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Antibody-Drug Conjugates in Breast Cancer: a Comprehensive Review

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Opinion Statement

Antibody-drug conjugates are an elegant approach to cancer treatment that couples the specificity of monoclonal antibodies to the cytotoxicity of classic chemotherapy agents, permitting, at least in theory, increased activity and reduced toxicity. In breast cancer, the early success of trastuzumab-emtansine (T-DM1) in the HER2-positive metastatic setting led to great hopes, later dashed by results in the early setting (KRISTINE trial) and in combination with pertuzumab (MARIANNE trial). Parallel to this, development of ADCs in breast cancer has suffered other setbacks, including the recent failure of other agents (MM-302) as well as the suspension of a few programs (XMT-1522, ADCT-502) with the overall effect of dampening the impetus of this concept and halting/delaying the progress of drugs associated with it, particularly when immunotherapy is at the center of so many efforts. Numerous antibody-drug conjugates remain, however, in development, and could prove successful. Critically, ADCs could permit the introduction of novel concepts such as the expansion of potent anti-HER2 therapy to HER2-low breast cancer, treatment beyond resistance to T-DM1, and synergy in combination with immune checkpoint blockade. In the early setting, the ATEMPT trial may show that T-DM1 reduces toxicity while maintaining good outcomes for lower risk HER2+ patients. ADCs based on bispecific antibodies are also in development. Finally, breakthroughs are occurring in the orphan triple-negative breast cancer subtype with agents targeting surface proteins. The recent results of *Sacituzumab govitecan* suggest substantial activity in heavily pre-treated patients and underscore the enduring relevance of antibody drug conjugates as a path towards better outcomes.

Introduction

Breast cancer is the most common form of cancer among women worldwide [1] and cure rates of early breast cancer continue to improve [2]. Metastatic breast cancer, on the other hand, remains incurable, despite recent improvements in outcomes [3]. These gains are connected to a deeper understanding of cancer biology and to the development of a new generation of anti-cancer agents designed to act upon specific molecular targets [4]. The most important of these is the anti-human epidermal growth factor receptor 2 (HER2) antibody trastuzumab, which changed the natural history of an aggressive subtype of breast cancer defined by its reliance on signaling via HER2—dubbed HER2-positive breast cancer [5].

Trastuzumab is remarkable for its specificity—its ability to bind to only one receptor epitope [5]. This specificity, largely absent in other target agent classes [6], grants to trastuzumab its remarkable activity and favorable toxicity profile. This quality of antibodies has led to interest in using them as the carriers of other less specific anti-cancer drugs [7].

This principle has led to the creation of a new subclass of targeted agents, called antibody-drug conjugates (ADCs), which combine the specificity of an antibody and the cytotoxicity of classic chemotherapy agents [7]. The first agent in this class to come into clinical practice in breast cancer, trastuzumab-emtansine (T-DM1), has created great interest and pushed a myriad of new ADCs into development [8]. In this article, we will review the current state of the ADC field in breast cancer in both the advanced and early disease setting, including a detailed look on the most recent clinical data on ADCs currently in development.

Antibody Drug Conjugates

ADCs are composed by three elements—monoclonal antibody, cytotoxic agent (often referred to as the "payload"), and a linker. All three elements have impact on the activity of an ADC. These have been extensively reviewed elsewhere recently [7, 9]. We will briefly review here the core aspects of each of the three elements as well as the so-called "bystander effect" and the factors which define ADC toxicity.

Antibody

The antibody is responsible for hitting the specific molecular target. The target receptor should be tumor specific and hyperexpressed—thereby increasing the chance of binding. These target receptors, furthermore, can either be a vital part of cancer cell signaling or not [10]. Other targets—in surrounding tumor-associated cells or stroma, can also be used for the designing of ADCs [11]. Correspondingly, the antibody itself can be independently active as an anti-cancer agent or not. Though many different proteins are hyperexpressed on the surface of tumor cells, a more limited number have thus far proven to be useful as targets [8]. Inter-tumoral and intra-tumoral heterogeneity present a challenge to ADCs due to the presence of subpopulations which do not express the target receptor [12].

Payload

Few chemotherapy agents are suitable to be payloads. They must be particularly potent considering the limited number of molecules which will enter the cell. The two most commonly used payloads are auristatin and maytansine

analogues, both classic cytotoxic agents that act upon microtubules and both having proved to be prohibitively toxic to patients when used by themselves [13]. The payload must also be resistant to classical efflux pump-based mechanism of resistance—such as MDR1-Pgp-mediated multi-drug resistance (MDR), and retain its efficacy after linkage [9, 14].

Linker

The linker is responsible for binding monoclonal antibody to payload, and affects solubility, stability during manufacturing, and release [15]. ADCs can be divided between those which have cleavable linkers (e.g., SYD985) and those with non-cleavable linkers (e.g., T-DM1). Cleavable linkers release the drug depending on glutathione concentration, Ph, or via enzymatic proteolysis—and this can translate into higher systemic release. Non-cleavable linkers require degradation inside the lysosome after internalization, which increases specificity but may limit efficacy [15].

The Bystander Effect

The bystander effect is the cytotoxic effect exerted by the payload or its metabolites upon populations of cells which are not the targets of the ADC. This can occur due to multiple causes. The payload or its metabolites may be able, once internalized and freed from the monoclonal antibody component, to cross the cellular membrane and kill surrounding cells. Alternatively, cleavable linkers may permit the release of a portion of the payload in the extracellular space, leading to direct cytotoxic activity. It is important to note, however, that though the bystander effect can in theory lead to increased activity on non-targeted cancer cells, it can decrease activity on targeted cells (by decreasing the concentration of the payload intracellularly) and, more importantly, lead to a worse side effect profile which can limit the dose tolerable to patients [16].

ADC Toxicity

The "magic bullet" concept which underpins the ADC concept purports that these agents will be less toxic than regular cytotoxic agents. This, however, is often not the case with ADCs both on the market and in testing which show a substantial incidence of side effects [17].

Toxicity in an ADC is determined by the physiological function and prevalence of the target in non-cancer tissue, by the nature of the linker, the number of payload molecules and by the type of payload. Mostly, however, as shown by preclinical models and a recent meta-analysis, the toxicities associated with current ADCs are off-target and match the toxicity profile of the payload—and therefore are associated with release of the drug into the bloodstream or plasma by suboptimal linkers or due to an excessively prominent bystander effect [17, 18].

Antibody Drug Conjugates Approved for Breast Cancer

Trastuzumab-Emtansine

T-DM1 is the only approved ADC thus far for use in breast cancer. It is built on the monoclonal antibody trastuzumab, which binds to the HER2 receptor. The payload is emtansine (DM1), a derivate of maytansine. DM1 is a potent inhibitor of tubulin polymerization, necessary for cellular division, leading to

apoptosis. Maytansine had been tested as an anti-cancer agent but demonstrated very limited efficacy with substantial toxicity [19]. DM1 is linked to a lysine in trastuzumab through a non-reducible thioether and has an average drug antibody ratio (DAR) of 3.5. Lambert et al. have reviewed in depth the pre-clinical development of T-DM1 [20]. Table 1 summarizes the results of the most important trials with T-DM1.

Advanced Disease

Seven published phase I, II, and III trials provide evidence on the efficacy of T-DM1 in advanced HER2-positive breast cancer [21, 24, 27, 30–33]. FDA/EMA approval, however, is based principally on two pivotal phase III trials—EMILIA and TH3RESA.

In EMILIA, 991 patients with advanced HER2-positive breast cancer having previously received only one line of treatment with a taxane and trastuzumab (or having failed adjuvant trastuzumab within 6 months of completion) were randomized between T-DM1 and capecitabine + lapatinib. Primary outcome results showed the superiority of T-DM1 with a median progression-free survival (PFS) of 9.6 months, vs 6.4 months, an absolute gain of 3.2 months, with a hazard ratio (HR) of 0.65, 95% confidence interval (CI) 0.55 to 0.77, p <0.001 [21]. The response rate (ORR) also favored the T-DM1 arm (43.6% vs 30.8%, 95% CI 26.3 to 35.7, p <0.001), and the median duration of response (DoR) was longer (12.6 months vs 6.5 months) in the T-DM1 arm [21]. More recently, mature OS data was published showing an advantage to T-DM1 use (29.9 months vs 25.9 months, HR 0.75, 95% CI 0.64–0.88) [22••]. More grade 3 or higher events occurred in the capecitabine + lapatinib arm (57% vs 40.8%). Nausea (39.2%), fatigue (35.1%), thrombocytopenia (28%), diarrhea (23.3%), and elevated AST (22.4%) were the most commonly reported adverse events in the T-DM1 arm [21]. Quality of life (QoL) was also better in the T-DM1 arm, with longer times to deterioration (7.1 months vs 4.6 months, HR 0.80, 95% CI 0.67 to 0.95, p =0.012) and a trend favoring T-DM1 in symptom improvement (55.3% vs. 49.4%, p =0.0842) [23].

In TH3RESA, 602 patients with advanced HER2+ breast cancer having received trastuzumab and lapatinib previously were randomized between T-DM1 and physician's choice (PC). Most patients in the PC arm received chemotherapy with trastuzumab (68%) with vinorelbine being the most commonly used chemotherapy base (32%) and 67% of patients in the T-DM1 arm had received four or more lines of treatment. Primary outcomes results favored the T-DM1 arm, with a PFS of 6.2 months vs 3.3 months, HR 0.528, 95% CI 0.422–0.661, p <0.0001 [24]. Mature OS data likewise favors the T-DM1 arm, with a median of (22.7 months vs 15.8 months, HR 0.68, 95% CI 0.54–0.85, p =0.0007) [25••]. Once again, T-DM1 was shown to be less toxic—with less grade 3 or more adverse events (32% vs 43%) and less discontinuations due to adverse events (7% vs 11%) [24]. QoL favored numerically the T-DM1 arm, with a higher proportion of patients reported improvements in global health (57.8% vs 47.1%) [26].

Following these results, however, the MARIANNE study testing T-DM1 in first-line failed to attain its primary objective. In MARIANNE, 1095 patients in first line were randomized between trastuzumab + taxane, T-DM1 + placebo, or T-DM1 + pertuzumab. The T-DM1 arms had similar survival results to the

Table 1. Phase III T-DM1 trial results in early and advanced disease

Study	Indication	Design	Sample size	Efficacy	Safety
Advanced disease					
EMILIA [21, 22••, 23]	Second line after failure of taxane + trastuzumab	T-DM1 vs capecitabine + lapatinib	991	Median PFS 9,6 m vs 6.4 m HR 0.65, 95% CI 0.55 to 0.77, p <0.001 Median OS: 29·9 months vs 25·9 months, HR 0.75, 95% CI 0.64–0.88. **T-DM1 superior to capecitabine + lapatinib**	HRQoL: time to symptom worsening 7.1 m vs 4.6 m, HR 0.796, p = 0.0121. grade≥3 AEs: more frequent in the lapatinib–capecitabine group than in the T-DM1 group (57.0% vs 40.8%). ALT (16.9% v 8.8) and AST (22.4% vs 9.4%) elevations, thrombocytopenia (28% vs 2.5%) and fatigue (35.1% vs 27.9%) more common in the T-DM1 arm. **T-DM1 less toxic (for serious toxicity)**
TH3RESA [24, 25••, 26]	Any line, having received previous trastuzumab and lapatinib	T-DM1 vs physician's choice	602	Median PFS of 6.2 m vs 3.3 m, median HR 0·528 [95% CI 0·422–0·661], p <0·0001; OS 22.7 months vs 15·8 months, HR 0.68, 95% CI 0.54–0.85, p =0.0007. **T-DM superior to physician's choice**	HRQoL: T-DM1 improved global health status more: 57.8% vs 47.1%. Fewer grade 3 or more events in the T-DM1 arm (32% vs 43%). Higher incidence of thrombocytopenia in the T-DM arm (15% vs 3%). **T-DM1 less toxic (for serious toxicity)**
MARIANNE [27]	First line, no previous chemotherapy	Paclitaxel + trastuzumab (A) vs T-DM1 (B) vs T-DM1 + pertuzumab (C)	1095	Median PFS 13.7m vs 14.1m vs 15.2m, A vs B: HR 0.91, 97.5% CI 0.73 to 1.13, p =0.31; A vs C: T-DM1 plus pertuzumab vs trastuzumab plus taxane, 0.87, 97.5% CI 0.69 to 1.08, p =0.14. **B and C not superior to A**	grade≥3 AEs were numerically higher A (54.1%) than in B(45.4%) or C (46.2%). AEs that were more frequent in the B and C as compared to A were headache (32.1% vs 22.1%), nausea (47.1% vs 37.1%), and epistaxis (31.0% vs 14.7%). **T-DM1 less toxic than chemotherapy**

Table 1. (Continued)

Study	Indication	Design	Sample size	Efficacy	Safety
Early disease					
KATHERINE [28]	Post-neoadjuvant stage II or III with residual invasive disease after neoadjuvant treatment	T-DM1 vs trastuzumab	1486	3-year iDFS 88.3% vs 77% (HR 0.50, 95% CI 0.39 to 0.64, p <00.1). **T-DM1 superior to trastuzumab**	Most common AD of grade 3 or higher were thrombocytopenia (5.7% and hypertension (2%). Serious adverse events occurred in. 12.7% of patients in the T-DM1 arm and 8.1% in the trastuzumab arm. **T-DM1 was more toxic**
KRISTINE [29]	Neoadjuvant, stage II or III	T-DM1 + pertuzumab vs docetaxel + carboplatin + trastuzumab + pertuzumab	444	pCR achieved in 44% vs 56% (absolute difference −11.3%, 95% CI −20.5 to −2.0, p =0.016).**T-DM1 not superior to chemotherapy + dual blockade**	AEs: **less toxicity in T-DM1 arms**, diarrhea 33%, fatigue 29%, headache 24%, ALT elevation 21%, AST elevation 15%

pCR pathological complete response, HRQoL healthcare-related quality of life, ToD time to deterioration, AEs adverse events, ALT alanine aminotransferase increased, AST aspartate aminotransferase increased, PFS progression-free survival, HR hazard ratio, CI confidence interval

taxane + trastuzumab arms with better tolerance [27]. PFS was 13.7 months for taxane + trastuzumab, 14.1 months with T-DM1 + placebo, and 15.2 months with T-DM1 plus pertuzumab.

Several relevant open questions remain regarding T-DM1 use in the advanced setting [34•]. Considering that the standard of care today in first line is trastuzumab + pertuzumab + taxane [35], the actual efficacy of T-DM1 is unclear, though available data suggests that it is still meaningful, while diminished [36–39]. Biomarkers able to select patients who can benefit from T-DM1 have thus far not been identified despite significant translational efforts based on samples collected in the registration trials [40–42]. Finally, some data suggests that T-DM1 may cross the blood-brain barrier and have a direct therapeutic effect on brain metastasis—coming from sub-analysis of EMILIA and KAMILLA and small case series [43–45].

Early Setting

The success of T-DM1 in the advanced setting created significant excitement surrounding the results of the KRISTINE and KAITLIN (NCT01966471) trials, which tested T-DM1 in the neoadjuvant and adjuvant settings, respectively.

In KRISTINE, 444 patients were randomized between docetaxel, carboplatin, and trastuzumab + pertuzumab (TCHP) or T-DM1 + pertuzumab. Primary outcome results have shown the superiority of the TCHP arm—pathologic complete response (pCR) 55.7% vs 44.4%. Toxicity favored the T-DM1 arm substantially, however, with only 13% of patient experiencing grade 3 or 4 adverse events (vs 64% in the TCHP arm). The failure of the T-DM1 + pertuzumab regimen in both MARIANNE and KRISTINE led to the halt of accrual in KAITLIN (NCT01966471), an as yet unreported trial randomizing 1846 patients between taxanes and anthracyclines + trastuzumab + pertuzumab (the regimen tested in the APHINITY trial) and T-DM1 + pertuzumab following anthracyclines.

More recently, the results of the KATHERINE (NCT01772472) trial are likely to bring T-DM1 into use in the early setting with substantial impact on current treatment guidelines [28]. In KATHERINE, patients with residual invasive disease after neoadjuvant therapy were randomized between completing 1 year of trastuzumab (743 patients) or of T-DM1 (743 patients). Interim analysis data suggest the superiority of the T-DM1 arm with 88.3% of patients in the T-DM1 arm and 77% of patients in the trastuzumab arm free of invasive disease at 3 years (HR 0.50, 95% CI 0.39 to 0.64, p <0.001). All subgroups seem to benefit from T-DM1, though it is important to mention that only a small number of patients received dual-blockade as their neoadjuvant treatment (17.9%). Toxicity, while still rare, was more common in the T-DM1 arm (grade 3 or more AE occurred in 15.4% in the trastuzumab arm and in 25.7% in the T-DM1 arm).

These results add to an already intense debate on how to update the long-standing trastuzumab (neo)adjuvant standard, together with the results of the PERSEPHONE, ExteNET, and APHINITY trials [46–48]. Considering the trend towards more common use of neoadjuvant therapy in the early setting, the size of the benefit and the clear-cut patient selection, it is likely that the T-DM1 post-neoadjuvant regimen will be a new standard. Whether patients who do achieve a complete response truly require

the standard 1 year of trastuzumab, however, remains an open research question.

Antibody Drug Conjugates in Development for Breast Cancer

Several ADCs are currently in development for advanced breast cancer (Table 2 and Fig. 1). Most of the agents in development target HER2, a consequence of the long history of this receptor as a validated therapeutic target, the availability of trastuzumab as a backbone for building ADCs, the significant incidence of HER2+ breast cancer, and the fact that HER2 testing is part of the standard of care. In HER2+ disease the current focus of development is in ADCs capable of showing efficacy after a patient has received T-DM1 as standard of care. Patients with HER2 1+ or 2+ with a negative FISH, (HER2-negative) have also been at the focus of development for ADCs targeting HER2 under the classification of "HER2-low" despite the absence of efficacy of trastuzumab in this setting [63]. Indeed, early results with a novel and potent anti-HER2 ADC (SYD985) demonstrate promising activity in HER2-low ER+ and triple-negative breast cancer [64].

Triple-negative disease (TNBC) has also been the target of substantial efforts. The aggressive nature of the biologic behavior of TNBC—which leads to short times between start of trial and results as well as the restricted availability of TNBC-specific targeted agents render TNBC a nearly orphan disease in dire need of advances—with already some evidence of success with sacituzumab govitecan [65].

Anti-HER2

XMT–1522

XMT–1522 is an ADC built on the basis of a monoclonal antibody (HT-19) that does not compete with either trastuzumab or pertuzumab for epitope binding, bound to an auristatin analogue (dolaflexin) with pre-clinical evidence of activity in both HER2+ and HER2-low in vitro and in vivo models [66, 67]. XMT–1522 is notable for its high DAR (approximately 12), obtained via a polymer linker. Dolaflexin, which crosses the cell membrane and can kill surrounding cells, is also particular for being metabolized, once released inside the cell, into a still cytotoxic metabolite which is however incapable of leaving the cell—leading to an initial short yet tangible bystander effect.

One dose escalation study exposed 18 HER2+ and HER2-low breast cancer patients, with confirmed responses [62]. Though early safety data did not show important toxicity, recently a death occurred, leading the company to temporarily halt the study for investigation of this case, though subsequently the trial was resumed (NCT02952729).

SYD985

SYD985 is an ADC composed of trastuzumab and a synthetic duocarmycin analogue, bound by a cleavable link. Once uptake occurs, the payload is released, leading to irreversible DNA damage and cell death. Furthermore, cleavage can happen outside the cells and the toxin is released into the microenvironment. In pre-clinical experiments,

Table 2. Antibody drug conjugates—clinical trial results

Drug	Target	Phase	Design	Sample size
PF-06647263 [49]	EFNA4	I	Dose escalation in heavily pre-treated solid tumors (part1) and TNBC (part2)	TNBC: 14 patients
RC48-ADC [50, 51]	HER2	Phase I	Dose escalation in heavily pre-treated HER2+ patients (up to 2 mg/kg q2w)	30 evaluable patients
		Phase I	Dose escalation in heavily pre-treated HER2+ patients (up to 2.5 mg/kg q2w)	22 evaluable patients
PF-06647020 [52]	PTK7	Phase I	Dose escalation in heavily pre-treated solid tumors including TNBC	29 patients with TNBC, 112 patients for safety analysis
SGN-LIV1A [53]	LIV-1	Phase I	Dose escalation in heavily pre-treated in HER2-negative advanced breast cancer	81 patients (63 TNBC)
SAR566658 [54]	CA6	Phase I	Dose escalation in heavily pre-treated solid tumors expressing CA6 in ≥30% tumor cells with an intensity 2/3+ by immunohistochemistry were enrolled	114
Sacituzumab govitecan [55–57]	Trop-2	Phase I/II basket trial	TNBC or ER+/HER2– having progressed under at least one previous treatment	215 (148 TNBC, 54 ER+/ HER2-negative, 13 other)
Glembatumumab vedotin [58]	GPNMB	Phase I/II	Dose escalation with at least 2 prior chemotherapy regimens, any subtype of B breast cancer	26 evaluable, 42 safety
MEDI 4276 [59]	Two different HER2 epitopes	Phase I/II	HER2 positive heavily pre-treated advanced breast or gastric cancer	44 (30 breast cancer)
DS–8201a [60]	HER2	Phase I/II	Dose escalating followed by expansion cohort in heavily pre-treated patients	144 breast cancer patients (111 HER2+/34 HER2-low)
SYD0985 [61]	HER2	Phase I	Dose escalating in patients with solid tumors—both HER2+ and HER2-low	50 HER2+, 32 HER2-low
XMT–1522 [62]	HER2	Phase I	Dose escalation HER2+ and HER2-low,	

Table 2. (Continued)

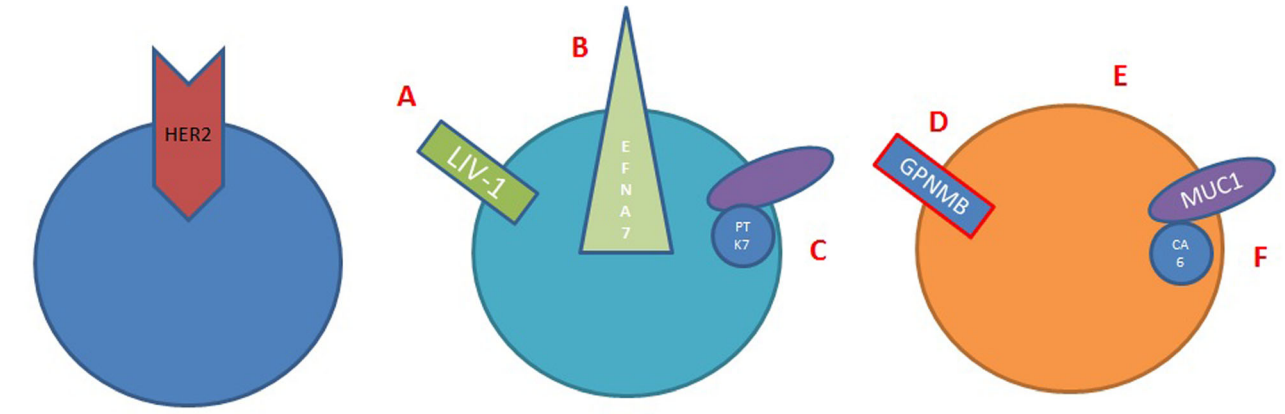
Drug	Target	Phase	Design	Sample size
			heavily pre-treated solid tumors, including breast	22 (18 breast cancer with 8 HER2+ and 10 HER2-low)

Drug	Efficacy results	Safety	Status
PF-06647263 [49]	2 partial responses, no other responses seen	32.7% of patients experienced a grade 3 or higher AE, with 1 AE-related death. Most common AEs included fatigues (56.9%), nausea (56.9%), decreased appetite (34.5%), thrombocytopenia (34.5%), vomiting (34.5%)	Development in TNBC terminated
RC48-ADC [50, 51]	Partial responses in 36.7% and stable disease in 60%. CBR in 46.7%	11.3% of patients experienced a grade 3 or higher AE. Most common AEs included ALT elevation (43.3%); AST elevation (43.3%), leucopenia (40%), neutropenia (33.3%), numbness (33.6%)	Phase II in comparison with lapatinib + capecitabine is ongoing
	In the 16 patients who received 1.5 mg/kg or more: partial responses in 56.3% and stable disease in 31.3%.	Most common AEs included leucopenia (54.2%), peripheral neuropathy (54.2%), ALT/AST elevation (50%), neutropenia (50%)	
PF-06647020 [52]	21% response rate, disease control rate 48%, median duration of response 2.6 m, median PFS 1.7 m	Chosen dose 2.8 mg/kg. Most common AEs included nausea (44.6%), alopecia (41.1%), fatigue (36.6%), headache (33%), neutropenia (27.7%)	Phase I in combination with gedatolisib is ongoing in TNBC and with avelumab in various solid tumors
SGN-LIV1A [53]	In TNBC with 2 mg/kg or more: 25% partial responses, 33.3% stable disease, CBR 28%, median duration of response: 13.3 weeks, media PFS 11 weeks. Recommended dose 2.5 mg/kg	In the entire safety population, the most common AEs were alopenia 40.7%, neutropenia 24.7%, vomiting 23.5%, anemia 21%, peripheral neuropathy 19.8%	Is investigated in a number of phase I and II studies, including I-SPY 2
SAR566658 [54]	One complete response (ovary), 8 partial responses (3 breast, 5 other tumors) and	Most common adverse event (AE) was grade 2 or 3 (36%) keratopathy, fatigue (32.6%),	Phase I in breast cancer CA6-positive is ongoing

Table 2. (Continued)

Drug	Efficacy results	Safety	Status
	39% stable disease were noted (all tumors combined)	peripheral neuropathy (31.6%), nausea (29%), abdominal pain (26%), diarrhea (25%)	
Sacituzumab govitecan [55–57]	ER/HER2-negative: 31% partial responses, CBR 48%, median duration of response 7.4 m, mPFS 6.8 m, in TNBC third line or more: 110 patients. Objective response rate 34%, CBR 45%, median duration of response 7.6 m, mPFS 5.5 m	Most common adverse events include neutropenia (64% all grades, 42% grade 3/4), anemia 36%, nausea 58%, diarrhea 40%, fatigue 46%	Has received breakthrough therapy designation. Phase II and III trials ongoing (ASCENT study)
Glembatumumab vedotin [58]	35% had not progressed at 12 weeks. Median PFS was 18.3 weeks in GNMB positive and 5.9 weeks in GPNMB negative. Phase II ORR 6% in general population	The most common AEs include fatigue (48%), rash (45%), nausea (45%), alopecia (33%), neutropenia (29%), with 2/3 of the neutropenia cases being grade 3	Phase II METRIC trial reported as negative, data yet to be presented formally
MEDI 4276 [59]	3 objective responses in breast cancer patients	53.2% experienced an event of grade 3 or 4. The most common adverse events included nausea (66%), fatigue (55.3%), vomiting (44.7%), diarrhea (42.6%), increased AST (40.1%), increased ALT (36.2%)	Unknown
DS–8201a [60]	HER2+: confirmed ORR 54.5%, disease control rate 93.9%. HER2-low: 50% ORR in, 85.3%	14.9% of patients experience treatment-related AEs of grade 3 or more. Most significant AEs were hematological or gastrointestinal	2 phase II trials ongoing
SYD0985 [61]	16 partial responses in HER2+ (33%) and 8 in HER2-low (27%). mPFS, respectively, 9.4 months and 4.1 months	Most common events were fatigue (32%), dry eyes (29%), conjunctivitis (25%)	Fast track denomination granted by FDA, TULIP phase III trial ongoing
XMT–1522 [62]	11 patients had disease control after 1 dose (including 6 breast cancer patients with one confirmed partial response in a HER2+ patient	Most common AEs were fatigue (27%), nausea (27%), vomiting (18%). Grade 3 events were rare (2 cases)	Phase I is ongoing

EFNA4 ephrin-A4, TNBC triple-negative breast cancer, CBR clinical benefit rate, ALT alanine aminotransferase increased, AST aspartate aminotransferase increased, HER2+ human epidermal growth factor receptor 2 positive by IHC or FISH, HER2-low HER2 1+ or 2+ with negative FISH



HER2

Agent	Payload	Status
T-DM1	maytansine	Approved for ABC
XMT – 1522	dolaflexin	Phase I
SYD985	duocarmycin	Phase III ongoing
DS8201a	deruxtecan	Phase II
MM – 302	liposomal doxorubicin	Terminated
MEDI 4276	tubulysin	unknown
RC48-ADC	auristatin	In Phase II

Other Targets I

Agent	Payload	Status
Ladiratuzumab Vedotin (A)	vedotin	In Phase II
PF-06647263 (B)	calicheamicin	Terminated
PF-06647020 (C)	auristatin	In Phase I

Other Targets II

Agent	Payload	Status
Sacituzumab Govitecan (D)	govitecan	Phase III
Glembatumumab vedotin (E)	vedotin	Phase II
SAR566658 (F)	DM4	Phase I

Fig. 1. Overview of antibody drug conjugates which have reached clinical development or regulatory approval for use in breast cancer. TKs tirosine kinase, HER2: human epidermal growth factor receptor 2, EFNA4: aphrin A4, PTK7 protein tyrosine kinase 7, GPNMB transmembrane glycoprotein NMB, TROP-2 trophoblast cell-surface antigen.

SYD985 was found to be more potent than T-DM1 and demonstrated cytotoxicity against low-HER2 cell lines via bystander killing [68]. Results of the breast cancer cohorts of a phase I trial (NCT02277717) including patients with advanced breast cancer [69] suggest activity (see Table 2) with responses seen in both HER2-low and HER2+ including previously exposed to pertuzumab and T-DM1. One notable yet manageable toxicity was ocular complications (conjunctivitis 25%, increased lacrimation 19%, dry eyes 29%, keratitis 19%, blurred vision 11%) [61, 69]. SYD985 received FDA fast track designation and a phase III study (TULIP) is currently ongoing in HER2-positive breast cancer patients (NCT03262935).

Trastuzumab Deruxtecan (DS8201a)

Trastuzumab deruxtecan combines an anti-HER2 antibody and an exatecan derivate, which can kill not only targeted cells but also surrounding cells (bystander effect), with some in vivo model evidence to confirm this hypothesis

[70, 71]. A phase I dose-escalation trial followed by a dose expansion, including both HER2+ (T-DM1 pre-treated) and HER2-low advanced breast cancer has been presented. Efficacy results were impressive, with a disease control rate 93.9% and 85.3% (see Table 2) in HER2+ and HER2– cases, respectively [60]. It is important to note, however, that safety results suggest intertitial lung disease (ILD) as a clinically meaningful side effect of DS8201a—with a recent combined analysis of 7 trials with 448 treated patients suggesting a rate as high as 9.8% with 2.2% of patients developing of grade 3 or higher potential ILD [72].

Trastuzumab deruxtecan is currently being tested in two phase 3 trials. In NCT03529110, 500 patients with advanced HER2+ disease having failed first line with a taxane and trastuzumab will be randomized between T-DM1 vs trastuzumab deruxtecan. In NCT03523585, 600 patients with advanced HER2+ disease having failed T-DM1 will be randomized between trastuzumab-deruxtecan, trastuzumab + capecitabine, and lapatinib + capacitabine. Further trials include testing combination with immunotherapy (NCT03523572).

MM-302

MM-302 is and ADC combining an anti-HER2 monoclonal antibody with liposomal doxorubicin. The goal behind the design of MM-302 was to permit, via better targeting, the use of higher doses of anthracycline, the quintessential chemotherapy agent used against breast cancer. Early pre-clinical studies demonstrated superior activity of MM-302 as compared to both regular anthracyclines and liposomal doxorubicin. Furthermore, evidence suggested that the combination of MM-302 and trastuzumab is synergestic [73].

Though phase I data showed activity in heavily pre-treated HER2-positive breast cancer without any evidence of cardiac toxicity, the phase II study HERMIONE failed to detect any benefit leading to closure of the study by the IDMC [74]. HERMIONE randomized patients between MM-302 + trastuzumab vs chemotherapy (gemcitabine, capecitabine, or vinorelbine) + trastuzumab [75].

MEDI 4276

MEDI4276 is a bi-paratopic (also called bi-specific) ADC, which targets two different epitopes in the HER2 extracellular domain. This bi-paratopic nature of the monoclonal antibody component of MEDI4276, which includes both the 39S Fv and trastuzumab scFV epitopes, leads to deeper inhibition of cancer cell proliferation than trastuzumab alone. The double binding leads, furthermore, to rapid receptor internalization and lysosomal destruction—and renders the antibody a valuable carrier for a payload as an ADC [76]. Initial in vitro and in vivo xenograft models have shown the potential of the agent. A phase I dose escalation trial have, however, not shown a large number of responses in breast cancer (see Table 2) and the future of the drug is currently unknown.

RC48-ADC

RC48-ADC is a novel HER2 targeted ADC, conjugating an auristatin (monomethyl auristatin E) derivate with a humanized anti-HER2 monoclonal antibody (hertuzumab) via a non-cleavable maleimidocaproyl

(mc) linker designed to only release the toxin once inside a lysosome. In cell lines and in vivo PDx mice models, RC48-ADC has shown higher potential than trastuzumab or lapatinib in impeding tumor growth [77]. Two phase I studies have been conducted in China, in heavily pre-treated advanced HER2+ disease with some signs of efficacy (results in Table 2) [50, 51]. A phase II (NCT03500380) trial is ongoing in patients who have received a taxane and trastuzumab vs lapatinib + capecitabine. The design of this trial, conducted exclusively in China, will render the interpretation of its results difficult as RC48-ADC is being tested against an old standard, unless a significant proportion of patients have been previously treated with T-DM1.

Other Targets

Sacituzumab Govitecan

Trophoblast cell-surface antigen (TROP-2) is a glycoprotein originally identified as a trophoblastic cell membrane marker but is now known to be hyperexpressed in a number of tumor types, including breast cancer. Mice models have suggested that TROP-2 signaling can play an important role in cancer cell behavior, including proliferation, angiogenesis, invasion, and dissemination [78]. Sacituzumab govitecan is composed of an anti-TROP2 (sacituzumab) antibody linked to a moderately potent irinotecan derivative (govitecan or SN-38). The relatively less potent cytotoxic effect of govitecan (as compared to auristain or maytansine analogues more commonly used) may be offset by the DAR of 7.6 (twice that of T-DM1). Additionally, sacituzumab has been shown to promote ADCC [79]. The pre-clinical potential has recently been confirmed in a large phase I in unselected TNBC (148) and ER+/HER2– [68] patients, with an ORR of approximately 30% overall though neutropenia was a significant issue (42% grade 3/4), potentially due to the relatively less stable linker which permits release of the drug in the blood stream [55, 56]. In the 108 TNBC patients having received at least two previous lines of treatment, who received the 10-mg/kg dose, the response rate was 33.3% and the PFS and OS were, respectively, 5.5 months and 13 months [65].

Based on its potential, this agent received breakthrough designation from the FDA and the phase III ASCENT (NCT02574455) trial was opened, planning to randomize 328 patients with advanced TNBC who have failed at least two previous lines of therapy (including at least on containing a taxane) between sacituzumab govitecan and physicians choice of therapy (including eribulin). The primary end point is PFS and results are awaited for 2019/2020.

Glembatumumab Vedotin

The glycoprotein NMB (GPNMB) is hyperexpressed in a large number of different tumors, including breast cancer (TNBC and HER2+), and is today recognized as a promoter of malignant behavior in breast cancer cells [80, 81]. Critically, in cancer cells, GPNMB is predominantly located on the membrane, while in normal cells it is more often intracellular,

making it a particularly interesting target for an ADC [82]. Glembatumumab vedotin conjugates the monoclonal anti-GPNMB antibody (glembatumumab) with an auristatin derivate (vedotin). Pre-clinical studies, conducted in cell lines and PDx mouse models, have suggested that anti-tumoral efficacy is highly correlated with GPNMB expression.

In breast cancer, a wealth of clinical data is today available on glembatumumab vedotin, suggesting limited efficacy, with two published trials—one phase I/II and one phase II totalizing over 150 treated patients (see Table 2 for detailed results), with the possibility that selected GPNMB+ patients derive a substantial benefit (ORR 6% in the general population vs 40% in GPNMB+ patients) [83, 84]. Recently, the results of the METRIC trial, a phase 2b trial comparing glembatumumab vedotin vs capecitabine in GPNMB+ advanced TNBC, were reported—with no discernible advantage of the ADC over capecitabine [85]. As a consequence, glembatumumab vedotin is no longer in active development.

SAR566658

CA6 is a Mucin 1-attached sialoglycotope that is expressed nearly exclusively in solid tumors, making it an interesting target for an ADC. The ADC SAR566658 conjugates huDS6, an anti-CA6 antibody with DM4, a maytansine derivated anti-microtubule agent [54]. In a dose escalation phase I trial in multiple solid tumors (114 patients) which hyperexpressed CA6. SAR566658 induced some responses, leading to a phase II study in CA6-positive TNBC (NCT02984683), in second to fourth line, which is currently ongoing.

Ladiratuzumab Vedotin SGN-LIV1A

LIV-1 is a transmembrane protein that promotes epithelial-to-mesenchymal transition (EMT). It is highly expressed in breast cancer and rarely in normal tissue [86]. Ladiratuzumab vedotin is an ADC conjugating a humanized anti-LIV-1 antibody and an auristatin analogue (vedotin), with a protease cleavable linker which has shown activity in vitro, as well as in mouse models of tumors with high LIV-1 expression [87].

In a phase I study, out of 614 screened samples for LIV-1 status, 90% were positive, with moderate to high expression being detected in 68% of TNBC cases, 82% of ER+/HER2− and 73% of HER2+ samples. Patients with high or moderate expression were eligible and had received at least two previous lines of therapy. Results presented in the TNBC cohort (63 patients) are promising (see Table 2), and the drug is now being investigated in multiple phase I and II studies—including within the I-SPY2 program [53].

PF-06647020

Protein tyrosine kinase 7 (PTK7) is a receptor tyrosine kinase in the Wnt pathway, highly enriched on tumor-initiating cells (TICs) of TNBC. Though it does not seem to play a role itself in tumor biology, its prevalence means the possibility of leveraging it as a target for ADCs. PTK7-ADC is composed of an anti-PTK7 antibody and an auristatin derivate (Aur0101), linked by a cleavable valine-citrulline-based linker. Following in vitro and PDx models showing cytotoxicity and tumor

regression PF-06647020 has entered clinical testing [88]. Phase I data in heavily pre-treated unselected solid tumors, including 29 TNBC patients, show a 21% ORR [52]. Phase I studies in combination with avelumab and gedatolisib are ongoing.

PF-06647263

Mutations in ephrin receptors (Eph) are often present in tumor tissue, and some evidence suggests tumor-suppressing activity in normal Eph signaling while other evidence suggests pro-tumorigenic effects [89, 90]. Their relevance in normal cell behavior and redundancy have made, however, Eph inhibition toxic and ineffective, but still potentially useful as a target for cytotoxic payload delivery [91].

PF-06647263 is an ADC conjugating an anti-EFNA4 (an ephrin receptor) with calicheamicin, a DNA-damaging agent. In vitro studies, conducted particularly in cell lines and PDX models of EFNA4 hyper-expressing TNBC cell lines, have confirmed the cytotoxic potential of PF-06647263 in vitro. In PDX mouse models, tumor regression has likewise been documented. Phase I results (Table 2), however, were frustrating, with only two responses, leading to the termination of development in TNBC [49].

Immunotherapy and ADC Combinations

Immunotherapy—in the form of immune checkpoint blockade targeting either PD(L)-1 (pembrolizumab, nivolumab, atezolizumab) or CTLA-4 (ipilimumab), has recently changed the natural history of multiple solid tumors [92]. In breast cancer, some data suggest the possibility of activity, particularly in TNBC (Impassion 130) and HER2+ disease (PANACEA), though thus far with activity that is not comparable to that seen in other diseases [93, 94]. Breast cancer, though still immunogenic, is relatively less so, particularly when compared with lung cancer, bladder cancer, or melanoma, with much lower median mutation burden, less lymphocyte infiltration, and less PD-L1 expression. Therefore, it is likely that in order to obtain substantial results in breast cancer, immune check point blockade agents will need to be combined, either sequentially or concomitantly, with other agents [95].

Some pre-clinical evidence suggests that ADCs can prime the tumor microenvironment and potentially improve responses to checkpoint blockade [96]. Biopsies taken 3 weeks after exposure to T-DM1 in the WSG-ADAPT trial suggest increased T cell infiltration. In mouse models, T cells and macrophages in the tumor microenvironment showed increased CTLA-4 and PD(L)-1 expression and T-DM1 + check point blockade showed synergistic activity [97].

The KATE2 trial is the first presented study to tests ADC and immunotherapy combination. Two-hundred and two patients having failed first-line treatment for advanced disease were randomized between T-DM + atezolizumab or T-DM1 + placebo. Though overall a benefit in terms of PFS was not detectable, a numerical difference was present for patients with PD-L1-positive disease (8.5 vs 4.1 m) [98]. Other ADCs, including

trastuzumab deruxtecan, are also being investigated in phase I trials in combination with immune-checkpoint blockade (NCT03523572).

Functional Imaging

As is the case with other anti-cancer agents, patients receive ADCs without a clear picture of whether they will derive any benefit from it because of both innate and acquired resistance as well as tumor heterogeneity. This leads to the possibility of needless toxicity, expenses as well as wasted time in which the patient could have received a more effective treatment [99].

Functional imaging holds the potential of addressing this issue. Whole body imaging using anti-HER2 specific probes, such as ^{89}Zr-trastuzumab (among many others), is able to identify tumors actively expressing HER2—a matter of potential clinical use as downregulation/structural receptor alterations are important mechanisms of trastuzumab resistance. For ADCs, this carries major consequences as without binding to target activity is marginal. Indeed, the ZEPHYR trial provides evidence that this concept is clinical useful, by combining traditional PET/CT with ^{89}Zr-trastuzumab PET/CT as means of response predictions in patients receiving T-DM1. The results of this study show that patients with positive HER2 PET/CTs and with an early response on the FDG-PET/CT have much better outcomes (time to treatment failure 15 m vs 2.8 months for patients with a negative HER2 PET/CT and a non-response on the first early FDG-PET/CT [100].

Conclusion

ADCs represent an elegant evolution of the concepts behind both chemotherapy and targeted therapy, which holds the promise to maximize efficacy while minimizing toxicity. The initial success of T-DM1 in breast cancer led to an acceleration in the field with over 60 new ADCs being in development. Nevertheless, the current panorama of ADCs also highlights the challenges of cancer drug development—multiple drugs with complex science, heavy investment behind it, and with sound pre-clinical evidence showing ultimately little or no activity in clinical situations. Furthermore, more recent ADCs, despite advances in linker technology, have displayed a toxicity profile that is similar or more intense than some types of chemotherapy. Cost, particularly when balanced against lower than expected efficacy and higher than anticipated toxicity, is also a substantial concern to the class. In coming years, though some ADCs may come into clinical use as monotherapy, combinations of ADCs, particularly with immunotherapy, are likely to further improve outcomes.

Compliance with Ethical Standards

Conflict of Interest

Noam Pondé has received travel support from Roche/Genentech, Janssen-Cilag, and Mundipharma, as well as speaker's fees from Mundipharma. The institute he works for has received research funding from AstraZeneca, Lilly,

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Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–86.
2. Cancer of the Breast (Female) - SEER Stat Fact Sheets [Internet]. [cited 2016 Oct 24]. Available from: http://seer.cancer.gov/statfacts/html/breast.html. Accessed 15 Sept 2018.
3. Cardoso F, Costa A, Senkus E, Aapro M, André F, Barrios CH, et al. 3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol. 2016;mdw544.
4. Sonnenblick A, Pondé N, Piccart M. Metastatic breast cancer: the Odyssey of personalization. Mol Oncol. 2016;10(8):1147–59.
5. Pegram M, Hsu S, Lewis G, Pietras R, Beryt M, Sliwkowski M, et al. Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers. Oncogene. 1999;18(13):2241–51.
6. Giansanti P, Preisinger C, Huber KVM, Gridling M, Superti-Furga G, Bennett KL, et al. Evaluating the promiscuous nature of tyrosine kinase inhibitors assessed in A431 epidermoid carcinoma cells by both chemical- and phosphoproteomics. ACS Chem Biol. 2014;9(7):1490–8.
7. Tolcher AW. Antibody drug conjugates: lessons from 20 years of clinical experience. Ann Oncol. 2016;27(12):2168–72.
8. Moek KL, de Groot DJA, de Vries EGE, Fehrmann RSN. The antibody–drug conjugate target landscape across a broad range of tumour types. Ann Oncol. 2017;28(12):3083–91.
9. Beck A, Goetsch L, Dumontet C, Corvaïa N. Strategies and challenges for the next generation of antibody–drug conjugates. Nat Rev Drug Discov. 2017;16(5):315–37.
10. Damelin M, Zhong W, Myers J, Sapra P. Evolving strategies for target selection for antibody-drug conjugates. Pharm Res. 2015;32(11):3494–507.
11. Visintin A, Knowlton K, Tyminski E, Lin C-I, Zheng X, Marquette K, et al. Novel anti-TM4SF1 antibody-drug conjugates with activity against tumor cells and tumor vasculature. Mol Cancer Ther. 2015;14(8):1868–76.
12. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012;366(10):883–92.
13. Issell BF, Crooke ST. Maytansine. Cancer Treat Rev. 1978;5(4):199–207.
14. Cianfriglia M. The biology of MDR1-P-glycoprotein (MDR1-Pgp) in designing functional antibody drug conjugates (ADCs): the experience of gemtuzumab ozogamicin. Ann Ist Super Sanita. 2013;49(2):150–68.
15. McCombs JR, Owen SC. Antibody drug conjugates: design and selection of linker, Payload and Conjugation Chemistry. AAPS J. 2015;17(2):339–51.
16. Staudacher AH, Brown MP. Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required? Br J Cancer. 2017;117(12):1736–42.
17. Masters JC, Nickens DJ, Xuan D, Shazer RL, Amantea M. Clinical toxicity of antibody drug conjugates: a meta-analysis of payloads. Investig New Drugs. 2018;36(1):121–35.
18. Ait-Oudhia S, Zhang W, Mager DE. A mechanism-based PK/PD model for hematological toxicities induced by antibody-drug conjugates. AAPS J. 2017;19(5):1436–48.
19. Ravry MJ, Omura GA, Birch R. Phase II evaluation of maytansine (NSC 153858) in advanced cancer. A

Southeastern Cancer Study Group trial. Am J Clin Oncol. 1985;8(2):148–50.
20. Lambert JM, Chari RVJ. Ado-trastuzumab emtansine (T-DM1): an antibody–drug conjugate (ADC) for HER2-positive breast cancer. J Med Chem. 2014;57(16):6949–64.
21. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783–91.
22.•• Diéras V, Miles D, Verma S, Pegram M, Welslau M, Baselga J, 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(6):732–4.
Updated results of the pivotal EMILIA trial.
23. Welslau M, Diéras V, Sohn J-H, Hurvitz SA, Lalla D, Fang L, et al. Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer: PROs from phase 3 T-DM1 HER2+ MBC study. Cancer. 2014;120(5):642–51.
24. Krop IE, Kim S-B, González-Martín A, LoRusso PM, Ferrero J-M, Smitt M, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(7):689–99.
25.•• Krop IE, Kim S-B, Martin AG, LoRusso PM, Ferrero J-M, Badovinac-Crnjevic T, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol. 2017;18(6):743–5.
Updated results of the pivotal TH3RESA trial.
26. Bartley K, Wildiers H, Kim S-B, Krop IE, Kang J, Yu R, et al. Patient-reported outcomes (PROs) from TH3RESA, a phase 3 study of trastuzumab emtansine (T-DM1) versus treatment of physician's choice (TPC) in patients with pretreated HER2-positive advanced breast cancer. J Clin Oncol. 2014;32(26_suppl):153.
27. Perez EA, Barrios C, Eiermann W, Toi M, Im Y-H, Conte P, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: primary results from the phase III MARIANNE study. J Clin Oncol. 2017;35(2):141–8.
28. von Minckwitz G, Huang C-S, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med [Internet]. 2018 5 [cited 2018 Dec 10]; Available from: http://www.nejm.org/doi/10.1056/NEJMoa1814017. Accessed 15 Sept 2018.
29. Hurvitz SA, Martin M, Symmans WF, Jung KH, Huang C-S, Thompson AM, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol [Internet]. 2017 Nov [cited 2017 Nov 30]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S1470204517307167. Accessed 15 Sept 2018.
30. Burris HA, Rugo HS, Vukelja SJ, Vogel CL, Borson RA, Limentani S, 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 Off J Am Soc Clin Oncol. 2011;29(4):398–405.
31. Krop IE, LoRusso P, Miller KD, Modi S, Yardley D, Rodriguez G, 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 Off J Am Soc Clin Oncol. 2012;30(26):3234–41.
32. Krop IE, Beeram M, Modi S, Jones SF, Holden SN, Yu W, et al. Phase I study of trastuzumab-DM1, an HER2 antibody-drug conjugate, given every 3 weeks to patients with HER2-positive metastatic breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28(16):2698–704.
33. Hurvitz SA, Dirix L, Kocsis J, Bianchi GV, Lu J, Vinholes J, et al. Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(9):1157–63.
34.• Pondé N, Brandão M, El-Hachem G, Werbrouck E, Piccart M. Treatment of advanced HER2-positive breast cancer: 2018 and beyond. Cancer Treat Rev. 2018;67:10–2.
Complete overview of the current results of the field.
35. Swain SM, Baselga J, Kim S-B, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724–34.
36. Fabi A, Giannarelli D, Moscetti L, Santini D, Zambelli A, Laurentiis MD, et al. Ado-trastuzumab emtansine (T-DM1) in HER2+ advanced breast cancer patients: does pretreatment with pertuzumab matter? Future Oncol. 2017;13(30):2791–7.
37. Vici P, Pizzuti L, Michelotti A, Sperduti I, Natoli C, Mentuccia L, et al. A retrospective multicentric observational study of trastuzumab emtansine in HER2 positive metastatic breast cancer: a real-world experience. Oncotarget. 2017 22 [cited 2018 Jul 18];8(34). Available from: http://www.oncotarget.com/fulltext/18176. Accessed 15 Sept 2018.
38. Conte B. Effectiveness of trastuzumab emtansine (TDM1) in patients with HER2-positive advanced breast cancer (ABC) progressing after taxane plus

pertuzumab plus trastuzumab. Ann Oncol. 2018;29(suppl_8):viii90–viii121. https://doi.org/10.1093/annonc/mdy272ESMO 2018; Munich.
39. Schneeweiss A. Ado-trastuzumab for the treatment of metastatic HER2-amplified breast cancer patients previously treated with pertuzumab. SABCS 2018; San Antonio, Texas.
40. Kim S-B, Wildiers H, Krop IE, Smitt M, Yu R, Lysbet de Haas S, et al. Relationship between tumor biomarkers and efficacy in TH3RESA, a phase III study of trastuzumab emtansine (T-DM1) vs. treatment of physician's choice in previously treated HER2-positive advanced breast cancer: Biomarker analyses in TH3RESA. Int J Cancer. 2016;139(10):2336–42.
41. Badve SS, Gokmen-Polar Y, Hoersch S, Xu J, Ruschoff J, de Haas S, et al. Role of tumor infiltrating lymphocytes (TILs) in HER2+ metastatic breast cancers (MBC) treated with trastuzumab emtansine (T-DM1) or lapatinib plus capecitabine (L+C) (EMILIA Trial). J Clin Oncol. 2016;34(15_suppl):607.
42. Baselga J, Lewis Phillips GD, Verma S, Ro J, Huober J, Guardino E, et al. Relationship between tumor biomarkers and efficacy in EMILIA, a phase III study of trastuzumab emtansine in HER2-positive metastatic breast cancer. Clin Cancer Res 2016 26.
43. Montemurro F, Ellis P, Delaloge S, Wuerstlein R, Anton A, Button P, et al. Safety and efficacy of trastuzumab emtansine (T-DM1) in 399 patients with central nervous system metastases: exploratory subgroup analysis from the KAMILLA study. San Antonio: SABCS; 2016.
44. Krop IE, Lin NU, Blackwell K, Guardino E, Huober J, Lu M, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. Ann Oncol. 2015;26(1):113–9.
45. Bartsch R, Berghoff AS, Vogl U, Rudas M, Bergen E, Dubsky P, et al. Activity of T-DM1 in Her2-positive breast cancer brain metastases. Clin Exp Metastasis. 2015;32(7):729–37.
46. Earl HM. PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): randomised phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results. Slide set. Chicago: ASCO; 2018.
47. Martin M, Holmes FA, Ejlertsen B, Delaloge S, Moy B, Iwata H, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(12):1688–700.
48. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med. 2017;377(2):122–31.
49. Garrido-Laguna I. A phase I study of PF-06647263, a novel EFNA4-ADC, in patients with metastatic triple negative breast cancer. Chicago: ASCO; 2017.
50. Xu B. An open-label, multicenter, phase Ib study to evaluate RC48-ADC in patients with HER2-positive metastatic breast cancer. Chicago: ASCO; 2018.
51. Wang J. An open-label, dose-escalation phase I study to evaluate RC48-ADC, a novel antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer. Chicago: ASCO; 2018.
52. Sachdev JC. PF-06647020 (PF-7020), an antibody-drug conjugate (ADC) targeting protein tyrosine kinase 7 (PTK7), in patients (pts) with advanced solid tumors:r of a phase I dose escalation and expansion study. Chicago: ASCO; 2018.
53. Modi S. Phase 1 study of the antibody-drug conjugate SGN-LIV1A in patients with heavily pretreated triple-negative metastatic breast cancer. Chicago: ASCO; 2018.
54. Gomez-Roca C. A phase I study of SAR566658, an anti CA6-antibody drug conjugate (ADC), in patients (Pts) with CA6-positive advanced solid tumors (STs) (NCT01156870). Chicago: ASCO; 2018.
55. Bardia A. Efficacy of sacituzumab govitecan (anti-Trop-2-SN-38 antibody-drug conjugate) for treatment-refractory hormone-receptor positive (HR+)/HER2– metastatic breast cancer (mBC). Chicago: ASCO; 2018.
56. Bardia A, Mayer IA, Diamond JR, Moroose RL, Isakoff SJ, Starodub AN, 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 Off J Am Soc Clin Oncol. 2017;35(19):2141–8.
57. Bardia A. Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate, as ≥3rd-line therapeutic option for patients with relapsed/refractory metastatic triple-negative breast cancer (mTNBC): efficacy results. San Antonio: SABCS; 2017.
58. Burris HA. A phase I/II study of CR011 vcMMAE (CDX 011), an antibody drug conjugate, in patients with locally advanced or metastatic breast cancer. San Antonio, Texas.
59. Pegram M. 47O - Phase 1 study of bispecific HER2 antibody-drug conjugate MEDI4276 in patients with advanced HER2-positive breast or gastric cancer. Paris: TAT; 2018.
60. Iwata H. Trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing solid tumors: long-term results of a large phase 1 study with multiple expansion cohorts. Chicago: ASCO; 2018.
61. Saura C. A phase I expansion cohorts study of SYD985 in heavily pretreated patients with HER2-positive or HER2-low metastatic breast cancer. In Chicago, IL, USA.
62. Hamilton EP. 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. Chicago: ASCO; 2018.
63. Fehrenbacher L. NSABP B-47 (NRG oncology): phase III randomized trial comparing adjuvant chemotherapy with adriamycin (A) and cyclophosphamide (C) → weekly paclitaxel (WP), or docetaxel (T) and C with or

without a year of trastuzumab (H) in women with node-positive or high-risk node-negative invasive breast cancer (IBC) expressing HER2 staining intensity of IHC 1+ or 2+ with negative FISH (HER2-low IBC). In San Antonio, Texas;
64. Saura C. Primary results of LORELEI: a phase II randomised double-blind study of neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with ER-positive/HER2-negative early stage breast cancer. Madrid: ESMO; 2017.
65. Bardia A, Mayer IA, Vahdat LT, Tolaney SM, Isakoff SJ, Diamond JR, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. N Engl J Med. 2019;380(8):741–51.
66. Bergstrom D. A novel, highly potent HER2-targeted antibody-drug conjugate (ADC) for the treatment of low HER2-expressing tumors and combination with trastuzumab-based regimens in HER2-driven tumors. Philadelphia: AACR; 2015.
67. Bergstrom D. XMT-1522 induces tumor regressions in preclinical models representing HER2 positive and HER2 low expressing breast cancer. San Antonio: SABCS; 2015.
68. van der Lee MMC, Groothuis PG, Ubink R, van der Vleuten MAJ, van Achterberg TA, Loosveld EM, et al. The preclinical profile of the duocarmycin-based HER2-targeting ADC SYD985 predicts for clinical benefit in low HER2-expressing breast cancers. Mol Cancer Ther. 2015;14(3):692–703.
69. Aftimos P. SYD985, a novel anti-HER2 ADC, shows promising activity in patients with HER2-positive and HER2-low metastatic breast cancer. San Antonio: SABCS; 2017.
70. Doi T, Iwata H, Tsurutani J, Takahashi S, Park H, Redfern CH, et al. Single agent activity of DS-8201a, a HER2-targeting antibody-drug conjugate, in heavily pretreated HER2 expressing solid tumors. J Clin Oncol. 2017;35(15_suppl):108.
71. Modi S. Safety and efficacy results from a phase 1 study of DS-8201a in patients with HER2 expressing breast cancers. San Antonio: SABCS; 2017.
72. Abstract P6-17-06: Characterization, monitoring and management of interstitial lung disease in patients with metastatic breast cancer: analysis of data available from multiple studies of DS-8201a, a HER2-targeted antibody drug conjugate with a topoisomer… | Cancer Res [Internet]. [cited 2019 Feb 26]. Available from: http://cancerres.aacrjournals.org/content/79/4_Supplement/P6-17-06. Accessed 15 Sept 2018.
73. Reynolds JG, Geretti E, Hendriks BS, Lee H, Leonard SC, Klinz SG, et al. HER2-targeted liposomal doxorubicin displays enhanced anti-tumorigenic effects without associated cardiotoxicity. Toxicol Appl Pharmacol. 2012;262(1):1–10.
74. LoRusso P, Krop I, Miller K, Ma C, Siegel BA, Shields AF, et al. Abstract CT234: a phase I study of MM-302, a HER2-targeted PEGylated liposomal doxorubicin, in patients with HER2+ metastatic breast cancer. Cancer Res. 2015;75(15 Supplement):CT234.
75. Miller K, Cortes J, Hurvitz SA, Krop IE, Tripathy D, Verma S, 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 [Internet]. 2016 Dec [cited 2017 Dec 5];16(1). Available from: http://bmccancer.biomedcentral.com/articles/10.1186/s12885-016-2385-z. Accessed 15 Sept 2018.
76. Li JY, Perry SR, Muniz-Medina V, Wang X, Wetzel LK, Rebelatto MC, et al. A biparatopic HER2-targeting antibody-drug conjugate induces tumor regression in primary models refractory to or ineligible for HER2-targeted therapy. Cancer Cell. 2016;29(1):117–29.
77. Yao X, Jiang J, Wang X, Huang C, Li D, Xie K, et al. A novel humanized anti-HER2 antibody conjugated with MMAE exerts potent anti-tumor activity. Breast Cancer Res Treat. 2015;153(1):123–33.
78. Goldenberg DM, Stein R, Sharkey RM. The emergence of trophoblast cell-surface antigen 2 (TROP-2) as a novel cancer target. Oncotarget [Internet]. 2018 Jun 22 [cited 2018 Jul 19];9(48). Available from: http://www.oncotarget.com/fulltext/25615. Accessed 15 Sept 2018.
79. Ocean AJ, Starodub AN, Bardia A, Vahdat LT, Isakoff SJ, Guarino M, et al. Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate for the treatment of diverse epithelial cancers: Safety and pharmacokinetics. Cancer. 2017;123(19):3843–54.
80. Rose AAN, Grosset AA, Dong Z, Russo C, MacDonald PA, Bertos NR, et al. Glycoprotein nonmetastatic B is an independent prognostic indicator of recurrence and a novel therapeutic target in breast cancer. Clin Cancer Res. 2010;16(7):2147–56.
81. Maric G, Annis MG, Dong Z, Rose AAN, Ng S, Perkins D, et al. GPNMB cooperates with neuropilin-1 to promote mammary tumor growth and engages integrin α5β1 for efficient breast cancer metastasis. Oncogene. 2015;34:5494–504.
82. Rose AAN, Biondini M, Curiel R, Siegel PM. Targeting GPNMB with glembatumumab vedotin: current developments and future opportunities for the treatment of cancer. Pharmacol Ther. 2017;179:127–41.
83. Bendell J, Saleh M, Rose AAN, Siegel PM, Hart L, Sirpal S, et al. Phase I/II study of the antibody-drug conjugate glembatumumab vedotin in patients with locally advanced or metastatic breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2014;32(32):3619–25.
84. Yardley DA, Weaver R, Melisko ME, Saleh MN, Arena FP, Forero A, et al. EMERGE: a randomized phase II study of the antibody-drug conjugate glembatumumab vedotin in advanced glycoprotein NMB-expressing breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2015;33(14):1609–19.
85. Vahdat LT, Forero-Torres A, Schmid P, Blackwell K, Telli ML, Melisko M, 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.
86. Taylor KM, Morgan HE, Smart K, Zahari NM, Pumford S, Ellis IO, et al. The emerging role of the LIV-1 subfamily of zinc transporters in breast cancer. Mol Med. 2007;13(7–8):396–406.
87. Sussman D, Smith LM, Anderson ME, Duniho S, Hunter JH, Kostner H, et al. SGN-LIV1A: a novel antibody-drug conjugate targeting LIV-1 for the treatment of metastatic breast cancer. Mol Cancer Ther. 2014;13(12):2991–3000.
88. Damelin M, Bankovich A, Bernstein J, Lucas J, Chen L, Williams S, et al. A PTK7-targeted antibody-drug conjugate reduces tumor-initiating cells and induces sustained tumor regressions. Sci Transl Med. 2017;9(372):eaag2611.
89. Lisabeth EM, Falivelli G, Pasquale EB. Eph receptor signaling and ephrins. Cold Spring Harb Perspect Biol. 2013;5(9):–a009159.
90. Barquilla A, Pasquale EB. Eph receptors and ephrins: therapeutic opportunities. Annu Rev Pharmacol Toxicol. 2015;55(1):465–87.
91. Damelin M, Bankovich A, Park A, Aguilar J, Anderson W, Santaguida M, et al. Anti-EFNA4 calicheamicin conjugates effectively target triple-negative breast and ovarian tumor-initiating cells to result in sustained tumor regressions. Clin Cancer Res. 2015;21(18):4165–73.
92. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359(6382):1350–5.
93. Loi S, Giobbie-Hurder A, Gombos A, Bachelot T, Hui R, Curigliano G, et al. Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA): a single-arm, multicentre, phase 1b–2 trial. Lancet Oncol [Internet]. 2019 Feb [cited 2019 Feb 26]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S147020451830812X. Accessed 15 Sept 2018.
94. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and Nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379(22):2108–21.
95. Swoboda A, Nanda R. Immune checkpoint blockade for breast cancer. Cancer Treat Res. 2018;173:155–65.
96. Martin K, Schreiner J, Zippelius A. Modulation of APC function and anti-tumor immunity by anti-cancer drugs. Front Immunol [Internet]. 2015 Sep 29 [cited 2018 Aug 1];6. Available from: http://journal.frontiersin.org/Article/10.3389/fimmu.2015.00501/abstract. Accessed 15 Sept 2018.
97. Müller P, Kreuzaler M, Khan T, Thommen DS, Martin K, Glatz K, et al. Trastuzumab emtansine (T-DM1) renders HER2+ breast cancer highly susceptible to CTLA-4/PD-1 blockade. Sci Transl Med. 2015;7(315):315ra188.
98. Emens LA, Esteva F, Beresford M, Saura C, Laurentiis MD, Kim S-B, et al. Abstract PD3-01: Results from KATE2, a randomized phase 2 study of atezolizumab (atezo)+trastuzumab emtansine (T-DM1) vs placebo (pbo)+T-DM1 in previously treated HER2+ advanced breast cancer (BC). Cancer Res. 2019;79(4 Supplement):PD3-01.
99. Gebhart G, Flamen P, De Vries EGE, Jhaveri K, Wimana Z. Imaging diagnostic and therapeutic targets: human epidermal growth factor receptor 2. J Nucl Med. 2016;57(Suppl 1):81S–8S.
100. Gebhart G, Lamberts LE, Wimana Z, Garcia C, Emonts P, Ameye L, et al. Molecular imaging as a tool to investigate heterogeneity of advanced HER2-positive breast cancer and to predict patient outcome under trastuzumab emtansine (T-DM1): the ZEPHIR trial. Ann Oncol. 2016;27(4):619–24.

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