Revolutionizing Breast Cancer Treatment: The Promise of Antibody-Drug Conjugates

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Abstract: Antibody-drug conjugates (ADCs) have significantly advanced the treatment of breast cancer by integrating the specificity of monoclonal antibodies with the cytotoxic efficacy of chemotherapy, thereby enabling a targeted therapeutic approach that reduces off-target toxicity to normal tissues. Currently, 4 ADCs—sacituzumab govitecan, trastuzumab deruxtecan, trastuzumab emtansine, and the more-recent datopotamab deruxtecan—are approved for clinical application, with several others in advanced stages of development. Although these agents have demonstrated promising clinical efficacy, challenges such as ADC resistance and associated toxicities have emerged, underscoring the need for continued research. Multiple strategies are under investigation to enhance therapeutic benefit through combination regimens with other classes of medications, as are approaches to mitigate resistance mechanisms. Progress in next-generation ADCs, incorporating novel linkers and more potent cytotoxic payloads, holds promise for further improvement in clinical outcomes. Additionally, biomarker-driven strategies to identify those patients most likely to benefit from ADC therapy will support more personalized approaches to treatment. This review explores the structural and mechanistic features of ADCs in breast cancer, highlighting their therapeutic potential, and discusses ongoing clinical trials exploring new-generation ADCs and combination therapies.

Introduction

Antibody-drug conjugates (ADCs) have revolutionized the therapeutic landscape in clinical oncology. By providing a targeted approach that combines the specificity of monoclonal antibodies with the potency of cytotoxic drugs, ADCs aim to enhance the efficacy of treatment while minimizing damage to normal tissue. In breast cancer, a heterogeneous disease comprising various subtypes, 4 ADCs are currently approved by the US Food and Drug Administration (FDA): sacituzumab govitecan (SG; Trodelvy, Gilead), trastuzumab deruxtecan (T-DXd; Enhertu, Daiichi-Sankyo/AstraZeneca), trastuzumab emtansine (T-DM1; Kadcyla, Genentech), and the more-recent datopotamab deruxtecan (Dato-DXd; Datroway, Daiichi Sankyo/AstraZeneca). Many additional ADCs are in development.

Keywords
Antibody-drug conjugates, breast cancer, datopotamab deruxtecan, sacituzumab govitecan, trastuzumab deruxtecan, trastuzumab emtansine

As research continues to elucidate the mechanisms of ADCs and their clinical applications, these therapies hold significant promise for improving outcomes in patients with breast cancer, transforming the landscape of treatment and offering new hope for the management of this complex disease. This review sheds light on the structure of ADCs, describes the mechanism of action of the 4 FDA-approved ADCs in breast cancer, and explores ongoing clinical trials of other ADCs in breast cancer (see eTable at www.hematologyandoncology.net).

The Structure of ADCs

The 3 components of the structure of an ADC are a monoclonal antibody (mAb), a cytotoxic payload, and a chemical linker that conjugates them.

The Antibody

The key to ADC identification of a tumor cell is the antigen expressed on the cell. Ideally, the antigen should be exclusive for tumor tissue and minimally expressed on normal cells to minimize the risk of systemic toxicity.[1] The most common targets for approved ADCs in breast cancer include human epidermal growth factor receptor 2 (HER2) and trophoblast cell surface antigen 2 (TROP2). The main components of the antibody include 2 antigen-binding fragments (Fabs), which recognize the target, and 1 constant fragment (Fc), which binds to Fc receptors on immune effector cells.[2] The optimal antibody in ADC would have low immunogenicity, high binding affinity, the ability to facilitate internalization, and a long half-life.[3] Given their low immunogenicity, fully humanized mAbs are employed in ADCs.[4] Immunoglobulin G (IgG) is the primary backbone of ADCs. Owing to its high binding affinity for Fc receptors—which induces antibody-dependent cell-mediated toxicity (ADCC), antibody-dependent phagocytosis, and complement-dependent cytotoxicity—IgG1 is the subclass most commonly used in ADCs.[5]

Although antigen expression is critical for ADC internalization into cancer cells, emerging clinical trial data indicate that levels of expression do not necessarily correlate with therapeutic response. In the ASCENT trial, SG demonstrated superior clinical outcomes vs chemotherapy in TROP2 subgroups stratified by H-score and membrane cell percentage.[6] Similarly, T-DXd has shown efficacy in HER2-low–expressing and HER2-ultra-low–expressing tumors,[7] underscoring the fact that HER2 overexpression is not essential for a significant therapeutic response. Moreover, it is estimated that only approximately 0.1% of the administered dose of an ADC reaches the targeted tumor cells; most is catabolized off site in nontargeted healthy cells, potentially leading to adverse toxicities.[8,9]

The Linker

The chemical linker binds the cytotoxic payload to the antibody. The ability to remain stable in the circulation is crucial because release of the payload in the bloodstream owing to premature cleavage can decrease efficacy and lead to an off-target effect. Linker chemistry and water solubility define the stability of ADCs and their ability to release payload metabolites, respectively.[10] Cleavable and noncleavable linkers are the 2 types of linkers that can be used in ADCs, according to their metabolic profile inside the cell.[3] Cleavable linkers depend on tumor-specific conditions, including lysosomal enzymes and PH changes. They are subdivided into chemical cleavage linkers (hydrazone and disulfide bonds) and enzyme cleavage linkers (glucuronide and peptide).[11] Premature cleavage can occur in the bloodstream, potentially resulting in systemic toxicity and decreased efficacy.[12] Noncleavable linkers (thioether or maleimidocaproyl group) have no sites for enzymatic or chemical cleavage. Given this fact, they are more stable in plasma and have a longer half-life and a reduced toxicity profile. The release of payload complex inside a tumor cell depends on hydrolysis of the antibody component by lysozymes. The bystander effect, which refers to the killing of neighboring cells that may not express the antigen target, is less frequently observed in ADCs with a noncleavable linker.[13]

The Cytotoxic Payload

The cytotoxic payload is the main agent of an ADC in regard to its efficacy and potency. Agents employed in ADC development aim to provide increased cytotoxicity with minimal intracellular concentration after drug internalization. The most common payload targets are DNA, microtubules, and topoisomerase I. DNA-damaging compounds include calicheamicin, pyrrolobenzodiazepines, and duocarmycin. Tubulin inhibitors include tubulysins, auristatins, and maytansinoids. Camptothecin, deruxtecan, and govitecan target topoisomerase, whereas α-amanitin inhibits RNA polymerase.[14] Payload conjugation to antibodies occurs through either cysteine or lysine residues.[15] The drug-antibody ratio (DAR), a significant ADC parameter, refers to the number of payload molecules attached to a single mAb. The higher the DAR, the higher the efficacy of an ADC but the lower its therapeutic index owing to rapid clearance and increased toxicity.[16]

ADCs in Breast Cancer

Trastuzumab Emtansine

T-DM1 was the first ADC approved for the treatment of breast cancer. T-DM1 is composed of the monoclonal antibody trastuzumab conjugated to a potent tubulin

polymerization inhibitor, DM-1, via a noncleavable maleimidomethyl cyclohexane-1-carboxylate (MCC) thioether linker through lysine residues. The average DAR of T-DM1 is approximately 3.5.[17] After selectively binding to tumor cells that overexpress the HER2 receptor, T-DM1 is internalized via endocytosis and transported to lysosomes. Thereafter, trastuzumab degradation by lysozymes leads to the release of lysin-MCC-DM1 and delivery into the cytoplasm, where it blocks tubulin polymerization and induces cell death without exhibiting bystander effect.[17]

Metastatic HER2+ Breast Cancer. T-DM1 was initially granted approval for the treatment of patients with metastatic HER2-positive (HER2+) disease who previously received trastuzumab and taxane therapy, either separately or in combination.[18] Approval was based on the EMILIA trial.[19] In comparison with lapatinib plus capecitabine, T-DM1 significantly improved median progression-free survival (PFS; 9.6 vs 6.4 months) and median overall survival (OS; 30.9 vs 25.1 months). In addition, the objective response rate (ORR) was 43.6% with T-DM1 vs 30.8% with lapatinib plus capecitabine.[19] The final analysis continued to show significant improvement in median OS (29.9 vs 25.9 months; hazard ratio [HR], 0.75), with a safety profile similar to those in prior analyses.[20]

Early-Stage HER2+ Breast Cancer. Further evaluation of T-DM1 was extended to early HER2+ disease. In the KATHERINE trial, patients who had residual invasive disease at surgery after neoadjuvant taxane and trastuzumab were randomized to T-DM1 vs trastuzumab.[21] The rate of invasive disease-free survival (iDFS) at 3 years, the primary endpoint, was 88.3% in the T-DM1 group vs 77% in the trastuzumab group (HR, 0.5; $P<.001$).[21] On the basis of these findings, the FDA expanded the use of T-DM1 to the adjuvant treatment of early HER2+ breast cancer for patients with residual invasive disease after neoadjuvant treatment based on a taxane and trastuzumab.[22] At 8.4-year follow-up, the rate of iDFS remained higher in the T-DM1 group than in the trastuzumab group (32.2% vs 19.7%; HR, 0.54), without new safety signals.[23] Real-world data from the KARMA study indicated a safety profile that was consistent and manageable, aligning with data from the KATHERINE trial.[24]

Trastuzumab Deruxtecan

T-DXd represents a significant advancement in the ADC landscape, with clinical applications expanding to a wider range of solid tumors. Although its monoclonal antibody component, trastuzumab, specifically targets HER2, T-DXd has proved effective not only in HER2+ breast cancer but also in HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+/in situ hybridization [ISH]–) and HER2-ultra-low (IHC 0 with membrane-staining) tumors.[7] This enhanced therapeutic effect is driven by the unique properties of the T-DXd linker and payload. The specialized, tetrapeptide-based cleavable linker in T-DXd avoids the premature release of payload in the circulation and allows a DAR of 8, higher than that of T-DM1.[25] The cytotoxic agent DXd is an exatecan derivative that inhibits topoisomerase I with potency10-fold higher than that of the active metabolite of irinotecan (SN-38).[26] In addition, a significant bystander effect is exhibited, given the lipophilic structure and high membrane permeability of DXd. This bystander effect allows the payload to enter surrounding cells and exert a cytotoxic effect in tumor cells that may not express HER2 receptor.[27] The potency of the payload, the bystander killing effect, and the relatively high DAR enhance the antitumor activity of T-DXd.[28]

Metastatic HER2+ Disease. In December 2019, T-DXd received accelerated approval for the treatment of metastatic HER2+ breast cancer after 2 or more HER2-directed therapies[29] on the basis of results of the single-arm, phase 2 DESTINY-Breast01 trial.[30] Among 184 patients, the response rate was 60.9%, with a median duration of response (DOR) of 14.8 months and median PFS of 16.4 months in the initial analysis.[30] When compared with T-DM1 in the confirmatory phase 3 DESTINY-Breast03 trial, T-DXd showed significant improvement in PFS (not reached vs 6.8 months; HR, 0.284) and the 12-month OS rate (94.1% vs 85.9%).[31] This finding led to approval in May 2022 for the treatment of unresectable or metastatic HER2+ disease in patients who have received a prior anti-HER2–based regimen either in the metastatic setting or in the neoadjuvant or adjuvant setting and in whom disease has recurred during or within 6 months after completion of therapy.[32] The updated results from DESTINY-Breast03 continued to show significant improvement with T-DXd vs T-DM1 in PFS and OS; median PFS was 29.0 vs 7.2 months (HR, 0.30; 95% CI, 0.24-0.38). The 36-month PFS rate was 45.7% vs 12.4%, and median OS was 52.6 vs 42.7 months (HR, 0.73).[33,34] In DESTINY-Breast02,[35] a comparison of T-DXd vs standard of care (SOC) in patients who had received T-DM1 revealed longer PFS with T-DXd (17.8 vs 6.9 months; $P<.0001$). This was the first randomized trial to demonstrate that an ADC can overcome resistance to prior ADCs.[35] In the DESTINY-Breast12 trial,[36] T-DXd demonstrated significant and durable overall and intracranial clinical activity in patients with HER2+ metastatic breast cancer, including a substantial cohort with stable or active brain metastases. The 12-month PFS rate was 61.6%, and the central nervous system PFS rate was 58.9%. These results were similar in patients with either stable (57.8%) or active (60.1%) brain metastases.[36]

Metastatic HER2-Low and HER2-Ultra-Low Disease. The quantitative expression of HER2 on tumor cells is assessed with IHC and ISH.[37] HER2-low disease, which refers to tumors with a HER2 IHC score of 1+ or 2+ in the absence of HER2 amplification, accounts for 45% to 55% of all cases of breast cancer.[35] Given the bystander effect, T-DXd was evaluated in the HER2-low setting and demonstrated promising antitumor activity, with an ORR of 37% in 54 patients and a median DOR of 10.4 months.[38] In August 2022, on the basis of results of the DESTINY-Breast04 trial, the FDA extended approval to include patients with HER2-low metastatic breast cancer who have received prior chemotherapy in the metastatic setting or in whom disease has recurred during or within 6 months after the completion of adjuvant chemotherapy.[39] Compared with the physician's choice of treatment, T-DXd significantly improved PFS (9.9 vs 5.1 months; *P*<.001) and OS (23.4 vs 16.8 months; *P*=.001).[39] Interestingly, clinically meaningful activity was also demonstrated in patients with HER2-null advanced breast cancer (best overall response rate, 29.7% in the DAISY trial.[40] As a first-line treatment after endocrine therapy, T-DXd outperformed chemotherapy in metastatic hormone receptor–positive (HR+) disease in the DESTINY-Breast06 trial. Significant improvement in PFS was demonstrated in HER2-low (13.2 vs 8.1 months; HR, 0.62) and HER2-ultra-low (13.2 vs 8.3 months; HR, 0.78) disease.[7] In addition, the ORR was significantly improved in both cohorts without any new safety signals. On the basis of these results, the FDA extended the approval of T-DXd to include unresectable or metastatic HR+/HER2-low or HER-2-ultra-low breast cancer that has progressed on one or more endocrine therapies in the metastatic setting.

Early-Stage HER2+ Disease. Ongoing trials are exploring T-DXd in early-stage disease. The TALENT trial is the first study to evaluate the efficacy of T-DXd in the neoadjuvant setting, randomizing 58 patients with HR+/HER2-low disease to T-DXd monotherapy (arm A) or T-DXd plus anastrozole (arm B). Among 17 patients who completed treatment in arm A, 1 had a pathological complete response (pCR) after 8 cycles and 2 had a residual cancer burden score of I after 6 cycles. In arm B, 1 of 16 patients had a residual cancer burden score of I after 8 cycles. The ORR was 75% in arm A and 63.2% in arm B.[41] In this pilot study, T-DXd demonstrated potential activity in the neoadjuvant setting; however, endocrine therapy did not appear to enhance its therapeutic benefit. Additionally, the SHAMROCK study[42] will enroll patients with stage II or III HER2+ disease to receive neoadjuvant T-DXd for up to 6 cycles. A repeat biopsy after 2 cycles will assess the RNA disruption index (RDI) score to determine the likelihood of pCR. The RDI score has been shown to predict pCR as early as after the first cycle of neoadjuvant chemotherapy in patients with HER2+ breast cancer.[43] On the basis of their RDI score, patients will receive either 4 or 6 cycles of T-DXd before imaging. Those achieving imaging complete response (iCR) will proceed to surgery, whereas those not achieving iCR may receive further systemic therapy or proceed to surgery.[42] DESTINY-Breast05 is a phase 3 trial comparing the efficacy and safety of adjuvant T-DXd with that of T-DM1 in patients with HER2+ invasive breast cancer who have residual disease after neoadjuvant therapy.[44] The trial aims to enroll approximately 1600 patients, randomized in a 1:1 ratio to receive either T-DXd (5.4 mg/kg) or T-DM1 (3.6 mg/kg) every 3 weeks for 14 cycles. The primary efficacy endpoint is iDFS, with secondary endpoints including OS and disease-free survival.[44] DESTINY-Breast11 will assess the efficacy of T-DXd monotherapy or T-DXd followed by paclitaxel, trastuzumab, and pertuzumab (Perjeta, Genentech; THP) vs that of dose-dense doxorubicin plus cyclophosphamide followed by THP in the neoadjuvant setting. Patients will be randomized in a 1:1:1 ratio and will be stratified by hormone receptor status and HER2 IHC score. Surgery will be performed 3 to 6 weeks after the administration of the last cycle of treatment, followed by adjuvant therapy according to local clinical standards. The primary endpoint is pCR.[45]

Sacituzumab Govitecan

High expression of TROP2, the antibody target in SG, has been associated with a poor prognosis, particularly in triple-negative breast cancer (TNBC).[46,47] The monoclonal antibody is connected to the payload, SN-38, via a hydrolyzable CLA2 linker. SN-38, the active metabolite of irinotecan, is a topoisomerase I inhibitor that causes double-stranded DNA breaks and cell death, exhibiting a bystander effect.[48]

Metastatic TNBC. SG was initially granted accelerated approval for previously treated metastatic TNBC in April 2020 on the basis of a phase 1/2 single-arm trial.[49] In patients with heavily pretreated metastatic TNBC, the response rate was 33.3% with SG. After results of ASCENT trial[50] demonstrating significant improvement vs chemotherapy in PFS (5.6 vs 1.7 months; *P*<.001) and OS (12.1 vs 6.1 months; *P*<0.001), SG was granted full approval by the FDA in April 2021.[51] In the final analysis, continued improvement was demonstrated in PFS (4.8 vs 1.7 months; HR, 0.41) and OS (11.8 vs 6.9 months; HR, 0.51).[6] In the first-line setting, SG is currently being evaluated in the randomized, phase 3 ASCENT-03 trial for programmed death ligand 1–negative (PD-L1–) TNBC. Patients will be randomized to SG vs chemotherapy (gemcitabine/carboplatin, paclitaxel, or nab-paclitaxel [Abraxane, Bristol Myers Squibb]) until disease progression or

unacceptable toxicity.[52] The ASCENT-04 trial is assessing the efficacy of SG plus pembrolizumab (Keytruda, Merck) vs standard chemotherapy as a first-line treatment in PD-L1+ disease. The key exclusion criterion is prior exposure to a topoisomerase inhibitor.[53]

Early-Stage TNBC. Further evaluation of SG is ongoing in early breast cancer. The NeoSTAR study demonstrated the efficacy of neoadjuvant SG in early-stage TNBC. Among 49 participants who completed 4 cycles of SG, the pCR rate was 30% and the ORR was 64%. At a median follow-up of 18.9 months, the 2-year event-free survival rate was 95% and was 100% in those achieving a pCR.[54] In the adjuvant setting, the combination of pembrolizumab plus SG will be evaluated in the phase 3 ASCENT-05 trial. Patients with residual disease after neoadjuvant therapy will be randomized to pembrolizumab plus SG vs pembrolizumab plus capecitabine. The primary endpoint is iDFS.[55]

Metastatic HR+ Disease. SG was also approved in metastatic HR+ disease[56] after the TROPiCS-02 study.[57] The ORR and the clinical benefit rate were higher in the SG group (21% vs 14%, respectively) than in the chemotherapy group (34% vs 22%, respectively). In addition, PFS was longer in the SG group than in the chemotherapy group (5.5 vs 4 months; *P*=.0003), with similar OS (13.9 vs 12.3 months; *P*=.143).[57] However, in the updated analysis, OS was significantly longer in the SG group (14.4 vs 11.2 months; *P*=.02), with a higher ORR (21% vs 14%; *P*=.03).[58] The ASCENT-07 trial will be assessing SG vs chemotherapy in patients with inoperable locally advanced disease or metastatic disease after endocrine therapy who are eligible for first chemotherapy. PFS is the primary endpoint.[59]

Datopotamab Deruxtecan

The humanized monoclonal antibody in Dato-DXd, like the one in SG, binds to TROP2 receptors on tumor cells. The payload, DXd, is conjugated with the antibody via a cleavable tetrapeptide-based linker, allowing stability in the bloodstream and an extended half-life.[60] A bystander effect is seen with Dato-DXd.[61]

Metastatic TNBC. Dato-DXd was initially evaluated in TROPION-PanTumor01, a first-in-human study of solid tumors. In the preliminary data on TNBC, Dato-DXd showed durable antitumor activity and manageable toxicity.[62,63] The ORR was 32% in all 44 patients, with the median DOR not reached.[63] In the BEGONIA trial, Dato-DXd plus durvalumab (Imfinzi, AstraZeneca) demonstrated a robust response in the first-line setting in 29 patients with unresectable locally advanced or metastatic TNBC.[64] Updated results from 53 treated patients revealed an ORR of 74%.[65] Further analysis[66] continued to show a durable response, with an ORR of 79% (49 of 62 patients); 6 patients had a complete response and 43 had a partial response. The median DOR was 15.5 months and the median PFS was 13.8 months.[66] The phase 3 TROPION-Breast02 trial[61] will evaluate the efficacy of Dato-DXd monotherapy in patients with treatment-naive locally recurrent or metastatic TNBC who are not eligible for programmed death 1/PD-L1 inhibitors. Patients will be randomized to Dato-DXd vs physician's choice of chemotherapy in a 1:1 ratio. The primary endpoints include PFS and OS.[61] In patients with inoperable locally recurrent disease or metastatic PD-L1+ disease not previously treated with chemotherapy, TROPION-Breast05 will compare Dato-DXd with or without durvalumab vs standard chemotherapy in a 3-arm study. Key exclusion criteria include active brain metastases and prior exposure to a topoisomerase I ADC or TROP2-targeted therapy.[67]

Metastatic HR+ Disease. The TROPION-Breast01 trial randomized patients with previously treated metastatic HR+ breast cancer to Dato-DXd vs chemotherapy.[68] Preliminary data demonstrated significant improvement in PFS vs placebo (6.9 vs 4.9 months; HR, 0.63). Although OS data were not yet mature, a trend favoring Dato-DXd was also observed (HR, 0.84; 95% CI, 0.62-1.14).[68,69] Given these results, Dato-DXd was FDA approved for treatment in patients with previously treated metastatic HR+/HER2– breast cancer.[70] Further analysis from the TROPION-Breast01 trial[71] indicated that adverse events of special interest were predominantly low grade, occurred during the initial treatment cycles, and were manageable. Furthermore, the rate of grade 3 or higher treatment-related adverse events (TRAEs) with Dato-DXd was less than half that observed with investigator's choice of chemotherapy, and fewer TRAEs necessitated dose interruptions or reductions. These findings suggest that Dato-DXd offers improved tolerability vs chemotherapy, highlighting its potential as a favorable treatment option in clinical practice.[71]

Early-Stage Disease. Given the compelling results observed in the metastatic setting, further investigation of Dato-DXd has been initiated in the early-stage context. The ongoing phase 3 TROPION-Breast03 trial[72] is assessing the efficacy and safety of Dato-DXd alone or in combination with durvalumab vs SOC therapy in patients with stage I to III TNBC who have residual invasive disease after neoadjuvant treatment. Eligible patients will be randomized in a 2:1:2 ratio to receive Dato-DXd (for 8 cycles) plus durvalumab (for 9 cycles), Dato-DXd monotherapy, or investigator's choice of therapy (capecitabine, pembrolizumab, or both). The primary endpoint is iDFS for the combination vs SOC. Key secondary endpoints include safety, distant disease–free survival, OS, and iDFS for Dato-DXd monotherapy vs SOC.[72] In the multicenter, phase 3 TROPION-Breast04 trial,[73]

neoadjuvant Dato-DXd with durvalumab followed by adjuvant durvalumab will be evaluated. Patients with treatment-naive stage II to III TNBC or HR-low (estrogen receptor and/or progesterone receptor expression from 1% to <10%)/HER2– disease will be randomized to receive Dato-DXd plus durvalumab vs SOC therapy and will be stratified by lymph node status, tumor stage, HR status, and region. The primary endpoints of the study include pCR and event-free survival. Key secondary endpoints encompass OS, distant disease–free survival, and safety/tolerability.[73]

ADCs in Clinical Development

Multiple other ADCs are being evaluated in breast cancer, including zanidatamab zovodotin, MEDI4276, disitamab vedotin, and ARX788.

Zanidatamab Zovodotin (ZW-49). Antibody modification plays a pivotal role in ADC development. For instance, biparatopic antibodies provide a promising approach to overcoming resistance by enabling increased binding, accelerated HER2 internalization, and enhanced lysosomal degradation. Zanidatamab (ZW25) is a novel, humanized bispecific monoclonal antibody targeting the juxta-membrane extracellular and dimerization domains of HER2. Its unique binding profile enables it to bind HER2 across varying levels of expression, induce receptor clustering and internalization, and downregulate HER2.[74,75] Zanidatamab also inhibits both growth factor–dependent and growth factor–independent tumor cell proliferation while activating immune responses, including ADCC, phagocytosis, and complement-dependent cytotoxicity.[76] Zanidatamab zovodotin, a HER2-based ADC using the biparatopic antibody zanidatamab, demonstrated antitumor activity in HER2+ and HER2-low breast cancer models.[77] When this finding was extended to a phase 1 study, the ADC showed manageable tolerability and efficacy in patients with HER2+ advanced breast and gastric cancers refractory to T-DM1.[78] Keratitis was the only dose-limiting toxicity. MEDI4276, another biparatopic ADC featuring site-specific conjugation, demonstrated limited clinical activity and unfavorable toxicity in a phase 1 trial.[79]

Disitamab Vedotin. Disitamab vedotin (RC48) is a novel HER2-based ADC composed of hertuzumab linked via a cleavable linker to monomethyl auristatin E (MMAE).[80] In HER2+ advanced and metastatic solid tumors, RC48 demonstrated promising efficacy, with an ORR of 37.5% in the subgroup with low to medium HER2 expression and 57.1% in the subgroup with higher HER2 expression. TRAEs included anemia, leukopenia, and elevated transaminases.[81] Pooled analysis of 2 studies in HER2+ and HER2-low breast cancer demonstrated consistent efficacy with different doses.[82]

ARX788. In addition to antibody engineering, linker modification has been developed to bypass multidrug resistance. In a study conducted by Kovtun and colleagues, the response of a PEG4Mal-linked ADC was more pronounced than the responses of non–polar-linked conjugates.[83] ADCs featuring noncleavable linkers, such as T-DM1 employing a thioether linker and ARX788 utilizing a maleimide linker, incorporate an active cytotoxic complex comprising a singular amino acid bound to the linker and the payload. However, this design presents limitations, including restricted membrane permeability and inadequate bystander effect,[84] thereby attenuating drug potency within tumors characterized by low or heterogeneous levels of HER2 expression. However, recent advancements have tackled this challenge, demonstrating promising efficacy in such patient populations. For example, T-DXd exhibited superior antitumor activity vs T-DM1 in individuals with HER2-low tumors and HER2 intratumoral heterogeneity owing to its cleavable linker, higher DAR, and more potent payload.[27] Unlike T-DM1, ARX788 displayed activity in patient-derived xenograft models of HER2-low breast cancer owing to its site-specific approach to conjugation, suggesting that efficient drug delivery might compensate for low antigen expression.[85] Traditional conjugation methods lead to heterogeneous products with variable DARs and conjugation sites. On the other hand, site-specific conjugation yields ADCs with moderate DARs, ensuring greater homogeneity and a favorable therapeutic index.[86] In addition, ARX788 contains a hydrophilic payload with minimal cell permeability to reduce side effects.[87] The ACE-Breast-02 trial[88] examined ARX788 vs lapatinib and capecitabine in patients with HER2+ disease pretreated with trastuzumab and a taxane. PFS was significantly longer with ARX788 than with the control treatment (11.33 vs 8.25 months; HR, 0.64). The most common TRAEs with ARX788 included interstitial lung disease, blurred vision, dry eye, and keratopathy. Interstitial lung disease occurred in 32.3% of patients and was primarily grade 1 or 2, with 3 cases potentially related to drug-induced deaths. Ocular events were observed in 74.5% of patients. These were mainly grade 1 or 2 (55.5%), with no grade 4 or 5 events reported.[88]

Other ADCs. Selection of the payload, a critical component of ADCs and a determinant of resistance, is another area of innovation. Beyond cytotoxic potency, resistance to drug efflux pump–mediated resistance is pivotal.[89] Dual-payload ADCs have emerged as a strategy to combat HER2 heterogeneity and drug resistance effectively. Equipped with both MMAE and MMAF, these ADCs can overcome resistance while maintaining efficacy; they demonstrate significant efficacy in preclinical models of refractory breast cancer with heterogeneous

HER2 expression and are poised for clinical advancement.[90] Payload diversification is one of the promising approaches to overcome payload-mediated resistance by modifying specific components in the cytotoxic agent. Belotecan derivative is an alternate topoisomerase I inhibitor in a novel TROP2-based ADC, SKB-264.[91] In addition, novel generations of HER2-targeted ADCs are in development, including trastuzumab duocarmycin (SYD985), BL-M07D1, TQB2102, and SHR-A1811.

Sequencing Treatment With ADCs

In evaluating individual ADCs, it is essential to consider how these therapies may be sequenced in clinical practice, particularly in relation to cross-resistance and the effectiveness of subsequent treatments. In a study of 32 patients receiving more than one ADC in the metastatic setting, PFS was significantly longer for the first ADC vs the second (ADC2; 7.55 vs 2.53 months; *P*=.006).[92] Subgroup analysis revealed no significant PFS difference between ADC2 with antibody target change vs ADC2 without antibody target change (3.25 vs 2.30 months; *P*=.16). Cross-resistance, defined as progressive disease at the first restaging on ADC2, was higher when ADC2 targeted the same antigen (69.2%) vs a different one (50%). These results suggest that although some patients experience cross-resistance to ADCs, others may demonstrate durable responses, particularly when a different antibody is employed.[92] Another study of patients with metastatic HR+/HER2– disease or TNBC who received multiple ADCs found that cross-resistance occurred in 59.4% of 68 patients at the first restaging. This resistance appeared to be driven more by the antibody target than the payload, emphasizing the heterogeneous nature of resistance mechanisms.[93]

Conclusion and Future Directions

ADCs have emerged as transformative agents in breast cancer therapy, offering targeted treatment that enhances efficacy while minimizing systemic toxicity. The promising clinical outcomes associated with ADCs suggest their potential to reshape treatment paradigms. However, the emergence of resistance to ADCs has highlighted the need for a deeper understanding of resistance mechanisms, underscoring the role of translational medicine. Next-generation sequencing, widely used in metastatic breast cancer to identify targeted genomic alterations, can be instrumental in uncovering resistance mechanisms, potentially involving the ADC pathway from antigen binding to cytotoxic payload effect. Integrating this approach is essential for predicting treatment response and identifying biomarkers of resistance on the basis of individual tumor characteristics and resistance profiles. Such efforts could optimize treatment outcomes through biomarker-driven strategies, enabling the identification of patients most likely to benefit from specific ADCs and the development of companion diagnostics to guide treatment selection. Addressing ADC resistance will be crucial in overcoming a critical challenge in this therapeutic landscape.

Future research should focus on key areas, including the exploration of combination therapies that synergize ADCs with immunotherapies and targeted agents, as well as the identification of predictive biomarkers for patient selection and personalized treatment. Advancing next-generation ADCs with novel linkers and cytotoxic agents will further expand their applicability. Long-term safety assessments and the use of real-world data are essential for understanding ADC effectiveness and tolerability across diverse patient populations. Innovative strategies to combat resistance to ADCs are also critical, such as enhancing antigen targeting through the development of novel ADCs with improved specificity, including the potential use of bispecific antibodies to target multiple antigens simultaneously. Concurrently, efforts are underway to develop payloads with greater cytotoxicity and reduced susceptibility to resistance.

Tailoring ADC therapy according to individual tumor characteristics and resistance profiles can optimize outcomes by incorporating biomarker-driven approaches that identify patients most likely to benefit, along with companion diagnostics for treatment selection. Additionally, combining ADCs with other modalities, such as chemotherapy and immunotherapy, may provide synergistic effects to overcome resistance. By strategically designing these combinations on the basis of insights into resistance mechanisms, it may be possible to improve efficacy while minimizing toxicities. Interdisciplinary collaboration among researchers, clinicians, and pharmaceutical partners will be essential for addressing these challenges and unlocking new opportunities in cancer therapy, ultimately enhancing the effectiveness of ADCs in breast cancer treatment.

Disclosures

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References

1. Khoury R, Saleh K, Khalife N, et al. Mechanisms of resistance to antibody-drug conjugates. *Int J Mol Sci.* 2023;24(11):9674.
2. Hoffmann RM, Coumbe BGT, Josephs DH, et al. Antibody structure and engineering considerations for the design and function of antibody drug conjugates (ADCs). *OncoImmunology.* 2017;7(3):e1395127.
3. Fu Z, Li S, Han S, Shi C, Zhang Y. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. *Signal Transduct Target Ther.* 2022;7(1):93.

4. Abdollahpour-Alitappeh M, Lotfinia M, Gharibi T, et al. Antibody-drug conjugates (ADCs) for cancer therapy: strategies, challenges, and successes. *J Cell Physiol.* 2019;234(5):5628-5642.
5. Natsume A, Niwa R, Satoh M. Improving effector functions of antibodies for cancer treatment: enhancing ADCC and CDC. *Drug Des Devel Ther.* 2009;3:7-16.
6. Bardia A, Rugo HS, Tolaney SM, et al. Final results from the randomized phase III ASCENT clinical trial in metastatic triple-negative breast cancer and association of outcomes by human epidermal growth factor receptor 2 and trophoblast cell surface antigen 2 expression. *J Clin Oncol.* 2024;42(15):1738-1744.
7. Curigliano G, Hu X, Dent RA, et al. Trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow metastatic breast cancer (mBC) with prior endocrine therapy (ET): primary results from DESTINY-Breast06 (DB-06) [ASCO abstract LBA1000]. *J Clin Oncol.* 2024;42(17)(suppl).
8. Baker MP, Reynolds HM, Lumicisi B, Bryson CJ. Immunogenicity of protein therapeutics: the key causes, consequences and challenges. *Self Nonself.* 2010;1(4):314-322.
9. Casi G, Neri D. Antibody-drug conjugates and small molecule-drug conjugates: opportunities and challenges for the development of selective anticancer cytotoxic agents. *J Med Chem.* 2015;58(22):8751-8761.
10. Saber H, Leighton JK. An FDA oncology analysis of antibody-drug conjugates. *Regul Toxicol Pharmacol.* 2015;71(3):444-452.
11. Bargh JD, Isidro-Llobet A, Parker JS, Spring DR. Cleavable linkers in antibody-drug conjugates. *Chem Soc Rev.* 2019;48(16):4361-4374.
12. Flygare JA, Pillow TH, Aristoff P. Antibody-drug conjugates for the treatment of cancer. *Chem Biol Drug Des.* 2013;81(1):113-121.
13. Erickson HK, Widdison WC, Mayo MF, et al. Tumor delivery and in vivo processing of disulfide-linked and thioether-linked antibody-maytansinoid conjugates. *Bioconjug Chem.* 2010;21(1):84-92.
14. Diamantis N, Banerji U. Antibody-drug conjugates—an emerging class of cancer treatment. *Br J Cancer.* 2016;114(4):362-367.
15. Qiu D, Huang Y, Chennamsetty N, Miller SA, Hay M. Characterizing and understanding the formation of cysteine conjugates and other by-products in a random, lysine-linked antibody drug conjugate. *MAbs.* 2021;13(1):1974150.
16. Sun X, Ponte JF, Yoder NC, et al. Effects of drug-antibody ratio on pharmacokinetics, biodistribution, efficacy, and tolerability of antibody-maytansinoid conjugates. *Bioconjug Chem.* 2017;28(5):1371-1381.
17. Hunter FW, Barker HR, Lipert B, et al. Mechanisms of resistance to trastuzumab emtansine (T-DM1) in HER2-positive breast cancer. *Br J Cancer.* 2020;122(5):603-612.
18. Kadcyla [package insert]. South San Francisco, CA: Genentech; 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125427s105lbl.pdf. Accessed April 22, 2024.
19. Verma S, Miles D, Gianni L, et al; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367(19):1783-1791.
20. Diéras 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(6):732-742.
21. von Minckwitz G, Huang CS, Mano MS, et al; KATHERINE Investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med.* 2019;380(7):617-628.
22. T-DM1 approval expanded to include some women with early-stage HER2-positive breast cancer. National Cancer Institute. https://www.cancer.gov/news-events/cancer-currents-blog/2019/kadcyla-fda-breast-her2-adjuvant. Posted May 23, 2019. Accessed May 12, 2024.
23. Loibl S, Mano M, Untch M, et al. Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis [SABCS abstract GS03-12]. *Cancer Res.* 2024;84(9)(suppl).
24. Antolín Novoa S, Escrivá-de-Romaní S, Tolosa Ortega P, et al. Real world data on the demographic and clinicopathological profile and management of patients with early-stage HER2-positive breast cancer and residual disease treated with adjuvant trastuzumab emtansine (KARMA study). *Cancer Treat Res Commun.* 2023;37:100772.
25. Mark C, Lee JS, Cui X, Yuan Y. Antibody-drug conjugates in breast cancer: current status and future directions. *Int J Mol Sci.* 2023;24(18):13726.
26. Schipilliti FM, Drittone D, Mazzuca F, La Forgia D, Guven DC, Rizzo A. Datopotamab deruxtecan: a novel antibody drug conjugate for triple-negative breast cancer. *Heliyon.* 2024;10(7):e28385.
27. Ogitani Y, Hagihara K, Oitate M, Naito H, Agatsuma T. 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(7):1039-1046.
28. Andrikopoulou A, Zografos E, Liontos M, Koutsoukos K, Dimopoulos MA, Zagouri F. Trastuzumab deruxtecan (DS-8201a): the latest research and advances in breast cancer. *Clin Breast Cancer.* 2021;21(3):e212-e219.
29. Narayan P, Osgood CL, Singh H, et al. FDA approval summary: fam-trastuzumab deruxtecan-nxki for the treatment of unresectable or metastatic HER2-positive breast cancer. *Clin Cancer Res.* 2021;27(16):4478-4485.
30. 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;382(7):610-621.
31. Cortés J, Kim SB, Chung WP, et al. Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (mBC): results of the randomized phase III DESTINY-Breast03 study [ESMO abstract LBA1]. *Ann Oncol.* 2021;32(5)(suppl).
32. Enhertu [package insert]. Basking Ridge, NJ: Daiichi Sankyo; 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s017s020lbl.pdf. Accessed April 22, 2024.
33. Hurvitz SA, Hegg R, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet.* 2023;401(10371):105-117.
34. Cortés J, Hurvitz SA, Im SA, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: long-term survival analysis of the DESTINY-Breast03 trial. *Nat Med.* 2024;30(8):2208-2215.
35. André F, Hee Park Y, Kim SB, et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2023;401(10390):1773-1785.
36. Lin N, Ciruelos EM, Jerusalem G, et al. Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2+ advanced/metastatic breast cancer (mBC) with or without brain metastases (BM): DESTINY-Breast12 primary results [ESMO abstract LBA18]. *Ann Oncol.* 2024;35(2)(suppl).
37. Press MF, Hung G, Godolphin W, Slamon DJ. Sensitivity of HER-2/neu antibodies in archival tissue samples: potential source of error in immunohistochemical studies of oncogene expression. *Cancer Res.* 1994;54(10):2771-2777.
38. 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(17):1887-1896.
39. Modi S, Jacot W, Yamashita T, et al; DESTINY-Breast04 Trial Investigators. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med.* 2022;387(1):9-20.
40. Diéras V, Deluche E, Lusque A, et al. Trastuzumab deruxtecan (T-DXd) for advanced breast cancer patients (ABC), regardless HER2 status: a phase II study with biomarkers analysis (DAISY) [SABCS abstract PD8-02]. *Cancer Res.* 2022;82(4)(suppl).
41. Bardia A, Hurvitz S, Press MF, et al. TRIO-US B-12 TALENT: neoadjuvant trastuzumab deruxtecan with or without anastrozole for HER2-low, HR+ early stage breast cancer [SABCS abstract GS2-03]. *Cancer Res.* 2023;83(5)(suppl).
42. Dowling GP, Toomey S, Bredin P, et al. Neoadjuvant trastuzumab deruxtecan (T-DXd) with response-directed definitive therapy in early stage HER2-positive breast cancer: a phase II study protocol (SHAMROCK study). *BMC Cancer.* 2024;24(1):91.
43. Toomey S, Eustace AJ, Pritzker LB, et al. RE: RNA disruption assay as a biomarker of pathological complete response in neoadjuvant trastuzumab-treated human epidermal growth factor receptor 2-positive breast cancer. *J Natl Cancer Inst.* 2016;108(8):djw111.
44. Geyer CE, Untch M, Prat A, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) vs trastuzumab emtansine (T-DM1) in high-risk patients with HER2-positive, residual invasive early breast cancer after neoadjuvant therapy: a randomized, phase 3 trial (DESTINY-Breast05) [SABCS abstract OT-03-01]. *Cancer Res.* 2021;81(4)(suppl).
45. Harbeck N, Boileau JF, Modi S, et al. A phase 3, open-label trial of neoadjuvant trastuzumab deruxtecan (T-DXd) monotherapy or T-DXd followed by THP compared with ddAC-THP in patients with high-risk HER2-positive early-stage breast cancer (DESTINY-Breast11) [SABCS abstract OT1-12-04]. *Cancer Res.* 2022;82(4)(suppl).

46. Liao S, Wang B, Zeng R, et al. Recent advances in trophoblast cell-surface antigen 2 targeted therapy for solid tumors. *Drug Dev Res.* 2021;82(8):1096-1110.
47. Ambrogi F, Fornili M, Boracchi P, et al. Trop-2 is a determinant of breast cancer survival. *PLoS One.* 2014;9(5):e96993.
48. Kopp A, Hofsess S, Cardillo TM, Govindan SV, Donnell J, Thurber GM. Antibody-drug conjugate sacituzumab govitecan drives efficient tissue penetration and rapid intracellular drug release. *Mol Cancer Ther.* 2023;22(1):102-111.
49. Bardia A, Mayer IA, Vahdat LT, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. *N Engl J Med.* 2019;380(8):741-751.
50. Bardia A, Hurvitz SA, Tolaney SM, et al; ASCENT Clinical Trial Investigators. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med.* 2021;384(16):1529-1541.
51. Sacituzumab govitecan earns full approval for triple-negative breast cancer. National Cancer Institute. https://www.cancer.gov/news-events/cancer-currents-blog/2021/sacituzumab-govitecan-tnbc-regular-approval. Posted May 12, 2021. Accessed May 12, 2024.
52. Bardia A, Punie K, Barrios CH, et al; D.H. Huynh. ASCENT-03: Phase III study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in first-line (1L) metastatic triple-negative breast cancer (mTNBC) [ESMO abstract 275TiP]. *Ann Oncol.* 2022;33(7)(suppl).
53. Tolaney SM, de Azambuja E, Emens LA, et al. ASCENT-04/KEYNOTE-D19: Phase III study of sacituzumab govitecan (SG) plus pembrolizumab (pembro) vs treatment of physician's choice (TPC) plus pembro in first-line (1L) programmed death-ligand 1-positive (PD-L1+) metastatic triple-negative breast cancer (mTNBC) [ESMO abstract 276TiP]. *Ann Oncol.* 2022;33(7)(suppl).
54. Spring LM, Tolaney SM, Fell G, et al. Response-guided neoadjuvant sacituzumab govitecan for localized triple-negative breast cancer: results from the NeoSTAR trial. *Ann Oncol.* 2024;35(3):293-301.
55. Tolaney SM, DeMichele A, Takano T, et al. ASCENT-05/OptimICE-RD (AFT-65): Phase 3, randomized, open-label study of adjuvant sacituzumab govitecan (SG) + pembrolizumab (pembro) vs pembro ± capecitabine (cape) in patients (pts) with triple-negative breast cancer (TNBC) and residual disease after neoadjuvant therapy (NAT) and surgery [ASCO abstract TPS619]. *J Clin Oncol.* 2023;41(16)(suppl).
56. FDA D.I.S.C.O. Burst Edition: FDA approval of Trodelvy (sacituzumab govitecan-hziy) for HR-positive breast cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-trodelvy-sacituzumab-govitecan-hziy-hr-positive-breast-cancer. Posted March 1, 2023. Accessed April 22, 2024.
57. Rugo HS, Bardia A, Marmé F, et al. Primary results from TROPiCS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with hormone receptor–positive/HER2-negative (HR+/HER2-) advanced breast cancer [ASCO abstract LBA1001]. *J Clin Oncol.* 2022;40(17)(suppl).
58. Rugo HS, Bardia A, Marmé F, et al. Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomized, open-label, multicenter, phase 3 trial. *Lancet.* 2023;402(10411):1423-1433.
59. Rugo H, Cortés J, Curigliano G, et al. ASCENT-07: A phase 3, randomized, open-label study of sacituzumab govitecan versus treatment of physician's choice in patients with HR+/HER2– inoperable, locally advanced, or metastatic breast cancer post-endocrine therapy [AACR abstract PO1-05-09]. *Cancer Res.* 2024;84(9)(suppl).
60. Nakada T, Masuda T, Naito H, et al. Novel antibody drug conjugates containing exatecan derivative-based cytotoxic payloads. *Bioorg Med Chem Lett.* 2016;26(6):1542-1545.
61. Dent RA, Cescon DW, Bachelot T, et al. TROPION-Breast02: datopotamab deruxtecan for locally recurrent inoperable or metastatic triple-negative breast cancer. *Future Oncol.* 2023;19(35):2349-2359.
62. Krop I, Juric D, Shimizu T, et al. Datopotamab deruxtecan in advanced/metastatic HER2- breast cancer: results from the phase 1 TROPION-PanTumor01 study [AACR abstract GS1-05]. *Cancer Res.* 2022;82(4)(suppl).
63. Bardia A, Krop I, Meric-Bernstam F, et al. Datopotamab deruxtecan (Dato-DXd) in advanced triple-negative breast cancer (TNBC): Updated results from the phase 1 TROPION-PanTumor01 study [AACR abstract P6-10-03]. *Cancer Res.* 2023;83(5)(suppl).
64. Schmid P, Jung KH, Wysocki PJ, et al. Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): initial results from BEGONIA, a phase Ib/II study [ESMO abstract 166MO]. *Ann Oncol.* 2022;33(3)(suppl).
65. Schmid P, Wysocki P, Ma C, et al. Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): updated results from BEGONIA, a phase 1b/2 study [AACR abstract PD11-09]. *Cancer Res.* 2023;83(5)(suppl).
66. Schmid P, Wysocki PJ, Ma CX, et al. Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): updated results from BEGONIA, a phase Ib/II study [ESMO abstract 379MO]. *Ann Oncol.* 2023;34(2)(suppl).
67. Schmid P, Oliveira M, O'Shaughnessy J, et al. TROPION-Breast05: Phase (Ph) III study of datopotamab deruxtecan (Dato-DXd) ± durvalumab (D) vs chemotherapy (CT) + pembrolizumab (pembro) in patients (pts) with PD-L1+ locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC) [ESMO Breast Cancer 261TiP]. *ESMO Open.* 2024;9(4)(suppl).
68. Bardia A, Jhaveri K, Im SA, et al. Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): primary results from the randomized phase III TROPION-Breast01 trial [ESMO abstract LBA11]. *Ann Oncol.* 2023;34(2)(suppl).
69. Bardia A, Jhaveri K, Im SA, et al; TROPION-Breast01 Investigators. Datopotamab deruxtecan versus chemotherapy in previously treated inoperable/metastatic hormone receptor-positive human epidermal growth factor receptor 2-negative breast cancer: Primary results from TROPION-Breast01. *J Clin Oncol.* 2025;43(3):285-296.
70. FDA approves datopotamab deruxtecan-dlnk for unresectable or metastatic, HR-positive, HER2-negative breast cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-datopotamab-deruxtecan-dlnk-unresectable-or-metastatic-hr-positive-her2-negative-breast. Posted January 17, 2025. Accessed February 17, 2025.
71. Jhaveri K, Bardia A, Im SA, et al. Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in pretreated, inoperable/metastatic HR+/HER2– breast cancer (BC): Additional safety analysis from TROPION-Breast01 [ESMO Breast Cancer LBA2]. *ESMO Open.* 2024;9(4)(suppl).
72. Bardia A, Pusztai L, Albain K, et al. TROPION-Breast03: a randomized phase III global trial of datopotamab deruxtecan ± durvalumab in patients with triple-negative breast cancer and residual invasive disease at surgical resection after neoadjuvant therapy. *Ther Adv Med Oncol.* 2024;16:17588359241248336.
73. Loibl S, Tolaney SM, Schmid P, et al. TROPION-Breast04: Phase (ph) III study of neoadjuvant (neoadj) datopotamab deruxtecan (Dato-DXd) + durvalumab (D) followed by adjuvant (adj) D vs standard of care (SoC) in treatment-naïve, triple-negative (TN) and HR-low/HER2- breast cancer (BC) [ESMO Breast Cancer abstract 159TiP]. *ESMO Open.* 2024;9(4)(suppl).
74. Weisser NE, Wickman G, Abraham L, et al. The bispecific antibody zanidatamab's (ZW25's) unique mechanisms of action and durable anti-tumor activity in HER2-expressing cancers [AACR abstract 1005]. *Cancer Res.* 2021;81(13)(suppl).
75. Weisser N, Wickman G, Davies R, Rowse G. Preclinical development of a novel biparatopic HER2 antibody with activity in low to high HER2 expressing cancers [AACR abstract 31]. *Cancer Res.* 2017;77(13)(suppl).
76. Meric-Bernstam F, Beeram M, Hamilton E, et al. Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or HER2-amplified cancers: a phase 1, dose-escalation and expansion study. *Lancet Oncol.* 2022;23(12):1558-1570.
77. Li JY, Perry SR, Muniz-Medina V, 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):117-129.
78. Jhaveri K, Han H, Dotan E, et al. Preliminary results from a phase I study using the bispecific, human epidermal growth factor 2 (HER2)-targeting antibody-drug conjugate (ADC) zanidatamab zovodotin (ZW49) in solid cancers [ESMO abstract 460MO]. *Ann Oncol.* 2022;33(7)(suppl).
79. Pegram MD, Hamilton EP, Tan AR, et al. First-in-human, phase 1 dose-escalation study of biparatopic anti-HER2 antibody-drug conjugate MEDI4276 in patients with HER2-positive advanced breast or gastric cancer. *Mol Cancer Ther.* 2021;20(8):1442-1453.
80. Chen Z, Yuan J, Xu Y, et al. From AVATAR mice to patients: RC48-ADC exerted promising efficacy in advanced gastric cancer with HER2 expression. *Front Pharmacol.* 2022;12:757994.
81. Wang P, Xia L. RC48-ADC treatment for patients with HER2-expressing locally advanced or metastatic solid tumors: a real-world study. *BMC Cancer.* 2023;23(1):1083.
82. Wang J, Liu Y, Zhang Q, et al. RC48-ADC, a HER2-targeting antibody-drug

conjugate, in patients with HER2-positive and HER2-low expressing advanced or metastatic breast cancer: a pooled analysis of two studies [ASCO abstract 1022]. *J Clin Oncol.* 2021;39(15)(suppl).
83. Kovtun YV, Audette CA, Mayo MF, et al. Antibody-maytansinoid conjugates designed to bypass multidrug resistance. *Cancer Res.* 2010;70(6):2528-2537.
84. Rock BM, Tometsko ME, Patel SK, Hamblett KJ, Fanslow WC, Rock DA. Intracellular catabolism of an antibody drug conjugate with a noncleavable linker. *Drug Metab Dispos.* 2015;43(9):1341-1344.
85. Skidmore L, Sakamuri S, Knudsen NA, et al. ARX788, a site-specific anti-HER2 antibody-drug conjugate, demonstrates potent and selective activity in HER2-low and T-DM1-resistant breast and gastric cancers. *Mol Cancer Ther.* 2020;19(9):1833-1843.
86. Junutula JR, Raab H, Clark S, et al. Site-specific conjugation of a cytotoxic drug to an antibody improves the therapeutic index. *Nat Biotechnol.* 2008;26(8):925-932.
87. Swain SM, Shastry M, Hamilton E. Targeting HER2-positive breast cancer: advances and future directions. *Nat Rev Drug Discov.* 2023;22(2):101-126.
88. Hu X, Wang L, Zhang J, et al. ACE-Breast-02: a pivotal phase II/III trial of ARX788, a novel anti-HER2 antibody-drug conjugate (ADC), versus lapatinib plus capecitabine for HER2+ advanced breast cancer (ABC) [ASCO abstract 1020]. *J Clin Oncol.* 2024;42(16)(suppl).
89. 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):315-337.
90. Yamazaki CM, Yamaguchi A, Anami Y, et al. Antibody-drug conjugates with dual payloads for combating breast tumor heterogeneity and drug resistance. *Nat Commun.* 2021;12(1):3528.
91. Conilh L, Sadilkova L, Viricel W, Dumontet C. Payload diversification: a key step in the development of antibody-drug conjugates. *J Hematol Oncol.* 2023;16(1):3.
92. Abelman RO, Spring L, Fell GG, et al. Sequential use of antibody-drug conjugate after antibody-drug conjugate for patients with metastatic breast cancer: ADC after ADC (A3) study [ASCO abstract 1022]. *J Clin Oncol.* 2023;41(16)(suppl).
93. Abelman RO, Spring L, Fell G, et al. Sequencing antibody-drug conjugate after antibody-drug conjugate in metastatic breast cancer (A3 study): multi-institution experience and biomarker analysis [AACR abstract PS08-03]. *Cancer Res.* 2024;84(9)(suppl).
94. Bardia A, Krop IE, Kogawa T, et al. Datopotamab deruxtecan in advanced or metastatic HR+/HER2- and triple-negative breast cancer: results from the phase I TROPION-PanTumor01 study. *J Clin Oncol.* 2024;42(19):2281-2294.
95. Saura C, Modi S, Krop I, et al. Trastuzumab deruxtecan in previously treated patients with HER2-positive metastatic breast cancer: updated survival results from a phase II trial (DESTINY-Breast01). *Ann Oncol.* 2024;35(3):302-307.
96. Mosele F, Deluche E, Lusque A, et al. Trastuzumab deruxtecan in metastatic breast cancer with variable HER2 expression: the phase 2 DAISY trial. *Nat Med.* 2023;29(8):2110-2120.
97. Garrido-Castro AC, Kim SE, Desrosiers J, et al. SACI-IO HR+: a randomized phase II trial of sacituzumab govitecan with or without pembrolizumab in patients with metastatic hormone receptor-positive/HER2-negative breast cancer [ASCO abstract LBA1004]. *J Clin Oncol.* 2024;42(17)(suppl).

eTable. Pertinent Trials of Dato-DXd, T-DXd, T-DM1, and SG

ADC	Trial, Disease Status	Phase	Experimental Agent(s)	Control	Identifier	Results
Dato-DXd	**Completed**					
	TROPION-PanTumor01: TNBC, HR+ BC	1			NCT03401385	**TNBC**[94]: ORR 31.8%, DOR 16.8 mo; **HR+ BC**[94]: ORR 26.8%, DOR not evaluable
	BEGONIA: TNBC	1b/2	+ Durvalumab		NCT03742102	ORR 79%, DOR 15.5 mo, mPFS 13.8 mo[66]
	TROPION-Breast01: HR+ BC	3			NCT05104866	mPFS 6.9 mo (HR 0.63, *P*<.001), mOS (HR 0.84)[68]
	Ongoing					
	TROPION-Breast03: stage I-III TNBC (adjuvant)	3	+/- Durvalumab	Immunochemotherapy	NCT05629585	
	TROPION-Breast04: stage II-III TNBC (neoadjuvant)	3	+ Durvalumab	Immunochemotherapy	NCT06112379	
	TROPION-PanTumor02: TNBC	1/2			NCT05460273	
	TROPION-Breast02: TNBC	3		Chemotherapy	NCT05374512	
	TROPION-Breast05: PD-L1+ TNBC	3	+ Durvalumab	Immunochemotherapy	NCT06103864	
	PETRA: advanced BC	1/2	+ Saruparib		NCT04644068	
T-DXd	**Completed**					
	DESTINY-Breast01: HER2+ BC	2			NCT03248492	ORR 62%, mDOR 18.2 mo, mPFS 19.4 mo, mOS 29.1 mo[95]
	DESTINY-Breast03: HER2+ BC	3		T-DM1	NCT03529110	mPFS 29.0 vs 7.2 mo (HR 0.30), mOS 52.6 vs 42.7 mo (HR 0.73)[34]
	DESTINY-Breast02: HER2+ BC	3		Chemotherapy	NCT03523585	mPFS 17.8 vs 6.9 mo (HR 0.36), mOS 39.2 vs 26.5 mo (HR 0.66)[35]
	DESTINY-Breast12: HER2+ BC +/BM	3b/4			NCT04739761	**BM:** 12-mo PFS 61.6%, 12-mo CNS PFS 58.9%; **non-BM:** ORR 62.7% [36]
	DESTINY-Breast04: HER2-low BC	3		Chemotherapy	NCT03734029	**HR+ cohort:** mPFS 10.1 vs 5.4 mo (HR 0.51), mOS 23.9 vs 17.5 mo (HR 0.64); **all population:** mPFS 9.9 vs 5.1 mo (HR 0.5), mOS 23.4 vs 16.8 mo (HR 0.64)[39]
	HER2-low BC	1b			NCT02564900	ORR 37%, mDOR 10.4 mo
	DESTINY-Breast06: HR+/HER2-low BC	2			NCT04132960	**ORR:**[96] HER2+ 70.6%, HER2-low 37.5%, HER2-null 29.7%
	DESTINY-Breast06: HR+/HER2-low BC			Chemotherapy	NCT04494425	**HER2-low:** mPFS 13.2 vs 8.1 mo (HR 0.62), ORR 56.5% vs 32.2%; **HER2-ultra-low:** mPFS 13.2 vs 8.3 mo (HR, 0.78), ORR 61.8% vs 26.3%[7]

eTable. (*Continued*) Pertinent Trials of Dato-DXd, T-DXd, T-DM1, and SG

ADC	Trial, Disease Status	Phase	Experimental Agent(s)	Control	Identifier	Results
T-DXd	**Ongoing**					
	TRIO-US B-12 TALENT: HR+/ HER2-low BC (neoadjuvant)	2	+/- Anastrozole		NCT04553770	**ORR:** T-DXd 75%, T-DXd + anastrozole 63.2%[41]
	SHAMROCK: HER2+ BC (neoadjuvant)	2			NCT05710666	
	DESTINY-Breast05: HER2+ BC (adjuvant)	3		T-DM1	NCT04622319	
	DESTINY-Breast11: HER2+ BC (neoadjuvant)	3	+/- In sequence with THP	ddAC-THP	NCT05113251	
	TRUDI: stage III HER2+ or HER2-low inflammatory BC	2	+ Durvalumab		NCT05795101	
	HER2CLIMB-04: HER2+ BC	2	+ Tucatinib		NCT04539938	
	HER2-low, HER2-ultra-low, or HER2-null BC	1b	+ Valemetostat (EZH1/2 inhibitor)		NCT05633979	
	DASH: HER2+ BC	1	+ AZD6738 (ATR inhibitor)		NCT04704661	
	DESTINY-Breast07: HER2+ BC	1/2	+/- Durvalumab, pertuzumab, paclitaxel, durvalumab/ paclitaxel, and tucatinib		NCT04538742	
	HER2+ or HER2-low BC	1	Pembrolizumab		NCT04042701	
	PRE-I-SPY-PI: HER2 IHC score > +1 BC	1	ALX148		NCT05868226	
	ALTER-BC-Ib-01: HER2-low BC	1	Anlotinib		NCT06331169	
	Morpheus-panBC: HER2+ or HER2-low BC	1/2	Inavolisib		NCT03424005	
	DESTINY-Breast08: HER2-low BC	1	+/- Capecitabine, capivasertib, durvalumab/ paclitaxel, anastrozole, fulvestrant		NCT04556773	
	Advanced BC	1/2	Hydroxychloroquine		NCT06328387	
	PETRA: advanced BC	1/2	Saruparib (AZD5305)		NCT04644068	

eTable. (*Continued*) Pertinent Trials of Dato-DXd, T-DXd, T-DM1, and SG

ADC	Trial, Disease Status	Phase	Experimental Agent(s)	Control	Identifier	Results
T-DM1	**Completed**					
	EMILIA: HER2+ BC	3		Lapatinib + capecitabine	NCT00829166	mPFS 9.6 vs 6.4 mo (HR 0.65),[19] mOS 29.9 vs 25.9 mo (HR 0.75),[20] ORR 43.6% vs 30.8%
	KATHERINE: HER2+ BC (adjuvant)	3		Trastuzumab	NCT01772472	iDFS 32.2% vs 19.7% (HR 0.54), 7-year OS rate 89.1% vs 84.4%
	Ongoing					
	Astefania: HER2+ BC (adjuvant)	3		T-DM1 monotherapy	NCT04873362	
	CompassHER2 RD: HER2+ BC (adjuvant)	3		T-DM1 monotherapy	NCT04457596	
	TUCATEMEB: HER2+ BC	2			NCT05673928	
	HER2CLIMB-02: HER2+ BC	3		T-DM1 monotherapy	NCT03975647	
	HER2+ BC	1b			NCT03032107	
	HER2+ metastatic BC	2			NCT05560308	
SG	**Completed**					
	TNBC	1/2			NCT01631552	ORR 33.3%, CBR 45.5%, mDOR 7.7 mo, mPFS 5.5 mo, mOS 13 mo[49]
	ASCENT: TNBC	3		Chemotherapy	NCT02574455	mPFS 4.8 vs 1.7 mo (HR 0.41), mOS 11.8 vs 6.9 mo (HR 0.51)[6]
	TROPiCS-02: HR+ BC	3		Chemotherapy	NCT03901339	ORR 21% vs 14%, CBR 34% vs 22%, PFS 5.5 vs 4 mo (HR 0.66),[57] OS 14.4 vs 11.2 mo (HR 0.79)[58]
	Ongoing					
	ASCENT-05: TNBC (adjuvant)	3	Pembrolizumab	Immunochemotherapy	NCT05633654	
	ASPRIA: TNBC (adjuvant)	2	Atezolizumab		NCT04434040	
	ASCENT-03L: TNBC (first-line)	3		Chemotherapy	NCT05382299	
	ASCENT-04: PD-L1+ TNBC (first-line)	3	Pembrolizumab	Chemotherapy	NCT05382286	
	ASCENT-07: HR+ BC	3		Chemotherapy	NCT05840211	
	Advanced BC	1/2	Hydroxychloroquine		NCT06328387	
	ASSET: HR+/HER2– BC, TNBC	1	Alpelisib		NCT05143229	
	PD-L1– metastatic TNBC	2	Pembrolizumab		NCT04468061	

eTable. (*Continued*) Pertinent Trials of Dato-DXd, T-DXd, T-DM1, and SG

ADC	Trial, Disease Status	Phase	Experimental Agent(s)	Control	Identifier	Results
SG	**Ongoing**					
	HER2+ BC, HR+/HER2– BC	1/2	DF1001 (immuno-therapy agent targeting NK cells)		NCT04143711	
	SACI-IO HR+: HR+/HER2– BC	2	Pembrolizumab	SG monotherapy	NCT04448886	PFS 8.4 vs 6.2 mo, OS 16.9 vs 17.1 mo (immature)[97]
	TNBC	1/2	Talazoparib		NCT04039230	
	HRD BC	1/2	Berzosertib (ATR inhibitor)		NCT04826341	
	InCITe: TNBC	2	Avelumab		NCT03971409	
	Morpheus-panBC: TNBC	1/2	Atezolizumab		NCT03424005	

BC, breast cancer; BM, brain metastases; CBR, clinical benefit rate; CNS, central nervous system; Dato-DXd, datopotamab deruxtecan; ddAC-THP, dose-dense doxorubicin plus cyclophosphamide followed by paclitaxel, trastuzumab, and pertuzumab; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+ BC, hormone receptor–positive breast cancer; HRD, homologous recombination–deficient; iDFS, invasive disease–free survival; IHC, immunohistochemistry; mDOR, median duration of response; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NK, natural killer; ORR, objective response rate; PD-L1, programmed death ligand 1; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine; TNBC, triple-negative breast cancer.