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Future potential targets of antibody-drug conjugates in breast cancer

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ABSTRACT

Metastatic breast cancer (BC) remains an incurable disease. Besides endocrine and targeted agents, chemotherapy is still a relevant therapeutic option for this disease. Recently, antibody-drug conjugates (ADCs) have shown to overcome the lack of tumor specificity and systemic toxicity typically associated with traditional chemotherapies, thus improving the therapeutic index. To effectively exploit this technological breakthrough, identification of optimal target antigens (Ags) is of utmost importance. To make the ideal target, differential expression of target Ags between healthy and cancer tissues, as well as specific mechanisms of ADC internalization after Ag-antibody interaction are required.

Therefore, several *in silico* strategies to identify and characterize new promising candidate Ags have been developed. If initial in vitro and in vivo positive data are documented, thus providing a biological rationale for further Ag investigation, early phase clinical trials are designed. In BC, these strategies have already led to the development of effective ADCs, namely trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG), primarily targeting HER2 and TROP-2. However, promising new Ags are currently under investigation, with encouraging results especially coming from targeting HER3, FRα, Tissue Factor, LIV-1, ROR1-2, and B7–H4.

In this review, we describe the landscape of emergent and future potential targets (i.e., other than HER2 and TROP-2) investigated in BC for ADC development. Predominant target expression, function, preclinical rationale, potential clinical implication, as well as preliminary clinical trial results are provided.

1. Introduction

1.1. Antibody-drug conjugates: a new anti-cancer technology

Metastatic breast cancer (BC) remains an incurable disease and a leading cause of cancer-related mortality amongst women worldwide [1,2]. Besides endocrine and targeted agents, chemotherapy is a commonly used treatment option in this disease [3]. However, lack of tumor specificity and the drug-specific therapeutic index may limit the manageability of cytotoxic agents [3]. In recent years, a groundbreaking class of anticancer drugs, namely antibody drug conjugates (ADCs), has paved the way to the targeted delivery of chemotherapy to solid tumors [4]. ADCs are made of three core components: the antibody, selective for a target antigen (Ag); the payload, typically a cytotoxic agent; and a linker, which connects the antibody to the payload [1]. Thus, by merging the target specificity of monoclonal antibodies (mAbs) with the cancer-killing abilities of cytotoxic warheads, chemotherapy is supposed to be mostly delivered to cells that express a selected target Ag, therefore sparing other healthy tissues [1].

Although the first clinical trials of ADCs for the treatment of patients with cancer disclosed unacceptable drug-related toxicities, this trend came to an end in the 2000s, with the first Food and Drug Administration (FDA) approval of the anti-CD33 gemtuzumab ozogamicin for the treatment of relapsed CD33-positive acute myeloid leukemia [5,6]. As for solid tumors, BC had a leading role in ADC development, since the human epidermal growth factor receptor 2 (HER2)-targeting ado-trastuzumab emtansine (T-DM1) was the first compound to be granted approval in 2013 for the treatment of trastuzumab-resistant metastatic BC [7].

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1.2. Approved antibody-drug conjugates for the treatment of breast cancer

1.2.1. HER2-targeting agents

T-DM1 merges the anti-HER2 assets of trastuzumab with DM1, a derivative of the maytansinoid toxin, which inhibits tubulin polymerization [1]. The linker is a non-cleavable stable thioether and the drug-to-antibody ratio (DAR) is about 3.5:1 [4]. The FDA drug approval in second treatment line for patients with HER2-positive metastatic BC was based on the results of the phase 3 EMILIA trial (Table 1) [8]. T-DM1

Table 1
Activity and toxicity of antibody-drug conjugates currently FDA-approved for the treatment of breast cancer.

Drug Name	Structure	Payload and DAR	Approval indication and date	Clinical trial specifics	Endpoints	Safety
Ado-trastuzumab Emtansine (T-DM1)	Antibody: IgG1 Target: HER2 Linker: NC	Payload: DM1 (maytansinoid antitubulin) DAR: 3.5 (mean)	HER2+ mBC (after taxane-trastuzumab) Year: 2013	EMILIA (Ph III): T-DM1 vs capecitabine-lapatinib	Primary: mOS 29.9 vs 25.9 mo (HR 0.75; 95% CI 0.64–0.88) mPFS 9.6 vs 6.4 mo (HR 0.65; 95% CI 0.55–0.77) Secondary:ORR 43.6% vs 30.8% mDOR 12.6 vs 6.5 mo	Any AE G ≥ 3 40.8% vs 57%; most common: thrombocytopenia (12.9% vs 0.2%), AST elevation (4.3% vs 0.8%)
			HER2+ eBC adjuvant therapy (if non-pCR) Year: 2019	KATHERINE (Ph III): T-DM1 vs trastuzumab	Primary: 3y iDFS 88.3% vs 77%; (HR 0.5; 0.39–0.64) Secondary: Distant recurrence as first iDFS event (10.5% vs 15.9%)	Any AE G ≥ 3 25.7% vs 15.4%; most common: thrombocytopenia (5.7% vs 0.3%), HBP (2% vs 1.2%)
Fam-trastuzumab Deruxtecan (T-DXd)	Antibody: IgG1 Target: HER2 Linker: C	Payload: Deruxtecan (DXd; camptothecin, topoisomerase-I inhibitor) DAR: 8 (mean)	HER2+ mBC (after 2 L or more for mBC) Year: 2019	DESTINY-Breast01 (Ph II): single-arm, non-randomized (confirmatory results in ph III DESTINY-Breast02)	Primary: ORR 61.4% Secondary: mPFS 19.4 mo mOS 24.6 mo mDOR 20.8 mo	Any AE G ≥ 3 48.4%; most common: neutropenia (19.6%), anemia (8.2%). Of special interest: ILD any G 13.6%, G ≥ 3 2.7%.
			HER2+ mBC (after 1 L) Year: 2022	DESTINY-Breast03 (Ph III): T-DXd vs T-DM1	Primary: PFS: 12-mo PFS rate 75% vs 34%; (HR 0.28, 95% CI 0.22–0.37) Updated mPFS: 28.8 mo vs. 6.8 mo (HR, 0.33) Secondary: ORR (80% vs 34%) Updated mOS: not reached in either group, HR 0.64 DOR, safety	Any AE G ≥ 3 45.1%; most common: neutropenia (19.1%), nausea (6.6%). Of special interest: ILD in 15% of patients receiving T-DXd vs 3% of patients receiving T-DM1
			HER2-low mBC (after 1 L) Year: 2022	DESTINY-Breast04 (Ph III): T-DXd vs TPC	Primary: mPFS (HR+): 10.1 mo vs 5.4 mo (HR 0.51; 95% CI, 0.40–0.64) Secondary: mPFS (overall): 9.9 mo vs 11.3 mo (HR, 0.50, 95% CI, 0.40–0.63) OS (HR+): 23.9 mo vs 17.5 mo (HR 0.64; 95% CI, 0.48–0.86; P = 0.003) OS (overall): 23.4 mo vs 16.8 mo (HR 0.64; 95% CI, 0.49–0.84; P = 0.001)	Any AE G ≥ 3 52.6%; most common: neutropenia (13.7%), anemia (8.1%), nausea (4.6%). Of special interest: ILD any G 12.1%, G ≥ 3 1.3%.
Sacituzumab govitecan (SG)	Antibody: IgG1 Target: TROP2 Linker: C	Payload: SN-38 (active irinotecan metabolite, camptothecin) DAR: 7.6 (mean)	mTNBC (after 2 L or more, at least 1 for mBC) Year: 2021	ASCENT (Ph III): SG vs ChT	Primary: mPFS in pts without brain metastasis 5.6 vs 1.7 mo (HR 0.41; 95% CI 0.32–0.52) Secondary: mOS 12.1 vs 6.7 mo (HR 0.48; 95% CI 0.38–0.59) ORR 35% vs 5%	Any AE G ≥ 3 64% vs 47%; most common neutropenia (51% vs 33%), leucopenia (10% vs 5%), diarrhea (10% vs <1%).
			HR + HER2- mBC after ET AND after ≥2 systemic therapies in the metastatic setting Year: 2023	TROPiCS-02 (Ph III): SG vs single agent ChT (eribulin, vinorelbine, gemcitabine, capecitabine)	Primary: mPFS: 5.5 mo vs 4 mo (HR 0.661, 95% CI, 0.529–0.826) Secondary: mOS: 14.4 mo vs 11.2 mo (HR 0.789, 95% CI, 0.646–0.964)	Any AE G ≥ 3 74% vs 60%; Most common neutropenia (51%) and diarrhea (10%)

Abbreviations: AE, adverse events; AST, Aspartate transaminase; C, cleavable; ChT, chemotherapy; CI, confidence interval; DAR, Drug-to-Antibody Ratio; eBC, early breast cancer; FDA, Food and Drug Administration; G, grade; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; iDFS, invasive disease free survival; IgG, ImmunoGlobulin G; ILD, interstitial lung disease; L, line of therapy for the advanced setting; mo, months; mBC, metastatic breast cancer; mDOR, median duration of response; MMAE, Monomethyl auristatin E; mOS, median overall survival; mPFS, median progression free survival; mTNBC, metastatic triple negative breast cancer; NC, non-cleavable; ORR, overall response rate; pCR, pathologic complete response; Ph, phase; SG, Sacituzumab govitecan; T-DM1, Ado-trastuzumab Emtansine; T-DXd, Fam-trastuzumab Deruxtecan; TPC, treatment of physician's choice; TROP2, trophoblast cell surface antigen 2.

(3.6 mg/kg) was compared to lapatinib plus capecitabine in 991 patients [8]. The experimental arm showed a significantly improved median overall survival (mOS, primary endpoint, 30.9 vs. 25.1 months; hazard ratio, HR 0.65), with an Objective Response Rate (ORR) of 43.6% (vs. 30.8%) [8]. In 2019, T-DM1 became the standard of care for patients with HER2-positive early BC and residual disease in the post-neoadjuvant setting, due to the significant improvement in 3-year invasive disease-free survival (iDFS) observed with the ADC (88.3% vs. 77%, HR: 0.50), compared with trastuzumab, together with a 40% reduction in the hazard rate of distant recurrences (phase 3 trial, KATHERINE) [9].

Besides T-DM1, trastuzumab deruxtecan (T-DXd), and sacituzumab govitecan (SG) have been FDA-approved for the treatment of BC [4]. T-DXd is composed of the anti-HER2 mAb trastuzumab and a cleavable tetrapeptide-based linker. The payload, an exatecan derivative, is a topoisomerase I inhibitor, with a DAR of 8:1 [10]. In December 2020, T-DXd (5.4 mg/kg) was granted accelerated approval by the FDA for patients with advanced or metastatic HER2-positive BC after at least two prior anti-HER2-based regimens, based on the efficacy results documented by the open-label phase 2 DESTINY-Breast01 clinical trial [11]. The primary endpoint was met, with an ORR of 61.4% and a median progression-free survival (mPFS) of 19.4 months, in a heavily pretreated patient population (median of 6 prior therapies for metastatic disease, including T-DM1) [11]. Importantly, 28 patients (15.2%) developed interstitial lung disease (ILD, grade 1, 3.2%; grade 2, 8.8%; grade 3, 0.5%; grade 5, 2.7%) [11]. The efficacy of T-DXd was later confirmed by the results of the phase 3 clinical trials DESTINY-Breast02 and DESTINY-Breast03, the latter paving the way for the indication of T-DXd (5.4 mg/kg) in second treatment line (Table 1) [3]. Indeed, T-DXd and T-DM1 underwent head-to-head comparison in 524 patients diagnosed with metastatic BC and previously treated with a taxane and trastuzumab [12]. The study met its primary endpoint, with an improved mPFS (not reached vs. 6.8 months; HR, 0.28) with the administration of T-DXd, compared to T-DM1 [12]. An almost doubled ORR was observed (79.7% vs. 34.2%), with a favorable trend for improved 12-month OS (94.1% vs. 85.9%; HR, 0.56) [12]. A recent updated analysis confirmed the positive report on mPFS for T-DXd (28.8 vs. 6.8 months, HR 0.33), as well as on mOS (not reached in either group, HR 0.64). The safety profile was consistent with previous reports, except for an encouraging lower rate of ILD in the phase 3 trial, which occurred in 15% of patients receiving T-DXd, compared with 3% of the participants receiving T-DM1 [12, 13]. As activity of T-DXd was detected even among 54 patients who had HER2-low BC (i.e., either a score of 1+ on immunohistochemical analysis or a score of 2+ with negative results on *in situ* hybridization), with an ORR of 37% and a mPFS of 11.1 months [12], DESTINY-Breast04 clinical trial has been designed to specifically investigate T-DXd in this patient population. Of note, the results of the phase 3 DESTINY-Breast04 were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2022, confirming favorable early results and allowing for regulatory approval on August 5, 2022 (Table 1) [14]. This study compared T-DXd with treatment of physician's choice (TPC) in patients with HER2-low mBC pretreated with endocrine treatment (if hormone receptor positive, HR-positive) and 1 to 2 lines of chemotherapy (n = 557) [14]. T-DXd (n = 331) demonstrated an improvement in PFS over chemotherapy (n = 163) among 494 randomized HR-positive patients (primary endpoint, 10.1 vs. 5.4 months, HR 0.51, $p < 0.001$), as well as in the overall study population (9.9 vs. 5.1 months, HR 0.50, $p < 0.001$) [14]. Median OS was also improved among HR-positive patients (23.9 vs. 17.5 months, HR 0.64, $p = 0.003$) and in the overall population (23.4 vs. 16.8 months, HR 0.64, $p = 0.001$) [14]. The ORR with T-DXd was 52.6% in the HR-positive subgroup, compared with 16.3% in the control arm. Results were consistent in an exploratory analysis restricted to triple-negative breast cancer (TNBC) patients (n = 58), with improved ORR (50% vs 16.7%), PFS (8.5 vs 2.9 months, HR 0.46) and mOS (18.2 vs 8.3 months, HR 0.48) [14]. Based on such positive results, DESTINY-Breast06 was conceived, and it is currently ongoing (NCT04494425). Several other anti-HER2 ADCs (e.g., RC48, B003, ALT-P7, BAT8001, FS-1502) are currently under evaluation for the treatment of BC in different settings. Updated results are awaited.

1.2.2. TROP-2 targeting agents

SG is an ADC built with an anti-TROP2 mAb linked, by means of a cleavable linker, to the cytotoxic agent SN-38, which is the active membrane-permeable metabolite of the topoisomerase I inhibitor irinotecan (DAR, 7.6–8:1) [4]. In April 2021, the FDA granted approval to SG (10 mg/kg) in patients with metastatic TNBC who had received ≥2 prior systemic therapies (with at least one in the metastatic setting), based on positive results of the confirmatory phase 3 ASCENT clinical trial) [15]. ASCENT compared the efficacy of SG to that of TPC in 468 patients with relapsed or refractory, metastatic TNBC after ≥2 prior regimens. SG determined an ORR of 35% (vs. 5% in the TPC arm), a longer mPFS (primary endpoint; 5.6 vs. 1.7 months; HR, 0.41) and longer mOS (12.1 vs. 6.7 months; HR, 0.48). Notably, no pre-specified biomarker selection had been performed for enrolment, as TROP-2 expression was only assessed for correlative analyses [16]. With such limitations taken into account, improved efficacy was observed in TROP-2-high and TROP-2-median BC patients treated with the experimental compound, in comparison with TPC [16]. The most common grade ≥3 treatment-related AEs with SG were neutropenia (51%), leukopenia (10%), diarrhea (10%), anemia (8%), and febrile neutropenia (6%) [15]. For HR-positive HER2-negative advanced BC, SG significantly reduced the risk of disease progression by 34% over TPC, based on the results of the phase III TROPiCS-02 trial [17]. This clinical trial included 543 patients who received a median of three prior chemotherapy regimens in the metastatic setting and reported an improved PFS (5.5 versus 4.0 months, HR, 0.66, 95% CI 0.53–0.83), with a nonsignificant trend towards improved OS (13.9 versus 12.3 months; HR 0.84) [17]. Consistently, on February 3, 2023, the FDA approved SG for patients with unresectable locally advanced or metastatic HR-positive, HER2-negative BC who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting (Table 1).

Another promising ADC targeting TROP2 is datopotamab deruxtecan (Dato-DXd), that is constituted of humanized TROP-2-directed mAb, a tetrapeptide-based linker and a topoisomerase 1 inhibitor warhead [4]. The open-label first-in-human phase 1 basket trial TROPION-PanTumor01 is investigating the ADC, in patients with advanced solid tumors [4]. For the cohort of TNBC patients, an ORR of 43% was highlighted, with a disease control rate of 95% among 21 highly pretreated patients [18]. As 30% of the patients in this study had received prior treatment with topoisomerase 1 inhibitor-based ADCs and, consequently, cross-resistance is possible, the subgroup of patients not previously treated with one of these agents was analyzed. For that subset of 27 patients with TNBC, after a median follow-up of 8.8 months, the ORR was 52%, including 13 patients (48%) with confirmed complete or partial responses. Nine patients (33%) had stable disease, yielding a disease control rate of 81% [18]. In the HR-positive HER2-negative cohort, as of April 29, 2022, 41 heavily pretreated patients (median of 5 prior regimens for the advanced setting, range: 3–10; almost 95% of patients treated with prior cyclin-dependent kinase 4/6 inhibitor) received Dato-DXd, with 9 patients undergoing treatment at the data cutoff [19]. The ORR was 29%, with a disease control rate (DCR) of 85% (35/41), and a clinical benefit rate (CBR) of 41% (17/41). The safety profile included treatment-emergent adverse events (TEAEs) in 98% (any grade) and 41% (grade ≥3) of cases, with thew most common events being stomatitis (any, 80%; grade ≥3, 10%), nausea (any, 56%; grade ≥3, 0%), fatigue (any, 46%; grade ≥3, 2%), and alopecia (any, 37%; grade ≥3, 0%) [19].

In this context, BC not only has played a major role in ADC development, but it is currently boosting further research efforts aiming at describing novel target Ags for ADCs. For these reasons, here we

describe the landscape of emergent and future potential target Ags, currently under investigation in BC. Predominant target expression, function, preclinical rationale, potential clinical implication, as well as preliminary clinical trial results are provided.

2. Potential targets for antibody-drug conjugates in breast cancer

The majority of ADCs recognize tumor cell surface Ags [20]. An ideal target should be homogeneously expressed on tumor cells, thus, in theory, letting the ADC spare healthy tissues. Besides, a good target should promptly trigger the internalization of the ADC. Certainly, this is a dynamic process, so the size, location and type of vesicles containing the ADC, once it has been internalized, contribute to the interconnected nature of the anti-cancer response. Other potential contributions may come from the specific function of the Ag, together with the downstream cellular changes induced by the ADC binding to the target. As a matter of fact, the amount of Ag expressed may change in response to treatment and the rate of internalization of an ADC may be influenced by other factors, either on the tumor cell or in the tumor microenvironment (TME) [4,20].

2.1. Nectin cell adhesion molecule 4

Nectin cell adhesion molecule 4 (Nectin-4) is a cell adhesion molecule that regulates diverse events mediated by cell adhesion, cell migration, proliferation, differentiation, and survival [21]. Among the well-known molecular interaction of nectin-4, the most investigated are those with the platelet-derived growth factor receptor, the fibroblast growth factor receptor, the vascular endothelial growth factor receptor, the prolactin receptor, ErbB3, ErbB4, and integrins [4]. Nectin-4 is upregulated in various neoplasms, such as breast, lung, ovarian, pancreatic, gallbladder, and gastric cancer, promoting cell proliferation and metastasis via phosphatidylinositol 3-kinase (PI3K)-Akt and Wnt-β-catenin and Rac small G protein pathways [21].

In this light, enfortumab vedotin (EV), an ADC conjugated to monomethyl auristatin E, an anti-microtubule agent, via a protease cleavable linker has been the first anti-nectin4 ADC ever investigated. Originally, EV was granted accelerated approval by FDA in 2019, specifically for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC), who either received both platinum-based chemotherapy and an immune checkpoint inhibitor (Programmed death-1, PD-1/Programmed death-ligand 1, PD-L1) or who were ineligible for cisplatin-containing chemotherapy, based on the efficacy data from the phase 2 clinical trial EV-201 [22]. Then, regular FDA approval has been granted based on the confirmatory positive results of the phase 3 clinical trial EV-301 [23]. The safety profile showed 51.4% of patients in the experimental arm experiencing grade ≥3 treatment-related AEs, with the most frequent being early-onset maculopapular rash (7.4%), fatigue (6.4%), and decreased neutrophil count (6.1%) [23].

In TNBC and, more broadly, basal-like subtypes, high nectin-4 mRNA expression has been described as an independent negative prognostic factor for metastasis-free survival [24]. In a recent analysis, membranous protein expression has been found in 62% of TNBCs for which immunohistochemistry (IHC) was available (n = 61), with strong correlation with mRNA expression [24]. *In vitro* analyses have shown that a nectin-4-targeted ADC not only binds with high affinity and specificity to its target, but it is also able to induce its internalization, as well as dose-dependent cytotoxicity on nectin-4-expressing BC cell lines [24]. *In vivo*, rapid, complete, and durable responses on nectin-4-positive xenograft TNBC samples (including primary tumors, metastases, and local relapses) have been detected [24]. Therefore, in a histology-agnostic perspective, a phase 2 basket trial EV-202 (NCT04225117) aims at investigating the activity of EV across multiple neoplasms that are known for their high expression of nectin-4, including BC, as shown in Table 2. The estimated primary completion date is in April 2024.

2.2. Tissue factor

Besides its well-known role in hemostasis, the transmembrane protein Tissue Factor (TF), also known as thromboplastin or CD142, has been observed to play a role in several physiological and pathological processes, including cancer, potentially favoring metastatization [25]. Tumor progression may be facilitated especially by exploiting TF procoagulant activity and protease-activated receptor-2 (PAR-2) signaling. TF expression has been found across various tissues and neoplasms, including ovarian, prostate, bladder, esophageal, breast, endometrial, and lung cancer.

Tisotumab vedotin (TV) is an ADC composed of an anti-TF mAb conjugated to the tubulin inhibitor monomethyl auristatin E, via a protease cleavable linker. Besides direct cytotoxicity, its anticancer activity is hypothesized to be due to Ab-dependent cellular phagocytosis, Ab-dependent cellular cytotoxicity (ADCC) and immunogenic cell death (ICD), possibly contributing to triggering an immune response against cancer. In September 2021, TV was granted accelerated approval based on the results of the phase 2 innovaTV-204 clinical trial, which investigated the compound in women with previously treated recurrent or metastatic cervical cancer (n = 101) [26]. The clinical trial showed an ORR (primary endpoint) of 24% (95% CI, 15.9–33.3) with a mPFS of 4.2 months (95% CI 3.0–4.4) and mOS of 12.1 months (95% CI 9.6–13.9) [26]. Grade ≥3 AEs occurred in 28% of cases, the most common being neutropenia (3%), fatigue (2%), ulcerative keratitis (2%), and peripheral neuropathy (2%). In a tumor agnostic perspective, anti-TF ADCs have been explored across different histologies, including BC. Indeed, XB002, an ADC composed of an anti-TF mAb conjugated to the tubulin inhibitor monomethyl auristatin E, via a protease cleavable linker, is currently under investigation in a phase 1 basket trial, either alone or in combination with the immune checkpoint inhibitor nivolumab (NCT04925284, Table 2). The estimated primary completion date is in June 2024.

2.3. Mesothelin

Mesothelin is a glycosylphosphatidylinositol-anchored cell surface protein, potentially involved in cell adhesion [27]. Although mesothelin expression is restricted to mesothelial cells of the pleura, including pericardium, peritoneum, cornea, and conjunctiva, mesothelin overexpression can occur in up to 30% of all cancers [27,28]. Increased mesothelin expression has also been associated with poor overall survival in patients with lung and BC, possibly because aberrant mesothelin expression plays a relevant role in promoting metastatization [27,29,30]. Although the development of anti-mesothelin ADCs is currently focused on ovarian cancer, mesothelioma, non-small cell lung cancer (NSCLC), pancreatic and gastric cancer, ongoing trials are including BC as well. For example, anetumab ravtansine (AR) is an ADC constituted by an anti-mesothelin mAb conjugated to the maytansinoid DM4 (microtuble inhibitor), via a reducible glutathione-based linker. Though displaying a manageable safety profile, AR did not perform better than vinorelbine in a randomized, open-label phase 2 trial, including patients with pre-treated advanced mesothelioma [31]. Another mesothelin-targeted ADC is RC88, which is composed of a microtuble-distrupting payload (MMAE), via a cleavable linker [32]. Currently, two phase 1/2 basket trials are investigating the activity of AR and RC88, respectively, in solid tumors, including advanced TNBC. The estimated primary completion date is in December 2023 (NCT04175847, Table 2).

2.4. LIV-1

LIV-1 belongs to the family of transmembrane zinc transporter proteins [33]. In healthy tissues, LIV-1 family expression is heterogeneous [33]. LIV1 is typically found in hormonally regulated tissues, such as breast, where its expression seems to be sensitive to estrogen levels [34].

Table 2
Ongoing clinical trials investigating novel potential targets (i.e., other than HER2 and TROP-2) for antibody-drug conjugates in breast cancer.

Antigen	Trial Name and Identifier	Ph	Setting	Drug(s)	Sample Size (estimated for ongoing trials)	Primary Endpoint(s)	Organ
Mesothelin	ARCS-Multi (NCT03102320, **Recruitment completed**)	1	Mesothelin Expressing Advanced or Recurrent Malignancies	Anetumab Ravtansine alone or + CDDP (if cholangiocarcinoma) or + gemcitabine (if pancreatic adenocarcinoma)	173	MTD, ORR, durable disease control	Basket trial (solid tumors)
	NCT04175847, **Recruiting**	1	Locally advanced or metastatic mesothelin-positive solid tumors	RC88	31	MTD, AEs	Basket trial (solid tumors)
Tissue Factor	NCT04925284, **Recruiting**	1	Locally advanced or metastatic solid tumors	XB002 alone or + Nivolumab	451	MTD, ORR	Basket trial (solid tumors)
Nectin-4	EV-202 (NCT04225117, **Recruiting**)	2	Treatment refractory advanced solid tumors	Enfortumab vedotin	280	ORR	Basket trial (solid tumors)
cMet	NCT03859752, **Active, not recruiting**	1	Unspecified adult solid tumors that express c-Met and have progressed/intolerant to all available therapies	TR1801-ADC	40	Safety, MTD	Basket trial (solid tumors)
	NCT04617314, **Recruiting**	1	Unspecified adult solid tumors that express c-Met and have progressed/intolerant to all available therapies	RC108	32	Safety, MTD	Basket trial (solid tumors)
LIV-1	NCT04032704, **Recruiting**	2	Unresectable Locally Advanced or Metastatic Refractory Solid Tumors	SGN-LIV1A (Ladiratuzumab Vedotin) alone or + Trastuzumab	264	ORR or PSA RR (cohort 7 only)	Basket trial (solid tumors)
	NCT01969643, **Recruiting**	1	Locally advanced or metastatic breast cancer	SGN-LIV1A (Ladiratuzumab Vedotin) alone or + Trastuzumab	448	AEs, DLT	Breast
	NCT03310957, **Recruiting**	1–2	Metastatic or locally-advanced TNBC	SGN-LIV1A (Ladiratuzumab Vedotin) + Pembrolizumab	211	ORR, AEs, DLT	Breast
5T4	NCT04202705, **Recruiting**	1	Patient with histologically - confirmed, locally advanced or metastatic cancer who has progressed on standard therapy	SYD1875	31	DLTs	Basket trial (solid tumors)
	NCT04410224, **Recruiting**	1	Advanced malignant solid tumor	ASN004	43	MTD	Basket trial (solid tumors)
FRα	NCT04300556, **Recruiting**	1–2	Metastatic, platinum-resistant disease (TNBC, endometrial, ovarian or NSCLC)	MORAb-202 (Farletuzumab ecteribulin)	196	RP2D, ORR, DLTs, AEs	Breast, endometrium, ovary, lung
ROR1	NCT04441099, **Recruiting**	1–2	Locally advanced or metastatic solid malignant tumor	NBE-002	100	RP2D, ORR	Basket trial (solid tumors)
ROR2	NCT03504488, **Recruiting**	1–2	Locally advanced unresectable or metastatic solid tumor and have failed all available standard of care (SoC) therapy	BA3021/CAB-ROR2-ADC alone or + PD-1 inhibitor	420	MTD, AEs, ORR	Basket trial (solid tumors)
B7–H3	NCT03729596, **Recruiting**	1–2	Locally advanced or metastatic solid tumors for whom no therapy with demonstrated clinical benefit is available	MGC018 alone or + Retinfalimab	182	AEs, MTD	Basket trial (solid tumors)
B7–H4	NCT05194072, **Recruiting**	1	Locally advanced unresectable or metastatic solid tumor	SGN-B7H4V	355	AEs, DLT	Breast, ovarian, uterus, lung, gallbladder
	NCT05123482, **Recruiting**	1–2	Metastatic or locally advanced/recurrent breast cancer, ovarian cancer, CCA or endometrial cancer	AZD8205	198	AEs, SAEs, DLT	Breast, ovarian, cholangiocarcinoma, endometrium
CEACAM5	NCT04659603, **Recruiting**	2	Metastatic, refractory, CAECAM-5 expressing breast or pancreatic cancer	SAR408701 (Tusamitamab ravtansine)	64	ORR	Breast, pancreas
	NCT02187848, **active, not recruiting**	1–2	Locally advanced or metastatic solid malignant tumor disease for which no standard alternative therapy is available	SAR408701 (Tusamitamab ravtansine)	263	DLTs, ORR	Basket trial (solid tumors)
HER3	NCT04965766, **Recruiting**	2	HER3-pos, HER2-neg, unresectable locally advanced or metastatic breast cancer that HRc- pos is at the time of the first diagnosis	U3-1402 (Patritumab Deruxtecan)	100	ORR	Breast
	NCT04610528, **Recruiting**	1	HR-pos and HER2-neg tumor with non-metastatic primary invasive breast cancer untreated and recently diagnosed	U3-1402 (Patritumab Deruxtecan)	80	CelTIL score	Breast

(*continued on next page*)

Table 2 (*continued*)

Antigen	Trial Name and Identifier	Ph	Setting	Drug(s)	Sample Size (estimated for ongoing trials)	Primary Endpoint(s)	Organ
	NCT04699630, **Recruiting**	2	Locally advanced or metastatic HR-pos/HER2-neg and TNBC	U3-1402 (Patritumab Deruxtecan)	120	ORR, PFS-6	Breast
	NCT02980341, **Active, not recruiting**	1–2	Refractory, advanced/unresectable metastatic breast cancer	U3-1402 (Patritumab Deruxtecan)	184	AEs, anti-tumor response	Breast
STING	NCT05070247, **Recruiting**	1	Locally advanced or metastatic solid tumors	TAK-500 alone or + Pembrolizumab	106	AEs, DLT	Breast, gastroesophageal, pancreas, liver, lung, head and neck
FOLR1; PSMA	NCT04928612, **Active, not recruiting**	1	Locally advanced or metastatic solid tumors	CBP-1018	170	AEs, RP2D, ORR	Basket trial (solid tumors)
Globo H (globohexaosylceramide)	NTC04084366, **Recruiting**	1	Locally advanced or metastatic high Globo H expressing solid tumors (H-score ≥100)	OBI-999	NA	NA	Basket (solid tumors)
KAAG1	NCT04972981, **Recruiting**	1	Locally advanced or metastatic solid tumors	ADCT-901	76	AEs, DLT	Breast, ovary, prostate, kidney, cholangiocarcinoma
CD205/Ly75	NCT04064359, **Recruiting**	1	Metastatic CD205+ve solid tumors who progressed on standard therapy	OBT076	70	AEs, DLT	Basket trial (solid tumors)

Abbreviations: Ab, antibody; ADC, antibody-drug conjugate; AEs, adverse events; B7–H3, B7 homolog 3; B7–H4, B7 homolog 4; CD, cluster of differentiation; CDDP, cisplatin; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; CelTIL, tumor cellularity and TILs; DLT, dose-limiting toxicity; FOLR1, Folate receptor 1; FRα, Folate receptor alpha; Globo-H, globohexaosylceramide H; HER2, human epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; KAAG1, kidney associated antigen 1; Ly75, Lymphocyte Antigen 75; MTD, maximum tolerated dose; NA, not applicable; Nectin-4, Nectin cell adhesion molecule 4; ORR, objective response rate; PD-1, programmed cell death protein 1; PFS, progression-free survival; Ph, phase; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; ROR1, receptor tyrosine kinase-like orphan receptor 1; ROR2, receptor tyrosine kinase-like orphan receptor 2; RP2D, recommended phase 2 dose.RR, response rate; SAE, severe adverse event; STING, Stimulator of interferon genes; TILs, tumor-infiltrating lymphocytes.

Indeed, LIV1 was firstly identified as an estrogen-induced gene in BC cell lines; then, it was associated with node involvement in HR-positive BC [34]. In this light, ladiratuzumab vedotin (LV or SGN-LIV1A) is an anti-LIV1 humanized mAb with a MMAE warhead, coupled by means of a cleavable linker [1]. This compound binds to the extracellular domain of LIV1 and, after internalization, is trafficked to lysosomes where the cytotoxic payload is released by proteolysis [35]. Cancer cells apoptosis is achieved via inhibition of microtubulin polymerization [35]. In TNBC, SGN-LIV1A may induce an effective ICD, potentially improving the benefit from immunotherapy, according to preclinical models [1,36]. SGN-LIV1A is currently investigated in a phase 1 clinical trial for patients with LIV1-positive metastatic HR-positive/HER2-negative and triple-negative BC (NCT01969643, Table 1) [37]. At the first data collection, the ORR was 32%, with a mPFS of 11.3 weeks in patients with TNBC treated in the combined dose-escalation and expansion cohorts (n = 44) [38]. In terms of safety, the most common all-grade AEs were fatigue (59%), nausea (51%), peripheral neuropathy (44%), alopecia (36%), decreased appetite (33%), constipation (30%), neutropenia (25%), diarrhea (25%) and abdominal pain (25%) [37,39]. As for grade ≥3 AEs, the most frequent were represented by neutropenia (25%) and anemia (15%) [37]. In early-stage BC, LV was one of the neoadjuvant treatments planned in the I-SPY2 trial (NCT01042379) and it was administered every 3 weeks for four cycles before doxorubicin/cyclophosphamide (AC) regimen, given every 2–3 weeks for four cycles [39]. Unfortunately, the experimental drug did not improve pathologic complete response (pCR) rates compared to the control arm [39]. The combination of SGN-LIV1A and immunotherapy has been explored, with two ongoing clinical trials: a combination treatment of ADC plus pembrolizumab as first-line treatment for metastatic TNBC (SGNLVA-002, KY-721, NCT03310957) and the ADC plus atezolizumab as second-line treatment (one arm of the Morpheus-TNBC, NCT03424005) [39]. In KY-721, among patients who were assessed for efficacy, the ORR was 54% (n = 26) [1]. The toxicity profile was manageable, with the most common grade ≥3 AEs represented by neutropenia (8%), diarrhea (8%), fatigue (8%), hypokalemia (8%) and maculopapular rash (8%) [1].

Specifically in BC, two ongoing phase 1/2 clinical trials are currently investigating LV, alone (SGNLVA-001, NCT01969643) or in combination with targeted treatments such as trastuzumab or immune checkpoint inhibitors (SGNLVA-002 NCT03310957), and final results are awaited (Table 2). SGNLVA-001 is an ongoing phase 1 clinical trial investigating the safety and tolerability of LV, either alone or in combination with trastuzumab, in patients with metastatic BC. The eligible population was made up of either patients with first- or second-line endocrine therapy refractory HR-positive/HER2-negative metastatic BC or patients with second-line treatment refractory TNBC [40]. Importantly, LIV-1 expression was not required for enrollment. Concerning preliminary results for patients with metastatic TNBC, ORR and disease control rate were 32% and 64%, respectively, with a mPFS of 11.3 weeks [40]. Most treatment-related AEs were grade 1 or 2, including fatigue (59%), nausea (51%), peripheral neuropathy (44%), and alopecia (36%) [40]. The updated results confirmed the promising activity of this agent, with an ORR of 28% for LV administered at a dose of 1.25 mg/kg in patients with second-line refractory metastatic TNBC [41]. The estimated primary completion date is in July 2022.

SGNLVA-002 is an ongoing global single-arm, open-label phase 1b/2 study of LV plus pembrolizumab as first-line therapy for patients with either unresectable locally advanced or metastatic TNBC. The primary endpoints are safety and ORR, with patients not being selected according to LIV-1 expression or PD-L1 status. In this clinical trial, LV has been delivered once every 3 weeks plus pembrolizumab and the combination has already demonstrated acceptable tolerability, with encouraging antitumor activity in patients with metastatic TNBC [42]. As a matter of fact, preliminary results showed an ORR of 35% among 66 patients, including 2 cases of complete response and 21 partial responses. Stable disease was achieved in 32 subjects. As for the safety profile, diarrhea,

nausea, fatigue, peripheral neuropathy, and neutropenia were the most commonly observed treatment-related toxicities. Additionally, interim results of weekly LV monotherapy at doses up to 1.5 mg/kg were clinically active and generally well tolerated [43]. Due to an unmet medical need for patients with metastatic TNBC who are PD-L1 low or negative, Part D will specifically focus on this patient population and immunotherapy-naïve patients with a PD-L1 combined positive score <10. Safety, tolerability and ORR are the primary endpoints [44]. The estimated primary completion date is in April 2023.

2.5. Receptor tyrosine kinase-like orphan receptor 1 and 2

Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is implicated in the neuronal growth that takes place in the central nervous system (CNS). Although ROR1 is limitedly expressed in healthy adult tissues, it is highly and uniformly expressed in both hematologic malignancies and solid tumors, including TNBC (~22%), with associated poor prognosis [45]. Specifically, ROR1 expression appears increased in TNBC as compared to other BC subtypes [46].

Moreover, ROR1 expression seems to correlate with signature genes in TNBC, like cancer stem cell phenotype and Transforming Growth Factor-β (TGFβ)/suppressor of mothers against decapentaplegic (SMAD) pathway [46]. Recently, a potential crosstalk between WNT5A/ROR1 and TGFβ/SMAD pathways has been described [46]. Indeed, WNT5a promotes SMAD2/3 activation in a ROR1-and TGFβR1-dependent manner [46]. Furthermore, WNT5a/ROR1 signaling may have a role in progression of TNBC, through potentiation of the TGFβ/SMAD/SNAI1/2 pathway, thus promoting epithelial mesenchymal transition (EMT) and stem-like phenotype [46]. Because inhibiting ROR1 shifts cancer stem cells of TNBC to a more luminal-like phenotype, anti-ROR1 agents have been developed and are currently under investigation, including ADCs [46]. In this regard, NBE-002 is an ADC targeting ROR1, obtained by site-specific, enzymatic, conjugation of the anthracycline-derivative PNU-159682 to a humanized recombinant IgG1 monoclonal antibody (XBR1-402), via a non-cleavable linker [47]. Direct anti-tumor activity of NBE-002 was evaluated in immunodeficient, ROR1 expression-low/-intermediate/-high patient-derived xenograft (PDX) models of several carcinoma and sarcoma subtypes [47]. The most pronounced anti-tumor effect was achieved in TNBC, at doses as low as 0.033 mg/kg, suggesting a best-in-class therapeutic index, also considering the high tolerability in preclinical toxicology models. Administration in a fully immune competent setting (EMT6/ROR1 orthotopic BC model) led to a strong anti-tumor response and a long-lasting anti-tumor immune protection [47]. Currently, NBE-002 is being investigated in a first-in-human, open-label, multi-center, phase 1/2 clinical trial in adult patients with advanced solid tumors (NCT04441099, Table 2). NBE-002 is given intravenously once every three weeks until disease progression, unacceptable toxicity or withdrawal of consent. Phase 1 dose escalation started on 17 July 2020, while phase 2 is planned for early 2023. The latter is planned to include two parallel expansion cohorts, enrolling patients with advanced TNBC (Cohort 1) or other solid tumors (Cohort 2) [47].The estimated primary completion date is in June 2025.

Although receptor tyrosine kinase-like orphan receptor 2 (ROR2) has been historically considered involved in bone and cartilage growth, it has recently been described as an active player in BC carcinogenesis, mainly via a WNT11/ROR2 signaling pathway [48]. This pathway comprises 19 secreted WNT ligands that can interact with ten different Frizzled (FZD) receptors and various co-receptors [48]. WNT ligands activate different intracellular signaling cascades, depending on the specific combination of locally available ligands, receptors and co-receptors [48]. Binding of a canonical WNT ligand to a FZD receptor and lipoprotein receptor-related proteins (LRP)5/6 co-receptor activates a β-catenin-dependent, canonical signaling which results in the expression of WNT-responsive target genes [48]. Other WNT ligands such as WNT5a/b, or WNT11 can bind FZDs and alternative co-receptors, such as ROR2, and trigger a multitude of β-catenin-dependent, non-canonical WNT signaling cascades [48]. Active non-canonical WNT signaling has been linked to the aggressive behavior of basal-like BCs [48]. In contrast to ROR1, ROR2 was not only found to be highly expressed in basal-like BCs, but in 87% of all BCs, and high levels were associated with shorter OS [48]. Apart from primary tumor tissue, elevated levels of ROR2 are detectable in lymph node and brain metastases, suggesting its involvement in tumor progression and metastatization [49]. In this context, BA3021, a conditionally active biologic (CAB) ROR2-targeted ADC is currently under investigation in a phase 1/2 basket clinical trial, enrolling patients with TNBC. After the completion the phase 1, a phase 2 study will assess safety and activity of BA3021 alone or in combination with an anti-PD-1 inhibitor. The estimated primary completion date is in March 2023 (NCT03504488, Table 2).

2.6. Human epidermal growth factor receptor 3

Human epidermal growth factor receptor 3 (HER3) is a member of the HER family characterized by weak tyrosine kinase activity. To transduce signals downstream, HER3 has to heterodimerize. In this context, HER2 is the most important partner for dimerization [50]. Other high affinity ligands of HER3 are represented by neuregulins (NRG-1 and NRG-2) [51]. A wide variety of cancer histologies overexpress HER3, such as head and neck carcinoma, colorectal cancer, bladder, melanoma, lung, ovarian, prostate and BC [52]. HER3 is believed to be involved in resistance to targeted therapies, not only those against other receptors of the HER family, but also hormonal agents and PI3K-inhibitors [1]. Finally, some oncogenic potential has also been shown by *ERBB3* somatic mutations [53]. In this framework, patritumab deruxtecan is a novel anti-HER3 ADC that is composed by the humanized mAb patritumab and deruxtecan. The mAb is linked to the payload via a peptide-based cleavable linker, with a DAR of 8 [1]. This experimental compound has been investigated in a phase 1/2 multicenter, open-label, first-in-human clinical trial enrolling heavily pretreated patients with HER3-positive metastatic BC (n = 182, NCT02980341, Table 2) [54]. Patients harboring HER3-high/HR-positive/HER2-negative neoplasms were enrolled in two cohorts to receive the drug at a dose of 4.8 mg/kg or 6.4 mg/kg. In contrast, HER3-low/HR-positive/HER2-negative metastatic BC patients as well as HER3-high metastatic TNBC patients received 6.4 mg/kg of the ADC. At the data cutoff, drug activity was evaluable in 64 patients with HER3-high/HR-positive/HER2-negative metastatic BC. In this group, the ORR was 30% and 13% for patients treated with 6.4 and 4.8 mg/kg, respectively. Among the 31 patients with HER3-low/HR-positive/HER2-negative metastatic BC and the 31 patients with HER3-high metastatic TNBC, the ORR was 33 and 16%, respectively [54]. An updated analysis was presented at the ASCO annual meeting 2022 and revealed an ORR of 30.1% (95% CI, 21.8–39.4, n = 113) in the HER3-high&low/HR-positive/HER2-negative subgroup (all doses) [55]. HER3-high/TNBC and HER3-high/HER2-positive groups reached an ORR of 22.6% (95% CI, 12.3–36.2, n = 53) and 42.9% (95% CI, 17.7–71.1, n = 14), respectively (all doses) [55]. No complete responses were reported [55]. The safety profile documented 130 patients (71.4%) experiencing grade ≥3 treatment-related AEs. The most common AEs (≥15%) were decreased neutrophil count (39.6%), decreased platelet count (30.8%), anemia (18.7%), and decreased white blood cell count (18.1%). Treatment-related ILD was observed in 12 patients (6.6%), including 1 fatal event [55].

2.7. Globohexaosylceramide

Globohexaosylceramide (Globo-H) is a tumor-associated carbohydrate antigen that is overexpressed in a variety of epithelial cancer cell types, including human pancreatic, gastric, lung, colorectal, esophageal, and BC [56]. In BC, Globo-H has been extensively investigated and adopted to develop therapeutic cancer vaccines, with promising results [56,57]. In this context, the novel ADC OBI-999, that is composed of a humanized IgG1 mAb, which targets Globo-H, and conjugated with MMAE via a cleavable linker, is currently in early phase clinical

development. A first-in-human, phase 1, dose-escalation clinical trial has been conducted in patients with advanced solid neoplasms (NTC04084366, Table 2). OBI-999 was administered intravenously at doses of 0.4, 0.8, 1.2, and 1.6 mg/kg on Day 1 of a 21-day cycle. Overall, 15 adult patients were treated, with good tolerability at a dose up to 1.2 mg/kg. Treatment-related AEs were described in 40% (6/15) of patients. AEs ≥ Grade 3 occurred in 27% (4/15) of patients (neutropenia in 3 patients, anemia in 2 patients). Dose-dependent, non-cumulative neutropenia was dose limiting. A retrospective validated automated immunohistochemistry assessment indicated that 50% of patients with advanced solid tumors had high Globo-H staining (H-score cutoff ≥100). Five patients (33.3%) displayed stable disease, while no complete responses were collected. The dose expansion phase is currently ongoing, and it is enrolling patients with high Globo H expressing solid tumors (H-score ≥100). Primary study completion is estimated in 2023.

2.8. Folate receptor alpha

Folate receptor alpha (FRα) is a glycosylphosphatidylinositol (GPI)-linked membrane protein that binds to folic acids and mediates their intracellular transport [58,59]. This molecule is expressed in 70–86% of metastatic TNBC, in which is related to a poor prognosis, but it is generally not expressed in healthy tissues [59]. Conversely, a recent study highlighted a prevalence of FRα expression in ~71% of early TNBC samples being associated with improved disease-free survival (DFS) [56]. These findings led to the initiation of phase 2 clinical study investigating an FRα-directed peptide-based vaccine candidate in patients with high-risk, early TNBC (NCT03012100) [56]. Coherently, also FRα-directed ADCs are currently in early clinical development. MORAb-202 is an investigational ADC, composed of farletuzumab, a humanized IgG1 mAb that binds to the FRα, and the microtubule inhibitor eribulin as warhead, conjugated via a protease-cleavable linker. *In vitro* studies have been conducted on seven BC and nine NSCLC cell lines treated with MORAb-202, in order to elucidate FRα expression, cell proliferation, bystander killing effects, and apoptosis, with promising results [60]. Indeed, MORAb-202 was associated with inhibited cell proliferation, with specific selectivity toward FRα-expressing BC cell lines [60]. Eribulin, the payload of MORAb-202, was unleashed in HCC1954 cells, diffused into intercellular spaces, and then killed the non-FRα-expressing MCF7 cells in co-culture systems [60]. In orthotopic xenograft mouse models, FRα-expressing T47D and non-FRα-expressing MCF7 cell lines were suppressed upon MORAb-202 administration, showing promising anti-cancer effects in BC. On this basis, the investigational compound is currently in early drug development. Between November 2017 and June 2019, a first-in-human, phase 1 clinical trial investigated MORAb-202 in solid tumors, with safety and tolerability as primary endpoints [61]. A total of 22 patients were enrolled, and treatment-related AEs occurred in 21 (95%) patients, with leukopenia and neutropenia in 10 (45%) of patients. One patient (0.9 mg/kg cohort) experienced two grade 3 dose-limiting toxicities: serum alanine aminotransferase and γ-glutamyl transferase increased. Grade 1/2 ILD was identified in five (23%) patients. Complete response, partial response, and stable disease were observed in one, nine, and eight patients, respectively. Therefore, the drug is now investigated in a phase 1/2 clinical trial, which focuses on advanced ovarian, endometrial, NSCLC and TNBC (NCT04300556, Table 2). ORR is the primary study endpoint, and the estimated primary completion date is in March 2025.

2.9. B7 homolog 4 protein

B7 homolog 4 protein (B7–H4), a member of the CD28/B7 family of co-inhibitory immune checkpoint ligands, is a transmembrane protein that binds to an unknown receptor on activated T cells, inhibiting their function. It is highly expressed by a wide variety of tumors including cholangiocarcinoma (CCA) and breast, ovarian and endometrial cancers, and is associated with poor prognosis [62]. The relationship of tumor and stromal B7–H4 protein expression with PD-L1, tumor-infiltrating lymphocytes (TILs) and its association with clinicopathological variables are yet to be fully elucidated in BC [63]. However, recent findings highlighted that B7–H4 is highly expressed in both cancer cells and stromal cells in BC, irrespective of intrinsic subtypes. Moreover, B7–H4 expression seems to behave in a mutually exclusive pattern with respect to PD-L1 expression, although such findings need further validation [63]. On this basis, development of B7–H4-targeted ADCs began with SGN-B7H4V and AZD8205 as first-in-class compounds. SGN-B7H4V is composed of a fully human IgG1 anti-B7-H4 mAb conjugated to the microtubule disrupting agent MMAE via a protease-cleavable peptide linker. In *vitro*, upon binding to SGN-B7H4V, the immune checkpoint ligand B7–H4 is rapidly internalized and delivered the cytotoxic payload MMAE. Here, SGN-B7H4V kills B7–H4-expressing tumor cells by MMAE-mediated cytotoxicity, ADCC, and antibody-dependent cellular phagocytosis (ADCP). *In vivo*, SGN-B7H4V demonstrated strong anti-tumor activity in multiple xenograft BC models. Interestingly, activity was observed in models with both uniformly high and heterogeneous expression of B7–H4, consistent with robust bystander activity of vedotin-based ADCs [63,64]. Finally, SGN-B7H4V was tolerated in both rat and non-human primate toxicology studies at doses consistent with approved vedotin ADCs [64]. Hence, SGN-B7H4V is currently under investigation for safety and tolerability in a phase 1 clinical trial involving patients affected by advanced breast, ovarian, endometrial, lung and gallbladder neoplasms (NCT05194072, Table 2). The estimated primary completion date is in June 2025.

AZD8205 is an ADC composed by a human anti-B7-H4 mAb conjugated via a cleavable linker to a topoisomerase I inhibitor warhead. In preclinical studies, AZD8205 has shown favorable antitumor activity in various PDXs models and an acceptable toxicity profile [62]. In this context, a phase 1/2 open-label, dose-escalation and dose-expansion clinical trial is currently evaluating the safety and tolerability of AZD8205 for the treatment of selected advanced neoplasms, including BC, ovarian cancer, cholangiocarcinoma, and endometrial cancer (NCT05123482, Table 2). In the escalation phase, patients receive AZD8205 followed by 21 days of observation for dose-limiting toxicities. The estimated primary completion date is in May 2025.

3. Conclusion and future perspectives

Recent progress in ADC engineering and technology platforms has unlocked the development of new warheads as well as novel linkers, thus enabling new generations of ADCs. This means that future ADCs not only will be equipped with higher DARs but might also benefit from the conjugation with compounds that go beyond chemotherapeutical payloads. For example, early clinical trials are investigating radionuclide-conjugated ADCs, that aim to selectively deliver radioactive agents, like Yttrium-90 [10]. Another example is the possibility to conjugate ADCs with immune-stimulant molecules, potentially able to induce targeted antitumoral immune responses and/or to synergize with immune checkpoint inhibition. Remarkable progress is also impacting the conjugation manufacturing process, thus allowing for the conjugation of two distinct payloads to the same mAb (dual-payload ADCs). This strategy would perhaps be able to overcome Ag heterogeneity, as depicted by promising early results obtained in HER2-positive metastatic BC [65]. Finally, the conjugation of payloads to bispecific Abs promises to be able to inhibit multiple pathways as well as to modulate the interface between immune effector and cancer cells [10,66].

To effectively exploit such ongoing technological breakthrough, identifying optimal targets is becoming of utmost importance. Indeed, sparing healthy tissues while hitting cancer cells with local high doses of an anti-cancer drug can be achieved only if an Ag is homogeneously expressed only on cancer cells (Fig. 1).

Besides differential expression between neoplastic and healthy tissues, surface location as well as internalization triggering after

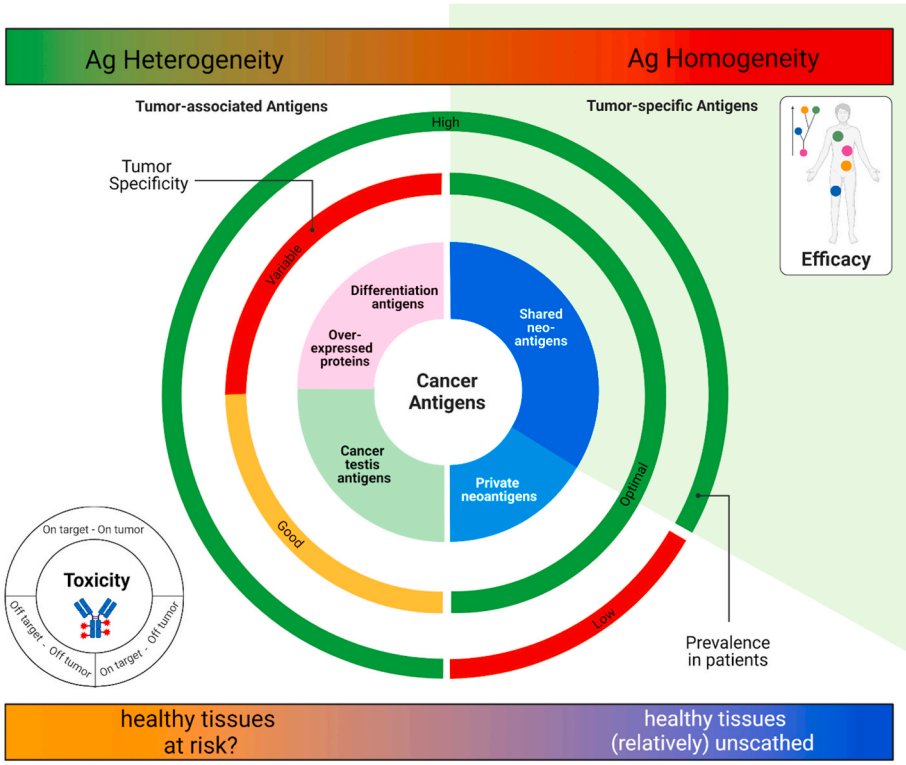

Fig. 1. Overview of the main characteristics of cancer antigens, optimized for antibody-drug conjugate development. The ideal target antigen should prompt ADC internalization upon interaction with the ligand. Besides, research efforts are focusing on finding cell surface Ags that show high expression on cancer cells, while displaying low or no expression on healthy tissues. Theoretically, such antigens would favor anti-cancer activity, while avoiding on-target off-tumor toxicities. Certainly, the complexity of ADC design and development goes far beyond seeking the ideal target. In fact, complex manufacturing issues related to linker stability, payload charge and membrane-permeability, as well as the overall interaction of the three core components are major issues to tackle. Abbreviations: Ag, antigen. Created with biorender.com (2023).

interaction with the ligand are required [1]. To identify and characterize promising candidate Ags, *in silico* strategies have been developed, involving RNA sequencing and protein-expression data to predict the most suitable Ag for targeting [67]. These strategies could inform the design of ADCs in the future, allowing the development of Ag maps of cancers and the identification of histologies most likely to benefit from particular conjugates. Finally, combinatorial strategies involving ADCs are being evaluated for the treatment of a wide variety of solid tumors, including BC, and will clarify the utility of this approach in the years to come.

In conclusion, the search for better target Ags, particularly for solid tumors, is ongoing, as well as an effort to develop better linkers and payloads for ADCs. Given the speed of progress in each of these areas, it is likely that new and active ADCs will continue to be developed and evaluated. However, "old" challenges may still threaten ADCs development, like patient selection and biomarker assessment. So, tackling these aspects should be prioritized in order to best exploit this promising drug class.

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