through an acid-cleavable hydrazone linker [4-(4-acetylphenoxy)butanoic acid], relatively stable at neutral pH but rapidly hydrolyzed in the acidic environment of lysosomes within tumor cells. The linker also includes a disulfide linkage (Ricart, 2011) that is stable in the bloodstream but efficiently reduced to free thiols intracellularly, thanks to high levels of reduced glutathione.

After ten years of clinical use, gemtuzumab ozogamicin was withdrawn from the market in 2010, due to a potentially fatal hepatotoxicity, occurring in the form of veno-occlusive disease. Such condition was shown to derive from the obstruction of small blood vessels in the liver, caused by the ADC binding to its target, CD33, also expressed on the surface of healthy sinusoidal endothelial cells (Tack et al., 2001). At the end of the revision process, the high dose as well as the relative instability of the linker in the blood circulation with consequent unexpected early systemic drug release, were considered as the main factors in determining gemtuzumab ozogamicin hepatotoxicity (Wolska-Washer and Robak, 2019).

Thereafter, gemtuzumab ozogamicin, in combination with daunorubicin and cytarabine, obtained a new marketing authorization at a lower and fractionated dose (3 mg/m^2 on days 1, 4, 7 rather than 9 mg/m^2 14 days apart in 28-day cycles) to improve treatment safety and prevent the rapid re-expression of CD33 on leukemia cells (Pilorge et al., 2014). Updated indications include newly diagnosed *de novo* CD33-positive AML in adults (FDA, in 2017), pediatric patients 1 month and older (FDA, in 2020) or ≥15 years old patients (EMA, in 2018), based on the results of phase 3 studies [i.e., ALFA-0701 (NCT00927498; 2007-002933-36) and AAML0531 (NCT00372593) in adult and pediatric populations, respectively] (Castaigne et al., 2012; Gamis et al., 2014). In the ALFA-0701 trial performed in 280 patients aged 50-70 years, the median event-free survival (EFS; primary endpoint of the study) and overall survival (OS) at 2 years were 40.8% [95% confidence intervals (CI) 32.8-50.8; hazard ratio (HR) = 0.58, 95% CI 0.43-0.78; P = 0.0003] and 53.2% (95% CI 44.6-63.5) in the gemtuzumab ozogamicin plus chemotherapy group *versus* 17.1% (95% CI 10.8-27.1) and 41.9% (95% CI 33.1-53.1) in the control group treated with chemotherapy only (HR = 0.69, 95% CI 0.49-0.98; P = 0.0368), respectively (Castaigne et al., 2012). The final results of this trial confirmed that addition of gemtuzumab ozogamicin to standard chemotherapy, as frontline therapy of *de novo* AML, significantly prolongs EFS by reducing the risk of an event compared to control treatment and has an acceptable safety profile. However, final median OS in the ADC plus chemotherapy arm was not statistically significantly different from that in the control

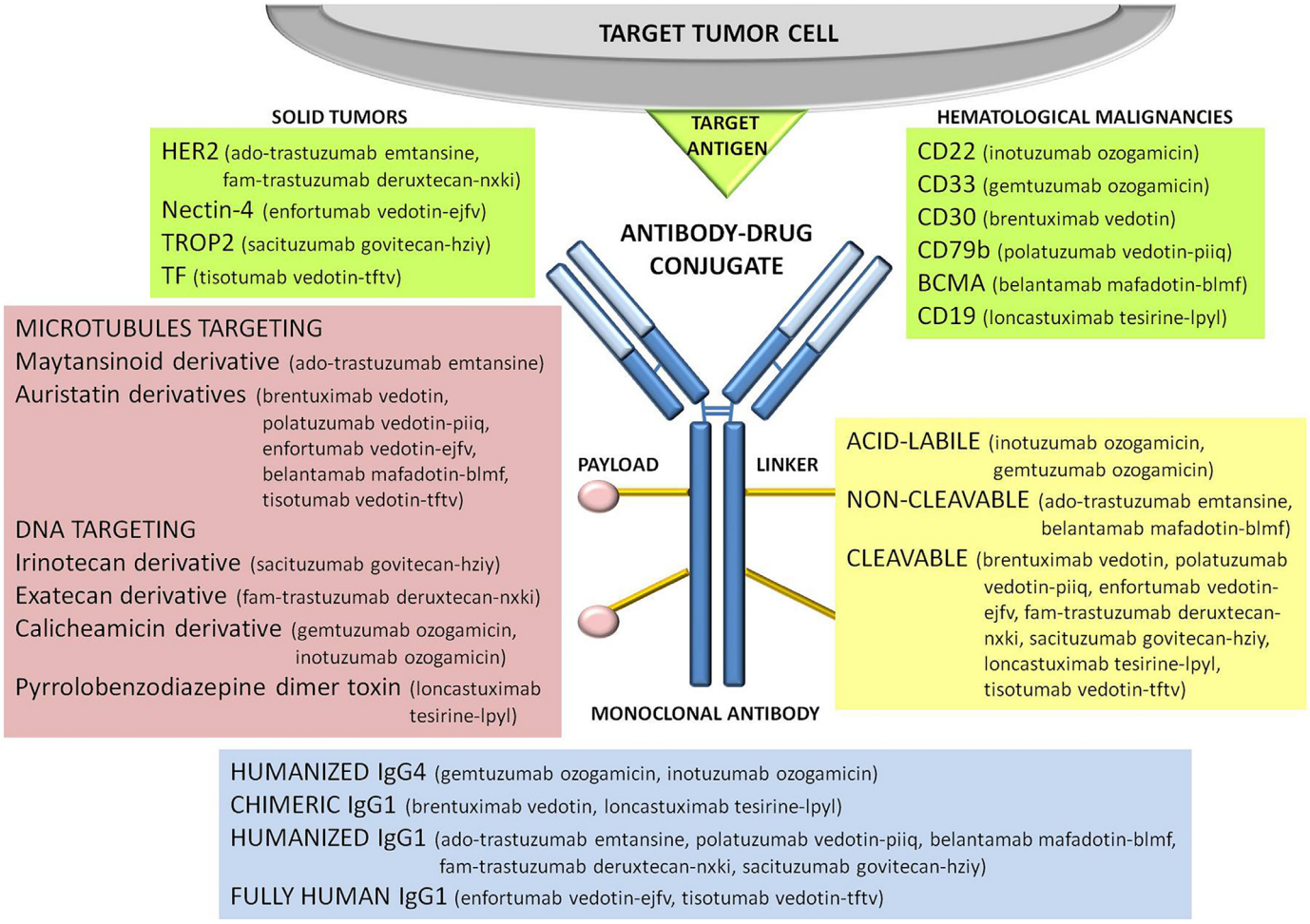

Fig. 1. Main properties of approved ADCs. Antibody drug conjugates (ADCs) are made of three major components: a mAb recognizing a target present on tumor cells, a cytotoxic drug (payload), and a linker. In approved ADCs, the cytotoxic drug conjugated to the mAb belongs to two possible families of chemotherapeutics: microtubules or DNA targeting agents, both eventually inducing apoptosis as a result of mitotic spindle disruption or DNA breaks, respectively. The linker (i.e., the component connecting the mAb to the payload) has chemical properties such that it prevents drug detachment in the bloodstream, allowing its release only in tumor cells, after ADC internalization. The payload release occurs upon ADC exposure to the lysosomal acidic pH (acid-labile linker) or to protease-mediated cleavage. In case of non-cleavable linkers, proteolytic degradation of the mAb component takes place in the lysosome and the linker remains attached to the cytotoxic drug. The mAbs present within ADCs are classified according to the level of sequence humanization (chimeric, humanized and fully human).

arm [27.5 months (95% CI 21.4–45.6) *versus* 21.8 months (95% CI 15.5–27.4); HR = 0.81, 95% CI 0.60-1.09; $P = 0.16$] (Lambert et al., 2019). Gemtuzumab ozogamicin was also approved by FDA as single agent for newly diagnosed *de novo* CD33-positive AML in elderly patients or adults ineligible for or unwilling to receive intensive chemotherapy, at a higher dose (6 mg/m^2) in the first administration of the induction cycle and at a lower dose in the continuation phase (2 mg/m^2) (AML-19 (NCT00091234) (Amadori et al., 2016). Another approved indication is relapsed or refractory CD33-positive AML in adults and children aged 2 years and older.

Resistance development has been recognized as a factor limiting the success of gemtuzumab ozogamicin, due to overexpression of P-glycoprotein (Matsumoto et al., 2012) and Bcl-2 and Bcl-x antiapoptotic proteins or down-regulation of Bak and Bax proapoptotic proteins (Haag et al., 2009).

In regard to adverse effects of gemtuzumab ozogamicin, besides the sinusoidal obstruction syndrome (black box warning), infusion-related reactions, prolonged thrombocytopenia with hemorrhages, and hypersensitivity reactions in the form of transient shortness of breath have been reported (Bross et al., 2001; Norsworthy et al., 2018). On the other hand, the lack of CD33 expression on pluripotent hematopoietic stem cells represents an advantage, allowing the reversal of the myelosuppression induced by a multi-drug chemotherapeutic regimen including myelotoxic agents.

To address the pharmacokinetic profile of gemtuzumab ozogamicin, several population studies have been done that revealed no differences depending on patients' age and sex (Hibma and Knight, 2019; Masters et al., 2019). Once released by hydrolysis, the calicheamicin derivative is subject to non-enzymatic reduction of its disulfide bonds. Therefore, no substantial effect on drug exposure is observed if gemtuzumab ozogamicin is co-administered with CYP450 inducers and/or inhibitors. Moreover, the produced metabolites exert little anti-neoplastic activity. Plasma $T_{1/2}$ of the ADC is approximately 160 hours at the recommended dosage of 3 mg/m^2 and patients with mild-to-moderate renal impairment do not show any alteration in the pharmacokinetics (Hibma and Knight, 2019).

Besides being recognized by gemtuzumab ozogamicin, CD33 is also targeted by other ADCs that reached clinical evaluation in recent years, such as IMGN779 and vadastuximab talirine (SGN-CD33A). IMGN779 utilizes the humanized anti-CD33 mAb Z4681A joined, through a cleavable disulfide linker, to a DNA-alkylating payload, DGN462, consisting of an indolinobenzodiazepine dimer with a monoimine moiety. This payload, characterized by potent antitumor effects, is a prototype of a new class of purpose-created indolinobenzodiazepine pseudodimers, termed IGNs and characterized by a tight DNA binding (Kovtun et al., 2018a). Also in vadastuximab talirine an anti-CD33 antibody, with engineered cysteine residues, is conjugated to DNA cross-linking synthetic pyrrolobenzodiazepine dimers (PBDs) via a highly

Table 1
FDA- and EMA-approved ADCs for solid tumors and hematological malignancies.

ADC	Target antigen	Approval status and regulatory history		Company	Approved indications
		FDA	EMA		
Gemtuzumab ozogamicin (Mylotarg)	CD33	- 1999: orphan drug designation; - 2000: first accelerated approval; - 2017: new approval at a lower and fractionated dosage.	- 2000: orphan drug designation; - 2018: first approval.	Pfizer	- Relapsed or refractory acute myeloid leukemia (AML) for 60 years of age or older patients not candidate for standard chemotherapy (FDA, 2000; withdrawn from the market by Pfizer in 2010); - newly-diagnosed CD33-positive AML in adults, and relapsed or refractory CD33-positive AML, in adults and children aged 2 years and older, as monotherapy (FDA, 2017); - newly diagnosed, *de novo* CD33-positive AML, in adults (2017, FDA), patients aged 15 years and above (2018, EMA), and pediatric patients 1 month and older (2020, FDA), in combination with daunorubicin and cytarabine.
Brentuximab vedotin (Adcetris)	CD30	- 2011: first accelerated approval; - 2017: breakthrough therapy designation as first-line therapy for patients with advanced classical Hodgkin lymphoma (cHL); - 2018: breakthrough therapy designation as first-line therapy for systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas.	- 2009: orphan drug designation; - 2012: first conditional marketing authorization.	Seattle Genetics, Millennium Pharmaceuticals, Takeda	- sALCL after failure of at least one prior multi-agent chemotherapy regimen (FDA, 2011; EMA, 2012); - cHL after failure of autologous-hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidates for auto-HSCT (FDA, 2011; EMA, 2012); - cHL at high risk of relapse or progression as post-auto-HSCT consolidation treatment (FDA, 2015; EMA, 2016); - primary cutaneous ALCL or CD30-expressing mycosis fungoides in patients who have received prior systemic therapy (FDA, 2017; EMA, 2017); - previously untreated stage III or IV cHL in combination with chemotherapy (FDA, 2018; EMA, 2019); - previously untreated sALCL or other CD30-expressing peripheral T-cell lymphomas, in combination with cyclophosphamide, doxorubicin, and prednisone (FDA, 2018; EMA, 2020).
Ado-trastuzumab emtansine or T-DM1 (Kadcyla)	HER2	- 2013: first accelerated approval; - 2019: breakthrough therapy designation for early-stage breast cancer.	- 2013: first approval.	Roche	- HER2-positive, late-stage (metastatic) breast cancer in patients pretreated with trastuzumab and taxanes, as monotherapy (2013, FDA and EMA); - HER2-positive, early-stage breast cancer as adjuvant in patients with residual disease after neoadjuvant treatment (FDA and EMA, 2019).
Inotuzumab ozogamicin (Besponsa)	CD22	- 2013: orphan drug designation; - 2015: breakthrough therapy designation; - 2017: first approval.	- 2013: orphan drug designation; - 2017: first approval.	Pfizer	- Relapsed or refractory B cell precursor acute lymphoblastic leukemia (B-ALL) in adults, as monotherapy (FDA and EMA, 2017).
Polatuzumab vedotin-piiq (Polivy)	CD79b	- 2016: orphan drug designation; - 2017: breakthrough therapy designation; - 2019: first accelerated approval.	- 2018: orphan drug designation; - 2020: first conditional market authorization.	Roche	- Relapsed or refractory diffuse large B-cell lymphoma (DLBCL), in adults who are ineligible for HSCT, in combination with rituximab and bendamustine (FDA, 2019; EMA, 2020).
Enfortumab vedotin-ejfv (Padcev)	Nectin-4	- 2018: breakthrough therapy designation for locally advanced or metastatic urothelial cancer in patients previously treated with immune checkpoint inhibitors; - 2019: first accelerated approval; - 2020: breakthrough therapy designation in combination with the anti-PD-1 pembrolizumab for unresectable locally advanced or metastatic urothelial cancer in patients who are unable to receive cisplatin-based chemotherapy, for the first-line setting.	- 2021: accepted a marketing authorization application in locally advanced or metastatic urothelial cancer.	Astellas Pharma	- Locally advanced or metastatic urothelial cancer in adult patients who have previously received a PD-1/L1 inhibitor and a platinum-containing chemotherapy in a neoadjuvant/adjuvant setting (FDA, 2019).

Table 1 (*continued*)

ADC	Target antigen	Approval status and regulatory history			
		FDA	EMA	Company	Approved indications
Fam-trastuzumab deruxtecan-nxki (Enhertu)	HER2	- 2019: first accelerated approval; - 2020: orphan designation for gastric cancer; - 2020: breakthrough therapy designation for HER2-positive unresectable or metastatic gastroesophageal junction adenocarcinoma; - 2021: breakthrough therapy designation for HER2-positive non–small cell lung cancer (NSCLC).	- 2021: first conditional market authorization.	AstraZeneca and Daiichi Sankyo Company	- HER2-positive unresectable or metastatic breast cancer following two or more prior anti-HER2 based regimens (FDA, 2019; EMA, 2021); - locally advanced or unresectable metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma in patients who have received a prior trastuzumab-based regimen (FDA, 2021).
Sacituzumab govitecan-hziy (Trodelvy)	TROP-2	- 2020: first approval for triple-negative breast cancer (TNBC); - 2021: accelerated approval for urothelial cancer.	- 2021: approval for metastatic TNBC.	Gilead Sciences (Immunomedics)	- Unresectable locally advanced or metastatic TNBC patients, who have received two or more prior systemic therapies, at least one of them for the metastatic disease (FDA, 2020; EMA, 2021); - locally advanced or metastatic urothelial cancer previously treated with platinum-containing chemotherapy and either anti-PD-1 or anti-PD-L1 mAbs (FDA, 2021).
Belantamab mafodotin-blmf (Blenrep)	BCMA	- 2017: orphan designation; - 2020: first accelerated approval.	- 2017: orphan designation; - 2020: first conditional marketing authorization.	GlaxoSmithKline	- Relapsed and refractory multiple myeloma that no longer responds to treatment with an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 mAb (after at least 4 prior therapies).
Loncastuximab tesirine-lpyl (Zynlonta)	CD19	- 2021: first approval.	- 2021: orphan designation and marketing authorization application.	ADC Therapeutics	- Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low grade lymphoma and high-grade B-cell lymphoma
Tisotumab vedotin-tftv (Tivdak)	TF	- 2021: first accelerated approval.		Seagen Inc.	- Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

Data updated to December 2021

stable, cathepsine B cleavable, maleimidocaproyl-valinealanine (MC-VC) dipeptide linker. This ADC has been tested in phase 1 clinical trials for CD33-positive AML as monotherapy or in combination with hypomethylating agents (azacitidine or decitabine) (Fathi et al., 2018; Stein et al., 2018). However, the Cascade phase 3 trial (NCT02785900) comparing vadastuximab talirine plus hypomethylating agents *versus* placebo plus hypmethylating agents in the frontline setting of newly diagnosed AML in elderly patients was discontinued due to increase in deaths in the vadastuximab arm (https://www.adcreview.com/news/phase-iii-cascade-clinical-trial-vadastuximab-talirine-frontline-acute-myeloid-leukemia-discontinued).

2.2. Brentuximab vedotin

The second approved ADC is brentuximab vedotin, a chimeric IgG1 mAb targeting CD30 (cAC10), conjugated via a cathepsin cleavable linker (valine-citrulline linker), to monomethyl auristatin E (MMAE). MMAE is a synthetic antimitotic agent, 100–1000 times more potent than vincristine (Burke et al., 2020; Dornan et al., 2009), which binds to tubulin and disrupts the microtubule network in dividing cells, thus causing G2/M phase cell cycle arrest (Francisco et al., 2003).

The cathepsin B-sensitive linker of brentuximab vedotin is cleaved only after cell internalization, because of the high pH and absence outside the cell of cathepsin B that is a lysosomal enzyme. This particular property of the linker offers an advantage over the hydrazone linker of gemtuzumab ozogamicin that instead may undergo occasional nonspecific breakdown outside of the target cell (Maruani, 2018; Wolska-Washer and Robak, 2019). Cytotoxic effects with brentuximab vedotin are also observed in neighboring tumor cells that do not bind the ADC (bystander effect), due to diffusion of the payload from the targeted cell into adjacent untargeted cells (Khera et al., 2021; Yu and Liu, 2019). In addition, an antibody-dependent cellular cytotoxicity (ADCC), typically induced by IgG1 mAbs, seems to contribute to the efficacy of brentuximab vedotin (Chen et al., 2017; Staudacher and Brown, 2017). ADCC is a mechanism involved in the antitumor activity of therapeutic mAbs whereby a target cell, with antibody-coated antigens, is attacked by effector cells of the innate immunity that express Fc receptors, [i.e. natural killer (NK) cells, eosinophils, and, to a lesser extent, neutrophils, monocytes, and macrophages] (Ma and Sawas, 2018; Shingleton and Dave, 2020).

In 2011 and 2012, FDA and EMA approved brentuximab vedotin for hematological malignancies expressing CD30, such as relapsed or refractory systemic anaplastic large-cell lymphoma (sALCL), after failure of at least one prior line of chemotherapy, and classical Hodgkin lymphoma (cHL) after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or at least two chemotherapy regimens in patients not eligible for auto-HSCT.

Its first approval for patients with sALCL was based on a multinational, open-label, single-arm phase 2 study (NCT00866047), in which 50 out of 58 enrolled patients [86%, 95% CI 74.6-93.9] had an objective response, and 33 patients (57%, 95% CI 43.2-69.8) showed a complete response. The median objective response duration was 12.6 months (95% CI 5.7-not estimable) (Pro et al., 2012). In the case of cHL, the first approval was related to data from another single-arm phase 2 study (NCT00848926), showing an overall objective response rate (ORR) of 75% (95% CI 64.9-82.6), with 34% complete responses (95% CI 25.2-44.4) and median response duration of 6.7 months (95% CI 3.6-14.8) (Younes et al., 2012a). The initial approval for cHL was then extended, by both regulatory authorities, to patients at high risk of relapse or progression after auto-HSCT. Thereafter, approved indications

included primary cutaneous ALCL and CD30 expressing mycosis fungoides previously treated with systemic therapy, on the basis of the results of the phase 3 ALCANZA study (NCT01578499), which investigated brentuximab vedotin in comparison with oral methotrexate or bexarotene (physician's choice), showing an improvement in ORR with the ADC [56.3% (36 of 64 patients) *versus* 12.5% (8 of 64 patients)] and a between-group difference of 43.8% (95% CI 29.1–58.4; $P < 0.0001$). The reported median progression-free survival (PFS) according to EMA criteria was 16.7 months with brentuximab vedotin and 3.5 months with the physician's choice (HR = 0.270, 95% CI 0.169–0.430; $P < 0.0001$) (Prince et al., 2017).

Between 2018 and 2020, FDA and EMA approved brentuximab vedotin in the frontline setting of adult patients with previously untreated stage III or IV cHL and sALCL in combination with chemotherapy (doxorubicin, vinblastine, and dacarbazine, or AVD protocol, in the case of cHL, and cyclophosphamide, doxorubicin, and prednisone, or CHP protocol, in the case of sALCL), based on the results of the phase 3 ECHELON-1 (NCT01712490) and ECHELON-2 trials, respectively. The ECHELON-1 trial evaluated the AVD protocol in combination with brentuximab vedotin ($n = 250$) *versus* AVD plus bleomycin (ABVD; $n = 247$). The results of this study showed an improvement of modified PFS with AVD plus brentuximab vedotin compared to the ABVD regimen, consisting in a 40% decrease of the risk of progression or death (HR = 0.60, 95% CI 0.40–0.90; $P = 0.012$). The 2-year modified PFS was 84.3% (95% CI 78.7–88.5) in the brentuximab vedotin containing arm *versus* 73.7% (95% CI 67.3–79.1) in the ABVD arm (Ramchandren et al., 2019). After five years of follow-up, the significantly higher clinical benefit obtained with the addition of brentuximab vedotin to the AVD protocol compared to ABVD was still maintained [5-year PFS 82.2% (95% CI 79–85) *versus* 75.3% (95% CI 71.7–78.5) (HR = 0.68, 95% CI 0.53–0.87; $P = 0.0017$). These data confirmed that brentuximab vedotin plus AVD should be preferred over ABVD in the frontline setting of patients with stage III or IV cHL (Straus et al., 2021). The ECHELON-2 trial compared brentuximab vedotin plus CHP ($n = 226$) with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP; $n = 226$) for sALCL, showing a median PFS improvement in the brentuximab vedotin containing group (48.2 months *versus* 20.8 months; HR = 0.71, 95% CI 0.54–0.93; $P = 0.011$). This trial also showed a significant clinical benefit in terms of OS associated with the brentixumab vedotin plus CHP regimen (HR = 0.66, 95% CI 0.46-0-95; $P = 0.0244$) (Horwitz et al., 2019). Moreover, a recent update indicated an estimated 5-year OS of 68.7% (95% CI 61.3-75.0) for the brentuximab vedotin plus CHP arm *versus* 60.3% (95% CI 52.8-67.0) for the CHOP arm (Horwitz et al., 2020).

Results from clinical studies with brentuximab vedotin indicated that once a week administration of a relatively low dose of ADC is associated with tumor regression and manageable toxicity, most common side effects being fatigue, nausea, diarrhea, arthralgia, and pyrexia. Nevertheless, immunogenicity has been reported, in the form of infusion reactions. The main dose-limiting toxicity has been identified in neutropenia, while repeated administrations have been associated with an increased occurrence of peripheral neuropathy, thrombocytopenia and hyperglycemia (Chen et al., 2010; Gopal et al., 2012; Younes et al., 2012a). Hepatotoxicity, opportunistic infections, fatal cases of progressive multifocal leukoencephalopathy associated with the John Cunningham virus have all been reported.

Brentuximab vedotin is cleared via proteolytic catabolism with a $T_{1/2}$ of 4–6 days (Younes et al., 2012a), while the elimination of the payload MMAE is limited by its rate of release from the ADC, with a $T_{1/2}$ of 3–4 days in patients who received a dose of 1.8 mg/kg. In regard to drug-drug interactions, being MMAE metabolized via oxidation by CYP3A4/5, strong CYP3A4 inhibitors (i.e. clarithromycin, ketoconazole, nefazodone, ritonavir, nelfinavir, voriconazole) can increase MMAE exposure by 73%, leading to increased incidence of neutropenia (Wolenski et al., 2018). Moreover, impaired hepatic and renal functions can significantly affect the exposure to both the ADC and the released payload and increase the frequency of grade ≥3 adverse reactions (Chen et al., 2015b; Flerlage et al., 2016; Zhao et al., 2016). In fact, exposure to MMAE was increased by 2.3-fold and 1.9-fold in patients with severe hepatic and renal impairment, respectively, while exposure to the intact ADC was reduced in both groups.

F0002-ADC is an investigational ADC, which interacts with the same target antigen of brentuximab vedotin, designed to improve the safety of the latter ADC by enhancing the linker stability and changing the payload. It consists of the anti-CD30 mAb cAC10, chemically conjugated with another antimitotic agent, a semi-synthetic derivative of the ansamycin antibiotic maytansine or mertansine, i.e. DM1 (the same cytotoxic molecule present in ado-trastuzumab emtansine; see below), through the stable linker succinimidyl trans-4-(maleimidylmethyl) cyclohexane-1-carboxylate (SMCC) (Shen et al., 2019).

2.3. Ado-trastuzumab emtansine

The first approved ADC for solid tumors was ado-trastuzumab emtansine (T-DM1), which consists of trastuzumab, a humanized anti-human epidermal growth factor receptor 2 (HER2, or-ErbB2) IgG1 mAb, linked by a non-cleavable thioether linker to the anti-microtubule agent DM1. HER2 is a member of the membrane-spanning type I receptor tyrosine kinase family that is overexpressed in 15–30% of breast cancers and 10–30% of gastric/gastroesophageal cancers, as a consequence of gene amplification. Although less commonly, HER2 overexpression can also be detected in other solid tumors, such as ovary, lung, colon, biliary, bladder cancers (Iqbal and Iqbal, 2014). In T-DM1, the thioeter non-cleavable linker [maleimidomethyl cyclohexane-1-carboxylate (MCC), bound to lysine amines of the mAb] remains attached to the payload after proteolytic degradation of the ADC in the lysosome (Lewis Phillips et al., 2008).

An interesting aspect of the treatment with T-DM1 was shown in a HER2 expressing orthotopic murine model of breast cancer, where the ADC was shown to induce intratumoral T lymphocyte infiltration, thus increasing the susceptibility to checkpoint blockade immunotherapy in this normally immune-resistant tumor (Müller et al., 2015). The observation by Müller et al. that T-DM1 elicits antitumor immunity is in line with the more recent results from a study focused on the evaluation of a peripheral blood biomarker, the neutrophil-to-lymphocyte ratio (NLR), as a predicting factor of T-DM1 treatment efficacy. By retrospectively recruiting 53 advanced or metastatic breast cancer patients treated with T-DM1, and setting the NLR cutoff at median value of 2.56, it was demonstrated that the PFS of patients with low NLR (n = 26; median, not reached) was significantly better than that of patients with high NLR (n = 27; median, 4.13 months; HR = 0.226, 95% CI 0.112–0.493; $P = 0.0001$). A low NLR was also associated with a significantly longer OS (HR = 0.384, 95% CI 0.170-0.910; $P = 0.0296$), allowing to conclude that the antitumor activity of T-DM1 may be at least in part mediated by activation of the immune system (Imamura et al., 2019).

Based on the demonstrated clinical efficacy in the phase 3 EMILIA trial (NCT00829166) enrolling 991 patients (Verma et al., 2012), T-DM1 was approved in 2013 by both FDA and EMA as monotherapy to treat adult patients with HER2-positive, unresectable, locally advanced or metastatic breast cancer, who previously received trastuzumab and a taxane (alone or combined, but not the small molecule HER2 kinase inhibitor lapatinib) or who developed disease recurrence during or within 6 months of completing adjuvant therapy. The EMILIA trial compared T-DM1 with lapatinib plus the antimetabolite capecitabine, showing improvements in PFS (9.6 months *versus* 6.4 months; HR = 0.65, 95% CI 0.55-0.77; $P < 0.0001$) and OS (interim results: 30.9 *versus* 25.6 months; HR = 0.68, 95% CI 0.55-0.85; $P = 0.0006$) in favor of the T-DM1 arm. Descriptive analysis of the final OS in the EMILIA trial confirmed the survival advantage with T-DM1 over control treatment despite crossover from control to the experimental group [29.9 months, (95% CI 26.3-34.1) *versus* 25.9 months (95% CI 22.7-28.3); HR = 0.75,

95% CI 0.64-0.88] (Diéras et al., 2017). The TH3RESA trial, in patients with disease progression on two or more HER2-directed regimens including lapatinib, confirmed the higher survival benefit of T-DM1 *versus* treatment of physician's choice [median OS 22.7 months (95% CI 19.4-27.5) *versus* 15.8 months (13.5-18.7); HR = 0.68 (95% CI 0.54-0.85); $P = 0.0007$] (Krop et al., 2017). Also concerning the side effects profile, T-DM1 was demonstrated to offer advantages compared to lapatinib plus capecitabine treatment: the incidence of grade ≥3 adverse events was 41% *versus* 57%, respectively. Lapatinib and capecitabine group was more frequently associated with higher incidence of diarrhea, nausea, vomiting, and palmar–plantar erythrodysesthesia, while T-DM1 was associated with higher incidence of thrombocytopenia and increased serum aminotransferase levels (Verma et al., 2012).

In 2019, the interim results of the phase 3 KATHERINE trial (NCT01772472) allowed approval of T-DM1 as adjuvant treatment for early stage HER2-positive breast cancer with residual invasive disease, in the breast or axillary lymph nodes, after completion of neoadjuvant therapy containing a taxane (with or without anthracycline) and trastuzumab (von Minckwitz et al., 2019). This study recruited 1486 patients who were randomly assigned to receive T-DM1 (n = 743) or trastuzumab (n = 743) after surgery and the primary endpoint was the invasive-disease free survival. The results indicated that the risk of recurrence of invasive breast cancer or death with T-DM1 adjuvant therapy was 50% lower than with the naked mAb trastuzumab (HR = 0.50, 95% CI 0.39-0.64; $P < 0.001$). Grade 3 or higher adverse effects were also more common in the T-DM1 arm than in the trastuzumab arm (25.7% of patients *versus* 15.4%). With T-DM1 the most common adverse events of grade ≥3 were decreased platelet count (5.7% of the patients) and hypertension (2.0%). Peripheral sensory neuropathy of any grade was reported in 138 patients who received T-DM1 (18.6%) and 50 patients who received trastuzumab (6.9%); pneumonitis of any grade occurred in 19 patients in the T-DM1 group (2.6%) and 6 patients in the trastuzumab one (0.8%).

T-DM1 exhibits favorable pharmacokinetics, with $T_{1/2}$ of approximately 4 days, and minimal systemic accumulation following repeated administrations (Lu et al., 2014). T-DM1 catabolites are mainly eliminated in the bile, with minimal urinary excretion; therefore, mild-to-moderate renal impairment does not alter T-DM1 pharmacokinetic profile. However, *in vitro* studies suggested that emtansine is a P-glycoprotein substrate and is mainly metabolized by CYP3A4 (to a lesser extent also by CYP3A5), so that strong CYP3A4 inhibitors should be avoided in combination with T-DM1, in order to reduce the risk of increased drug exposure and toxicity (Corrigan et al., 2014; Davis et al., 2012).

The most common adverse effects of T-DM1, generally grade 1-2 and reversible, include severe thrombocytopenia (in 54.2% of patients), followed by elevated transaminases, fatigue, anemia, nausea, musculoskeletal pain, headache, and constipation (Krop et al., 2010). Severe hepatobiliary disorders were also reported from clinical trials, with at least two fatal cases of liver failure and encephalopathy (Diéras et al., 2017; Kim et al., 2016). Moreover, almost 20% of patients presented cardiotoxicity in the form of left ventricular dysfunction (Amiri-Kordestani et al., 2014). Finally, T-DM1 can harm the fetus when administered to pregnant women or even within seven months prior to conception (National Institute of Health, 2013), since several complications, including oligohydramnios, and fetal/neonatal death have been documented, likely due to the cytotoxic component, emtansine.

Among trastuzumab-based ADCs under clinical development, (vic-) trastuzumab duocarmazine (SYD985) consists of the anti-HER2 mAb carrying the alkylating agent duocarmycin, through a cleavable linker, and was designed to overcome resistance to T-DM1 (Van Der Lee et al., 2015; Xu et al., 2019). Other anti-HER2 ADCs under clinical evaluation, even in phase 3 clinical trials, are RC48-ADC and BAT8001. RC48-ADC (disitamab vedotin) is a novel humanized anti-HER2 antibody conjugated with MMAE via a cleavable linker (Sheng et al., 2021b) that received FDA breakthrough therapy designation for the treatment of urothelial cancer in September 2020. In a phase 2 trial, enrolling patients with HER2-positive locally advanced or metastatic urothelial cancer who had failed ≥1 lines of systemic chemotherapy, RC48-ADC showed promising antitumor activity and manageable safety profile (Sheng et al., 2021b). Moreover, a phase 1 study for advanced solid tumors with HER2 expression, including gastric cancer, indicated that RC48-ADC was well tolerated and had promising clinical activity (Xu et al., 2021). BAT8001 is, instead, a trastuzumab biosimilar product (BAT0606) bound through an uncleavable linker to batansine (a derivative of maytansine) that in a phase 1 study has shown therapeutic potential for HER2-positive locally advanced or metastatic breast cancer (Hong et al., 2021). Noteworthy, many other HER2 targeting ADCs are currently under evaluation in different tumors, at advanced or earlier disease stages (Xu et al., 2019): FS-1502, A166, XMT-1522, MEDI-4276, ARX788, PF-06804103, ZW49, ALT-P7, BDC-1001, RG6148, GQ1001, NJH395, and SBT6050. Among these, BDC-1001, NJH395, and SBT6050 represent a particular subgroup of next-generation ADCs, i.e. the subgroup of immune stimulator antibody conjugates (ISACs), designed to activate the innate immune system by carrying a potent immune-stimulatory agent rather than a cytotoxic molecule (Gerber et al., 2016). In particular, ISAC molecules deliver a potent agonist of toll-like receptor 7 and/or 8 (TLR7/8) broadly expressed on myeloid dendritic cells and other antigen-presenting cells (APCs) (Evans et al., 2019; Metz et al., 2020; Sharma et al., 2021). Thus, treatment with ISAC molecules is expected to inhibit tumor growth by immune mediated mechanisms comprising not only ADCC (through the Fc region of IgG1 mAbs) but also adaptive immune responses, as a consequence of stimulation of tumor-associated antigen presentation to T cells.

2.4. Inotuzumab ozogamicin

Inotuzumab ozogamicin is an ADC composed of a recombinant humanized IgG4 anti-CD22 mAb, linked to the DNA-damaging cytotoxic agent ozogamicin (Wynne et al., 2019; Yilmaz et al., 2015). As in the case of gemtuzumab ozogamicin, an acid-sensitive linker (4-(4′-acetylphenoxy) butanoic acid linker) is used to join the anti-CD22 mAb to the calicheamicin derivative. In particular, this linker contains a hydrazone moiety and a disulfide linkage (Ricart, 2011), another possible component of non-enzymatic cleavable linkers, which remains stable in the bloodstream but is efficiently reduced to free thiols by intracellular glutathione.

Being CD22 a B-cell-specific transmembrane protein involved in B cell activation, it is mainly expressed on mature B lymphocytes and acute lymphoblastic leukemia (ALL) (Troussard and Cornet, 2017). Accordingly, inotuzumab ozogamicin was approved in 2017 by FDA and EMA as monotherapy for the treatment of relapsed or refractory B cell precursor ALL (B-ALL), on the basis of primary intent-to treat analysis of data from the randomized phase 3 INO-VATE trial (NCT01564784) obtained in the first 218 of the 326 randomized patients. Adult patients with Philadelphia chromosome positive B-ALL were required to have failed treatment with at least one or more second-generation BCR-ABL tyrosine kinase inhibitors. This analysis demonstrated a clinically and statistically significant increase in complete remission rate with inotuzumab ozogamicin (n = 109), compared to standard intensive chemotherapy (n = 109) (80.7%, 95% CI 72.1-88 *versus* 29.4%, 95% CI 21-39, $P < 0.001$). Also the median PFS (5.0 months, 95% CI 3.7-5.6 *versus* 1.8 months, 95% CI 1.5-2.2; HR = 0.45, 97.5% CI 0.34-0.61; $P < 0.001$) and the median OS (7.7 months, 95% CI 6.0-9.2 *versus* 6.7 months, 95% CI 4.9-8.3; HR = 0.77, 97.5% CI 0.58-1.03; $P = 0.04$) were significantly longer in the inotuzumab ozogamicin group (Kantarjian et al., 2016). The final results of the INO-VATE trial (with ≥2 years of follow-up) in 326 patients confirmed the higher complete remission rate in the inotuzumab ozogamicin group compared to the control group (73.8% *versus* 30.9%; $P < 0.0001$) and showed 2-year OS rates of 22.8% and 10.0%, respectively (HR = 0.75, 97.5% CI 0.57-0.99; $P = 0.0105$)

(Kantarjian et al., 2019). In both arms, the most frequent all-grade and grade ≥3 adverse events were hematological toxicities: neutropenia (47%), thrombocytopenia (41%), leukopenia (27%), and febrile neutropenia (27%) with inotuzumab ozogamicin; thrombocytopenia (59%), febrile neutropenia (54%), neutropenia (44%), and anemia (44%) with standard chemotherapy. Conversely, the veno-occlusive disease was more frequent with inotuzumab ozogamicin (14.0% *versus* 2.1%). Of interest, since the loss of other B-cell antigens, like CD19, is a major mechanism of resistance developed by hematological tumors, CD22 targeting is expected to provide new therapeutic options for the treatment of B-cell malignancies refractory to anti-CD19 mAbs like, for instance, blinatumomab (Ormhøj et al., 2019).

About inotuzumab ozogamicin clearance, the elimination $T_{1/2}$ at the end of cycle 4, when steady-state is achieved with the recommended starting dose of 1.8 mg/m^2/cycle, is approximately 12.3 days [https://www.accessdata.fda.gov]. The payload calicheamicin derivative is metabolized via non-enzymatic reduction and its levels do not appear to be reduced or altered in patients with hepatic or renal impairment (DeAngelo et al., 2017). Unfortunately, overexpression of P-glycoprotein in leukemia cells may result in increased efflux of the cytotoxic drug, thus reducing the ADC efficacy.

Similarly to gemtuzumab ozogamicin, the most common non-hematological toxicity with inotuzumab ozogamicin is hepatotoxicity that has been associated with a possible premature ADC breakdown prior to entering the target cell (Wolska-Washer and Robak, 2019). In particular, veno-occlusive disease has been diagnosed in patients who underwent HSCT after inotuzumab ozogamicin treatment. Other adverse events are represented by myelosuppression, increased transaminases, headache, nausea and fatigue (Kantarjian et al., 2016, 2019). Thus, particular attention must be given to the dose and dosing regimen when using this ADC.

Among novel CD22 targeting ADCs under clinical investigation, ADCT-602 (epratuzumab-cys-tesirine) is composed of a cysteine-engineered version of epratuzumab (hLL2), a humanized anti-CD22 mAb derived from the murine IgG2a mAb LL2 (EPB-2). The cytotoxic agent, tesirine (SG3249), includes a cathepsin B-cleavable valine-alanine PBD that binds to guanines on opposite strands of DNA, thus inducing inter-strand cross-links and inhibition of DNA replication (Zammarchi et al., 2016). Another ADC having CD22 as target, is pinatuzumab vedotin (DCDT2980S), containing a cathepsin-cleavable maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl (mc-val-cit-PABC) type linker, and MMAE as payload. This ADC has shown clinical activity in combination with the anti-CD20 rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma [DLBCL, the most common type of non-Hodgkin lymphoma (non-HL)] and follicular lymphoma that represent a difficult-to-treat population (Morschhauser et al., 2014, 2019). Furthermore, TRPH-222 (CD22-4AP) is a clinically investigated ADC, composed of an anti-CD22 humanized mAb site-specifically conjugated, via formylglycine residues and a protease insensitive linker, to a cytotoxic microtubule-targeting maytansinoid payload.

2.5. Polatuzumab vedotin-piiq

In polatuzumab vedotin-piiq, a humanized IgG1 anti-CD79b mAb is linked to the tubulin inhibitor MMAE through the same protease-cleavable linker (valine-citrulline linker cleaved by lysosomal cathepsin B) found in brentuximab vedotin (Maruani, 2018). Although the mechanism of action of polatuzumab vedotin-piiq is mostly based on MMAE-induced cell death, antibody opsonization and ADCC also play an important role in inhibiting tumor growth (Ma and Sawas, 2018; Shingleton and Dave, 2020). Polatuzumab vedotin-piiq received accelerated approval by FDA in 2019 and conditional market authorization by EMA in 2020 for the treatment of relapsed or refractory DLBCL, in combination with rituximab and bendamustine, after two prior therapies. Similarly to CD22, CD79b is a marker of the B-cell lineage; specifically, it is a B cell receptor complex component, but unlike CD22, it is virtually expressed in both immature and mature B cells (Chu and Arber, 2001). Approval was based on the early promising results of the phase 1b/2 GO29365 study (NCT02257567) evaluating polatuzumab vedotin-piiq in combination with bendamustine and rituximab, compared to bendamustine and rituximab, for relapsed/refractory DLBCL. In the ADC combination group, 16 out of 40 patients achieved a complete response *versus* 7 out of 40 patients in the bendamustine and rituximab group (40% *versus* 18%, $P = 0.026$). Moreover, after a median follow-up of 22.3 months, the OS was significantly improved by polatuzumab vedotin-piiq, with a death risk reduction of 58% (HR = 0.42, 95% CI 0.24-0.75) and longer median OS (12.4 months, 95% CI 9.0-not evaluable *versus* 4.7 months, 95% CI 3.7-8.3 months). Patients treated with the ADC in combination with bendamustine and rituximab had higher rates of grade 3-4 neutropenia (46.2% *versus* 33.3%), anemia (28.2% *versus* 17.9%), and thrombocytopenia (41% *versus* 23.1%), compared to those treated with bendamustine and rituximab, but similar grade 3-4 infections (23.1% *versus* 20.5%). In addition, grade 1-2 peripheral neuropathy was associated with polatuzumab vedotin-piiq (43.6% of patients), but resolved in most patients (Sehn et al., 2020).

Generally associated with a favorable safety profile, the most common adverse effects with polatuzumab vedotin-piiq are fatigue, diarrhea, nausea, peripheral neuropathy, neutropenia, constipation, decreased appetite. Grade ≥3 adverse events include neutropenia, diarrhea, dyspnea, febrile neutropenia, hyperglycemia, fatigue, and thrombocytopenia (Morschhauser et al., 2014; Sehn et al., 2020).

In regard to pharmacokinetics and drug-drug interactions, a recent phase 1b/2 open-label study (NCT01992653) indicated that when polatuzumab vedotin-piiq is used in combination with rituximab (or the other anti-CD20 mAb obinutuzumab), cyclophosphamide, doxorubicin, and prednisone in patients with DLBCL, no clinically meaningful differences are observed between treatment arms or depending on the line of therapy (Shemesh et al., 2020). In particular, polatuzumab vedotin-piiq shows a long terminal $T_{1/2}$, of approximately 12 days at cycle 6 of treatment, whereas $T_{1/2}$ of the unconjugated payload, MMAE, is about 4 days after the first dose [https://www.accessdata.fda.gov].

Like polatuzumab vedotin-piiq, also the experimental ADC iladatuzumab vedotin (DCDS0780A) targets CD79b, through a humanized IgG1 mAb linked to MMAE by a cleavable linker (Herrera and Molina, 2018). This mAb is evaluated in early stage clinical trials for relapsed/ refractory B-cell non-HL.

2.6. Enfortumab vedotin-ejfv

Enfortumab vedotin-ejfv is a fully humanized IgG1 mAb directed against nectin-4, and conjugated via a valine-citrulline protease-cleavable linker to the microtubule disruptor MMAE. Nectins are a class of Ig-like proteins that play a critical role in cell-cell adhesion and intracellular communication, recently associated with oncogenic processes like cell growth, invasion, and survival (Mandai et al., 2015). In particular, nectin-4 is highly expressed across several carcinomas, including gastric (Zhang et al., 2018a), breast (Lattanzio et al., 2014), lung (Takano et al., 2009), and bladder (Heath and Rosenberg, 2021) cancers, where it seems to be involved in the establishment of adherens junctions and apico-basal cell polarity (Rikitake et al., 2012). Although nectin-4 is largely expressed in many normal epithelial tissues, enfortumab vedotin-ejfv has an acceptable safety profile due the higher levels of nectin-4 present in the tumor tissue (Challita-Eid et al., 2016; Rosenberg et al., 2019). As demonstrated in a preclinical study, the unconjugated form of enfortumab is able to inhibit nectin-4 homo- and heterodimerization but it does not affect cell viability. On the contrary, the derived ADC inhibits *in vitro* proliferation of nectin-4 expressing cancer cell lines [i.e., breast, prostate, and small-cell lung cancer (SCLC)], and *in vivo* growth of several tumor xenografts, including

patient-derived xenografts from bladder, breast, and pancreatic cancer (Challita-Eid et al., 2016).

In December 2019, FDA granted accelerated approval to enfortumab vedotin-ejfv for the treatment of platinum- and immune checkpoint inhibitor-refractory, locally advanced or metastatic urothelial carcinoma, previously treated with an anti-PD-1 or anti-PD-L1 mAb and platinum-based chemotherapy in the neoadjuvant or adjuvant settings. Clinical data supporting approval derived from the EV-201 trial (NCT03219333), a single arm phase 2 study testing enfortumab vedotin-ejfv monotherapy in 125 patients (Rosenberg et al., 2019) that reported a confirmed ORR of 44% (95% CI 35.1-53.2%). The most common treatment-related adverse events were fatigue (50%), and peripheral sensory neuropathy (50%), alopecia (49%), rash (48%), reduced appetite (44%), and dysgeusia (40%). Peripheral neuropathy and hyperglycemia (reported in 11% of patients) have been described also for other MMAE carrying ADCs, like brentuximab vedotin and polatuzumab vedotin-piiq, and therefore have been attributed to the payload (Masters et al., 2018). Conversely, the skin toxicity is an example of on-target/off-tumor toxicity of enfortumab vedotin-ejfv, being nectin-4 highly expressed also by cutaneous cells (Chang et al., 2021a). In 2021, enfortumab vedotin-ejfv received full approval based on the EV-301 phase 3 trial (NCT03474107) with OS as primary endpoint. This study showed an increase of OS in patients treated with enfortumab vedotin-ejfv group (N = 301) compared to the chemotherapy arm (N = 307) (median OS, 12.88 *versus* 8.97 months; HR = 0.70, 95% CI 0.56-0.89; $P = 0.001$) (Powles et al., 2021). Approval was extended to include patients ineligible for cisplatin after at least one line of treatment.

Recently, in 2020, based on the initial promising results of the phase 1b/2 EV-103 clinical trial (NCT03288545) (Hoimes et al., 2019), enfortumab vedotin-ejfv in combination with the anti-PD-1 mAb pembrolizumab received breakthrough therapy designation in the first-line treatment of patients with unresectable, locally advanced or metastatic bladder cancer patients who cannot tolerate cisplatin.

Enfortumab vedotin-ejfv and the carried payload MMAE exhibit an elimination $T_{1/2}$ of 3.4 and 2.4 days, respectively, when used at the recommended dosage of 1.25 mg/kg [https://www.accessdata.fda.gov]. As in the case of brentuximab vedotin and polatuzumab vedotin-piiq, the rate of MMAE release from the ADC affects its elimination and metabolism by CYP3A4. Thus, concomitant administration with a strong CYP3A4 inhibitor may increase free MMAE exposure and the risk of toxicity with enfortumab vedotin-ejfv [https://www.accessdata.fda.gov].

2.7. Fam-trastuzumab deruxtecan-nxki

This ADC is composed of the humanized IgG1 anti-HER2 mAb trastuzumab, conjugated through a protease-cleavable tetrapeptide linker to an exatecan derivative acting as a topoisomerase I inhibitor (Ogitani et al., 2016a). Fam-trastuzumab deruxtecan-nxki received accelerated approval in 2019 by FDA for the treatment of HER2-positive advanced/metastatic breast cancer patients who have received at least two prior HER2-directed therapies (Modi et al., 2020), while in Europe it received conditional approval by EMA for the same indication on January 2021. Recently, FDA also approved this ADC for locally advanced or unresectable metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma and granted it a breakthrough therapy designation for non–small cell lung cancer (NSCLC).

The first approved indication was based on data from the DS8201-A-U201 (DESTINY-Breast01; NCT03248492) and DS8201-A-J101 (NCT02564900) trials (Narayan et al., 2021). DESTINY-Breast01 is a phase 2 study that evaluated fam-trastuzumab deruxtecan-nxki in adults with pathologically documented HER2-positive metastatic breast cancer who had received previous treatment with T-DM1. Response to the therapy was reported in 112 out of the 184 treated patients (60.9%; 95% CI 53.4-68.0). At a median follow-up of 11.1 months (range 0.7-19.9), the median response duration was 14.8 months (95% CI 13.8-16.9) and the median duration of PFS was 16.4 months (95% CI 12.7-not reached). The most common adverse events of grade 3 or higher were decrease of neutrophil count (20.7%), anemia (8.7%), and nausea (7.6%). Moreover, in 13.6% of cases interstitial lung disease was reported (Modi et al., 2020). Of interest, according to the results of the multi-cohort phase 1 DS8201-A-J101 study, in patients with other advanced solid tumors, including gastric cancer (Doi et al., 2017), responses were observed also in low-HER2 expressing tumors. More recently, the results of DESTINY-Gastric01 (NCT03329690) phase 2 trial promoted approval of fam-trastuzumab deruxtecan-nxki for the treatment of HER2-positive gastric or gastroesophageal junction adenocarcinoma (Shitara et al., 2020). This study compared fam-trastuzumab deruxtecan-nxki (n = 125) with physician's choice of chemotherapy (the topoisomerase I inhibitor irinotecan or the antimitotic agent paclitaxel; n = 62) reporting higher ORR (51% *versus* 14%; $P < 0.001$) and longer OS (median, 12.5 *versus* 8.4 months; HR for death = 0.59, 95% CI 0.39-0.88; $P = 0.01$) in patients treated with the ADC than in those receiving chemotherapy.

Compared to T-DM1, fam-trastuzumab deruxtecan-nxki is characterized by a higher drug-to-antibody ratio, thus allowing a significantly increased drug concentration in the target tumor cells and accounting for its efficacy even in low-HER2 expressing tumors. Another biochemical improvement that differentiates fam-trastuzumab deruxtecan-nxki from the previously approved anti-HER2 ADCs, and justifies its activity across several cancer types, is the linker, which consists in a novel lysosome-cleavable peptide sensitive to enzymes commonly detected in the TME, like cathepsins (T-DM1, instead, includes a non-cleavable thioether linker). Additionally, the payload is permeable to cell membranes and can easily diffuse into cells adjacent to the target cell, maximizing the bystander effect of fam-trastuzumab deruxtecan-nxki, and contributing to its efficacy also against HER2-negative tumor cells (Ogitani et al., 2016b).

The most common toxicities were gastrointestinal disturbances (nausea), hematological toxicities (myelosuppression), alopecia, and cough. Remarkably, fam-trastuzumab deruxtecan-nxki was also associated with interstitial lung disease (Modi et al., 2020).

The pharmacokinetics of fam-trastuzumab deruxtecan-nxki, following a single intravenous administration of 3 mg/kg, is similar to that of the naked mAb ($T_{1/2}$ 8.23±1.39 and 10.3±1.5 days, respectively), while the payload deruxtecan is rapidly cleared from the circulation ($T_{1/2}$ 1.35 h) and excreted mainly through the feces as intact form without involvement of enzymatic metabolism (Okamoto et al., 2020), excluding the risk of enzyme-mediated drug-drug interactions.

2.8. Sacituzumab govitecan-hziy

Sacituzumab govitecan-hziy is an ADC comprised of a humanized IgG1 mAb directed against human trophoblast cell surface marker 2 (TROP-2, also known as tumor-associated calcium signal transducer), conjugated via a pH-sensitive (hydrolysable) linker to the topoisomerase I inhibitor SN-38, the active metabolite of irinotecan (Goldenberg and Sharkey, 2020). SN-38 is about 1000 times more potent than the parental compound, demonstrating activity even at nanomolar concentrations (Kawato et al., 1991). However, SN-38 cannot be administered as a free drug, due to its toxicity and poor solubility (Beck et al., 2017); in this case, the ADC formulation offers the additional advantage to act as vehicle of this highly potent drug, overcoming solubility limitations. Moreover, this ADC has a high drug-to-antibody ratio (7.5–8) and the hydrolysable linker can cause the release of the cytotoxic molecules into the TME, extending its killing activity to nearby tumor cells via the bystander effect (Goldenberg and Sharkey, 2020).

The ADC target TROP-2 is a transmembrane glycoprotein implicated in cell growth and migration, shown to be overexpressed in a variety of solid tumors (Cardillo et al., 2011; Trerotola et al., 2013) and associated with worse prognosis (Cubas et al., 2010). In particular, while expressed

on breast, cervix, ovary, prostate, pancreas, colon and rectum, kidney, liver, and lung cancer cells, TROP-2 has limited expression in normal human tissues.

In April 2020, FDA granted accelerated approval and, one year later, full approval to sacituzumab govitecan-hziy for unresectable, locally advanced or metastatic triple-negative breast cancer (TNBC; i.e., HER2, estrogen receptor and progesterone receptor negative), after at least two prior therapeutic regimens for the metastatic disease, based on the data of the phase 3 ASCENT study (NCT02574455). This trial, enrolling 468 patients affected by TNBC without brain metastases, demonstrated a statistically significant reduction in the risk of disease progression or death (HR = 0.41, 95% CI 0.32-0.52; $P < 0.001$) in patients treated with sacituzumab govitecan-hziy (n = 235) compared to chemotherapy (the antimitotic agents eribulin and vinorelbine and the antimetabolites capecitabine and gemcitabine) (n = 233), extending median PFS to 5.6 months (95% CI 4.3-6.3) from 1.7 months (95% CI 1.5-2.6). Treatment with the ADC was also associated with an improvement in OS (12.1 months, 95% CI 10.7-14.0 *versus* 6.9 months, 95% CI 5.8-7.7; HR = 0.48, 95% CI 0.38-0.59; $P < 0.001$). The grade ≥3 adverse effects, more frequently associated with sacituzumab govitecan-hziy, were myelotoxicity with neutropenia (51% *versus* 33% with chemotherapy) and diarrhea (10% *versus* <1%) (Bardia et al., 2021a). In November, 2021 also EMA approved this ADC for the same indication.

In April 2021, sacituzumab govitecan-hziy received accelerated approval for the treatment of unresectable locally advanced or metastatic urothelial cancer progressing after platinum-containing chemotherapy and either anti-PD-1 or anti-PD-L1 mAbs. Approval was based on data from the phase 2 TROPHY-U-01 study (NCT03547973), in which 27.7% of patients (31 out of 113; 95% CI 19.5-36.6) treated with sacituzumab govitecan-hziy responded to treatment, with a median duration of response of 7.2 months (95% CI 4.7-8.6). Also in this case, grade ≥3 treatment-related adverse events were neutropenia and diarrhea (Tagawa et al., 2021). Thus, sacituzumab govitecan-hziy prescribing information has a boxed warning about the risk of severe or life-threatening neutropenia and severe diarrhea [https://www.accessdata.fda.gov].

At 8-10 mg/kg, sacituzumab govitecan-hziy has a predictable pharmacokinetics, with a $T_{1/2}$ for the IgG component of antibody of about 103-114 hours and for total SN-38 (bound and free drug) of 16-19 hours (Ocean et al., 2017). Comparable $T_{1/2}$ values were reported in a more recent study (Bardia et al., 2021b). No metabolism and drug-drug interaction studies have been conducted with sacituzumab govitecan-hziy, but since SN-38 is metabolized via uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), inhibitors or inducers of this enzyme are expected to increase or decrease SN-38 exposure, respectively (Bardia et al., 2021b) [https://www.accessdata.fda.gov]. Moreover, *UGT1A1* gene polymorphisms, associated with reduced enzymatic activity (e.g., Gilbert's syndrome), may lead to increased SN-38 toxicity and, in clinical trials testing sacituzumab govitecan-hzi, Gilbert's syndrome is often listed among the exclusion criteria.

Datopotamab deruxtecan (DS-1062) is a novel ADC currently investigated in different clinical trials (Okajima et al., 2021), including another humanized anti-TROP2 IgG1 mAb, a tetrapeptide-based linker and a topoisomerase I inhibitor as payload. This ADC, according to a recent press release by Astra-Zeneca (2021, January 29; "Datopotamab deruxtecan and Enhertu show promising early clinical activity in patients with advanced non-small cell lung cancer") seems to have promising clinical activity in patients with advanced or metastatic NSCLC, according to the results of the phase 1 TROPION-PanTumor01 trial (NCT03401385). SKB264 is another new TROP2 targeting ADC with a belotecan-derived payload (a camptothecin derivative that like SN-38 inhibits topoisomerase I) and a stable conjugation chemistry to obtain a drug-to-antibody ratio of 7.4. A first-in-human study is testing SKB264 in patients with locally advanced unresectable or metastatic solid tumors, refractory to available standard therapies (NCT04152499) (Liu et al., 2020).

2.9. Belantamab mafodotin-blmf

Belantamab mafodotin-blmf comprises an IgG1 that targets the cell surface B cell maturation antigen (BCMA), involved in the growth and survival of plasma cells and expressed on multiple myeloma cells (Trudel et al., 2019). Moreover, BCMA serum levels have been correlated with response to therapy and OS in multiple myeloma patients (Sanchez et al., 2012). The antibody is conjugated to the antimitotic drug monomethyl auristatin F (MMAF) via a non-cleavable protease-resistant maleimidocaproyl linker (Lee et al., 2016). The presence of a negative charge at the C-terminus renders MMAF less liposoluble and membrane-permeable than MMAE, the payload found in brentuximab vedotin, polatuzumab vedotin-piiq, and enfortumab vedotin-ejfv. As a consequence, MMAF showed a higher IC_{50} value and limited bystander killing effects *in vitro,* compared to MMAE. Due to these properties, MMAF-mediated killing effect is restricted to the target cell and a high tumor expression of the target antigen is required for its antitumor activity (Li et al., 2016). On the other hand, the same additional negative charge located in the C-terminus of MMAF confers it a higher affinity for the target protein tubulin, compared to MMAE (Waight et al., 2016).

Belantamab mafodotin-blmf received accelerated approval in 2020 by FDA and conditional market authorization by EMA, as monotherapy for the treatment of patients with relapsed or refractory multiple myeloma who have received at least four prior therapies, including an anti-CD38 mAb, a proteasome inhibitor and an immunomodulatory agent (Tzogani et al., 2021).

Approval of belantamab mafodotin-blmf was based on the results of ORR and response duration of the DREAMM-2 study (NCT03525678). This phase 2 trial enrolled patients with relapsed or refractory multiple myeloma, worsened despite three or more lines of current standard of therapy, resistant to immunomodulatory agents and proteasome inhibitors, and refractory and/or intolerant to an anti-CD38 mAb. Treatment with belantamab mafodotin-blmf as single-agent induced a clinically important ORR of 31% (97.5% CI 21-43). The median duration of response had not been reached at the six-month analysis, but 73% of responders had a response duration equal to or greater than six months. The most commonly reported adverse events (≥20%) were keratopathy, with or without symptoms (leading to treatment discontinuation in 2.1% of patients), decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue (Lonial et al., 2020). Considering the corneal risks associated with belantamab mafodotin-blmf, a boxed warning has been added to the prescription information stating that the ADC may induce changes in the corneal epithelium and that treated patients should undergo periodic ophthalmic examinations [https://www.accessdata.fda.gov].

The pharmacokinetic profile of belantamab mafodotin-blmf has been described according to a two-compartment model, with linear elimination and time-varying clearance, influenced by disease-related factors and body weight (Markham, 2020). In particular, administration of belantamab mafodotin-blmf 2.5 mg/kg to patients with multiple myeloma gives a mean $T_{1/2}$ of 12 and 14 days after the first dose and at steady state, respectively. *In vitro*, the payload attached to the protease-resistant maleimidocaproyl linker (cys-mcMMAF), is mainly hydrolyzed and dehydrated to a cyclized isomeric form of cys-mcMMAF, but no data are available concerning its *in vivo* metabolism and elimination [https://www.accessdata.fda.gov].

Among ADCs in clinical development targeting BCMA, AMG 224 is formed by an IgG1 conjugated, through the noncleavable linker 4-(N-maleimidomethyl) cyclohexane-1-carboxylate, with DM1 (Lee et al., 2021). In a phase 1 dose-escalation study (NCT02561962) for relapsed/refractory multiple myeloma, AMG 224 demonstrated favorable pharmacokinetics, manageable safety, and durable antitumor activity in some patients (23% ORR, 95% CI 11–39; median duration of response of 14.7 months) (Lee et al., 2021). CC-99712 is another anti-BCMA ADC, linked through a dibenzocyclooctyne non-cleavable linker to a

maytansinoid moiety, to which FDA has granted orphan drug designation for adult patients with relapsed/refractory multiple myeloma. Finally, HDP-101 is an anti-BMCA ADC under clinical evaluation, which belongs to the new class of antigen-targeted amanitin-conjugates (ATACs). In ATACs the mAb is conjugated through a cleavable linker to the payload amanitin, a small bicyclic peptide naturally occurring in the death cap mushroom that inhibits RNA polymerase II complex and, consequently, gene transcription (Figueroa-Vazquez et al., 2021). Differently from microtubule targeting payloads, alpha-amanitin exerts cytotoxic effects independently of the proliferation status of tumor cells; thus, it is active also against resting tumor cells.

2.10. Loncastuximab tesirine-lpyl

Loncastuximab tesirine-lpyl (ADCT-402) is a recently FDA-approved ADC comprising a humanized anti-CD19 mAb conjugated to a pyrrolobenzodiazepine (PBD) dimer toxin, namely SG3199 (a DNA cross-linking agent), through a cathepsin-cleavable valine-alanine linker (Hamadani et al., 2021a). CD19, also known as B lymphocyte surface antigen B4, is a suitable target for the immunotherapy of B-cell non-HL because it is expressed on B-cell malignancies and during B-cell development, but not on hematopoietic stem cells and terminally differentiated plasma cells. Moreover, CD19 is rapidly internalized and does not spread into the general circulation, rendering it an ideal target for ADCs (Zammarchi et al., 2018).

Accordingly, loncastuximab tesirine-lpyl has been granted first accelerated approval by FDA in 2021 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma, after two or more lines of systemic therapy, including DLBCL of non-specified origin and DLBCL arising from low- or high-grade B-cell lymphoma, thus representing the second ADC clinically available for DLBCL treatment. Approval was based on the data of LOTIS-2 (NCT03589469), a phase 2 single-arm clinical trial that enrolled adult patients ($n = 184$) with relapsed/refractory DLBCL following two or more prior lines of systemic therapy, including patients non eligible for or progressing after CD19 directed CAR-T therapy. The results of the trial demonstrated that 70 out of the 145 eligible patients achieved complete or partial response (ORR 48.3%, 95% CI 39.9-56.7), with a complete response rate of 24.1% (95% CI 17.4-31.9). Median time to response was 1.3 months and the median duration of response for the 70 responders was 10.3 months. The most common grade ≥3 treatment-emergent adverse events were represented by hematological toxicity (26% neutropenia, 18% thrombocytopenia, 10.3% anemia) and increased gamma-glutamyltransferase (17%) (Caimi et al., 2021). A randomized phase 3 trial is currently comparing loncastuximab tesirine-lpyl plus rituximab with standard immunochemotherapy (NCT04384484).

The reported mean $T_{1/2}$ of loncastuximab tesirine-lpyl at steady state is 20.8 ± 7 days. The mAb portion is metabolized by proteolytic pathways, while the small molecule SG3199 is metabolized by CYP3A4/5 *in vitro* but the mechanisms involved in its excretion in humans have not been investigated yet [https://www.accessdata.fda.gov].

Among novel experimental anti-CD19 ADCs, coltuximab ravtansine (SAR3419) (Younes et al., 2012b; Carol et al., 2013; Coiffier et al., 2016; Trněny et al., 2018) and denintuzumab mafodotin (SGN-CD19A or HBU12-491) (Jones et al., 2020) have been also studied in clinical trials for DLBCL, including patients refractory to rituximab.

2.11. Tisotumab vedotin-tftv

The last FDA-approved ADC, on September 2021, is tisotumab vedotin-tftv, a tissue factor (TF) targeting mAb conjugated with MMAE through a protease cleavable linker (de Bono et al., 2019). TF is a transmembrane glycoprotein normally detected in fibroblasts and sub-endothelial cells, with a crucial role in hemostasis regulation (Rondon et al., 2019). Indeed, its binding to factor VII (FVII) generates the active TF-FVIIa complex, which is responsible for the activation of the coagulation extrinsic cascade. TF is frequently expressed by tumor cells, and evidence exists that it promotes tumor growth, angiogenesis, metastasis and thrombosis (Van Den Berg et al., 2012). FDA has granted accelerated approval to tisotumab vedotin-tftv as the first ADC for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy, a clinical condition that lacks a standard of care after failure of the first-line treatment. Approval was based on the results of the innovaTV 204 trial (NCT03438396), an open-label, single-arm, multicenter phase 2 study with confirmed objective response rate as primary endpoint (Coleman et al., 2021). One hundred and two patients were treated with at least one dose of the ADC and, after a medium follow-up of 10 months, the ORR was 20% (95% CI 16-33) of which 7% and 14% were complete and partial responses, respectively. The median PFS was 4.2 months (95% CI 3.0-4.4) and OS was 12.1 months (95% CI 9.6-13.9). The most common (2-3%) grade ≥3 treatment-related adverse effects included neutropenia, fatigue, ulcerative keratitis (boxed warning for ocular toxicity in the drug label), and peripheral neuropathies. A phase 3 trial that compares tisotumab vedotin-tftv with the investigator's choice chemotherapy, in the same clinical setting (i.e., recurrent/metastatic cervical cancer) and with OS as primary endpoint, is currently ongoing (NCT04697628).

Analysis of the pharmacokinetics deriving from a dose-escalation study indicated that low concentrations of free MMAE were detected in the bloodstream (de Bono et al., 2019).

In addition to tisotumab vedotin-tftv, a second experimental ADC targeting TF (i.e., MRG004A) is under clinical investigation (Matiash et al., 2021).

2.12. Ongoing clinical trials with approved ADCs

The aforementioned approved ADCs are currently evaluated in a number of ongoing phase 2 and 3 clinical trials, as single agents or in combination with other therapeutic agents, in the frontline setting of newly diagnosed malignancies or after several lines of treatment for refractory tumors, and advanced/metastatic or early stages of disease. Phase 2 studies also include evaluation of the ADCs for tumor types different from those comprised in the approved indications. Conversely, the currently active-not recruiting or recruiting phase 3 trials are evaluating these ADCs for the same tumor types for which they have received approval but at different disease stages, within different combination protocols or compared to other treatments (Table 2).

3. Novel ADCs under clinical investigation

The interest in new potential targets for ADCs has recently grown due to the need of find alternative and safer therapeutic opportunities especially for advanced/metastatic solid tumors. In fact, solid tumor-associated antigens targeted by approved ADCs are often present also in normal cells. This implies an increased toxicity towards healthy tissues and a reduced amount of intra-tumoral drug delivery (Boni et al., 2020). Lineage-specific antigens expressed by hematological malignancies have been widely investigated as targets of the approved ADCs and just a limited number of experimental ADCs are evaluated for these tumor types.

To date, a growing number of experimental ADCs, under preclinical and clinical investigation, are directed against either the same antigens of approved ADCs or novel therapeutically unexploited antigens expressed by cancer cells. Moreover, many ADCs under clinical development target cancer stem cells or antigens that are abundantly found in the cells of the TME, such as immunosuppressive regulatory T cells (Tregs) and cancer associated fibroblasts (Fig. 2, Table 3).

Table 2
Not yet recruiting, recruiting, or active not recruiting phase 3 clinical trials with approved ADCs.

ADC	Clinicaltrials.gov identifier[a]	Status	Tumor	Investigated treatment
Gemtuzumab ozogamicin	NCT04093505	Recruiting	Newly diagnosed AML	Gemtuzumab ozogamicin in combination with chemotherapy (cytarabine and daunorubicin) in induction therapy; chemotherapy plus or minus glasdegib (inhibitor of the Hedgehog pathway) in maintenance/consolidation therapy.
	NCT04168502	Recruiting	Previously untreated *de novo* favorable/intermediate risk AML	Gemtuzumab ozogamicin in combination with daunorubicin and cytarabine in induction and consolidation therapy; post-transplant maintenance with or without glasdegib.
	NCT02724163	Recruiting	AML pediatric patients	Gemtuzumab ozogamicin in combination with cytarabine plus mitoxantrone or liposomal daunorubicin in induction therapy.
	NCT04293562	Recruiting	Newly diagnosed AML with or without mutated FLT3	Standard therapy (cytarabine, daunorubicin, etoposide, methotrexate, etc.), including gemtuzumab ozogamicin *versus* CPX-351(liposome-encapsulated daunorubicin-cytarabine), plus gemtuzumab ozogamicin and addition of the FLT3 inhibitor gilteritinib for patients with FLT3 mutations.
Brentuximab vedotin	NCT02684292	Active not recruiting	Relapsed or refractory cHL	Brentuximab vedotin *versus* pembrolizumab.
	NCT03907488	Recruiting	Newly diagnosed stage III or IV cHL	Brentuximab vedotin plus standard chemotherapy (doxorubicin, vinblastine, and dacarbazine) *versus* the anti-PD-1 mAb nivolumab plus standard chemotherapy.
	NCT04685616	Not yet recruiting	Early stage cHL	Radiotherapy plus AVD chemotherapy (doxorubicin, vinblastine and dacarbazine) and brentuximab vedotin plus growth factor support *versus* radiotherapy plus ABVD chemotherapy (doxorubicin, bleomycin, vinblastine and dacarbazine).
	NCT01712490[b]	Active not recruiting	Previously untreated advanced (stage III or IV) cHL	AVD plus brentuximab vedotin *versus* ABVD.
	NCT02166463	Active not recruiting	Newly diagnosed stage IIB or IIIB-IVB cHL in children and young adults	Brentuximab vedotin plus chemotherapy (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) *versus* chemotherapy alone.
	NCT04404283	Recruiting	Relapsed or refractory DLBCL	Brentuximab vedotin plus lenalidomide and rituximab *versus* lenalidomide and rituximab plus placebo.
	NCT02661503	Recruiting	Advanced stage cHL	BrECADD treatment (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) *versus* BEACOPP treatment (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone).
Ado-trastuzumab emtansine or T-DM1	NCT04622319	Recruiting	High-risk HER2-positive patients with residual invasive breast cancer following neoadjuvant therapy	T-DM1 *versus* trastuzumab deruxtecan after treatment with trastuzumab- and taxane-based therapy.
	NCT03529110	Active not recruiting	HER2-positive, unresectable and/or metastatic breast cancer	T-DM1 *versus* fam-trastuzumab deruxtecan-nxki in patients previously treated with trastuzumab- and taxane-based therapy.
	NCT04740918	Recruiting	HER2- and PD-L1-positive locally advanced or metastatic breast cancer	T-DM1 plus the anti-PD-L1 mAb atezolizumab *versus* T-DM1 plus placebo in patients with disease progression either during or after prior trastuzumab- and taxane-based therapy.
	NCT03084939	Active not recruiting	HER2-positive, unresectable, locally advanced or metastatic breast cancer	T-DM1 *versus* lapatinib plus capecitabine regimen, after prior trastuzumab-based therapy.
	NCT03975647	Recruiting	Unresectable, locally-advanced or metastatic HER2-positive breast cancer	T-DM1 alone *versus* its combination with the HER2 tyrosine kinase inhibitor tucatinib, after prior treatment with trastuzumab- and taxane-based therapy.
	NCT04873362	Recruiting	HER2-positive primary breast cancer at high risk of recurrence	T-DM1 plus atezolizumab *versus* atezolizumab plus placebo, following preoperative HER2-directed therapy, including trastuzumab, and in the presence of residual invasive disease, as adjuvant therapy.
	NCT01772472[b]	Active not recruiting	HER2-positive primary breast cancer with residual tumor in the breast or axillary lymph nodes following preoperative therapy	T-DM1 *versus* trastuzumab as adjuvant therapy.
	NCT04457596	Recruiting	High risk, HER2-positive breast cancer with residual disease after neoadjuvant HER2-directed therapy	T-DM1 in combination with tucatinib *versus* T-DM1 alone.
Inotuzumab ozogamicin	NCT03959085	Recruiting	Newly diagnosed high-risk B-ALL	Inotuzumab ozogamicin added to post-induction chemotherapy (cyclophosphamide, cytarabine, dexamethasone, doxorubicin, daunorubicin, methotrexate, mercaptopurine, prednisone, thioguanine, vincristine, and pegaspargase) *versus* other treatment arms without inotuzumab ozogamicin.
	NCT03150693	Recruiting	Newly diagnosed B-ALL in young adults	Inotuzumab ozogamicin added to frontline chemotherapy (cytarabine, daunorubicin, vincristine, dexamethasone, pegaspargase, methotrexate, cyclophosphamide, mercaptopurine, rituximab, doxorubicin, thioguanine) *versus* chemotherapy.
	NCT04307576	Recruiting	Newly diagnosed ALL in children and young adults	Inotuzumab ozogamicin plus standard maintenance therapy *versus* other treatment arms without inotuzumab ozogamicin.

Table 2 (*continued*)

ADC	Clinicaltrials.gov identifier[a]	Status	Tumor	Investigated treatment
Polatuzumab vedotin-piiq	NCT03274492	Active not recruiting	Previously untreated DLBCL	Polatuzumab vedotin-piiq plus R-CHP (rituximab-cyclophosphamide, doxorubicin, prednisone) *versus* R-CHOP (rituximab- cyclophosphamide, doxorubicin, vincristine, prednisone).
	NCT04182204	Recruiting	Relapsed or refractory DLBCL	Polatuzumab vedotin-piiq plus R-GemOx (rituximab, gemcitabine, and oxaliplatin) *versus* R-GemOx.
	NCT04236141	Active not recruiting	Relapsed or refractory DLBCL	Polatuzumab vedotin-piiq plus bendamustine and rituximab *versus* bendamustine and rituximab.
	NCT04833114	Recruiting	Relapsed or refractory DLBCL	Polatuzumab vedotin-piiq plus Pola-R-ICE (rituximab, ifosfamide, carboplatin and etoposide) *versus* R-ICE (rituximab, ifosfamide, carboplatin and etoposide), as second line treatment.
	NCT04332822	Recruiting	Previously untreated DLBCL in elderly patients	R-miniCHOP (rituximab plus attenuated dose of cyclophosphamide, doxorubicin, vincristine, and prednisone) *versus* R-pola-miniCHP, where vincristine is replaced by polatuzumab vedotin-piiq.
Enfortumab vedotin-ejfv	NCT03474107[c]	Active not recruiting	Previously treated locally advanced or metastatic urothelial cancer.	Enfortumab vedotin-ejfv plus chemotherapy (docetaxel, paclitaxel, vinflunine) *versus* chemotherapy.
	NCT04223856	Recruiting	Untreated locally advanced or metastatic urothelial cancer	Enfortumab vedotin-ejfv plus pembrolizumab *versus* standard chemotherapy (cisplatin or carboplatin and gemcitabine) or enfortumab vedotin-ejfv plus pembrolizumab and cisplatin or carboplatin.
	NCT04960709	Recruiting	Muscle invasive bladder cancer, in patients ineligible for cisplatin undergoing radical cystectomy	Enfortumab vedotin-ejfv plus the anti-PD-L1 mAb durvalumab and the anti-CTLA-4 mAb tremelimumab *versus* enfortumab vedotin-ejfv plus durvalumab as perioperative treatment.
	NCT03924895	Recruiting	Muscle invasive bladder cancer, in patients ineligible for cisplatin	Enfortumab vedotin-ejfv plus pembrolizumab *versus* pembrolizumab as preoperative and postoperative treatments *versus* cystectomy alone.
	NCT04700124	Recruiting	Cisplatin-eligible muscle invasive bladder cancer	Enfortumab vedotin-ejfv plus pembrolizumab as perioperative treatment [radical cystectomy (RC) plus pelvic lymph node dissection (PLND)] followed by adjuvant pembrolizuam *versus* neoadjuvant chemotherapy with gemcitabine plus cisplatin before RC and PLND.
Fam-trastuzumab deruxtecan-nxki	NCT04622319	Recruiting	High-risk HER2-positive patients with residual invasive breast cancer following neoadjuvant therapy	Fam-trastuzumab deruxtecan-nxki *versus* T-DM1.
	NCT04704934	Recruiting	HER2-positive gastric or gastro-esophageal junction adenocarcinoma progressed on or after trastuzumab-based therapy	Fam-trastuzumab deruxtecan-nxki *versus* the anti-VEGFR-2 mAb ramucirumab plus paclitaxel.
	NCT04739761	Recruiting	Advanced/metastatic HER2-positive breast cancer, with or without brain metastasis, progressed on prior anti-HER2-based therapy after no more than 2 lines/regimens of therapy	Fam-trastuzumab deruxtecan-nxki.
	NCT04494425	Recruiting	HER2-low, hormone receptor (HR) positive metastatic breast cancer after progression on endocrine therapy	Fam-trastuzumab deruxtecan-nxki *versus* investigator's choice chemotherapy (capecitabile, paclitaxel or nab-paclitaxel).
	NCT04784715	Recruiting	Untreated HER2-positive metastatic breast cancer	Fam-trastuzumab deruxtecan-nxki *versus* trastuzumab plus pertuzumab *versus* standard of care (taxane, trastuzumab and pertuzumab) as first-line.
	NCT03529110	Active not recruiting	Unresectable and /or metastatic HER2-positive breast cancer previously treated with trastuzumab and taxane	Fam-trastuzumab deruxtecan-nxki *versus* T-DM1.
	NCT03734029	Active not recruiting	Unresectable and/or metastatic HER2-low breast cancer previously treated with chemotherapy	Fam-trastuzumab deruxtecan-nxki *versus* treatment of physician's choice (capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel).
	NCT03523585	Active not recruiting	Unresectable and/or metastatic HER2-positive breast cancer previously treated with anti-HER2 therapies including T-DM1	Fam-trastuzumab deruxtecan-nxki *versus* standard of care (capecitabine plus trastuzumab or lapatinib plus trastuzumab).
	NCT05048797	Recruiting	Unresectable, locally advanced or metastatic NSCLC with HER2 mutations as first treatment option	Fam-trastuzumab deruxtecan-nxki *versus* standard of care (cisplatin or carboplatin plus pembrolizumab and pemetrexed).
	NCT05113251	Recruiting	High-risk, HER2-positive early-stage non-metastatic breast cancer	Fam-trastuzumab deruxtecan-nxki, alone or in combination with THP (paclitaxel, trastuzumab, pertuzumab) *versus* standard neoadjuvant treatment ddAC-THP (paclitaxel, trastuzumab, pertuzumab doxorubicin, cyclophosphamide).
Sacituzumab govitecan-hziy	NCT04527991	Recruiting	Metastatic or locally advanced unresectable urothelial cancer progressed after prior therapy with platinum-based regimen and anti-PD-1/PD-L1 mAbs	Sacituzumab govitecan-hziy *versus* treatment of physician's choice (paclitaxel, docetaxel, or vinflunine).
	NCT03901339	Active not recruiting	Metastatic HR-positive, HER2-negative breast cancer with disease progression	Sacituzumab govitecan-hziy *versus* treatment of physician's choice (capecitabine, eribulin, gemcitabine or vinorelbine).
	NCT04595565	Recruiting	Primary HER2-negative breast cancer with residual disease after neoadjuvant chemotherapy	Sacituzumab govitecan-hziy *versus* treatment of physician's choice (capecitabine or platinum-based chemotherapy).
	NCT04639986	Recruiting	Metastatic or locally recurrent unresectable, HR-positive/HER2-negative metastatic breast cancer after failure of at least 2, and no more than 4, prior chemotherapy regimens for metastatic disease	Sacituzumab govitecan-hziy *versus* treatment of physician's choice (capecitabine, eribulin, gemcitabine or vinorelbine).

(*continued on next page*)

Table 2 (*continued*)

ADC	Clinicaltrials.gov identifier[a]	Status	Tumor	Investigated treatment
Belantamab mafodotin-blmf	NCT04549363	Recruiting	Multiple myeloma	Characterization of corneal epitheliopathy in patients treated with belantamab mafodotin-blmf.
	NCT04162210	Recruiting	Relapsed/refractory multiple myeloma	Belantamab mafodotin-blmf *versus* pomalidomide plus low dose dexamethasone.
	NCT04484623	Recruiting	Relapsed/refractory multiple myeloma	Belantamab mafodotin-blmf plus the immunomodulatory drug pomalidomide and dexamethasone *versus* pomalidomide plus the proteasome inhibitor bortezomib and dexamethasone.
	NCT04246047	Active not recruiting	Relapsed/refractory multiple myeloma	Belantamab mafodotin-blmf plus bortezomib and dexamethasone *versus* the anti-CD38 mAb daratumumab, bortezomib and dexamethasone.
Loncastuximab tesirine-lpyl	NCT04384484	Recruiting	Relapsed/refractory DLBCL	Loncastuximab tesirine-lpyl plus rituximab *versus* standard immunochemotherapy treatment consisting of rituximab, gemcitabine and oxaliplatin
	NCT05144009 (part 2)	Not yet recruiting	Previously untreated DLBCL in frail/unfit patients	Loncastuximab tesirine-lpyl plus rituximab *versus* standard immunochemotherapy treatment with R-mini-CHOP
Tisotumab vedotin-tftv	NCT04697628	Recruiting	Recurrent or metastatic cervical cancer	Tisotumab vedotin-tftv *versus* chemotherapy (investigator's choice among topotecan, vinorelbine, gemcitabine, or irinotecan).

[a] NCT number or https://ClinicalTrials.gov identifier; data from https://clinicaltrials.gov, accessed on December 2021.
[b] Registration trial.
[c] Confirmatory trial.

3.1. New potential targets expressed in solid tumors

3.1.1. Tyrosine kinase and G-protein coupled receptors

Receptors present on the surface of cancer cells that are involved in the modulation of cell proliferation and survival, are ideal candidates as ADCs targets. Among them, receptor tyrosine kinases are often dysregulated in a wide range of tumors (Yamaoka et al., 2018). For instance, over-activation of the hepatocyte growth factor receptor (HGFR or c-Met), due to gene mutation/amplification, has been associated with malignant cell transformation and disease progression in different tumor types, such as thyroid, colorectal, pancreatic, breast, ovarian, gastric cancers, NSCLC, medulloblastoma, glioblastoma, and renal papillary carcinoma (Zhang et al., 2018b). Under normal conditions, the HGFR, upon binding to its ligand, activates different signaling pathways implicated in cell motility, embryogenesis, and wound repair. In the recent years, several anti-HGFR ADCs have been developed and are now at the clinical stage of investigation (i.e. ABBV-399 or telisotuzumab vedotin, TR1801-ADC, RC108-ADC, HTI-1066). In phase 1 studies telisotuzumab vedotin was safe and showed antitumor activity in c-Met positive NSCLC and is currently investigated in a phase 3 trial (NCT04928846) for non-squamous NSCLC in pretreated patients, compared to the antimitotic agent docetaxel (Camidge et al., 2021; Strickler et al., 2018). Conversely, in a phase 2 trial (NCT03574753), telisotuzumab vedotin failed to meet the prespecified response during an interim analysis in patients with squamous cell lung cancer and enrollment was discontinued due to lack of clinical efficacy (Waqar et al., 2021).

Regarding the HER receptor tyrosine kinases family, HER2 is the most widely characterized member, targeted by clinically approved naked mAbs (i.e., trastuzumab, pertuzumab and margetuximab) and ADCs (i.e., T-DM1 and fam-trastuzumab deruxtecan-nxki) as well as by investigational ADCs (i.e., SYD985, FS-1502, RC48-ADC, BAT8001, A166, XMT-1522, MEDI-4276, PF-06804103, ARX788, ZW49, ALT-P7, BDC-1001, RG6148, GQ1001, NJH395, SBT6050) (see Chapter 2.3). This family of receptor tyrosine kinases offers other opportunities by means of targeting HER3 (ErbB3) and HER1 [also known as epidermal growth factor receptor (EGFR)]. Overexpression of HER3 characterizes a variety of human cancers, including breast, ovarian, prostate, bladder, colorectal, lung cancer, melanoma and head and neck squamous cell carcinoma (Mishra et al., 2018). Moreover, several studies demonstrated that HER3 has a role in mediating resistance to therapies directed against other members of the HER family, PI3K-inhibitors or hormonal agents (Kiavue et al., 2020). Similarly, HER1 overexpression is correlated with a poor prognosis in different malignancies of epithelial origin (Bergado Báez et al., 2018). U3-1402 (patritumab deruxtecan) is the only anti-HER3 ADC currently investigated in clinical trials, while ABBV-321 (serclutamab talirine), AMG-595, ABT-414 (depatuxizumab mafodotin) and M1231 are investigational ADCs that target HER1. ABT-414 has shown acceptable safety profile and encouraging activity in combination with the methylating agent temozolomide in patients affected by recurrent glioblastoma with HER1 amplification (Lassman et al., 2019; Narita et al., 2021; Padovan et al., 2021; Van Den Bent et al., 2020; von Achenbach et al., 2020). Of note, M1231 is a first-in-class bispecific ADC, targeting both HER1 and mucin-1 (MUC1), a transmembrane glycoprotein aberrantly glycosylated and overexpressed in a variety of carcinomas (Nath and Mukherjee, 2014). Moreover, MUC1 is attracting the interest of investigational therapies because of its differential function in normal and tumor cells (Nath and Mukherjee, 2014). In fact, in healthy cells MUC1 exerts a structural function providing protection to the underlying epithelia, whereas in cancer cells it participates to intracellular signal transduction pathways and regulates the expression of target genes, involved in proliferation, metabolism and extracellular matrix (ECM) invasion.

The insulin-like growth factor type 1 receptor (IGF-1R) is another tyrosine kinase receptor with a role in tumorigenesis (Pollak, 2008) and overexpressed in several cancer types, including NSCLC (Fu et al., 2016), head and neck squamous cell carcinoma (Dale et al., 2015), breast cancer (Heskamp et al., 2015), prostate cancer (Hellawell et al., 2002), and osteosarcoma (Liang et al., 2015). An ADC targeting IGF-1R (W0101), has been generated and at present is in clinical stage of development.

Differently from the above mentioned receptors, the receptor tyrosine kinase-like orphan receptor (ROR) family (name given in the past years for the absence of a known ligand, currently identified in Wnt5a), comprising ROR1 and ROR2, offers the opportunity to target both solid and hematological malignancies. Indeed, the association of ROR1 with cancer was first shown in B-cell malignancies (DaneshManesh et al., 2008) and then reported in pancreatic, breast, and ovarian cancers as well as in melanoma and hepatocellular

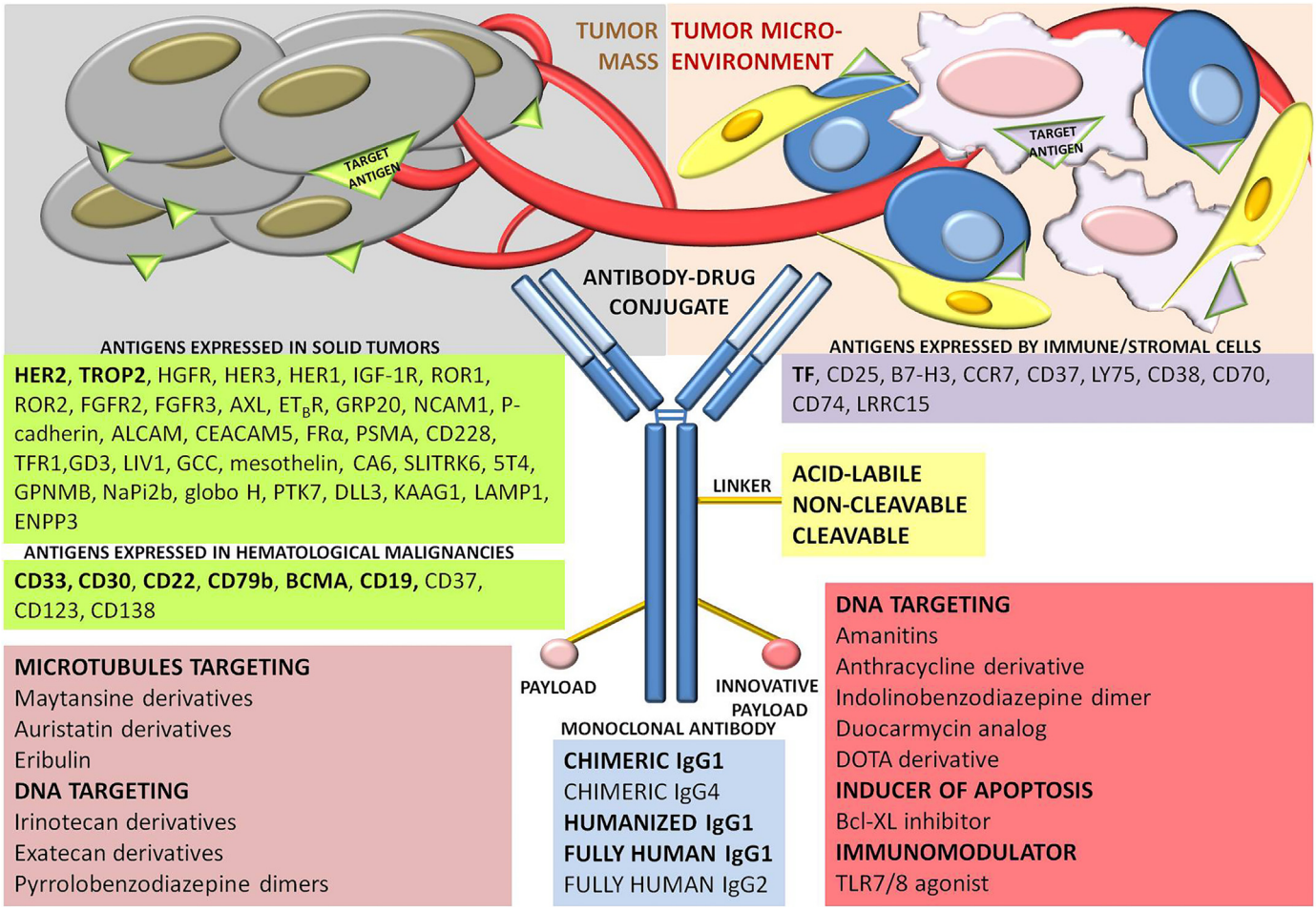

Fig. 2. Main properties of investigational ADCs. Experimental ADCs that reached the clinical stages of investigation may share the target antigens with approved ADCs (antigens indicated in bold in the green boxes) or recognize novel tumor-associated antigens typically expressed by solid tumors (not in bold antigens listed in the green boxes) or by immune/stromal cells present in the tumor microenvironment (TME) (purple box). A minority of these ADCs are directed against emerging cell-lineage specific antigens, selectively expressed by certain hematological malignancies. As in the case of approved ADCs, acid labile, non-cleavable or cleavable linkers, join the mAb moiety to the cytotoxic payload. Cytotoxic compounds delivered by investigational ADCs are in most cases different from those delivered by approved ADCs (common payloads are listed in the pink box; innovative payloads are listed in the red box). The mAb component of investigational ADCs is represented by chimeric, humanized or fully human IgG1, IgG2 or IgG4 (common IgG subclasses also present within approved ADCs are indicated in bold).

carcinoma (Cetin et al., 2019; Zhang et al., 2012). While ROR1 has been detected also in normal tissues (Balakrishnan et al., 2017), ROR2 is highly expressed during embryonic development but only minimally expressed on normal adult cells, and correlates with a poor prognosis in cancer, where it seems to control cell migration and invasion (Dai et al., 2017; Wright et al., 2009). NBE-002 and VLS-101 are ADCs in clinical stage targeting ROR1 and BA3021 is the only clinically investigated ADC targeting ROR2. The latter represents an interesting evolution in the field of ADCs, being an example of conditionally active biologics (CABs). The CAB technology allows the development of antibodies that bind to target antigens in cancer tissues, but not in healthy tissues, by taking advantage of the acidic pH that characterizes the cancer microenvironment, mainly as a result of the Warburg effect (increased rate of glucose uptake and production of lactate) (Liberti and Locasale, 2016). In detail, under the acidic conditions that characterize the tumor mass, a reversible chemical switch within the CAB structure takes place allowing antibody interaction with the antigen. At physiological pH, CABs are instead unable to bind the target antigen (Chang et al., 2021b).

Another transmembrane receptor tyrosine kinase is the fibroblast growth factor receptor (FGFR) that is normally required for tissue repair and embryonic development (Wesche et al., 2011). Activating mutations or overexpression of the gene encoding for the type 2 receptor (FGFR2) have been reported in TNBC, NSCLC, esophageal, gastric, colorectal, hepatocellular, pancreatic, ovarian, cancer and glioma (André and Cortés, 2015; Dienstmann et al., 2014; Matsuda et al., 2014). In contrast to the typically high levels detected in tumors, FGFR2 is generally scarcely expressed in normal tissues. Aprutumab ixadotin (BAY 1187982) is a novel ADC comprising a fully human anti-FGFR2 mAb (Sommer et al., 2016). However, a first-in-human phase 1 dose-escalation study conducted in adult patients with advanced, refractory solid tumors demonstrated that this ADC was poorly tolerated; therefore, the trial was terminated early (Kim et al., 2019). Also FGFR3 has been associated with several types of cancer, including multiple myeloma, bladder cancer, NSCLC, and oropharyngeal squamous cell carcinoma (Koole et al., 2016; Salazar et al., 2014; Theelen et al., 2016; Tomlinson et al., 2007). Moreover, FGFR3 mutations correlate with disease progression in some hematological malignancies (Onwuazor et al., 2003). LY3076226 is a novel ADC composed of a human IgG1 mAb against FGFR3 clinically evaluated in patients with advanced or metastatic cancer (Kollmannsberger et al., 2021a).

Another target opportunity for ADCs among receptor tyrosine kinases is represented by AXL, a member of the TYRO3, AXL and MERTK (TAM) family, associated with the switching from a proliferative to an invasive tumor phenotype, epithelial-mesenchymal transition (EMT), and aberrantly expressed in a variety of malignancies (Feneyrolles

Table 3
Experimental ADCs in clinical investigation: antigen classification and main properties of ADC components (mAb, payload, linker).

ADC target antigen	ADC name	IgG subclass	Payload	Linker	Reference
Antigens shared with approved ADCs					
CD33	IMGN779	Humanized IgG1	DGN462 (PBD derivative)	Cleavable disulfide sulfo-(SPDB) linker	(Kovtun et al., 2018a)
	SGN-CD33A (vadastuximab talirine)	Chimeric IgG1	SGD-1882 (PBD dimer)	Cleavable dipeptide maleimidocaproyl-valine-alanine (MC-VC linker)	(Fathi et al., 2018; Stein et al., 2018)
CD30	F0002-ADC	Chimeric IgG1	DM1 or mertansine (maytansine derivative)	Non-cleavable succinimidyl trans-4-(maleimidylmethyl) cyclohexane-1-carboxylate (SMCC)	(Shen et al., 2019)
HER2	SYD985 (vic-trastuzumab duocarmazine)	Humanized IgG1	Seco-duocarmycin-hydroxybenzamide-azaindole (seco-DUBA)	Cleavable, N-[2-(2 maleimidoethoxy) ethoxycarbonyl]-L-valyl-L-citrullinyl-p-aminobenzyloxycarbonyl-N-[2-(2-hydroxyethoxy)ethyl]-N-[2-(methylamino)ethyl]carbamoyl	(Van Der Lee et al., 2015)
	RC48-ADC (disitamab vedotin)	Humanized IgG1	Monomethylauristatin E (MMAE)	Cleavable maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl (MC-val-cit-PABC)	(Sheng et al., 2021a; Xu et al., 2021)
	BAT8001	Humanized IgG1	Batansine (maytansine derivative)	Soluble 6-maleimidocaproic acid	(Hong et al., 2021)
	FS-1502 (trastuzumab MMAF)	Humanized IgG1	Monomethylauristatin F (MMAF)	Unknown	(Hafeez et al., 2020)
	A166	Humanized IgG1	Duostatin-5 (MMAF derivative)	Cleavable val-cit peptide	(Lopez et al., 2019)
	XMT-1522	Fully human IgG1	Auristatin F-hydroxypropylamide (AF-HPA)	Biodegradable polymer-based conjugation platform (Dolaflexin®)	(Hamilton et al., 2018)
	MEDI-4276	Trastuzumab-selected single chain fragment variable (scFv)	Methyl Mep N-ethyl tubulysin aniline (mc-Lys-MMETA)	Maleimidocaproyl linker	(Pegram et al., 2021)
	PF-06804103	Fully Human IgG1	Aur0101 (auristatin derivative)	Cleavable val-cit dipeptide	(Graziani et al., 2020)
	ARX788	Engineered IgG1 with a p-acetylphenylalanine (pAcPhe) residue	MMAF	Para-acetyl-phenylalanine (pAcF)	(Skidmore et al., 2020)
	ZW49	Humanized IgG1	N-acyl sulfonamide auristatin cytotoxin	Proprietary cleavable linker	(Hamblett et al., 2019)
	ALT-P7	Humanized IgG1	MMAE	Cleavable	(Park et al., 2020)
	BDC-1001[a]	Investigational trastuzumab biosimilar	TLR7/8 agonist	Non-cleavable linker	(Sharma et al., 2021)
	RG6148 (DHES0815A)	Engineered IgG1	Pyrrolo[2,1- c][1,4]benzodiazepine monoamide (PBD-MA)	Cleavable	(Rinnerthaler et al., 2019)
	GQ1001	Unknown	DM1	Unknown	www.adcreview.com
	NJH395[a]	Unknown	TLR7/8 agonist	Unknown	(Boni et al., 2020)
	SBT6050[a]	Unknown	TLR8 agonist	Unknown	(Metz et al., 2020)
CD22	ADCT-602 (epratuzumab tesirine)	Humanized IgG2	Tesirine (PBD derivative)	Cleavable val-ala dipeptide	(Gaudio et al., 2020)
	DCDT2980S (pinatuzumab vedotin)	Humanized IgG1	MMAE	Cleavable MC-val-cit-PABC	(Li et al., 2013)
	TRPH-222 (CD22-4AP)	Humanized mAb*	Maytansine	Proprietary non-cleavable 4AP	www.adcreview.com
CD79b	DCDS0780A (iladatuzumab vedotin)	Humanized IgG1	MMAE	MC-val-cit-PABC	(Herrera and Molina, 2018)
TROP2	DS-1062 (datopotamab deruxtecan)	Humanized mAb*	Topoisomerase I inhibitor	Tetrapeptide-based	(Okajima et al., 2021)
	SKB264	Unknown	Camptothecin derivative	Stable chemistry	(Liu et al., 2020)
BCMA	AMG 224	Fully human IgG1	DM1	Non-cleavable 4-(N-maleimidomethyl) cyclohexane-1-carboxylate	(Lee et al., 2021)
	CC-99712	Unknown	Maytansine derivative	Non-cleavable dibenzocyclooctyne	www.adcreview.com
	HDP-101	Unknown	Amanitin	Cleavable	www.adcreview.com

CD19	SAR3419 (coltuximab ravtansine)	Chimeric IgG1	DM4	SPDB linker	(Carol et al., 2013; Coiffier et al., 2016; Trněny et al., 2018; Younes et al., 2012b)
	SGN-CD19A (denintuzumab mafodotin)	Humanized IgG1	MMAF	Unknown	(Jones et al., 2020)
TF	MRG004A	Fully human mAb*	Unknown	Proprietary conjugation technology	www.adcreview.com
Antigens overexpressed by cancer cells in solid tumors: tyrosine kinase and G-protein coupled receptors					
HGFR (c-Met)	ABBV-399 (telisotuzumab vedotin)	Humanized IgG1	MMAE	MC-val-cit-PABC	(Camidge et al., 2021; Strickler et al., 2018)
	TR1801-ADC	Humanized IgG2	PBD toxin	Val-ala peptide	(Gymnopoulos et al., 2020)
	RC108-ADC	Unknown	MMAE	Unknown	www.clinicaltrials.gov
	HTI-1066 (SHR-A1403)	Humanized IgG2	SHR152852 (auristatin analog)	Proprietary uncleavable thioether linker	(Jin et al., 2021)
HER3	U3-1402 (patritumab deruxtecan)	Fully human mAb*	Exatecan (DX-8951, camptothecin derivative)	Cleavable, tetrapeptide-based linker	(Hashimoto et al., 2019)
HER1 (EGFR)	ABBV-321 (serclutamab talirine)	Humanized IgG1	SGD-1882	MC-Val-Ala	(Anderson et al., 2020)
	AMG-595	Fully human IgG1	DM1	Non-cleavable SMCC linker	(Hamblett et al., 2015)
	ABT-414 (depatuxizumab mafodotin)	Humanized IgG1	MMAF	Non-cleavable MC linker	(Lassman et al., 2019; Narita et al., 2021; Padovan et al., 2021; Van Den Bent et al., 2020; von Achenbach et al., 2020)
	M1232	Unknown	Hemiasterlin-related toxic compound	Val-cit-based linker	www.clinicaltrials.gov
IGF-1R	W0101	Humanized mAb*	Auristatin derivative	Non-cleavable MC linker	(Akla et al., 2020)
ROR1[b]	NBE-002	Humanized IgG1	Anthracycline-derivative PNU-159682	Non-cleavable linker	(Tolcher et al., 2021a)
	VLS-101	Humanized IgG1	MMAE	MC-val-cit-PABC	(Vaisitti et al., 2021)
ROR2	BA3021[c]	Unknown	Unknown	Unknown	(Sharp et al., 2018)
FGFR2	BAY1187982 (aprutumab ixadotin)	Fully human IgG1	Auristatin W derivative	Non-cleavable	(Sommer et al., 2016)
FGFR3	LY3076226	Fully human IgG1	DM4	Unknown	(Kollmannsberger et al., 2021a)
AXL	AXL-107-MMAE (enapotamab vedotin)	Fully human IgG1	MMAE	MC-val-cit-PABC	(Boshuizen et al., 2018, 2021; Koopman et al., 2019)
	BA3011	Humanized IgG1	MMAE	Cleavable linker	(Rodon Ahnert et al., 2018)
ET_BR	DEDN6526A	Humanized IgG1	MMAE	Peptide linker	(Sandhu et al., 2020)
GRP20	DS-6157[a]	Humanized mAb*	Exatecan derivative	Tetrapeptide-based linker	(Iida et al., 2021)
Antigens overexpressed by cancer cells in solid tumors: cell adhesion molecules					
P-cadherin	PCA062	Unknown	DM1	SMCC	(Sheng et al., 2021b)
NCAM-1 (CD56)[b]	IMGN901 (lorvotuzumab mertansine)	Humanized IgG1	DM1	Thiopentanoate linker	(Ailawadhi et al., 2019; Geller et al., 2020; Shah et al., 2016; Socinski et al., 2017)
ALCAM (CD166)	CX-2009 (praluzatamab ravtansine)	Humanized IgG1	DM4	SPDB linker	(Garcia-Corbacho et al., 2017)
CEACAM5	SAR408701 (tusamitamab ravtansine)	Humanized mAb*	DM4	SPDB linker	(Decary et al., 2020; Gazzah et al., 2020)
	IMMU-130 (labetuzumab govitecan)	Humanized IgG1	SN-38	pH-sensitive	(Dotan et al., 2017)

(continued on next page)

Table 3 (*continued*)

ADC target antigen	ADC name	IgG subclass	Payload	Linker	Reference
Antigens overexpressed by cancer cells in solid tumors: members of the folate system					
FRα	IMGN-853 (mirvetuximab soravtansine)	Chimeric IgG1	DM4	SPDB linker	(Moore et al., 2016; Moore et al., 2021; O'Malley et al., 2020; Ponte et al., 2016)
	MORAb-202	Humanized IgG1	Eribulin	Cathepsin B-cleavable linker	(Furuuchi et al., 2021)
	STRO-002	Fully human IgG1	Hemiasterlin analogue	Proprietary cleavable linker	(Naumann et al., 2021)
PSMA	PSMA-ADC	Fully human IgG1	MMAE	Val-cit dipeptide	(Petrylak et al., 2020)
Antigens overexpressed by cancer cells in solid tumors: iron binding proteins					
Melanotransferrin (CD228/MFI2/MELTF)	SGN-CD228A	Humanized IgG1	MMAE	β-glucuronidase-cleavable linker incorporating a polyethylene glycol (PEG) side chain and self-stabilizing maleimide	(Sandall et al., 2019)
TFR1 (CD71)	CX-2029	Unknown	MMAE	Unknown	(Johnson et al., 2021a)
Antigens associated with cancer cells of specific tumor types					
GD3	PF-06688992	Unknown	Unknown	Unknown	www.adcreview.com
LIV1	SGN-LIV1A (ladiratuzumab vedotin)	Humanized IgG1	MMAE	MC-val-cit-PABC	(McGuinness and Kalinsky, 2021)
GCC	MLN0264 (indusatumab vedotin or TAK-264)	Fully human IgG1	MMAE	MC-val-cit-PABC	(Almhanna et al., 2016, 2017; Bang et al., 2018)
ENPP3	AGS-16C3F	Fully human IgG2	MMAF	Non-cleavable MC linker	(Kollmannsberger et al., 2021b; Thompson et al., 2018)
Other antigens overexpressed by cancer cells					
Mesothelin	BAY94-9343 (anetumab ravtansine)	Fully human IgG1	DM4	SPDB linker	(Golfier et al., 2014; Hassan et al., 2020)
	DMOT4039A	Humanized IgG1	MMAE	Val-cit linker	(Weekes et al., 2016)
	RC88	Humanized mAb*	MMAE	Unknown	(Criscitiello et al., 2021)
	BMS-986148	Fully human IgG1	Tubulysin	Unknown	(Clarke et al., 2019; Rottey et al., 2021)
CA6	SAR566658	Humanized IgG1	DM4	Unknown	(Nicolazzi et al., 2020)
SLITRK6	ASG-15ME (sirtratumab vedotin)	Fully human IgG2	MMAE	Unknown	(Morrison et al., 2016)
GPNMB (HGFIN)	CDX-011 (glembatumumab vedotin)	Fully human IgG2	MMAE	MC-val-cit-PABC	(Keir and Vahdat, 2012)
NaPi2b	DNIB0600A (lifastuzumab vedotin)	Humanized IgG1	MMAE	MC-val-cit-PABC	(Banerjee et al., 2018)
	XMT-1536 (upifitamab rilsodotin)	Humanized IgG1	Auristatin derivative	Biodegradable polymer-based conjugation platform (Dolaflexin®)	(Bodyak et al., 2021)
	XMT-1592	Humanized IgG1	Auristatin derivative	Proprietary technology platform (Dolasynthen)	(Fessler et al., 2020)
CD205 (LY75)	MEN1309 (OBT076)	Humanized IgG1	DM4	N-succinimidyl-4-(2-pyridyldithio) butanoate linker	(Merlino et al., 2019)
Antigens overexpressed by cancer stem cells					
5T4	SYD1875	Humanized, HC41-cysteine-engineered IgG1	Synthetic duocarmycin	Proprietary cleavable linker	(Groothuis et al., 2021)
	ASN004	Single-chain Fv-Fc ab	Auristatin analog	Biodegradable polymer-based conjugation platform (Dolaflexin®)	(Smith et al., 2021)
Globo H	OBI-999	Humanized IgG1	MMAE	Cleavable linker	(Yang et al., 2021)
PTK7 (CCK4)	PF-06647020 (cofetuzumab pelidotin)	Humanized IgG1	Auristatin-0101	MC-val-cit-PABC	(Maitland et al., 2021)

DLL3	SC16LD6.5 (rovalpituzumab tesirine)	Humanized IgG1	SC-DR002 (PBD-dimer toxin)	Maleimide-containing linker with val-ala dipeptide	(Blackhall et al., 2021; Johnson et al., 2021b; Morgensztern et al., 2019; Udagawa et al., 2019)
KAAG1	ADCT-901	Humanized mAb*	SG3199 (PBD–dimer cytotoxin)	Cathepsin-cleavable	www.adcreview.com
LAMP-1	SAR428926	Humanized IgG1	DM4	SPDB linker	www.adcreview.com
Antigens expressed by cells of the tumor microenvironment					
CD25	ADCT-301 (camidanlumab tesirine)	Humanized IgG1	PBD-based toxin (SG3199)	Cathepsin-cleavable val-ala dipeptide	(Flynn et al., 2016)
B7-H3 (CD276)	DS-7300	Humanized mAb*	Deruxtecan	Tetrapeptide-based linker	(Yamato et al., 2020)
	MGC018	Humanized IgG1	Duocarmycin analog	Val-cit linker	(Scribner et al., 2020)
	ABBV-155 (mirzotamab clezutoclax)	Chimeric/humanized IgG1	Clezutoclax	Val-ala linker	(Tolcher et al., 2021b)
CD70	SGN-CD70A	Engineered cysteine mAb*	PBD dimer	Peptide-based linker	(Pal et al., 2019; Phillips et al., 2019)
CCR7	JBH492	Unknown	DM4	Unknown	www.adcreview.com
CD74	STRO-001	Aglycosylated fully human IgG1	Maytansine derivative	Non-cleavable	(Zhao et al., 2019)
LRRC15	ABBV-085	Humanized IgG1	MMAE	Val–cit linker	(Demetri et al., 2021)
CD38	STI-6129	Fully human IgG1	MMAF derivative (duostatin)	Proprietary linker	(Li et al., 2020)
Antigens overexpressed in hematological malignancies					
CD37	IMGN529 (naratuximab emtansine)	Humanized IgG1	DM1	SMCC linker	(Stathis et al., 2018)
CD123	IMGN632	Humanized IgG1	Indolinobenzodiazepine pseudodimer	Peptide-based linker	(Angelova et al., 2019; Kovtun et al., 2018b)
CD138	BT062 (indatuximab ravtansine)	Chimeric IgG4	DM4	SPDB linker	(Jagannath et al., 2019; Kelly et al., 2021)

[a] Immune stimulator antibody conjugate (ISAC).
[b] Antigen expressed in both solid and hematological malignancies.
[c] Conditionally active biologic (CAB).
* Not disclosed IgG subclass.

et al., 2014; Gay et al., 2017). AXL is the target of AXL-107-MMAE (enapotamab vedotin) (Koopman et al., 2019), a MMAE carrying ADC that recently demonstrated promising antitumor effects in patient-derived xenograft models from a variety of solid tumors, including melanoma, lung, thyroid, pancreatic esophageal, and cervical cancer (Boshuizen et al., 2018, 2021). Moreover, a CAB directed against AXL (BA3011 or CAB-AXL-ADC) is currently investigated and consists in a humanized mAb conjugated with MMAE by a cleavable linker that binds to AXL under conditions found within the TME (Rodon Ahnert et al., 2018).

G protein coupled receptors are also targeted by novel ADCs. In particular, endothelin B receptor (ET_BR) is a member of the G protein coupled receptor superfamily that mediates tissue differentiation, growth, and repair (Bagnato et al., 2004) and is implicated in malignant transformation of melanocytes to melanoma. Compared to normal skin, ET_BR expression is increased in metastatic melanoma, where it promotes proliferation and metastatic spread (Asundi et al., 2011; Saldana-Caboverde and Kos, 2010). Thus, ET_BR overexpression in the tumor offers the opportunity of a targeted therapeutic approach through the use of DEDN6526A ADC (Sandhu et al., 2020).

The G protein-coupled receptor 20 (GPR20) is another novel target, specifically expressed in gastrointestinal stromal tumor (GIST). The ADC DS-6157a, directed against this antigen, exhibited GPR20 expression-dependent antitumor activity in preclinical GIST xenograft models, even in those resistant to the c-Kit tyrosine kinase inhibitors imatinib, sunitinib, and regorafenib. A phase 1 clinical trial is assessing its safety, efficacy, and pharmacokinetics in patients with GIST (Iida et al., 2021).

3.1.2. Cell adhesion molecules

Cell adhesion molecules (CAMs) are cell-surface proteins that account for cell-to-cell or cell-to-ECM interactions, molecularly divided into cadherins, integrins, selectins, and members of the Ig superfamily. Changes in the expression or function of CAMs characterize tumor progression. In particular, alterations in the adhesion properties of cancer cells endow them with invasive and migratory phenotypes (Cavallaro and Christofori, 2004; Makrilia et al., 2009). These findings rendered CAMs potential therapeutic targets in oncology.

P-(placental) cadherin, a member of the subfamily of classic cadherins highly expressed in a number of malignancies, including those arising in the epithelium of the bladder, breast, esophagus, lung and upper aerodigestive tract (Vieira and Paredes, 2015), is the target of a novel ADC, named PCA062 that is at an early stage of clinical development for tumors expressing P-cadherin (Sheng et al., 2021a).

The neural cell adhesion molecule-1, or NCAM-1, also known as CD56, is another CAM highly expressed in several solid malignancies, particularly in those with neuronal or neuroendocrine differentiation, including SCLC, ovarian cancer, and neuroblastoma. However, CD56 expression is also found in the hematopoietic system, where it can be associated with natural killer (NK), gamma delta ($\gamma\delta$) T, activated $CD8^+$ T and dendritic cells (Van Acker et al., 2017). In the bone marrow, CD56 exerts a pivotal role and its aberrant expression is observed in hematological malignancies such as multiple myeloma and leukemia (Pan et al., 2016; Xu et al., 2015). Lorvotuzumab mertansine (IMGN901) is an ADC composed of a humanized anti-CD56 antibody, extensively studied in clinical trials involving both solid and hematological malignancies, as well as adult and pediatric patients, with promising results (Ailawadhi et al., 2019; Geller et al., 2020; Shah et al., 2016). However, in the case of extensive-stage SCLC the combination of lorvotuzumab mertansine with carboplatin and etoposide did not improve efficacy, compared to the doublet therapy, and increased systemic toxicity (Socinski et al., 2017).

Activated leukocyte cell adhesion molecule (ALCAM or CD166), is a cell surface glycoprotein structurally related to the Ig superfamily members, that is involved in angiogenesis, monocytes and leukocytes migration, T cell activation, hematopoiesis, osteogenesis, neurite extension and embryonic implantation (Ferragut et al., 2021; Von Lersner et al., 2019). ALCAM also acts as a modulator of cancer cell proliferation, adhesion, migration and invasion and is regarded as a prognostic marker of disease progression and poor survival in several solid tumors (Weidle et al., 2010). Moreover, CD166/ALCAM has been identified as a putative cancer stem cell marker (Darvishi et al., 2020). CX-2009 (praluzatamab ravtansine) is an emerging probody-drug conjugate (PDC) composed of a recombinant anti-CD166 mAb, hidden by a cleavable masking peptide, and conjugated with the cytotoxic agent maytansinoid DM4 (Garcia-Corbacho et al., 2017). PDCs represent an interesting evolution of traditional ADCs since they are designed to remain inactive until proteolytically unmasked and activated by multiple tumor associated proteases located in the TME.

Finally, among CAMs with potential therapeutic significance, the carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) are Ig-related proteins expressed in epithelial tissues, involved not only in cell adhesion, but also in cell differentiation, proliferation and survival (Tchoupa et al., 2014). They act as important signal modulators in cancer progression and metastasis (Beauchemin and Arabzadeh, 2013). In particular, CEACAM5 has attracted interest as potential ADCs target antigen since it is detected at high levels in various cancers, including colorectal, lung and gastric cancer, with limited expression in normal tissues. Actually, SAR408701 (Decary et al., 2015; Gazzah et al., 2020) and labetuzumab govitecan (IMMU-130) (Dotan et al., 2017) are the first examples of experimental CEACAM5-targeting ADCs of clinical interest.

3.1.3. Members of the folate system

Rapidly proliferating cells, including cancer cells, need a sufficient intake of folate for DNA biosynthesis (Locasale, 2013). A glycosylphosphatidylinositol (GPI)-anchored membrane protein named folate receptor α [FRα, also known as FOLR1 or folate binding protein (FBP)] that coordinates the transport of the active form of folate, 5-methyltetrahydrofolate (Kelemen, 2006), has been found overexpressed in different solid tumors, such as ovarian and breast carcinomas, mesothelioma, NSCLC, and endometrial cancer (Boogerd et al., 2016; Shi et al., 2015). FRα overexpression may promote tumor growth, through both folate intake-dependent and independent mechanisms (O'Shannessy et al., 2012; Siu et al., 2012). On the other hand, FRα is expressed at low levels in normal tissues, including kidney, breast, colon and bladder epithelium, thyroid and salivary glands, lung and choroid plexus (Kelemen, 2006). Mirvetuximab soravtansine (IMGN-853), MORAb-202, and STRO-002 represent emerging promising ADCs that target FRα and have reached clinical investigation (Furuuchi et al., 2021; Naumann et al., 2021; Ponte et al., 2016). The results of a phase 1 study in patients with platinum-resistant ovarian cancer indicated that treatment with mirvetuximab soravtansine, as single agent, was well tolerated (NCT01609556) (Moore et al., 2016). However, in a phase 3 trial (NCT02631876) in patients with platinum-resistant epithelial ovarian cancer expressing FRα, mirvetuximab soravtansine did not improve PFS compared to chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan) (Moore et al., 2021). Conversely, in a phase 1b study (NCT02606305) enrolling patients with the same tumor type, treatment with mirvetuximab soravtansine in combination with the anti-VEGF-A mAb bevacizumab showed promising results in term of efficacy (O'Malley et al., 2020).

Another key player in the folate system, significantly upregulated in both primary and metastatic prostate cancer and accordingly named prostate-specific membrane antigen (PSMA), is a unique folate hydrolase, i.e. an enzyme able to hydrolyze polyglutamated folates, thus increasing the available folate pool for cancer cells, and consequently their proliferative potential (Yao et al., 2010). Recently identified also in urothelial cell carcinoma (Schreiber et al., 2020), PSMA is the target of the novel ADC, indicated as PSMA-ADC, that has shown efficacy in a phase 2 study (NCT01695044) recruiting patients with progressive, metastatic, castration-resistant prostate cancer after failure of the anti-androgens abiraterone and enzalutamide (Petrylak et al., 2020).

3.1.4. Iron binding proteins

Compared to normal cells, cancer cells differ in the expression and/or activity of many iron-related proteins, proved to play a role in tumor initiation, proliferation, and metastasis. Due to their contribution in maintaining relatively high intracellular iron levels and in facilitating the functions of iron-dependent proteins, involved in DNA synthesis and repair, cell cycle regulation, and angiogenesis, these iron-related proteins have been considered as suitable targets for cancer treatment (Wang et al., 2019).

Melanotransferrin (CD228/MFI2/MELTF) is a membrane glycoprotein of the transferrin iron-binding proteins family (Suryo Rahmanto et al., 2007) that acts as an iron-transport protein and is considered an oncofetal antigen with low expression in normal tissues. This protein is highly expressed in several tumor types, including melanoma, mesothelioma, NSCLC, pancreatic, breast, and colorectal cancer (Duś-Szachniewicz et al., 2015). Although its biological function in cancer remains unclear, emerging data indicate that CD228 is involved in tumor cell proliferation and angiogenesis (Dunn et al., 2006; Sala et al., 2002). SGN-CD228A is a humanized anti-CD228 mAb to which MMAE has been conjugated via a β-glucuronidase–cleavable linker, ensuring a fast cleavage of the payload and activity even in low–CD228-expressing cells. Moreover, the characteristic trafficking/recycling of this target contributes to increase the internalization rate of the payload (Sandall et al., 2019).

From the same family of melanotransferrin, transferrin receptor 1 (TFR1, or CD71) is required for iron cellular intake and has been reported to be abnormally expressed in various cancers (Shen et al., 2018). In particular TFR1 overexpression has been detected in breast cancer (Pizzamiglio et al., 2017), glioma (Weston et al., 2016), hepatocellular carcinoma (Adachi et al., 2019), lung cancer (Kukulj et al., 2010). CX-2029 is an investigational PDC that targets TFR1 and releases MMAE after exposure to proteases present in the TME. This property allows target engagement only by tumor cells and avoids the interaction with normal cells where TFR1 is highly expressed (Johnson et al., 2021a), since the anti-CD71 PDC remains in a relatively inactive form in the bloodstream and in normal tissues. In fact, a phase 1 study indicated that CX-2029 had an acceptable toxicity profile being anemia and neutropenia the most common dose-dependent adverse effects (Johnson et al., 2021a).

3.1.5. Antigens associated to cancer cells of specific tumor types

Lineage-restricted antigens are largely expressed by a single cancer histotype. Several tumors exhibit enhanced synthesis of gangliosides (glycosphingolipids present in the outer leaflet of plasma membrane, consisting of sialic acid–containing carbohydrates attached to ceramide). An example of gangliosides is GD3, which is widely expressed in human malignant melanoma, where it is involved in the promotion of cell proliferation and invasion (Ohmi et al., 2018) and brain metastasis (Ramos et al., 2020). This ganglioside is the target of the investigational ADC PF-06688992 [www.adcreview.com].

A subfamily of transmembrane proteins belonging to the ZIP superfamily of zinc transporter, i.e. the LIV1 family (Taylor et al., 2003), comprises another promising ADC target: LIV1 (or ZIP6), mainly detected in hormonally controlled tissues. In particular, LIV1 has been first identified in breast cancer cell lines as an estrogen-sensitive gene, and subsequently associated to EMT and node involvement in hormone receptor (HR)-positive breast cancer (Manning et al., 1994). Subsequently, in addition to breast cancer, it has been revealed in other hormone-dependent tumors, like pancreatic, prostate, cervical and uterine carcinomas, and melanoma (Sussman et al., 2014). Concerning melanoma, although classically considered a non-hormone-related cancer, increasing evidence supports a direct correlation between sex hormones, in particular estrogens, and tumor malignant behavior (Dika et al., 2019). In detail, estrogen receptor beta (ERβ) has been regarded as a marker of metastatic potential and prognosis in malignant melanoma (de Giorgi et al., 2009). By evaluating its expression in stage and age-matched melanoma patients, higher ERβ levels were found in women compared to men, especially in the case of melanoma occurring during pregnancy (Schmidt et al., 2006). SGN-LIV1A (ladiratuzumab vedotin) is a MMAE-releasing anti-LIV1 ADC currently under clinical evaluation especially for breast cancer including metastatic TNBC (McGuinness and Kalinsky, 2021; Sussman et al., 2014).

Guanylyl cyclase C (GCC) is a transmembrane receptor whose expression has been detected throughout the gut, where it is activated by the endogenous hormones guanylin and uroguanylin, as well as by bacterial heat-stable enterotoxins (Bose et al., 2021). This receptor plays a central role in the regulation of intestinal homeostasis, mucosal barrier function, and modulation of intestinal cell proliferation (Blomain et al., 2016). GCC expression has also been detected in various gastrointestinal epithelial malignancies, including colorectal cancer (Chang et al., 2015), esophageal, and pancreatic adenocarcinomas (Camci et al., 2011; Park et al., 2002), thus suggesting a role as a potential target for the treatment of these tumors. Indeed, GCC is scarcely expressed in normal tissues, with the only exception of intestinal epithelial cells; furthermore, in these cells, access to GCC (localized in the apical side of polarized epithelium) from the vascular compartment is restricted by the epithelial tight junctions. Conversely, in malignant cells, the apical localization is disrupted, enabling agents targeting GCC, such as the novel ADC indusatumab vedotin (TAK-264 or MLN0264), to easily access solely tumor cells (Almhanna et al., 2017; Wolfe et al., 2002). Indeed, MLN0264 is evaluated for advanced gastrointestinal carcinomas, gastric or gastroesophageal junction adenocarcinoma and pancreatic cancer (Almhanna et al., 2016; Bang et al., 2018).

Finally, ectonucleotide pyrophosphatase/phosphodiesterase 3 (ENPP3, also known as CD203a) is a basophil activation marker, normally expressed on activated basophils/mast cells and a subset of renal tubules, and, among cancers, in renal cell carcinomas (about 94% of clear cell histology and 60% of those with papillary histology) (Doñate et al., 2016). However, the functional role for ENPP3 in cancer has not been elucidated so far. Although a limited expression of ENPP3 has been also reported in mast cell-derived tumors (Hauswirth et al., 2008), acute basophilic leukemia (Staal-Viliare et al., 2007), colon cancer (Yano et al., 2003), and biliary tract tumor cells (Yano et al., 2004), the novel anti-ENPP3 ADC, AGS-16C3F is presently investigated only for renal carcinoma (Kollmannsberger et al., 2021b; Thompson et al., 2018).

3.1.6. Other antigens associated to cancer cells

Among novel target antigens for ADCs that cannot be included in the previously described groups, mesothelin is a membrane glycoprotein, with unknown biological function, normally expressed by mesothelial cells lining the pleura, pericardium and peritoneum. Its overexpression has been observed in several malignancies, including mesothelioma, NSCLC, pancreatic adenocarcinoma, cholangiocarcinoma, breast, ovarian and gastric cancer. However, the role for mesothelin in cancer development and metastasis has been defined only for ovarian cancer (Rump et al., 2004). From a therapeutic point of view, the high expression levels of mesothelin found in cancer cells, in addition to its low expression in normal tissues, make this protein an ideal tumor-related antigen. Thus, ADCs against mesothelin have been developed (Hassan and Ho, 2008), such as anetumab ravtansine (BAY94-9343), DMOT4039A, RC88 and BMS-986148, all currently under clinical evaluation (Clarke et al., 2019; Hassan et al., 2020; Rottey et al., 2021; Weekes et al., 2016).

Frequently, cancer is associated with deregulation of glycosylation, a complex multienzyme-related process that can result in the generation of novel tumor surface–specific glycotopes potentially targetable by specific antibodies. CA6, a MUC1-associated sialoglycotope highly detected in breast, ovarian, lung, and bladder carcinomas, is the target of the ADC SAR566658 evaluated in phase 1/2 clinical trials (Nicolazzi et al., 2020), recently discontinued due to limited clinical benefit.

SLITRK6, a member of the SLITRK family of type I transmembrane proteins, was discovered as a bladder cancer antigen but found

expressed to a lesser extent in other epithelial tumors (lung, breast, and glioblastoma). This antigen is the target of ASG-15ME (sirtratumab vedotin) currently in a phase 1 study in patients with metastatic urothelial cancer (Morrison et al., 2016).

gpNMB (glycoprotein non-metastatic B, also known as hematopoietic growth factor inducible neurokinin-1 type, HGFIN), is a type I transmembrane protein that contributes to the initiation and malignant progression of breast cancer through induction of EMT (Rose et al., 2010). Glembatumumab vedotin (CDX-011) is a novel ADC that, based on the results of clinical trials, in 2010 received FDA fast track designation for the treatment of advanced, refractory, or resistant gpNMB-expressing breast cancer (Vaklavas and Forero, 2014). However, a phase 2 study enrolling patients with gpNMB overexpressing, advanced breast cancer, including TNBC, did not meet the primary endpoint of improved PFS over investigator's choice chemotherapy or capecitabine (NCT01156753; NCT0199733) (Vahdat et al., 2014; Yardley et al., 2015). Interestingly, a recent phase 1/2 study indicated that glembatumumab has activity in patients with unresectable stage III or stage IV melanoma refractory to immune checkpoint inhibitors and MEK/BRAF inhibitors (Ott et al., 2019).

Among transporters, sodium-dependent phosphate transport protein 2B (NaPi2b) is involved in phosphate cell internalization, in association with sodium co-transport, and has attracted interest as a putative ADC target due to its high expression in non-squamous NSCLC and ovarian cancer (Lin et al., 2015). DNIB0600A (lifastuzumab vedotin) and XMT-1536 (upifitamab rilsodotin) both target NaPi2b through a humanized mAb linked to MMAE (DNIB0600A) (Banerjee et al., 2018) or to auristatin F-hydroxypropylamide payload, using the Dolaflexin platform that yields a high drug-to-antibody ratio (XMT-1536) (Bodyak et al., 2021). XMT-1592 is a third NaPi2b targeting ADC created on the Dolasynthen technology platform, a synthetic scaffold for precise control of drug-to-antibody ratio and site-specific antibody bioconjugation, that showed greater efficacy in preclinical studies when compared to the Dolaflexin platform (Fessler et al., 2020; Nurgalieva et al., 2021). These anti-NaPi2b ADCs are all investigated for ovarian cancer and/or NSCLC.

Finally, LY75 (CD205) is another type I transmembrane protein belonging to the macrophage mannose receptor (MMR) family of C-type lectin endocytic uptake receptors, predominantly expressed by the thymic cortical epithelium and dendritic cells (Gliddon et al., 2004), as well as by T and B lymphocytes and several other tissues, including intestine and lung epithelia. This protein plays an important role in antigen uptake for presentation to T cells and initiation of the antitumor immune response and is strongly expressed in a variety of solid malignancies, like pancreatic cancer, bladder cancer, and TNBC (Mahnke et al., 2000). MEN1309 (OBT076) is a first-in-class ADC, including a humanized anti-CD205 mAb, currently tested in a phase 1 trial for advanced/recurrent solid tumors expressing CD205 and for HER2-negative breast cancer (Merlino et al., 2019).

3.2. New potential antigens associated to cancer stem cells

Cancer stem cells (CSCs) are a subpopulation of tumor cells that can originate from either differentiated cells or adult tissue resident stem cells, driving tumor initiation and causing disease relapse. Several CSCs biomarkers have been identified and correlated to diagnosis, therapy and prognosis of cancer. Indeed, biological properties like self-renewal and differentiation capacity, high invasiveness, resistance to treatment, underline their importance in tumorigenesis and reinforce the need for targeted therapies aimed at eradicating CSCs (Walcher et al., 2020).

Surface molecules shared by human trophoblast and cancer cells represent potentially interesting CSCs-associated therapeutic targets: they may allow survival of the fetus as a semi-allograft in the mother, like a tumor in its host. In this regard, the 5T4 onco-fetal antigen is considered a potential CSCs marker in NSCLC (Damelin et al., 2011) and its expression has been reported in many different cancers where it correlates with poorer clinical outcome, especially in the case of colorectal, gastric and ovarian cancers (Stern and Harrop, 2017). The expression of 5T4 is associated with the directional movement of cells through EMT. Potentiation of the CXCL12/CXCR4 chemotactic pathway has been considered the putative mechanism involved in the 5T4 promotion of tumor growth and metastasis; however, 5T4 can also modulate tumor cell proliferation and migration *per se* (Puchert et al., 2018; Southgate et al., 2010). Inhibition of canonical Wnt/beta-catenin signaling, with concomitant activation of non-canonical Wnt pathways, is another possible mechanism involved in 5T4 effects on cancer cell invasive phenotype (Kagermeier-Schenk et al., 2011). In different malignancies, these processes are associated with CSCs properties that help to drive cancer cell dissemination (Harrop et al., 2019). The novel anti-5T4 ADC, SYD1875, has shown marked antitumor activity in a variety of patient-derived tumor xenografts expressing 5T4 and is presently tested in a dose-finding phase 1 trial (Groothuis et al., 2021). A second ADC that targets 5T4, evaluated in a not yet recruiting phase 1 clinical trial, is ASN004 that carries an auristatin analog as cytotoxic payload and was obtained by the Dolaflexin drug-linker technology (Smith et al., 2021).

Globo H is a tumor-associated carbohydrate antigen found on breast CSCs, highly expressed on the surface of epithelial cancers cells (Chang et al., 2008), but not in normal tissues. It is a potent inducer of angiogenesis and its expression has been reported to correlate with poor prognosis in many cancers of epithelial origin (e.g., breast, colon, endometrial, gastric, pancreatic, lung, and prostate cancers) and with the presence of CSCs (Cheng et al., 2014). OBI-999, a novel first-in-class ADC, linking a humanized anti-globo H mAb (OBI-888) to MMAE (Yang et al., 2021), was granted orphan drug designation for pancreatic and gastric cancer by FDA.

The protein tyrosine kinase 7 (PTK7), also known as colon carcinoma kinase 4 (CCK4), exerts important functions in developmental biology and is involved in the maintenance of intestinal and hematopoietic stem cells (Katoh, 2017). Accordingly, high PTK7 levels are associated with increased self-renewal potential (Jung et al., 2015). Structurally, PTK7 shares a common domain architecture with vascular endothelial growth factor receptors (VEGFR-1 and VEGFR-2), although its tyrosine kinase domain is significantly divergent from those of VEGFRs (Katoh, 2016; Lacal and Graziani, 2018). This structural analogy reflects a functional involvement of PTK7 in VEGF-A-induced VEGFR-2 phosphorylation and angiogenic sprouting of endothelial cells (Shin et al., 2015). Particularly abundant also in CSCs, PTK7 may contribute to treatment resistance/relapse and to poor prognosis in patients with TNBC and NSCLC (Ataseven et al., 2013; Chen et al., 2015a; Tian et al., 2016). Cofetuzumab pelidotin (PF-06647020, ABBV-647) is an investigational ADC including an anti-PTK7 mAb, currently tested in the clinic (NCT02222922) and demonstrating an interesting therapeutic activity in previously treated patients with ovarian cancer, NSCLC, and TNBC (Maitland et al., 2021).

The Notch pathway plays a critical role in the correlation between CSCs self-renewal and angiogenesis: its crosstalk with fibroblast growth factor (FGF) and WNT signaling cascades contributes to maintain CSCs survival and to remodel TME, thus receiving increased attention as a putative target to eliminate CSCs. Actually, the Notch signaling network exerts oncogenic and tumor-suppressive effects in a cancer stage- or subtype-dependent manner, being aberrantly activated in breast cancer, NSCLC and hematological malignancies, and inactivated in SCLC and squamous cell carcinomas (Katoh and Katoh, 2020). Interestingly, a cell-autonomous inhibitor of Notch signaling, devoid of the conserved N-terminal module of the agonistic Notch ligands, and highly expressed in CSCs of SCLC [i.e., delta-like ligand 3 (DLL3)], has been shown to promote cell migration and invasion through a mechanism involving PI3K/Akt signaling and the EMT protein Snail (Deng et al., 2017; Furuta et al., 2019). DLL3 plays a role in neuroendocrine tumorigenesis and is minimally expressed in normal tissues (Owen et al., 2019). Moreover,

while normally localized in the Golgi apparatus, DLL3 emerges on cell surfaces when overexpressed. All these properties, have made this protein a candidate target of a novel ADC, namely rovalpituzumab tesirine, tested in clinical studies especially for extensive-stage-SCLC, a neuroendocrine tumor with a low 5-year survival rate (Matsuo et al., 2021; Morgensztern et al., 2019; Saunders et al., 2015; Udagawa et al., 2019). Unfortunately, in a phase 3 trial (NCT03033511) recruiting patients with extensive-stage SCLC, rovalpituzumab, used as maintenance therapy after platinum-based chemotherapy, did not improve either PFS or OS compared to placebo (Johnson et al., 2021b). Moreover, the results of another phase 3 trial (NCT03061812) in advanced/metastatic SCLC overexpressing DLL3 indicated that treatment with rovalpituzumab was associated with a lower survival compared to the topoisomerase I inhibitor topotecan that represents the standard second-line therapy for this tumor type (Blackhall et al., 2021).

The kidney-associated antigen 1 (KAAG1), encoded by the reverse strand of the housekeeping gene doublecortin (DCX) domain containing 2 (*DCDC2*), has been also identified as a novel tumor-associated antigen, expressed in ovarian, prostate and breast cancer. This protein is known to be involved in brain development, microtubule assembly and neuronal migration (Reiner et al., 2006), whereas it is not expressed in most adult tissues (Coquelle et al., 2006; Longoni et al., 2013). Although KAAG1 is an intracellular protein, it becomes exposed on the surface of tumor cells when overexpressed. Moreover, when recognized by the investigational ADC ADCT-901, it is internalized and co-localizes with lysosomal-associated membrane protein 1 (LAMP-1 or CD107a). This means that the conjugate is efficiently transported to the lysosomal cellular compartment, where an efficient release of the payload occurs [www-adcreview.com]. An anti-LAMP-1 ADC (i.e., SAR428926) has also been developed and is currently clinically investigated in patients with advanced solid tumors [www.adcreview.com; www.clinicaltrials.com]. This heavily glycosylated protein is involved in protecting the lysosomal membrane from intracellular proteolysis (Parkinson-Lawrence et al., 2005). Although primarily expressed in the endosome-lysosomal membrane system, LAMP-1 is also expressed in the plasma membrane and, at high levels, in the cell surface of metastatic tumor cells.

3.3. New potential antigens associated to the tumor microenvironment

The targets for ADCs in clinical development discussed until now are mainly localized on cancer cells. Targeting the TME, i.e. antigens expressed on immune cells, endothelial cells, and fibroblasts, is a novel approach that provides several advantages: *i*) antigens may have greater accessibility to the ADC delivered through the circulation; *ii*) nonmalignant cells constituting the TME are less frequently affected by somatic mutations conferring drug resistance; *iii*) ADCs targeting the TME could potentially synergize with antiangiogenic agents as well as with immune checkpoint inhibitors. Moreover, as in the case of antigens expressed on malignant cells, TME-associated proteins are minimally or not expressed on healthy tissues (Mathur and Weiner, 2013).

Among the antigens associated to the TME, CD25 (interleukin-2 receptor) is a protein expressed by immunosuppressive Tregs infiltrating the tumor, and found to be overexpressed in both cHL and non-HL (Sakaguchi et al., 1995). ADCT-301, also known as camidanlumab tesirine, is an ADC composed of an antibody directed against CD25 that in a phase 1 study (NCT02432235) has shown antitumor activity against cHL and non-HL warranting further evaluation (Flynn et al., 2016; Hamadani et al., 2021b).

A crucial role in immune cells activation is played by immune checkpoints, molecules acting as gatekeepers of immune responses that gained therapeutic interest as they offer the opportunity to modulate the efficacy of the immune system in eradicating malignant cells. B7-H3 (CD276) is an immune checkpoint belonging to the B7 family of membrane proteins, normally expressed on activated APCs and regulating T cell responses. Up-regulated in several kinds of cancer (lung, breast, renal cell, and prostate cancers), B7-H3 has been found to inhibit T-cell proliferation (Castellanos et al., 2017), decrease cytokines secretion and promote tumor immune evasion (Chapoval et al., 2001; Dong et al., 2002; Yang et al., 2020; Ye et al., 2016). Interestingly, B7-H3 is overexpressed during pathological but not physiological angiogenesis; thus, ADCs targeting this protein can also inhibit tumor-associated vessels (Seaman et al., 2017). Emergent anti-B7-H3 ADCs in early clinical development include DS-7300 (Yamato et al., 2020), MGC018 (Powderly et al., 2020), and ABBV-155 (mirzotamab clezutoclax) (Tolcher et al., 2021b).

The CD70–CD27 signaling pathway represents another interesting targetable system to enhance the antitumor immune response. CD70, which belongs to the tumor necrosis factor (TNF) superfamily of molecules, is the ligand for CD27 and is expressed upon activation on dendritic cells. CD27, a TNF receptor superfamily member, is a marker of highly suppressive Tregs and its interaction with CD70 has been found to increase the frequency of Tregs and to promote tumor growth (Arroyo Hornero et al., 2020; Claus et al., 2012; Starzer and Berghoff, 2020). Thus, CD70/CD27 interaction may contribute to tumor escape from immune responses. Moreover, CD70 expression has been detected in different tumors of hematological origin as well as in several solid tumors (Jacobs et al., 2015). In particular, high levels of CD70 expression are found in lymphomas, renal cell carcinoma (Jilaveanu et al., 2012), nasopharyngeal carcinoma, Epstein–Barr virus-induced carcinomas (Boursalian et al., 2009), and are associated with poor prognosis in B cell lymphoma and breast cancer (Petrau et al., 2014). Conversely, CD27-expressing cells have not been demonstrated to date in solid tumors but only in hematological malignancies. Nonetheless, persistent CD27 signaling can occur in the TME thanks to its expression on tumor-infiltrating lymphocytes, which have been shown to communicate with CD70 present in carcinoma cells (Agathanggelou et al., 1995). In this context, an ADC directed against CD70 (i.e., SGN-CD70A) has been produced that, however, has shown modest activity against metastatic renal cell carcinoma or in DLBCL and mantle cell lymphoma (Pal et al., 2019; Phillips et al., 2019).

CCR7, the major receptor for chemokine C ligand 19 (CCL19) and chemokine C ligand 21 (CCL21), mainly expressed on B, naive T and memory T lymphocytes, and mature dendritic cells, plays a vital role in lymphocyte cell trafficking and homing to lymph nodes. CCR7 is also highly expressed by various hematological malignancies, and contributes to cell proliferation, invasion, metastasis, and angiogenesis in several solid tumors. Strong evidence suggests that lymphatic metastasis of TNBC is mediated by the CCR7/CCL21 crosstalk between tumor cells and the lymphatic system. Thus, it has been hypothesized that CCR7 is a key immune modulator in the TME and its local blockade might inhibit TNBC lymphatic metastasis (An et al., 2019). JBH492 is an ADC specific for CCR7 that has recently reached the phase 1 of clinical investigation for non-HL and chronic lymphocytic leukemia (CLL) [www.adcreview.com].

CD74, also known as HLA-DR-associated invariant chain, is a type II transmembrane glycoprotein that acts as an MHC class II chaperone with an important role in antigen presentation. As a receptor for the pro-inflammatory cytokine macrophage migration inhibitory factor (MIF), it is an important regulator of the innate immune system inducing an immunosuppressive environment that supports melanoma progression (Gil-Yarom et al., 2017; Yaddanapudi et al., 2016). Upon binding to MIF, the CD74-intracellular domain migrates to the nucleus where it acts together with NF-κB pathway members to induce B-cell proliferation and survival. CD74 is overexpressed on multiple myeloma and non-HL but its expression in normal tissues is limited to B cells, monocytes, macrophages, dendritic cells, Langerhans cells, activated T-cell subsets, and thymic epithelium (Stein et al., 2007). Thus, CD74-MIF signaling is another emerging attractive target for immunotherapy and for the novel ADC STRO-001 (Abrahams et al., 2018; Zhao et al., 2019).

Moving to antigens expressed on another cell population homing the TME, the membrane protein leucine-rich repeat containing 15

(LRRC15) is an example of novel ADCs target. This protein is highly expressed on cancer-associated fibroblasts in the stromal microenvironment of many solid tumors (e.g., breast, head and neck, lung, pancreatic cancer) and in a subset of cancer cells of mesenchymal origin (e.g., sarcoma, melanoma, glioblastoma), with limited expression in normal tissues. ABBV-085 (samrotamab vedotin) is a MMAE-releasing ADC directed against LRRC15 that showed efficacy in tumors of mesenchymal origin or with LRRC15-positive stromal desmoplasia (Demetri et al., 2021; Purcell et al., 2018).

CD38 is a nicotinamide adenine dinucleotide (NAD^+) glycohydrolase and adenosine diphosphate (ADP)-ribosyl cyclase involved in chronic inflammatory conditions such as asthma, diabetes, obesity, heart disease, aging, and cancer (Chini et al., 2018). Targeting stromal CD38 in melanoma increases cell death and reduces the density of tumor-associated fibroblasts, as well as neoangiogenesis (Baruch et al., 2018; Blacher et al., 2015) and melanoma metastasis. Accordingly, CD38-expressing fibroblasts infiltrating the tumor mass have been shown to promote cancer cell migration/invasion and blood vessel formation *in vitro*, enabling the expression of key metastatic and angiogenic factors like VEGF-A, FGF-2, CXCL-12, matrix metallopeptidase-9 and HGF (Baruch et al., 2020). STI-6129 is an emergent ADC including a novel cytotoxic payload derived from MMAF and a chemical linker that reduces the premature systemic release of the payload, thus avoiding the risk of toxicity observed with first-generation ADCs (Li et al., 2020).

A part from ADCs directed against B7-H3, ADCs specifically designed to target tumor associated-endothelium are still investigated at a preclinical level, such as CD105-DM1 that interacts with endoglin (CD105) (Huang et al., 2020), a type I transmembrane protein upregulated on proliferating endothelial cells and expressed on tumor-associated vessels of several tumor types (e.g., breast, colon, lung, stomach and brain cancers) (Burrows et al., 1995; Minhajat et al., 2006).

3.4. New potential targets with exclusive expression in hematological malignancies

As mentioned before, some investigational ADCs are directed against lineage-specific antigens expressed by blood cells, even though they are also recognized by already approved ADCs, i.e. CD33, CD30, CD22, CD79b, BCMA, and CD19 (see Tables 1 and 3).

Among new potential targets under clinical evaluation for hematological malignancies, CD37 is a B-cell surface antigen, belonging to the tetraspanin protein family, expressed in most B-cell malignancies, including B-cell non-HL and CLL, with a demonstrated prognostic value in DLBCL (Deckert et al., 2013; Xu-Monette et al., 2016). Naratuximab emtansine (IMGN529) is a clinically investigated ADC comprising a CD37-binding mAb (Stathis et al., 2018) for which in 2016 FDA granted orphan drug designation for the treatment of DLBCL. Actually, a recent press release from Debiopharm on the results of a phase 2 trial indicates that heavily pre-treated patients with relapsed/refractory DLBCL may derive clinical benefit from the treatment with this anti-CD37 ADC in combination with rituximab (2021, June 14; "Debiopharm's CD37 antibody drug conjugate shows promising phase 2 results for the treatment of B-cell malignancies").

CD123, the interleukin-3 receptor α-chain, plays a critical role in leukemogenesis. This protein is mainly present in T-lymphocytes and involved in the regulation of hematopoietic cell production by stimulating cell cycle progression, differentiation, and inhibiting apoptosis. Expressed at various levels in hematological malignancies, but at low level or absent in normal hematopoietic stem cells, CD123 is an attractive cell surface receptor for ADCs such as the IMGN632 that was designed to selectively kill AML blasts sparing bone marrow cells (Angelova et al., 2019; Kovtun et al., 2018b).

CD138, also known as syndecan-1, is a protein overexpressed on multiple myeloma cells belonging to the syndecan family of type I transmembrane proteoglycans. This protein acts as co-receptor for the binding of growth factors, such as HGF and epidermal growth factor (EGF), and to promote cell survival and proliferation in the bone marrow. Accordingly, an increase in serum levels of soluble CD138 is related with poor overall survival in multiple myeloma patients (Mahtouk et al., 2006). Indatuximab ravtansine (BT062) is a clinically investigated ADC that binds to CD138 (Jagannath et al., 2019). In a phase 1/2 study (NCT01638936), indatuximab ravtansine combined with dexamethasone plus the immunomodulatory drugs lenalidomide or pomalidomide was tolerated and active against heavily pretreated patients with relapsed/refractory multiple myeloma (Kelly et al., 2021).

Table 4 recapitulates some of the clinical trials investigating the above mentioned ADCs, recently completed or terminated, still recruiting, or not yet recruiting cancer patients.

4. Conclusions and future directions

Approval of seven new ADCs (polatuzumab vedotin-piiq, enfortumab vedotin-ejfv, fam-trastuzumab deruxtecan-nxki, sacituzumab govitecan-hziy, belantamab mafodotin-blmf, loncastuximab tesirine-lpyl, and tisotumab vedotin-tftv) from 2019 to date is a clear indication of the resurgence of an almost twenty years old anticancer prototype. Indeed, despite initial challenges related to non-tumor specific target recognition and/or premature payload release due to linker instability, the progress made in recent years in the field of drug design and engineering technologies has allowed to overcome these drawbacks and to affirm the great potential of these therapeutic agents against cancer. Even more surprising is the magnitude of investigational ADCs and the continuously growing number of registered clinical trials (more than two hundreds so far).

Innovative prototypes like ISACs, PDCs and CABs represent a step forward in the design of second-generation ADCs. In the first case, the mAb is not conjugated to a cytotoxic compound, but to an immune-stimulatory agent, i.e. a drug that mainly acts as toll-like receptor agonist, thus activating dendritic cells and antigen presentation within the tumor mass (Ackerman et al., 2021). PDCs are characterized by the addition of a masking peptide that allows the PDC to remain inactive until proteolytically unmasked through tumor associated proteases cleavage. In the case of CABs, this technology exploits the unique acidic microenvironment of cancer that allows antibody activation in close proximity to the tumor, while promoting their reversible inactivation away from the tumor when exposed to physiological pH.

In addition to the promoting role in ADCs evolution played by the optimization of mAb or linker technologies and by the introduction of new payloads, this very productive moment is closely related to the constant expansion of the pool of ADCs target antigens. Novel ADCs not only try to avoid systemic adverse effects by leaving healthy tissues unaffected, but also offer the possibility to target, besides cancer cells, stromal and immune cells constituting the TME. In turn, antigens expressed in the TME offer the advantage to be more easily accessible by circulating ADCs and, since the TME plays a pivotal role in tumor growth and metastasis (Ceci et al., 2020; Lacal et al., 2020), its targeting by anticancer therapies may lead to significant and long-lasting benefits. Among potential ADCs targets, present both in tumor cells and in TME cellular components, VEGFR-1 appears to be a suitable candidate being expressed not only by tumor cells (e.g., melanoma and glioblastoma) but also by the endothelium of tumor-associated vessels and by pro-tumoral myeloid cells (i.e., M2 macrophages). Thus, an ADC targeting VEGFR-1 might represent a multi-targeted therapeutic approach to directly kill tumor cells and to inhibit neovessel formation as well as tumor infiltration by immunosuppressive immune cells (Lacal et al., 2020; Lacal and Graziani, 2018).

Moreover, emerging ADCs carrying immunomodulatory payloads, like ISACs, or those targeting the TME, may promote immunogenic cell death and synergize with immune checkpoint inhibitors. Not surprisingly, some clinical studies among those listed in Table 3, are assessing the safety and therapeutic potential of ISACs in combination with

Table 4
Clinical trials involving novel experimental ADCs.

ADC target antigen	ADC name	ClinicalTrials.gov Identifier[a]	Status	Phase	Tumor type
Antigens shared with approved ADCs					
CD33	IMGN779	NCT02674763	Completed	1	AML
	SGN-CD33A (vadastuximab talirine)	NCT02706899	Terminated	1/2	Myelodysplastic syndrome
		NCT02614560	Terminated	1/2	AML
		NCT02785900	Terminated	3	AML
		NCT02326584	Completed	1	AML
		NCT01902329	Completed	1	AML
CD30	F0002-ADC	NCT03894150	Recruiting	1	Hematological malignancies
HER2	SYD985 (vic-trastuzumab duocarmazine)	NCT04602117	Recruiting	1	Metastatic cancers
		NCT04205630	Recruiting	2	Endometrial cancer
		NCT04235101	Recruiting	1	Metastatic solid tumors
		NCT02277717	Completed	1	Metastatic cancers
		NCT03262935	Active, not recruiting	3	Breast cancer
		NCT04983238	Not yet recruiting	1/2	Metastatic breast cancer
	RC48-ADC (disitamab vedotin)	NCT04329429	Recruiting	2	Biliary tract cancer
		NCT04280341	Not yet recruiting	1	Advanced solid tumors
		NCT04965519	Not yet recruiting	2	Gynecological malignancies
		NCT04879329	Not yet recruiting	2	Urothelial carcinoma
		NCT02881190	Completed	1	Advanced solid tumors
		NCT02881138	Completed	1	Advanced solid tumors
		NCT03809013	Active, not recruiting	2	Urothelial cancer
		NCT04714190	Recruiting	3	Gastric cancer
		NCT04073602	Active, not recruiting	2	Urothelial cancer
		NCT03507166	Completed	2	Urothelial cancer
		NCT04264936	Recruiting	1/2	Urothelial cancer
		NCT03556345	Active, not recruiting	2	Gastric cancer
		NCT04400695	Recruiting	3	Breast cancer
		NCT03052634	Active, not recruiting	1/2	Breast cancer
		NCT03500380	Recruiting	2/3	Breast cancer
		NCT04311034	Active, not recruiting	1/2	NSCLC
		NCT05135715	Not yet recruiting	2	Advanced melanoma
		NCT05134519	Not yet recruiting	2	Breast cancer
		NCT05115500	Not yet recruiting	2	Advanced solid tumors
		NCT05016973	Not yet recruiting	2	Myometrial invasive bladder cancer
	BAT8001	NCT04151329	Unknown	1/2	Advanced solid tumors
		NCT04189211	Unknown	1	Breast cancer or gastric cancer
		NCT04185649	Active, not recruiting	3	Breast cancer
	FS-1502 (trastuzumab MMAF)	NCT03944499	Recruiting	1	Advanced solid tumors and breast cancer
	A166	NCT03602079	Recruiting	1/2	Advanced solid tumors
	XMT-1522	NCT02952729	Completed	1	Breast cancer, NSCLC, gastric cancer
	MEDI-4276	NCT02576548	Completed	1	Breast cancer, gastric cancer
	PF-06804103	NCT03284723	Completed	1	Breast and gastric cancer
	ARX788	NCT04829604	Recruiting	2	Breast cancer
		NCT03255070	Recruiting	1	Advanced solid tumors
		NCT05041972	Not yet recruiting	2	Solid tumors
		NCT05018676	Not yet recruiting	2	Breast cancer
		NCT05018702	Recruiting	2	Metastatic breast cancer
		NCT04983121	Not yet recruiting	2	Breast cancer

(continued on next page)

Table 4 (*continued*)

ADC target antigen	ADC name	ClinicalTrials.gov Identifier[a]	Status	Phase	Tumor type
	ZW49	NCT03821233	Recruiting	1	Advanced or metastatic tumors
	ALT-P7	NCT03281824	Active, not recruiting	1	Breast cancer
	BDC-1001	NCT04278144	Recruiting	1/2	Advanced solid tumors
	RG6148 (DHES0815A)	NCT03451162	Completed	1	Breast cancer
	GQ1001	NCT04450732	Recruiting	1	Advanced solid tumors
	NJH395	NCT03696771	Completed	1	Non-breast advanced tumors
	SBT6050	NCT04460456	Recruiting	1	Advanced solid tumors
		NCT05091528	Not yet recruiting	1/2	Solid tumors
CD22	ADCT-602 (epratuzumab tesirine)	NCT03698552	Recruiting	1/2	B-ALL
	DCDT2980S (pinatuzumab vedotin)	NCT01209130	Completed	1	Non-HL, CLL
		NCT01691898	Completed	1/2	B-cell non-HL
	TRPH-222 (CD22-4AP)	NCT03682796	Recruiting	1/2	B-cell non-HL
CD79b	DCDS0780A (iladatuzumab vedotin)	NCT02453087	Completed	1	B-cell non-HL
TROP2	DS-1062 (datopotamab deruxtecan)	NCT04484142	Recruiting	2	NSCLC
		NCT04656652	Recruiting	3	NSCLC
		NCT04940325	Recruiting	2	NSCLC
		NCT03401385	Recruiting	1	Advanced solid tumors
		NCT04612751	Recruiting	1	NSCLC
		NCT04526691	Recruiting	1	NSCLC
		NCT03742102	Recruiting	1/2	TNBC
		NCT05104866	Recruiting	3	Breast cancer
	SKB264	NCT04152499	Recruiting	1/2	Advanced solid tumors
BCMA	AMG 224	NCT02561962	Active, not recruiting	1	Multiple myeloma
	CC-99712	NCT04036461	Recruiting	1	Multiple myeloma
	HDP-101	NCT04879043	Not yet recruiting	1/2	Multiple myeloma
CD19	SAR3419 (coltuximab ravtansine)	NCT01472887	Completed	2	DLBCL
		NCT00796731	Completed	1	Non-HL
		NCT00549185	Completed	1	Non-HL
		NCT01470456	Completed	2	DLBCL
		NCT01440179	Terminated	2	ALL
	SGN-CD19A (denintuzumab mafodotin)	NCT01786135	Completed	1	B-lineage non-HL
		NCT01786096	Completed	1	Burkitt Lymphoma, Precursor B-cell Lymphoblastic Leukemia-Lymphoma
		NCT02592876	Terminated	2	DLBCL
		NCT02855359	Terminated	2	DLBCL or follicular lymphoma
TF	MRG004A	NCT04843709	Recruiting	1/2	Advanced solid tumors
Antigens overexpressed by cancer cells in solid tumors: tyrosine kinase and G-protein coupled receptors					
HGFR (c-Met)	ABBV-399 (telisotuzumab vedotin)	NCT03539536	Recruiting	2	NSCLC
		NCT04928846	Not yet recruiting	3	Non squamous NSCLC
		NCT04830202	Expanded access available		
		NCT02099058	Recruiting	1	Advanced solid tumors
		NCT03311477	Completed	1	Advanced solid tumors
		NCT03574753	Completed	2	Squamous cell lung carcinoma
	TR1801-ADC	NCT03859752	Active, not recruiting	1	Solid tumors
	RC108-ADC	NCT04617314	Recruiting	1	Advanced solid tumors
	HTI-1066 (SHR-A1403)	NCT03398720	Unknown	1	Advanced solid tumors
		NCT03856541	Unknown	1	Advanced solid tumors
HER3	U3-1402 (patritumab deruxtecan)	NCT04699630	Recruiting	2	Breast cancer
		NCT04479436	Terminated	2	Colorectal cancer
		NCT04610528	Recruiting	1	Breast cancer
		NCT04965766	Recruiting	2	Breast cancer
		NCT03260491	Active, not recruiting	1	NSCLC
		NCT02980341	Active, not recruiting	1/2	Breast cancer
		NCT04619004	Recruiting	2	NSCLC
		NCT04676477	Recruiting	1	NSCLC

Table 4 (*continued*)

ADC target antigen	ADC name	ClinicalTrials.gov Identifier[a]	Status	Phase	Tumor type
HER1 (EGFR)	ABBV-321 (serclutamab talirine)	NCT03234712	Completed	1	Advanced solid tumors
	AMG-595	NCT01475006	Completed	1	Glioblastoma
	ABT-414 (depatuxizumab mafodotin)	NCT01741727	Completed	1	Advanced solid tumors
		NCT01800695	Completed	1	Glioblastoma
		NCT02343406	Completed	2	Glioblastoma
		NCT02590263	Completed	1/2	Glioblastoma, malignant glioma
		NCT02573324	Active, not recruiting	2/3	Glioblastoma, gliosarcoma
	M1231	NCT04695847	Recruiting	1	Advanced solid tumors
IGF-1R	W0101	NCT03316638	Recruiting	1/2	Advanced solid tumors
ROR1	NBE-002	NCT04441099	Recruiting	1/2	Advanced solid tumors
	VLS-101 (zilovertamab vedotin)	NCT04504916	Recruiting	2	Metastatic solid tumors
		NCT03833180	Recruiting	1	Hematological cancers
		NCT05139017	Recruiting	2/3	DLBCL
ROR2	BA3021 (CAB-ROR2 ADC)	NCT03504488	Recruiting	1/2	Solid tumors (phase 1); locally advanced unresectable or metastatic NSCLC, TNBC and soft tissue sarcoma (phase 2)
		NCT04918186	Recruiting	2	Ovarian cancer
				1/2	Solid tumors
FGFR2	BAY 1187982	NCT02368951	Terminated	1	Advanced solid tumors
FGFR3	LY3076226	NCT02529553	Completed	1	Advanced or metastatic tumors
AXL	AXL-107-MMAE (enapotamab vedotin)	NCT02988817	Completed	1/2	Solid tumors
	BA3011	NCT04681131	Recruiting	2	NSCLC
		NCT03425279	Recruiting	1/2	Solid tumors
		NCT04918186	Recruiting	2	Ovarian cancer
ET_BR	DEDN6526A	NCT01522664	Completed	1	Melanoma
GRP20	DS-6157a	NCT04276415	Active, not recruiting	1	Gastrointestinal stromal tumor
Antigens overexpressed by cancer cells in solid tumors: cell adhesion molecules					
P-cadherin	PCA062	NCT02375958	Completed	1	Tumors expressing P-cadherin
NCAM-1 (CD56)	IMGN-901 (lorvotuzumab mertansine)	NCT02452554	Active, not recruiting	2	Wilms tumor, rhabdomyosarcoma, neuroblastoma, pleuropulmonary blastoma, malignant peripheral nerve sheath tumor, or synovial sarcoma
		NCT02420873	Completed	2	Leukemia
		NCT01237678	Terminated	1/2	Advanced solid tumors and extensive stage SCLC
		NCT00346255	Completed	1	Multiple myeloma
		NCT00991562	Completed	1	Multiple myeloma
		NCT00346385	Completed	1	Ovarian cancer, Merkel cell carcinoma, SCLC SCLC
		NCT00065429	Completed	1/2	
ALCAM (CD166)	CX-2009 (praluzatamab ravtansine)	NCT03149549	Completed	1/2	Solid tumors
		NCT04596150	Recruiting	2	Advanced breast cancer
CEACAM5	SAR408701 (tusamitamab ravtansine)	NCT04659603	Recruiting	2	Advanced solid tumors
		NCT04394624	Recruiting	2	Non squamous NSCLC
		NCT04524689	Recruiting	2	Non squamous NSCLC
		NCT03324113	Active, not recruiting	1	Advanced solid tumors
		NCT04154956	Recruiting	3	Non squamous NSCLC
		NCT05071053	Recruiting	2	Gastric cancer
		NCT02187848	Active, not recruiting	1/2	Advanced solid tumors
	IMMU-130 (labetuzumab govitecan)	NCT01270698	Completed	1	Colorectal cancer
Antigens overexpressed by cancer cells in solid tumors: members of the folate system					
FRα	IMGN-853 (mirvetuximab soravtansine)	NCT03832361	Recruiting	2	Endometrial cancer
		NCT01609556	Completed	1	Ovarian cancer and other FRα positive solid tumors
		NCT03106077	Completed	2	Breast cancer
		NCT04296890	Active, not recruiting	3	Ovarian cancer, primary peritoneal, or fallopian tube cancer
		NCT03552471	Active, not recruiting	1	Endometrial, ovarian, fallopian tube or primary peritoneal cancer
		NCT03835819	Recruiting	2	Endometrial cancer
		NCT04209855	Recruiting	3	Epithelial ovarian cancer, primary peritoneal, or fallopian tube cancer

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Table 4 (*continued*)

ADC target antigen	ADC name	ClinicalTrials.gov Identifier[a]	Status	Phase	Tumor type
		NCT05041257	Recruiting	2	Ovarian, primary peritoneal or fallopian tube cancer
		NCT04606914	Recruiting	2	Ovarian cancer, primary peritoneal, or fallopian tube cancer
		NCT02606305	Completed	1/2	Ovarian cancer, primary peritoneal, or fallopian tube cancer
		NCT02631876	Completed	3	Epithelial ovarian cancer, primary peritoneal, or fallopian tube cancer
		NCT04274426	Recruiting	2	Ovarian cancer
		NCT02996825	Recruiting	1	Epithelial ovarian cancer, primary peritoneal, or fallopian tube cancer or TNBC
	MORAb-202	NCT04300556	Active, not recruiting	1/2	Selected solid tumors
		NCT03386942	Active, not recruiting	1	Solid tumors
	STRO-002	NCT03748186	Recruiting	1	Ovarian and endometrial cancer
PSMA	PSMA-ADC	NCT01695044	Completed	2	Prostate cancer
		NCT02020135	Completed	2	Prostate cancer
		NCT01414283	Completed	1	Prostate cancer
		NCT01414296	Completed	1	Prostate cancer
		NCT01856933	Completed	2	Glioblastoma
Antigens overexpressed by cancer cells in solid tumors: iron binding proteins					
Melanotransferrin (CD228/MFI2/MELTF)	SGN-CD228A	NCT04042480	Recruiting	1	Advanced solid tumors
TFR1 (CD71)	CX-2029	NCT03543813	Recruiting	1/2	Solid tumors or DLBCL
Antigens associated with cancer cells of specific tumor types					
GD3	PF-06688992	NCT03159117	Completed	1	Melanoma
LIV1	SGN-LIV1A (ladiratuzumab vedotin)	NCT04032704	Recruiting	2	Advanced solid tumors
		NCT03310957	Recruiting	1/2	Breast cancer
		NCT01969643	Recruiting	1	Breast cancer
		NCT03424005	Recruiting	1/2	TNBC
		NCT01042379	Recruiting	2	Breast cancer
GCC	MLN0264 (indusatumab vedotin or TAK-264)	NCT01577758	Completed	1	Advanced gastrointestinal malignancies
		NCT02391038	Terminated	1	Advanced gastrointestinal carcinoma, metastatic or recurrent gastric or gastroesophageal junction adenocarcinoma
		NCT02202785	Terminated	2	Pancreatic cancer
		NCT02202759	Terminated	2	Gastric or gastroesophageal junction adenocarcinoma
ENPP3	AGS-16C3F	NCT01672775	Completed	1	Renal cell carcinoma
		NCT02639182	Completed	2	Renal cell carcinoma
Other antigens overexpressed by cancer cells					
Mesothelin	BAY94-9343 (anetumab ravtansine)	NCT02751918	Completed	1	Ovarian neoplasms
		NCT03126630	Recruiting	1/2	Mesothelioma
		NCT03102320	Completed	1	Advanced solid tumors
		NCT03926143	Active, not recruiting	2	Solid tumors
		NCT03023722	Completed	2	Pancreatic cancer
		NCT03587311	Recruiting	2	ovarian, fallopian tube, or primary peritoneal cancer
		NCT02696642	Completed	1	Advanced solid cancers
		NCT02824042	Completed	1	Advanced solid cancers
		NCT02639091	Completed	1	Epithelial mesothelioma or non squamous NSCLC
		NCT03816358	Recruiting	1/2	Pancreatic cancer
		NCT02610140	Completed	2	Mesothelioma
		NCT01439152	Completed	1	Advanced solid tumors
		NCT02485119	Completed	1	Advanced solid tumors
		NCT02839681	Terminated	2	Lung adenocarcinoma
		NCT03455556	Terminated	1	Advanced NSCLC
	DMOT4039A	NCT01469793	Completed	1	Ovarian cancer
	RC88	NCT04175847	Recruiting	1	Advanced solid tumors
	BMS-986148	NCT02341625	Terminated	1/2	Advanced solid tumors
		NCT02884726	Completed	1	Advanced solid tumors
CA6	SAR566658	NCT02984683	Terminated	2	Metastatic TNBC
		NCT01156870	Completed	1	Solid tumors
SLITRK6	ASG-15ME (sirtratumab vedotin)	NCT01963052	Completed	1	Urothelial cancer
GPNMB (HGFIN)	CDX-011 (glembatumumab vedotin)	NCT01997333	Completed	2	TNBC
		NCT01156753	Completed	2	Breast cancer
		NCT02487979	Active, not recruiting	2	Osteosarcoma
		NCT02713828	Terminated	1/2	Advanced or metastatic squamous cell carcinoma of the lung
		NCT02363283	Completed	2	Uveal melanoma
		NCT02302339	Terminated	2	Advanced melanoma
		NCT00412828	Completed	1/2	Melanoma
		NCT00704158	Completed	1/2	Breast cancer

Table 4 (*continued*)

ADC target antigen	ADC name	ClinicalTrials.gov Identifier[a]	Status	Phase	Tumor type
NaPi2b	DNIB0600A (lifastuzumab vedotin)	NCT01363947	Completed	1	NSCLC, ovarian cancer
		NCT01991210	Terminated	2	Ovarian cancer
		NCT01995188	Completed	1	Non-squamous NSCLC
	XMT-1536 (upifitamab rilsodotin)	NCT03319628	Recruiting	1/2	NSCLC, ovarian cancer
		NCT04907968	Recruiting	1/2	Ovarian cancer
		NCT04396340	Recruiting	1/2	NSCLC, ovarian cancer
	XMT-1592	NCT04396340	Recruiting	1/2	NSCLC, ovarian cancer
CD205 (LY75)	MEN1309 (OBT076)	NCT04064359	Recruiting	1	Solid tumors, HER2-negative breast cancer
		NCT03403725	Terminated	1	Non-HL
Antigens overexpressed by cancer stem cells					
5T4	SYD1875	NCT04202705	Recruiting	1	Solid tumors
	ASN004	NCT04410224	Not yet recruiting	1	Advanced solid tumors
Globo H	OBI-999	NCT04084366	Recruiting	1/2	Advanced solid tumors
PTK7 (CCK4)	PF-06647020 (cofetuzumab pelidotin)	NCT02222922	Completed	1	Advanced solid tumors
		NCT03243331	Completed	1	TNBC
		NCT04189614	Recruiting	1	NSCLC
DLL3	SC16LD6.5 (rovalpituzumab tesirine)	NCT02674568	Completed	2	SCLC
		NCT01901653	Completed	1/2	SCLC
		NCT02874664	Completed	1	SCLC
		NCT03543358	Completed	2	Solid tumors
		NCT03086239	Completed	1	SCLC
		NCT02709889	Terminated	1/2	Advanced solid tumors
		NCT03061812	Completed	3	SCLC
		NCT02819999	Terminated	1	SCLC
		NCT03026166	Terminated	1/2	SCLC
		NCT03033511	Terminated	3	SCLC
		NCT03000257	Active, not recruiting	1	Advanced solid tumors
KAAG1	ADCT-901	NCT04972981	Recruiting	1	Advanced solid tumors
LAMP-1	SAR428926	NCT02575781	Completed	1	Advanced solid tumors
Antigens expressed by cells of the tumor microenvironment					
CD25	ADCT-301 (camidanlumab tesirine)	NCT04639024	Not yet recruiting	2	AML, myelodysplastic syndrome, myeloproliferative neoplasm
		NCT03621982	Recruiting	1	Advanced solid tumors
		NCT02588092	Terminated	1	ALL
		NCT04052997	Active, not recruiting	2	HL
		NCT02432235	Completed	1	HL, non-HL
B7-H3 (CD276)	DS-7300	NCT04145622	Recruiting	1/2	Advanced solid tumors
	MGC018	NCT03729596	Recruiting	1/2	Advanced solid tumors
	ABBV-155 (mirzotamab clezutoclax)	NCT03595059	Recruiting	1	Advanced solid tumors
CD70	SGN-CD70A	NCT02216890	Completed	1	Renal cell carcinoma, mantle-cell lymphoma, DLBCL, follicular lymphoma
CCR7	JBH492	NCT04240704	Recruiting	1	Non-HL, CLL
CD74	STRO-001	NCT03424603	Recruiting	1	Advanced B-cell malignancies
LRRC15	ABBV-085 (samrotamab vedotin)	NCT02565758	Completed	1	Advanced solid tumors
CD38	STI-6129	NCT04316442	Recruiting	1	Systemic amyloid light-chain amyloidosis
Antigens overexpressed in hematological malignancies					
CD37	IMGN529 (naratuximab emtansine)	NCT01534715	Completed	1	Non-HL, CLL
CD123	IMGN632	NCT03386513	Recruiting	1/2	AML, ALL, blastic plasmacytoid dendritic cell neoplasm, myeloproliferative neoplasm
		NCT04086264	Recruiting	1/2	AML
CD138	BT062 (indatuximab ravtansine)	NCT01638936	Completed	1/2	Multiple myeloma
		NCT01001442	Completed	1/2	Multiple myeloma
		NCT00723359	Completed	1	Multiple myeloma

[a] NCT number or ClinicalTrials.gov identifier; data from https://clinicaltrials.gov, accessed on December 2021

anti–PD-1/PD-L1 mAbs (e.g., NCT04278144 and NCT04460456 testing BDC-1001 and SBT6050, respectively, in combination with pembrolizumab) and are expected to further improve the outcome of advanced/metastatic tumors with limited therapeutic options.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

This review article was mainly focused on clinically approved and clinically investigated ADCs and not on ADCs that are still at a preclinical stage. Due to the growing number of published articles on this topic, we apologize to those colleagues whose work was not cited.

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