RESEARCH ARTICLE

Breast Cancer Treatment and Antibody Drug Conjugates: Beyond T-DM1

Authors

Mony Ung, Jean Louis Lacaze, Eleonora de Maio and Florence Dalenc

Affiliation

Medical oncology department, Institut Claudius Regaud, Institut Universitaire du Cancer de Toulouse-Oncopole, 31059 Toulouse, France

Correspondence
Mony Ung
Email: Ung.Mony@iuct-oncopole.fr

Abstract

Antibody–drug conjugates (ADCs) are a new class of anticancer agents that combine cytotoxic agents attached by a linker to a monoclonal antibody. These engineered drugs can selectively deliver a cytotoxic payload to targeted cancer cells and the local microenvironment (bystander effect), thereby increasing activity and reducing off-target toxicity. The association of ADCs with other anti-cancer therapies is therefore promising.

Trastuzumab-emtansine was the first approved ADC in breast cancer (BC), specifically for the management of human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer. New ADCs are in development in BC. Some have shown meaningful clinical benefit and have been recently approved, such as trastuzumab deruxtecan in HER2-positive trastuzumab emtansine (T-DM1) pretreated BC and Trop-2 guided sacituzumab govitecan in triple-negative BC. Trastuzumab deruxtecan also has potential clinical activity in HER2-low BC thanks to a bystander effect. In this article, we review the ADCs under development in advanced BC.

Keywords: antibody–drug conjugates, breast cancer, HER2-positive, HER2-low, triple-negative

Introduction

Breast cancer (BC) is the most common malignancy in women. Despite significant progress in terms of biology, diagnosis and therapeutics, it remains one of the major causes of cancer mortality worldwide.[1] The principles of treatment in a metastatic setting are based on combinations of chemotherapy with or without targeted therapy, or combinations of endocrine and targeted therapies for hormone receptor (HR)-positive tumors. However, the narrow therapeutic index of some combinations, particularly with chemotherapy, limits their benefit.

Antibody drug conjugates (ADC) are a new family of anti-cancer agents. They offer an attractive approach that resembles the "magic bullet" concept described by Paul Ehrlich by delivering a cytotoxic drug selectively to a tumor target, thus limiting “off target” toxicity.[2] The use of ADCs has become more widespread in recent years, particularly for the treatment of breast cancer. The three key components of an ADC are the monoclonal antibody (mab), the linker and the attached drug called the payload (Figure 1). The primary function of the mab is to bind selectively to a surface tumor antigen, ideally one that is not present on the surface of non-tumor cells in order to limit the off-target effect. The payload is a highly potent drug and ideally must be insensitive to efflux proteins in order to remain in the target cell. The drug-loading is expressed by the drug-to-antibody ratio (DAR). A higher DAR is not necessarily associated with greater efficacy, although a low DAR is less efficient.[3] Payloads currently under development belong to four major categories: antimitotic agents (monomethyl auristatin E (MMAE) and F (MMAF), microtubule inhibiting maytansinoids (DM1 and DM4), antibiotics inducing DNA breaks (calicheamicin and duocarmycin), and topo-isomerase 1 inhibitors (SN38 and derivatives). The linker connects the payload to the antibody and must be stable enough not to release the payload before the internalization of the ADC in the target cell.[4]

Fig 1

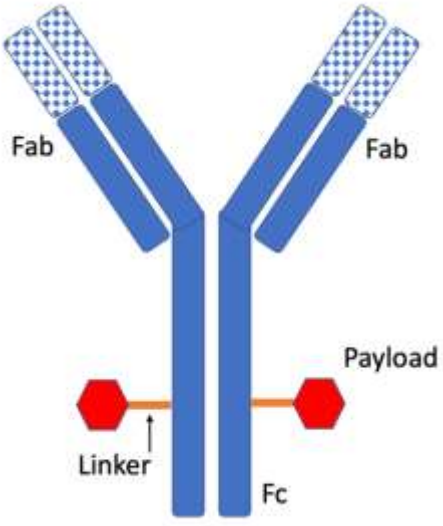

Figure 1: Structure of antibody-drug-conjugate
Fab: antigen-binding fragment
Fc: constant fragment

The ADC is administered by the venous route and binds to its membrane target. The complex is then internalized in the target cell by endocytosis. The endosome joins the lysosome where proteolytic enzymes degrade the antibody, and lysosomal acidic pH cleaves the linker, thereby releasing the payload into the cytoplasm (Figure 2). Ancillary mechanisms of action may potentially participate in the efficacy of some ADCs. Like some mabs, certain ADCs can also induce an antibody-dependent cellular

cytotoxicity (ADCC) phenomenon,[5] and complement-dependent cytotoxicity (CDC). In addition, a bystander effect is known to occur with some ADCs since they can cross the cell membrane of the payload. The heterogeneity of expression of the target antigen in the surrounding environment is overcome, leading to a local cytotoxic effect.[6] We review the clinical results ADCs that have led to their approval and discuss new ADCs under development in BC.

Fig 2

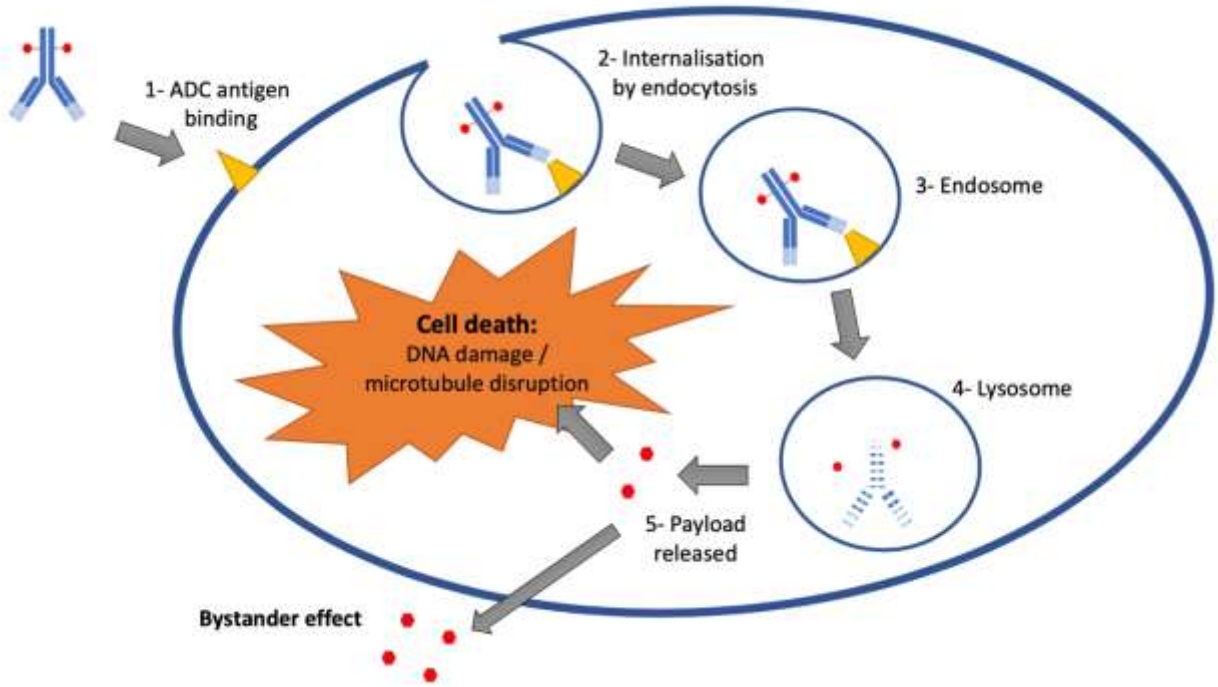

Figure 2: ADC mechanisms of action

ADCs APPROVED IN BREAST CANCER IN 2021

1. Ado-trastuzumab emtansine (T-DM1)

BC with membrane overexpression of human epidermal growth factor receptor 2 (HER2) or HER2 amplification represents about 20% of BCs and benefits from HER2-targeted therapies. The first ADC to gain approval in this setting was ado-trastuzumab emtansine, which consists of trastuzumab, a humanized mab targeting HER2, which is linked by a non-cleavable linker to a maytansinoid emtansine (DM1). The payload on each antibody (drug-to-antibody ratio (DAR) is approximately 3-4. Approval was obtained in 2013 following the results of the pivotal EMILIA study, which demonstrated a significant clinical benefit compared to capecitabine and lapatinib combination in terms of progression-free survival (PFS) and overall survival (OS).[7,8] The toxicity profile

was manageable with fatigue, diarrhea, hematologic toxicity and transaminase disturbances.

More recently, approval has been extended to early-stage BC in the event of absence of pathological complete response after neoadjuvant chemotherapy combined with trastuzumab plus pertuzumab or not following the results of the KATHERINE trial, with a reduced risk of recurrence compared to trastuzumab.[9] Nonetheless, T-DM1 does not have a disease-free survival or safety advantage over paclitaxel plus trastuzumab in the adjuvant setting for patients with stage 1 HER2-positive BC.[10]

2. Trastuzumab deruxtecan (DS- 8201a)

Trastuzumab deruxtecan is the second approved ADC in HER2-positive BC. It consists of trastuzumab, which is linked by a cleavable linker to a topoisomerase I inhibitor. The DAR is higher than for T-DM1, around 7-8. This higher DAR may partly explain its efficacy on T-DM1-resistant tumors, but also its higher bystander effect due to a higher payload membrane permeability. Clinical proof of concept was provided by the phase 2 DESTINY-Breast01 trial in 2019, with an overall response (OR) of 60.9% (95%CI, 53.4 to 68.0), and a median duration of PFS of 16.4 months (95% CI, 12.7 not reached) in a single arm of T-DM1 pre-exposed and heavily pretreated patients.[11] The toxicity profile was hematological, nausea, and most notably iatrogenic interstitial lung disease in 13.6% of the patients, so pulmonary symptoms require careful monitoring. The major results of this trial allowed approval of trastuzumab deruxtecan to be accelerated. Several phase III trials are ongoing or planned in advanced HER2-positive BC after failure of T-DM1 versus investigator treatment choice (NCT03523585), and versus T-DM1 in a second-line setting (NCT03529110).

Importantly ADCs could lead to novel concepts such as the expansion of potent anti-HER2 therapy to HER2-low BC. Indeed, HER2-low BC, which were previously known as HER2-negative, are defined by HER2 immunohistochemistry 1+ or 2+ without amplification of HER2 oncogene by in situ hybridization. They represent 40 to 50% of BC and are a heterogeneous population including both hormone receptor (HR)-positive and HR-negative tumors.[12] In this population, subgroup results with T-DM1 showed a lower efficacy rate than in HER2-positive patients.[13,14] The lower presence of HER2 protein on the cell membrane suggests the potential efficacy of trastuzumab deruxtecan, notably thanks to a bystander effect demonstrated with the molecule.[6] In a cohort of HER2 low BC in a phase Ib trial treated with trastuzumab deruxtecan, OR was 37% and median duration of response was 10.4 months.[15] Phase III trials are ongoing or planned in HER2 low advanced BC (NCT03734029, NCT04494425). A French phase II trial is currently being conducted in different cohorts (HER2-positive, HER2-low and HER2-negative) with biomarker analysis (NCT04132960).

3. Sacituzumab govitecan

This ADC is composed of an anti-trophoblast cell-surface (Trop-2) antibody conjugated with the topo-isomerase 1 inhibitor SN38 (active metabolite of irinotecan) by a cleavable linker, with an average DAR of 7.6. Trop-2 is a membrane glycoprotein originally described in trophoblastic cells and involved

in cell migration and anchorage-independent growth. Its expression in BC is associated with poor prognosis,[16] and it is highly expressed in many epithelial cancers, notably in 90% of triple-negative BC (TNBC) tumors.[17] The first efficacy data in TNBC came from a phase I-II trial in patients with TNBC who had received at least two prior therapies. Objective response was 33.3%, median PFS was 5.5 months, and median OS was 13.0 months.[17] The toxicity profile was hematological, diarrhea, fatigue, and was manageable. Outcomes in this cohort were better than expected in this setting. Hence, in April 2020, sacituzumab govitecan received accelerated approval in the USA for the treatment of patients with metastatic TNBC who have received at least two prior therapies for metastatic disease.

Results from the phase III, randomized, open-label, confirmatory ASCENT trial (NCT02574455) were presented in 2020 at the European Society of Medical Oncology (ESMO) congress and at the San Antonio Breast Cancer Symposium (SABCS). Five hundred twenty-nine patients with metastatic TNBC who received more than two lines of chemotherapy were assigned to treatment with either sacituzumab govitecan or to physician's choice of single-agent chemotherapy (eribulin, capecitabine, gemcitabine, or vinorelbine). The trial showed a significant benefit in PFS in the population without brain metastases (primary objective). Median PFS increased from 1.7 to 5.6 months with sacituzumab govitecan (HR = 0.41, CI95: 0.32-0.52, $p < 0.0001$) and OS (secondary outcome) from 6.7 to 12.1 months (HR = 0.48, CI95: 0.38-0.59, $p < 0.0001$). The OR increased from 5% to 35% ($p < 0.0001$).[18] There was no new toxicity signal compared with the previous phase II trial. Efficacy seemed to be greater with higher Trop-2 expression.[19]

As Trop-2 expression is present in other tumor types, sacituzumab govitecan is currently in clinical trials in HR-positive/HER2-negative cancers (NCT03901339, NCT04639986), in patients with BC with brain metastases (NCT04647916) and in early-stage HER2-negative BC with residual disease after neoadjuvant chemotherapy (NCT04595565).

Ongoing clinical trials with the three approved ADCs are shown in Table 1.

Table 1. Clinical development of the three approved ADCs in metastatic BC

Drug	combination partner	phase	population	status	ClinicalTrials.gov identifier
Trastuzumab emtansine		II	older patients HER2+ MBC	Active, not recruiting	NCT03587740
	taselisib	I	HER2+ MBC	Active, not recruiting	NCT02390427
	temozolomide	I-II	HER2+ MBC, Brain mets	Recruiting	NCT03190967
	tucatinib	III	HER2+ MBC	Recruiting	NCT03975647
	DZD1516	I	HER2+ MBC	Recruiting	NCT04509596
	neratinib	I-II	HER2+ MBC	Active, not recruiting	NCT02236000
	afatinib	II	HER2+ MBC, Brain mets	Recruiting	NCT04158947
	PD-0332991	I	HER2+ MBC	Active, not recruiting	NCT01976169
	palbociclib	II	HER2+ MBC	Recruiting	NCT03530696
	ribociclib	I-II	HER2+ MBC	Active, not recruiting	NCT02657343

	abemaciclib	II	HER2+ MBC	Recruiting	NCT04351230
	pembrolizumab	I	HER2+ MBC	Active, not recruiting	NCT03032107
	atezolizumab	III	HER2+ MBC	Active, not recruiting	NCT04740918
	BN-Brachyury, entinostat, M7824	I	MBC	Recruiting	NCT04296942
	utomilumab	I	HER2+ MBC	Active, not recruiting	NCT03364348
Trastuzumab deruxtecan		II	HER2+, HER2 low, HER2 0, with biomarker analysis	Active, not recruiting	NCT04132960
		II	HER2+ MBC, Brain mets	Recruiting	NCT04420598
		II	HER2+ MBC, Brain mets	Recruiting	NCT04752059
		IV	HER2+ MBC, Brain mets	Not yet recruiting	NCT04739761
		III	HER2+ MBC (vs T-DM1)	Active, not recruiting	NCT03529110
		III	HER2+ MBC (T-DM1 pre treated)	Active, not recruiting	NCT03523585
		III	HER2 low MBC	Active, not recruiting	NCT03734029
	tucatinib	II	HER2+ MBC	Recruiting	NCT04539938
	with /without pertuzumab + other drugs (durvalumab, paclitaxel, pertuzumab, tucatinib)	III	first line HER2+ MBC	Not yet recruiting	NCT04784715
		I-II	HER2+ MBC	Recruiting	NCT04538742
	+ other drugs (durvalumab, paclitaxel, capivasertib, anastrole, fulvestrant, capecitabine)	I	HER2 low MBC	Recruiting	NCT04556773
	nivolumab	I	HER2+ MBC	Active, not recruiting	NCT03523572
	pembrolizumab	I	HER2+/HER2 low BC and HER2+ or mutant NSCLC	Recruiting	NCT04042701
	ceralasertib	I	solid tumors	Not yet recruiting	NCT04704661
Sacituzumab govitecan		III	HR+/HER2-	Recruiting	NCT03901339
		III	HR+/HER2- (asian)	Recruiting	NCT04639986
		II	MBC brain mets	Recruiting	NCT04647916
	pembrolizumab	II	TN MBC	Recruiting	NCT04468061
	pembrolizumab	II	HR+/HER2-	Recruiting	NCT04448886
	atezolizumab	I-II	TN MBC	Recruiting	NCT03424005
	talazoparib	I-II	TN MBC	Recruiting	NCT04039230
	rucaparib	I-II	TN MBC and other tumors	Recruiting	NCT03992131

MBC: metastatic breast cancer
TN: triple negative
NSCLC: non-small cell lung cancer

OTHER ADCS UNDER DEVELOPMENT

Numerous ADCs are under development and could prove successful as monotherapy. Moreover, the synergy in combination with other therapies like immune checkpoint inhibitors could prove successful (Table 2).

Table 2: Clinical development of other ADCs in metastatic BC

Drug	Target	antibody	payload	combination partner	phase	population	status	Clinical Trials. gov identifier
SYD985	HER2	modified trastuzumab	duocarmycin		III	HER2+ BC	Active not recruiting	NCT03262935
				paclitaxel	I	HER2+ BC	Not yet recruiting	NCT04602117
RC48-ADC		hertuzumab	MMAE		II	HER2+ BC	Recruiting	NCT03500380
					III	HER2 low BC	Recruiting	NCT04400695
PF-06804103		HER2 targeted mab	Aur101		I	HER2+ and HER2- tumors	Active not recruiting	NCT03284723
ARX788		HER2 targeted mab	MMAF		I	HER2+ and HER2-low tumors	Recruiting	NCT03255070
DHES0815A		HER2 targeted mab	benzodiazepine monoamide		I	HER2+ BC	Active not recruiting	NCT03451162
ALT-P7		modified trastuzumab	MMAE		I	HER2+ BC	Not recruiting	NCT03281824
PF-06804103		HER2 targeted mab	Aur101		I	HER2+ and HER2- tumors	Active not recruiting	NCT03284723
FS-1502		modified trastuzumab	MMAF		I	HER2+ BC	Not yet recruiting	NCT03944499
GQ1001		HER2 targeted mab	DM1		I	HER2+ BC	Recruiting	NCT04450732
MRG002		HER2 targeted mab	MMAE		II	HER2 low BC	Not yet recruiting	NCT04742153
Patritumab deruxtecan (U3-1402)	HER3	patritumab	deruxtecan		II	BC	Not yet recruiting	NCT04699630
					I	expressed HER3 BC	Active not recruiting	NCT02980341
Ladiratuzumab vedotin (SGN-LIV1A)	LIV1A	LIV-1 targeted mab	MMAE	atezolizumab/ multiple agents	I-II	TNBC	Recruiting	NCT03424005
				pembrolizumab	I-II	TNBC	Recruiting	NCT03310957
Datopotamab deruxtecan	Trop-2	Trop-2 targeted mab	deruxtecan		I-II	TNBC	Recruiting	NCT03742102
PF-06647020	PTK7	PTK7 targeted mab	Aur101	gedatolisib	I	TNBC	Completed	NCT03243331
SAR566658	CA6	CA6 targeted mab	DM4		II	CA6+ TNBC	Completed	NCT02984683
AVID100	EGFR	EGFR targeted mab	DM1		I-II	solid tumors	Active not recruiting	NCT03094169
OBT076	CD205	CD205 targeted mab	DM4		I	CD205 positive BC	Recruiting	NCT04064359
ASN004	5T4 oncofetal antigen	5T4 targeted mab	Auristatin		I	Solid tumors	Not yet recruiting	NCT04410224
NBE-002	ROR1	ROR1 targeted mab	anthracycline PNU-159682		I	Solid tumors, TNBC	Recruiting	NCT04441099
VLS-101	ROR1	ROR1 targeted mab	MMAE		II	BC and NSCLC	Recruiting	NCT04504916

ABBV-085	leucine-rich repeat containing 15 (LRRC15)	LRRC15 targeted mab	MMAE		I	Solid tumors	Completed	NCT02565758

NSCLC: non small cell lung cancer

1. HER2-positive and HER2-low BC

1.1. Trastuzumab duocarmazine (SYD985)

Trastuzumab duocarmazine is composed of trastuzumab conjugated with a potent antimitotic antibiotic duocarmazine via a cleavable linker. In the HER2-positive BC cohort of a phase I trial, the OR was 33%. The most common adverse events were fatigue, conjunctivitis and dry eyes.[20] The United States Food & Drug Administration (FDA) has granted Fast Track designation for trastuzumab duocarmazine for the treatment of patients with HER2-positive metastatic BC who have progressed during or after at least two different HER2-targeting treatment regimens.

In an HER2-low BC cohort, the OR was 28% and 40% for HR-positive and HR-negative tumors, respectively, with more data needed due to small numbers. The compound is currently under investigation in HER2-positive BC versus treatment physician choice (TPC) in the phase III TULIP trial (NCT03262935).

1.2. MM-302

The compound MM-302 is an anti-HER2 monoclonal antibody conjugated with pegylated antibody-liposomal doxorubicin. Its specific interest is that it increases the delivery of anthracycline molecules to tumor cells while avoiding cardiotoxicity. Despite promising results in a phase 1 trial,[21] the phase 2 HERMIONE study failed to demonstrate any clinical benefit of MM-302 plus trastuzumab versus TPC in patients with refractory HER2-positive advanced/metastatic BC for whom there are no standard-of-care therapies.[22] Consequently, the development was prematurely terminated owing to a lack of efficacy.

1.3. RC48-ADC

RC48-ADC is a high-affinity anti-HER2 antibody (hertuzumab) conjugated via a cleavable linker to MMAE. In a phase Ib trial, RC48-ADC showed manageable safety and encouraging efficacy profiles in patients with HER2-positive metastatic BC.[23] Thirty patients pretreated with trastuzumab/chemotherapy were enrolled. Disease control (CR+PR+SD) was observed in 29 of 30 evaluable patients who received RECIST 1.1 assessment (96.7%), with 11 PR (ORR: 36.7%; 30-76% regression) and 18 SD (60.0%) The common treatment-related adverse events reported were AST and ALT elevation (50.0%, and 43.3%) and hematological. Phase II and III trials are ongoing (NCT04400695, NCT03500380).

1.4. MEDI4276

MEDI4276 is an ADC comprised of bispecific humanized HER2 antibody attached via a protease-cleavable linker to a tubulysin toxin (AZ13599185) with an approximate average DAR of 4. MEDI4276

demonstrated enhanced cellular internalization and cytolysis of HER2 positive, T-DM1-resistant tumor cells *in vitro*. In a phase I study in breast and gastric HER2- positive tumors, 43 patients received MEDI4276. Treatment showed clinical activity (disease control 32%), but with increased toxicity at escalation higher doses. Twelve patients (28%) had grade 3-4 drug-related adverse events, the most common being elevated transaminases.[24] Additional data are awaited.

1.5. XMT-1522

XMT-1522 is a humanized anti-HER2 antibody conjugated to MMAF, with a favorable safety and efficacy profile in a phase I trial.[25] However, the development of XMT-1522 was halted by the company due to the competitive environment for HER2-targeted therapies.

1.6. PF-06804103

PF-06804103 is an anti-HER2 antibody conjugated with a cleavable linker to the cytotoxic agent auristatin microtubule inhibitor Aur0101. A phase I trial in HER2-positive BC and gastric cancer showed manageable toxicity and promising anti-tumor activity in this small, heavily pretreated study population.[26]

1.7. Other ADCs

Other compounds targeting HER2 are under investigation: A166 (NCT03602079), ARX-788 (NCT03255070), ALT-P7 (NCT03281824), DHES0815A (NCT03451162), FS-1502 (NCT03944499), GQ1001 (NCT04450732), MRG002 (NCT04742153). To our knowledge, there are no clinical data have been published. The development of ADCT502 was terminated owing to a lack of efficacy.

2. Other targets

2.1. HER3: patritumab deruxtecan (U3-1402)

HER3 is highly expressed in various tumor types, is implicated in resistance to anti-HER2 agents,[27] and may be associated with poor prognosis in solid tumors.[28] U3-1402 is an anti-HER3 antibody conjugated with topoisomerase I inhibitor deruxtecan. Preliminary data from a phase I-II trial suggests that it has promising antitumor activity (OR 33% and disease control rate 95%) with manageable toxicity in patients with HER3-overexpressing metastatic BC.[29] A phase II trial is ongoing in metastatic BC. (NCT04699630)

2.2. LIV1A: ladiratuzumab vedotin (SGN-LIV1A)

LIV-1 is a transmembrane protein with a zinc transporter expressed in about 70% % of metastatic TNBC.[30] It is reported to be associated with metastatic progression by promoting epithelial-mesenchymal transition, suggesting an interest in developing targeted agents. SGN-LIV1A is composed of a LIV1A antibody conjugated with MMAE by a cleavable linker. Data from a phase I study in TNBC patients showed promising results, OR was 32% and the median PFS was 11.3 weeks.[31] Data from an expansion TNBC cohort are awaited. Combination strategies are being studied, in particular with immune checkpoint inhibitors such as pembrolizumab and atezolizumab, or other agents (NCT03310957, NCT03424005).

2.3. Trop-2: datopotamab deruxtecan

Datopotamab deruxtecan (anti-Trop-2 antibody conjugated with topoisomerase I inhibitor) showed interesting results in NSCLC patients in a phase I trial.[32] A phase I-II trial in TNBC is ongoing (NCT03742102)

2.4. Protein tyrosine kinase 7 : PF-06647020

Protein tyrosine kinase 7 (PTK7) is a receptor tyrosine kinase in the Wnt pathway. It is highly expressed on tumor-initiating cells and is thought to participate in tumor progression. PF-06647020 combines the PTK7 antibody with auristatin (Aur101). A phase I trial in solid tumors suggested encouraging OR and an acceptable safety profile.[33] A phase I trial combining PF-06647020 with the phosphoinositide 3-kinase(PI3K) inhibitor gedatolisib is ongoing in TNBC (NCT03243331).

2.5. CA6: SAR566658

The anti-CA6 ADC conjugated with DM4 showed efficacy in solid tumors overexpressing CA6, [34] a Mucin-1 (MUC1)-associated sialoglycotope that is highly detected in breast, ovarian, lung, and bladder carcinomas.[35] A phase II trial in CA6-positive metastatic TNBC is ongoing (NCT02984683).

2.6. Epidermal growth factor receptor: AVID100

Epidermal growth factor receptor (EGFR) is overexpressed in about 20% of TNBC. AVID100 is an anti-EGFR ADC that targets both wild-type and mutant forms of EGFR (both wild type and mutant) and is conjugated with DM1. A phase I trial in patients with solid tumors demonstrated encouraging results.[36] A phase II trial in overexpressed EGFR TNBC is ongoing (NCT03094169)

2.7. Other ADCs

Other compounds are under investigation: OBT076 (NCT04064359), VLS-101 (NCT04504916), ASN004 (NCT04410224), NBE002 (NCT04441099), BA3021 (NCT03504488). To our knowledge, no clinical data have been published to date.

The development of PF-06664178 (Trop2 ADC - Aur101) was discontinued owing to an unfavorable safety profile. Similarly, the development of glembatumumab vedotin (gpNMB ADC-MMAE) was discontinued since the drug failed to demonstrate any benefit versus capecitabine in overexpressing gpNMB TNBC in the phase 2 METRIC trial.[37]

CONCLUSION

The development of ADCs represents an important step forward in cancer treatment since they allow specific targeting while delivering a highly potent drug. Nevertheless, the efficacy/safety balance remains crucial, with many ADCs showing a debatable or even unfavorable therapeutic index.

In advanced BC, three ADCs now have approval, showing major clinical benefits with manageable side-effects. The bystander effect and immune functions of ADCs in the microenvironment suggest the value of associating ADCs with other anti-cancer therapies, e.g. immune checkpoint inhibitors or targeted agents, in order to circumvent possible resistance and to further improve outcome. For example, trastuzumab

deruxtecan in combination with the anti-PD-1 antibody showed benefit in xenograft models, possibly owing to increased T-cell activity and upregulated PD-L1 expression induced by trastuzumab deruxtecan.[38] Combination trials are currently underway (Table 1, 2). It will be important to develop biomarkers of sensitivity/resistance to each ADC to improve the therapeutic index.

Based on the results of these trials, it may be possible in the future to replace conventional chemotherapy with these more targeted and efficient ADC approaches

.

REFERENCES

1- Global Cancer Observatory, International Agency for Research on Cancer. Available from: https://gco.iarc.fr/

2- Chau CH, Steeg PS, Figg WD. Antibody – drug conjugates for cancer. *Lancet* 2019; 394:793 – 804.

3- Hamblett KJ. Effects of drug loading on the antitumor activity of a monoclonal antibody drug conjugate. *Clin Cancer Res* 2004; 10:7063–7070.

4- Lu J, Jiang F, Lu A, Zhang G. Linkers having a crucial role in antibody–drug conjugates. *Int J Mol Sci* 2016; 17:561.

5- Junttila TT, Li G, Parsons K, et al. Trastuzumab-DM1 (T-DM1) retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib insensitive breast cancer. *Breast Cancer Res Treat* 2011; 128: 347–356.

6- Ogitani Y, Hagihara K, Oitate M, et al. Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody–drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. *Cancer Sci* 2016; 107: 1039–1046.

7- Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; 367:1783 – 1791.

8- Dieras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2017; 18:732–742.

9- Von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med* 2019; 380:617–628.

10- Tolaney SM, Trippa L, Barry W, et al. TBCRC 033: A randomized phase II study of adjuvant trastuzumab emtansine vs paclitaxel in combination with trastuzumab for stage I HER2-positive breast cancer (ATEMPT). 2019 San Antonio Breast Cancer Symposium. Abstract GS1-05.

11- Modi S, Saura C, Yamashita T, et al; DESTINY-Breast01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N Engl J Med* 2020 Feb 13;382(7):610-621. doi: 10.1056/NEJMoa1914510. Epub 2019 Dec 11. PMID: 31825192; PMCID: PMC7458671.

12- Schalper KA, Kumar S, Hui P, et al: A retrospective population-based comparison of HER2 immunohistochemistry and fluorescence in situ hybridization in breast carcinomas: Impact of 2007 American Society of Clinical Oncology/College of American Pathologists criteria. *Arch Pathol Lab Med* 138:213-219, 2014

13- Burris HA, Rugo HS, Vukelja SJ, et al. Phase II study of the antibody drug conjugate

trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. *J Clin Oncol* 2011; 29:398 – 405.

14- Krop IE, LoRusso P, Miller KD, et al. A Phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. *J Clin Oncol* 2012; 30:3234 – 3241.

15- Modi S, Park H, Murthy RK, et al. Antitumor activity and safety of trastuzumab deruxtecan in patients with HER2-low – Expressing advanced breast cancer: results from a Phase Ib study. *J Clin Oncol* 2020; 38:1887 –1896.

16- Lin H, Huang JF, Qiu JR, et al. Significantly upregulated TACSTD2 and Cyclin D1 correlate with poor prognosis of invasive ductal breast cancer. *Exp Mol Pathol* 2013; 94: 73–78.

17- Bardia A, Mayer IA, Diamond JR, et al. Efficacy and safety of anti-trop-2 antibody drug conjugate sacituzumab govitecan (IMMU-132) in heavily pretreated patients with metastatic triple-negative breast cancer. *J Clin Oncol* 2017; 35: 2141–2148.

18- Bardia A et al. ASCENT: A randomized phase III study of sacituzumab govitecan versus treatment of physician's choice in patients with previously treated metastatic triple-negative breast cancer. ESMO virtual congress 2020, LBA17.

19- Hurvirtz SA et al. Biomarker evaluation in the phase 3 ASCENT study of sacituzumab govitecan versus chemotherapy in patient with metastatic triple-negative breast cancer. SABCS virtual congress 2020, GS3- 06.

20- Banerji U, van Herpen CM, Saura C, et al. Trastuzumab duocarmazine in & locally advanced and metastatic solid tumours and HER2-expressing breast cancer: a phase 1 dose-escalation and dose-expansion study. *Lancet Oncol* 2019; 20:1124–1135.

21- Munster P, Krop IE, LoRusso P, et al. Safety and pharmacokinetics of MM-302, a HER2-targeted antibody-liposomal doxorubicin conjugate, in patients with advanced HER2-positive breast cancer: a phase 1 dose-escalation study. *Br J Cancer* 2018 Oct;119(9):1086-1093.

22- Miller K, Cortes J, Hurvitz SA, et al. HERMIONE: a randomized Phase 2 trial of MM-302 plus trastuzumab versus chemotherapy of physician's choice plus trastuzumab in patients with previously treated, anthracycline-naïve, HER2-positive, locally advanced/metastatic breast cancer. *BMC Cancer*. 2016 Jun 3;16:352.

23- Xu B, Wang J, Zhang Q, et al. An open-label, multicenter, phase Ib study to evaluate RC48-ADC in patients with HER2-positive metastatic breast cancer. *J Clin Oncol* 2018; 36(15_suppl):1028 – 11028

24- Pegram M, Hamilton E, Tan AR, et al. Phase 1 study of bispecific HER2 antibody-drug conjugate MEDI4276 in patients with

advanced HER2-positive breast or gastric cancer. *Ann Oncol* 2018; 29:iii8.

25- Hamilton EP, Barve MA, Bardia A, et al. Phase 1 dose escalation of XMT- 1522, a novel HER2-targeting antibody-drug conjugate (ADC), in patients (pts) with HER2-expressing breast, lung and gastric tumors. *J Clin Oncol* 2018; 36(15_suppl):2546 – 12546.

26- Meric-Bernstam F, Calvo E, Moreno V, et al. A phase I dose escalation study evaluating the safety and tolerability of a novel anti-HER2 antibody-drug conjugate (PF-06804103) in patients with HER2-positive solid tumors. *J Clin Oncol* 2020 38:15_suppl, 1039-1039

27- Xia W, Petricoin EF III, Zhao S, et al. An heregulin-EGFR-HER3 autocrine signaling axis can mediate acquired lapatinib resistance in HER2+ breast cancer models. *Breast Cancer Res* 2013; 15: R85.

28- Ocana A, Vera-Badillo F, Seruga B, et al. HER3 overexpression and survival in solid tumors: a meta-analysis. *J Natl Cancer Inst* 2013; 105: 266–273.

29- Yonemori K, Masuda N, Takahashi S, et al. 151O. Single agent activity of U3-1402, a HER3- targeting antibody–drug conjugate, in HER3- overexpressing metastatic breast cancer: updated results from a phase I/II trial. *Ann Oncol* 2019; 30(Suppl. 3): iii48.

30- Taylor KM, Morgan HE, Johnson A, et al. Structure-function analysis of LIV-1, the breast cancer-associated protein that belongs to a new subfamily of zinc transporters. *Biochem J* 2003; 375: 51–59.

31- Modi S, Pusztai L, Forero A, et al. Phase 1 study of the antibody–drug conjugate SGN-LIV1A in patients with heavily pretreated triple-negative metastatic breast cancer. *Clin Cancer Res* 2018; 78(Suppl.): abstract PD3-14.

32- Lisberg AE, Sands J, Toshio Shimizu T, et al. Dose escalation and expansion from the phase I study of DS-1062, a trophoblast cell-surface antigen 2 (TROP2) antibody drug conjugate (ADC), in patients (pts) with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2020 38:15_suppl, 9619-9619

33- Sachdev JC, Maitland ML, Sharma M, et al. PF-06647020 (PF-7020), an antibody-drug conjugate (ADC) targeting protein tyrosine kinase 7 (PTK7), in patients (pts) with advanced solid tumors: results of a phase I dose escalation and expansion study [abstract]. *J Clin Oncol* 2018; 36(15_suppl): 5565–15565.

34- Gomez-Roca CA, Boni V, Moreno V, et al. A phase I study of SAR566658, an anti CA6- antibody drug conjugate (ADC), in patients (Pts) with CA6-positive advanced solid tumors (STs) (NCT01156870). *J Clin Oncol* 2016; 34(Suppl. 15): 2511.

35- Kearse KP, Smith NL, Semer DA, Eagles L, Finley JL, Kazmierczak S, et al. Monoclonal antibody DS6 detects a tumor-associated sialoglycotope expressed on human serous ovarian carcinomas. *Int J Cancer* 2000;88:

866–72.

36- Tolcher A , Papadopoulos K, Cole Y, et al. A Phase 1a/2a trial of AVID100, an anti-EGFR antibody-drug conjugate. *Ann Oncol* 2018; 29(Suppl. 3): iii8.

37- Vahdat L, Forero-Torres A, Schmid P, et al. Abstract P6-20-01: METRIC: a randomized international phase 2b study of the antibody-drug conjugate (ADC) glembatumumab vedotin (GV) in gpNMB-overexpressing, metastatic, triple-negative breast cancer (mTNBC). *Cancer Res* 2019; 79(4 Supplement)P6-20-01.

38- Iwata TN, Ishii C, Ishida S, et al. A HER2-Targeting Antibody-Drug Conjugate, Trastuzumab Deruxtecan (DS-8201a), Enhances Antitumor Immunity in a Mouse Model. *Mol Cancer Ther* 2018 Jul;17(7):1494-1503.

